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EDITORIAL

Our Dear Readers,

We are so happy to publish the new issue of JHSM with valuable new scientific articles. This year JHSM has been completed 5 years since its establishment and we are taking firm steps towards the goals we have set. As we have mentioned before, we are increasingly contributing to the international literature day by day. We are constantly working to raise our scientific bar and to increase the success of our journal by entering valuable international indexes such as SCIExp and PubMed. We would like to thank all the authors who contributed to the strengthening of our journal by sending articles from both domestic and abroad.

Sincerely Yours,

Assoc. Prof. Alpaslan TANOGLU, MD, PhD
Editor-in-Chief

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Role of systemic immune-inflammation index in predicting mortality in cancer patients in palliative care units

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ABSTRACT

Aim: In our study, we aimed to investigate whether the systemic immune-inflammation index (SII) can evaluate mortality in cancer patients treated in the palliative care unit (PCU).

Material and Method: Cancer patients who received palliative care treatments in the PCU were screened retrospectively, and 309 patients were included in the study. The patients were divided into two groups; hospitalizations ending with discharge as Group 1 (n=154) and hospitalizations ending with exitus as Group 2 (n=155). SII values of the two groups were compared. SII was calculated with the formula of neutrophil count x platelet count / lymphocyte count. To determine the best cut-off value for the mortality distinction ability of the SII, a Receiver Operating Curve (ROC) analysis was used.

Results: The mean age and distribution of genders of the two groups were similar (p=0.706, p=0.964). There was a statistically significant difference between the SII values of the two groups (p<0.001). SII was successful in predicting mortality in cancer patients hospitalized in PCU, and the probability of mortality in patients with an SII value of 1426.29 and above at the time of hospitalization was approximately 1.8 times higher than in patients with a value below 1426.29.

Conclusion: We found that high SII values could predict mortality in cancer patients receiving palliative care in PCU. We think that SII, which is inexpensive, easily accessible, and easily calculated with only peripheral blood cell count, will provide clinicians working in PCU with important benefits, such as achieving more accurate prognostic results for the selection of treatment modalities and mortality estimation when combined with their own clinical experience. We recommend that SII be calculated in all cancer patients hospitalized in PCUs and that patients with high SII values should be followed more closely.

Keywords: Palliative care, SII, cancer, mortality

INTRODUCTION

Palliative care is a multidisciplinary approach that aims to relieve symptoms of diseases with high morbidity and mortality and improve the quality of life of patients and their families (1,2). Cancers constitute a critical part of these severe diseases with high morbidity and mortality (3,4). It has been determined that systemic and local inflammation have a role in cancer initiation, development, and progression (5,6). This inflammation network is the target in the prevention and treatment of cancer (7). Prediction of cancer prognosis is vital in reducing preventable risks (8). SII, an inflammatory index, has been associated with mortality in many types of cancer. In more than one study, high SII was found to be associated with a significant increase in mortality and a decrease in survival time. Systemic immune-inflammatory index (SII) is calculated as neutrophil count x platelet count / lymphocyte count (9-11).

Clinicians aim to identify easily accessible and easily calculated reliable markers for predicting prognosis and mortality in cancer patients. In this study, we aimed to investigate whether SII can be used as an index to predict mortality in cancer patients under palliative follow-up.

MATERIAL AND METHOD

This study was planned as a retrospective study and carried out with the permission of Hitit University Faculty of Medicine Clinical Researches Ethics Committee (Date: 14.12.2022, Decision No: 2022-106). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. All malignancy-related hospitalizations at the Palliative Care Unit (PCU) between January 2018, and June 2022, were screened retrospectively. Patients under 18, patients with a known hematological disease, patients who are using drugs that

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could affect hematologic parameters (such as steroids, chemotherapeutic agents, and antibiotics), patients with acquired immune deficiency syndrome (AIDS), pregnancy, or breastfeeding status, and those whose blood results on the first day of hospitalization could not be obtained were excluded. A total of 309 palliative care patients were included in the study. The gender, age, hospitalization duration, serum neutrophil, lymphocyte, platelet counts, hemoglobin, and albumin levels of 309 patients, and the mortality status of the patients were obtained from the archive system retrospectively. All patients were divided into two groups: Hospitalizations ending with discharge as Group 1 and hospitalizations ending with exitus as Group 2. These groups were compared in terms of demographic characteristics, hospitalization duration, peripheral blood cell count, albumin, and SII values. The SII value was calculated as SII = Neutrophil count (10^9/L) x Platelet count (10^9/L) / Lymphocyte count (10^9/L).

Statistical Analysis

For statistical analysis IBM SPSS Statistics for Windows software was used (Version 26; IBM Corp., Armonk, N.Y., USA). Descriptive statistics were reported using numbers and percentages for categorical variables. Numerical variables were reported as mean ± standard deviation and median value in parentheses. Data distribution was evaluated using the Shapiro-Wilks test. Using Pearson and Spearman correlation coefficients, relationships between variables were analyzed. Distribution-based analysis was used to compare the numerical measures of two separate study groups. Age, length of hospital stay, serum neutrophil, lymphocyte, platelet counts, albumin level, and SII value were evaluated with the Mann-Whitney U test, and serum hemoglobin level was assessed using student t-test. The Chi-Square test was used to evaluate the statistical significance of categorical variable differences across groups. By drawing the Receiver Operating Curve (ROC) and determining the area under it, the cut-off values with the best sensitivity and specificity that separate the groups based on mortality were calculated using the Youden index. Sensitivity, specificity, PPV, NPV, test precision, and odds ratio were calculated for cut-off values. For the statistical significance level, $p<0.05$ was accepted as meaningful.

RESULTS

In the whole group, 191 (61.81%) patients were male, and 118 (38.19%) were female. The median age of all hospitalizations was calculated as 72 years. The median duration of hospitalization was 11 days.

The median neutrophil count of all patients was 6.69 109/L, the median lymphocyte count was 0.96 109/L, and the median platelet count was 212 109/L. The median hemoglobin was 10 g/dL, and the median albumin value was 2.6 g/dL.

In the whole group, 155 (50.16%) patients died in the same admission to the hospital. All patients' median SII value was 1536.56 (**Table 1**).

When types of cancer were investigated in the whole group, the most frequent cancer types in palliative care were lung cancer (17.80%), gastric cancer (14.56%), colorectal cancer (13.27%), pancreatic cancer (10.36%), and breast cancer (7.44%). Most deaths were seen in patients with cholangiocellular carcinoma (87.50%), ovarian carcinoma (66.67%), and bladder carcinoma (66.67%). Every malignancy's mean SII score and the standard deviation are shown in **Table 2**.

Comparison between Discharged and Exitus Patient Groups

61.69% (n=95) of the discharged patients and 61.94% (n=96) of the deceased patients were male, and no statistically significant difference was found between the two groups (p=0.964). When examined in terms of age differences between the two groups, the median of Group 1 was 73 years, while the median of Group 2 was 72 years. The median age of the two groups did not show a statistically significant difference (p=0.706).

Table 1: Evaluation of all patients and comparison between patient groups

Variables	All Hospitalizations (n=309)	Alive (n=154)	Exitus (n=155)	Statistical significance
Gender				0.964
Male	191 (61.81%)	95 (61.69%)	96 (61.94%)	
Female	118 (38.19%)	59 (38.31%)	59 (38.06%)	
Age (years)	70.14±14.31 (72)	70.18±14.87 (73)	70.1±13.78 (72)	0.706
Hospitalization Duration (days)	15.71±15.03 (11)	12.79±13.93 (8)	18.61±15.55 (15)	<0.001
Neutrophil count (10^9/L)	7.95±5.74 (6.69)	6.81±4.41 (5.95)	9.09±6.64 (7.78)	0.001
Lymphocyte count (10^9/L)	1.1±0.81 (0.96)	1.25±1 (1.13)	0.95±0.53 (0,84)	<0.001
Platelet count (10^9/L)	231.41±139.52 (212)	235.36±135.62 (209.5)	227.48±143.61 (213)	0.785
Hemoglobin (g/dL)	10.09±2 (10)	10.21±2.11 (10.1)	9.97±1.88 (9.8)	0.302
Albumin (g/dL)	2.77±0.67 (2.6)	3.08±0.69 (3)	2.45±0.46 (2,4)	<0.001
SII	2338.21±3134.14 (1536.56)	2095±3671.24 (1085.41)	2579.84±2477.34 (1891.23)	<0.001
Mortality	155 (50.16%)			

SII: systemic immune-inflammation index

Table 2: Types of malignancies in hospitalized patients

Types of Malignancy	Patient Count (Column Percent) (n=309)	Alive (Row Percent) (n=154)	Exitus (Row Percent) (n=155)	SII (Mean±SD)
Lung	55 (17.80%)	30 (54.55%)	25 (45.45%)	2234.82±2457.879
Gastric	45 (14.56%)	17 (37.78%)	28 (62.22%)	2366.97±1953.002
Colorectal	41 (13.27%)	25 (60.98%)	16 (39.02%)	1920.86±1858.45
Pancreas	32 (10.36%)	16 (50.00%)	16 (50.00%)	1747.66±1523.459
Breast	23 (7.44%)	11 (47.83%)	12 (52.17%)	2046.60±1930.764
Prostate	23 (7.44%)	10 (43.48%)	13 (56.52%)	2775.35±2389.322
Hepatocellular	13 (4.21%)	5 (38.46%)	8 (61.54%)	2530.57±1717.702
Ovarian	12 (3.88%)	4 (33.33%)	8 (66.67%)	2108.73±1437.407
Skin	9 (2.91%)	5 (55.56%)	4 (44.44%)	5156.59±6292.337
Larynx	9 (2.91%)	6 (66.67%)	3 (33.33%)	8441.31±11720.56
Brain	8 (2.59%)	6 (75.00%)	2 (25.00%)	1454.96±939.9612
Cholangiocellular	8 (2.59%)	1 (12.50%)	7 (87.50%)	1452.52±1307.536
Renal	6 (1.94%)	4 (66.67%)	2 (33.33%)	1827.49±1661.831
Head and Neck Tumors	5 (1.62%)	3 (60.00%)	2 (40.00%)	2675.26±1208.922
Cervix	5 (1.62%)	4 (80.00%)	1 (20.00%)	3260.31±5438.002
Endometrium	5 (1.62%)	2 (40.00%)	3 (60.00%)	5153.71±6621.9
Oesophagus	5 (1.62%)	2 (40.00%)	3 (60.00%)	2376.42±1444.313
Bladder	3 (0.97%)	1 (33.33%)	2 (66.67%)	3664.44±2450.972
Soft Tissue	2 (0.65%)	2 (100.00%)	0 (0.00%)	1798.43±1672.861

SD: Standard Deviation, SII: systemic immune-inflammatory index

While the discharged patients were hospitalized for a median of 8 days, the median hospitalization period of the patients who died was 15 days, and the patients who were discharged were hospitalized for significantly longer (p<0.001).

The median neutrophil count of surviving patients was 5.95, the median neutrophil count of the deceased patients was 7.78, and the median neutrophil count was statistically significantly higher in patients who died (p=0.001). The median lymphocyte count of Group 1 was 1.13, and the median of Group 2 was 0.84; the lymphocyte count of the patients who died was statistically significantly lower (p<0.001). There was no statistically significant difference between platelet counts (p=0.785).

When the SII values were calculated, the median SII value of the patients who did not die was 1085.41, and the median SII value of the patients with mortality was calculated as 1891.23. There was a statistically significant difference between the SII values of the two groups. (p<0.001) (**Table 1**).

Prognostic Value of the SII in Terms of Mortality

To determine the best cut-off value for the mortality distinction ability of the SII, a ROC curve analysis was used [AUC 0.623 (0.032), %95 CI = 0.560-0.685, p<0.001]. The cut-off value for the SII was found to be 1426.29 with 65.8% sensitivity, 59.7% specificity, 62.2% positive predictive value, 63.4% negative predictive value, and 62.8% test accuracy (OR = 2.856, %95 CI = 1.798-4.535, p<0.001) (**Table 3** and **Figure 1**).

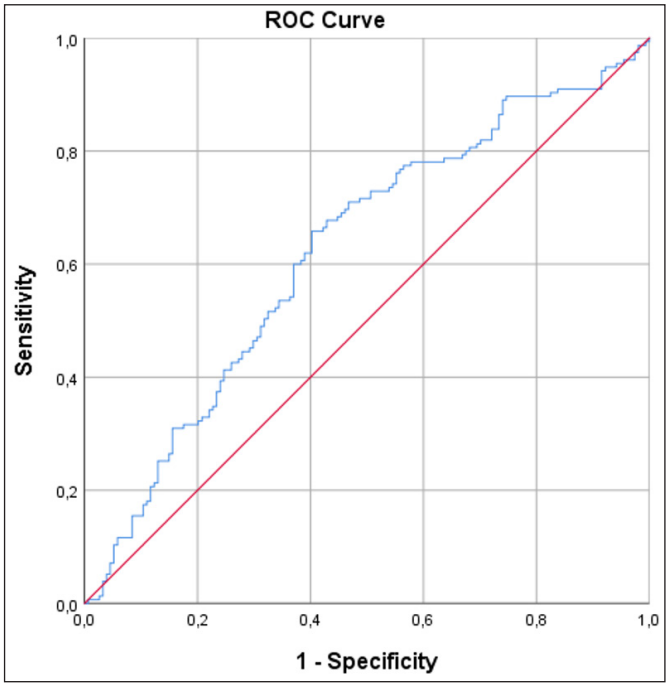

Figure 1: ROC analysis of SII and mortality

Table 3: SII cut-off values for mortality prediction in palliative care patients with malignancy

Variables	Cut-Off	Diagnostic Values					ROC Curve			Odds ratio		
		Sensitivity	Specificity	PPV	NPV	Accuracy	Area (SE)	%95 CI	p	Odds ratio	%95 CI	p
SII	≥1426.29	65.8%	59.7%	62.2%	63.4%	62.8%	0.623 (0.032)	0.560-0.685	<0.001	2.856	1.798-4.535	<0.001

SII: systemic immune-inflammation index CI: Confidence interval, PPV: positive predictive value, NPV: negative predictive value, SE: standard error, ROC: Receiver Operating Curve

The SII values predicted mortality in cancer patients hospitalized in the palliative care service. A patient with an SII value of 1426.29 or above was about 1.8 times more likely to die during hospitalization than a patient below 1426.29.

DISCUSSION

In the PCU, advanced-stage cancer patients who have no chance of curative cancer treatment and receive supportive or maintenance treatments are usually hospitalized (12). Therefore, high mortality in this patient population is an expected result. Predicting this mortality may benefit the patient, their relatives, and clinicians. Providing early palliative support in patients with advanced cancer using mortality predictors is very important in positively affecting the patient's quality of life and increasing survival (13-16). In this study, we investigated whether SII can evaluate and predict mortality in patients with cancer receiving palliative care in PCU. We demonstrated that SII could accurately predict death in this patient group. We found that the probability of mortality was 1.8 times higher in patients with an SII value of 1426.29 and above.

Markers that can predict mortality for cancer patients in PCU may provide clinicians with significant benefits in intensifying supportive treatments to support patients' quality of life and reduce mortality rates (17). For these purposes, some prognostic indexes have been developed and are also used by clinicians (18). Feliu Prognostic Nomogram (FPN), Palliative Performance Scale (PPS), Palliative Prognostic Index (PPI), and Palliative Prognostic (PaP) Score are some of the prognostic indexes used in cancer patients (19,20). PaP score is a score calculated by the parameters of Clinical Prediction of Survival (CPS), Karnofsky Performance Status (KPS), total white blood count (WBC), lymphocyte percentage, anorexia, and dyspnea. PPI is calculated according to the criteria of PPS, nutritional status of the patient, edema, delirium, and dyspnea. FPN is calculated based on the time from the initial diagnosis to detection of terminal fatal disease, serum albumin, lactate dehydrogenase, Eastern Cooperative Oncology Group (ECOG) performance status, and lymphocyte counts. PPS is a functional status measurement designed for use in palliative care. It has been shown that these indexes can successfully predict mortality in patients with cancer in palliative care (19). However, these indices are calculated based on clinician evaluations, laboratory parameters, clinical symptoms, signs, or combinations thereof. These calculations may present some difficulties and complexities for the clinician. The fact that SII can only be calculated with a simple peripheral blood cell count is an essential difference from other indices. From this perspective, we believe that SII will give a significant advantage to practitioners who cannot conduct further examinations and clinical assessments when estimating the mortality of cancer patients.

The SII, which can be easily calculated by the count of neutrophils, platelets, and leukocytes, is a biomarker showing systemic inflammatory activity (21). It is also useful in determining the balance between pro-tumor and anti-tumor immune status in cancer patients (10). Studies have found that SII is associated with mortality and prognosis in many cancer types, such as breast, stomach, esophagus, pancreas, and gastrointestinal stromal tumors (22-26). It has been found that it can be used as a prognostic marker in cancer patients, and its elevation is associated with poor outcomes (27,28). The results of our study are also in parallel with the results of these studies. In the literature, studies investigating the prognostic value of SII in cancer patients receiving palliative care regardless of cancer type are limited (29). In this study, we determined that SII could be a prognostic index independent of cancer subtype in cancer patients receiving palliative care.

The SII is a useful prognostic index for predicting mortality. However, the prognosis is not only related to the host's inflammatory response but also to the clinicopathological features of the tumor (30). The SII can evaluate the prognosis and mortality risk of cancer patients by reflecting the patient's immune-inflammatory status and may provide significant benefits to clinicians. In cancer patients, we think that more accurate prognostic predictions can be achieved by evaluating the patient's tumor characteristics, general condition, and additional comorbidities according to the clinician's experience and estimations, together with the SII.

The limitations of our study are that it was conducted retrospectively, was based on data from a single center, and involved a relatively small number of patients.

CONCLUSION

This study showed that high SII values could predict prognosis in cancer patients receiving palliative care in PCU. With this feature, SII can contribute to more reliable estimations when evaluated with clinicians' experience and other prognostic markers for estimating mortality in cancer patients receiving palliative care. The essential advantages of SII are that it can be easily calculated with only a peripheral blood cell count and that additional laboratory tests and clinical evaluations are unnecessary. We suggest calculating SII in all cancer patients hospitalized in PCUs, and monitoring patients with high values more closely. We believe that prospective studies with more patients should support our study results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Faculty of Medicine Clinical Researches Ethics Committee (Date: 14.12.2022, Decision No: 2022-106).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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MEDICINE

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Publication trends and global productivity about the anterior cruciate ligament: a bibliometric analysis between 1980-2021

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ABSTRACT

Aim: Due to anatomic, biomechanical, kinematic, biological and clinical data obtained as a result of many studies related to treatment and rehabilitation of injuries to the anterior cruciate ligament (ACL), among the most studied anatomic structures in the human body, the literature is continuously being updated and improved. In this study, the aim was to holistically analyze scientific articles about the ACL published between 1980 and 2021 using a variety of statistical methods.

Material and Method: Articles published from 1980 to 2021 about the ACL were obtained from the Web of Science (WoS) database and analyzed using statistical methods and bibliometric approaches. To identify trend topics and global cooperation, and to complete citation analysis, network visualization maps were used. The exponential smoothing predictor was used to predict the number of articles that will be published in the next 5 years. Spearman's correlation coefficient was used for correlation research.

Results: A total of 11,077 publications were identified. Of these publications, 9101 (82.1%) were articles. The top 3 countries contributing most to the literature were the USA (3894, 42.7%), Japan (879, 9.6%) and Germany (616, 6.7%). The top 3 active organizations were Pennsylvania Commonwealth System of Higher Education (n=468), University of Pittsburgh (440), and University of California system (279). The top 3 journals publishing most articles were the American Journal of Sports Medicine (n=1614), Knee Surgery Sports Traumatology Arthroscopy (1418), and Arthroscopy: The Journal of Arthroscopic and Related Surgery (915). The most effective journal according to mean number of citations per article was the Journal of Bone and Joint Surgery (average citation per document: 80.7). The most active author was Freddie H. Fu (n=278, from University of Pittsburgh).

Conclusion: In this comprehensive bibliometric research about the topic of ACL, with a trend toward increasing publication numbers in recent years, the summary information for 9101 articles published between 1980 and 2021 was shared. According to analysis results to determine trend topics, the keywords studied in recent years include return to sport, ACL injury, anterolateral ligament, pivot shift, quadriceps strength, KOOS, ACL tear, ACL repair, meniscal repair, knee ligaments, tibial slope, posterior tibial slope, return to play, adolescent, graft failure and lateral meniscus.

Keywords: Anterior cruciate ligament, ACL, bibliometric analysis, trends, injuries, global cooperation

INTRODUCTION

The anterior cruciate ligament (ACL) is the structure limiting the forward translation of the tibia and providing rotational stability of the knee in both the frontal and transverse planes (1). The ligament, with a strong fibrous structure, assists in controlling movement by limiting the mobility of the knee joint. The ACL is one of the four main ligaments in the knee and provides 85% of anterior tibial displacement limitation in knee flexion from 30 degrees to 90 degrees (2). In the body, the ACL is more susceptible to injury due to its structural properties and is one of the most studied injuries related to sports surgery in orthopedics (3). Most ACL tears are the result of a contact-free mechanism, like sudden direction changes causing the knee to turn inward (4). Sportswomen with increased dynamic valgus and high abduction loads are at higher risk in terms of ACL injury. During a landing task, knee movements and knee load are determinants of the ACL injury risk of sportswomen (5).

Biomechanical changes after ACL injury are associated with cartilage degeneration and progressive knee joint osteoarthritis development (6). ACL reconstructive surgery is recommended to ensure knee joint stability and return to function after ACL injury (1). Even if

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conservative treatment is applied to chosen patients in the general population, as a result of the inability to obtain the desired results from cases undergoing primary repair, currently the gold standard treatment for ACL injury in athletic individuals has emerged as ACL reconstruction surgery. The most frequently used autografts for ACL reconstruction are the bone patellar tendon bone (BPTB), hamstring tendon (HT) and quadriceps tendon (QT) (7). Though a variety of grafts and techniques have been defined for ACL reconstruction, currently the most popular methods are arthroscopic repairs using hamstring tendon and patellar tendon autografts (8). However, the optimal graft tissue selection for ACL reconstruction is still controversial (9,10). A meta-analysis study by Freedman et al. (9) determined that patellar tendon autografts had significantly lower graft failure rates compared to hamstring tendon autografts, better static knee stability and higher patient satisfaction. Additionally, they reported that anterior knee pain was higher in patellar tendon autograft reconstructions. The results of a meta-analysis study performed by Xie et al. (11) stated that ACL reconstruction with BPTB autografts may be superior to four-strand hamstring tendon (4SHT) autografts in sustaining rotational stability of the knee joint and higher activity levels of patients. They concluded that there was insufficient evidence to determine which of the two types of grafts were significantly superior for ACL reconstruction (10). In recent years, though there is increasing interest in biological agents focusing on platelet-rich plasma (PRP) and mesenchymal stem cells for conservative treatment for ACL tears, the evidence of benefit is still inadequate.

The incidence of ACL injuries is increasing due to the rapid increase from past to present in the numbers of people of every age playing sports. An incidence study by Mall et al. (3) in the United States stated that the incidence of ACL injuries significantly increased from 1994 to 2006, especially among women, those younger than 20 years of age and older than 40 years of age. In this study, the ACL injury incidence in the United States of America was 32.9 per 100,000 in 1994 and 43.5 per 100,000 in 2006. Every sportswoman is predicted to have nearly 10% ACL injury risk during their whole middle school and high school careers (12).

Bibliometrics is the statistical analysis of certain characteristics of publications such as author, subject, cited author, publication information, cited sources (13,14). Meta-analysis is a statistical analysis that combines the results of more than one scientific study (9,10,12). Bibliometric analysis and meta-analysis rely on quantitative techniques and can therefore reduce interpretation bias. Meta-analysis focuses on summarizing empirical evidence by analyzing the strength of effects and relationships between variables (9,10,12). In contrast, bibliometric analysis summarizes and maps the bibliometric and intellectual structure of a field by analyzing the social and structural relationships between different research components (e.g. authors, countries, institutions, topics). Therefore, well-done bibliometric studies provide scientists with a one-stop overview (13,14).

In parallel with the increasing number of publications in the literature, bibliometric research has been performed about many topics in the medical field (13-16). In addition to ACL injuries involving high health services use and high costs in financial terms, they lead to destructive outcomes for patient activity levels and quality of life. The literature is continuously updating and developing due to anatomic, biomechanical, kinematic, biological and clinical data obtained as a result of many studies related to treatment and rehabilitation of injuries to the ACL, one of the most studied anatomic structures in the human body. In this study, the aim was to holistically analyze scientific articles published about the ACL from 1980 to 2021 using a variety of bibliometric and statistical methods.

MATERIAL AND METHOD

Search Strategy

The Web of Science Core Collection (WoS by Clarivate Analytics) database was used for literature screening. The research period was determined to cover 1980 to 2021 (access date: 01.04.2022). As a result of publication screening using different keywords related to the ACL, all publications with statements related to ACL in the title were accessed. In order for the researchers to be able to access similar documents (research findings may change according to different access dates), repeatability codes were (Title=("ACL") or Title=("anterior cruciate ligament*") Refined by: Research area: (Orthopedics), Document Types: (Article), Timespan: 1980-2021). For this type of study ethics committee approval is not required. All procedures were carried out in accordance with the ethical rules and the principles.

Statistical Analysis

The exponential smoothing predictor in the Microsoft Office Excel program was used to predict the number of publications in future years according to previous publication trends. A website (https://app.datawrapper.de) was used to draw the world map. The VOSviewer (Version 1.6.16, Leiden University's Centre for Science and Technology Studies, Leiden, Netherlands) program was used to visualize bibliometric networks and for citation analysis (17). Statistical analyses were completed with the SPSS (version 22.00, SPSS Inc.,

Chicago, IL, USA, License: Hitit University) program. The fit of data to normal distribution was tested with the Shapiro-Wilks test. With the aim of assessing the correlation between global publication productivity about ACL and economic strength of countries, the correlation between the number of articles produced by countries with some markers of economic development (gross domestic product (GDP), gross domestic product per capita (GDP per capita) and human development index(HDI)) were investigated with the Spearman correlation coefficient (data obtained from the World Bank) (18). Statistical significance of a relationship was accepted as $p < 0.05$.

RESULTS

As a result of literature screening, a total of 17,343 publications published about ACL between 1980 and 2021 were found in the WoS database. Of these publications, only 11,077 studies published in the orthopedics research field were included in the study. The distribution of these studies according to publication categories were articles (9101, 82.1%), review articles (619, 5.8%), meeting abstracts (350, 3.6%), letters (320, 2.8%), proceedings papers (274, 2.4%) and the remainder were other publication types (editorial materials, early access, notes, book chapters, news items, corrections, additions, discussions, bibliographies, biographical items, books, book reviews). Bibliometric analyses were completed on 9101 publications in the article publication category from among the total of 11,077 publications. Of these articles, 97.5% (n=8880) were in English and the remainder were published in other languages (French (n=88), German (81), Czech (27), Russian (13), Turkish (7), Italian (2), Portuguese (2), Slovak (1)). Nearly all articles were included in the SCI-Expanded (n=8295, 91.1%) and Emerging Sources Citation Index (ESCI) (781, 8.5%) (the few remaining articles were indexed in the Social Sciences Citation Index (SSCI), Book Citation Index – Science (BKCI-S) and Conference Proceedings Citation Index – Science (CPCI-S)).

Development of Publications According to Year

The distribution of article numbers according to year is shown in **Figure 1**. The prediction values related to the results of the exponential smoothing prediction model used to estimate the number of articles that will be published in 2022 and later are shown in **Figure 1**. According to the estimation model results, it is predicted there will be 755 articles (confidence interval (CI) 705-806) published about ACL in 2022 and 966 (CI%: 897-1035) published in 2026 (**Figure 1**).

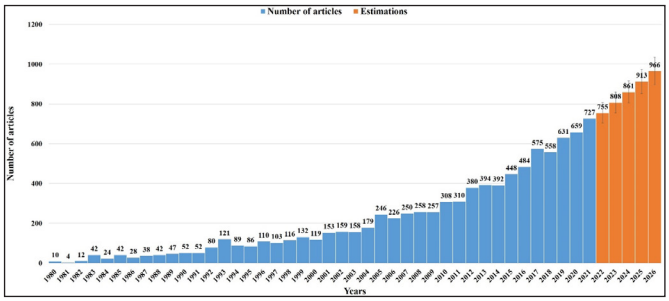

Figure 1. Bar chart showing the distribution of articles published about ACL by year and forecasts for the number of articles in the next 5 years

Active Countries

The distribution of article numbers according to country is shown in **Figure 2**. The top 20 countries publishing most articles were identified to be USA (3894, 42.7%), Japan (879, 9.6%), Germany (616, 6.7%), UK (489, 5.3%), France (417, 4.5%), South Korea (407, 4.4%), Sweden (388, 4.2%), Italy (382, 4.1%), Australia (380, 4.1%), China (352, 3.8), Canada (334, 3.6%), Switzerland (184, 2.0%), Norway (178, 1.9%), Netherlands (175, 1.9%), Turkey (167, 1.8%), Brazil (159, 1.7%), Austria (144, 1.5%), India (144, 1.5%), Spain (128, 1.4%), and Greece (123, 1.3%).

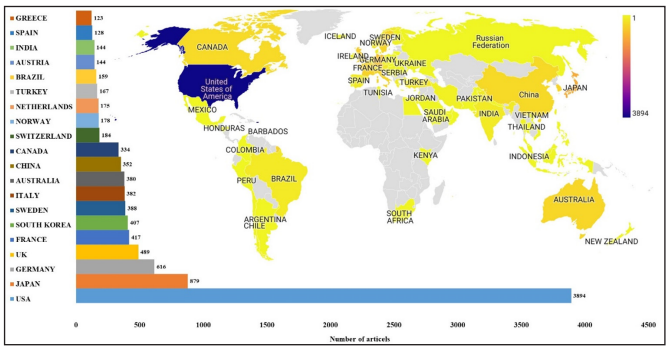

Figure 2. Global productivity world map showing the distribution of published articles about ACL by country and bar chart showing the top 20 most active countries

Cluster analysis was performed on the 50 countries producing at least 10 articles and with international cooperation between authors from among the 89 countries publishing articles about ACL and the results are shown in **Figure 3a.** According to the cluster analysis results, 9 different clusters related to international cooperation were identified (Cluster 1: Belgium, Czech Republic, England (in UK), India, New Zealand, Scotland, South Africa, United Arab Emirates, Wales. Cluster 2: Austria, Germany, Israel, Luxembourg, Netherlands, Poland, Russia. Cluster 3: Iran, Japan, Malaysia, South Korea, Taiwan, Thailand, USA. Cluster 4: Egypt, Greece, Kuwait, Qatar, Saudi Arabia, Turkey. Cluster 5: Canada, Denmark, Finland, Norway, Slovenia, Sweden. Cluster 6: Argentina, Brazil, Chile, Italy, Portugal, Spain. Cluster 7: Australia, China, Singapore. Cluster 8: Croatia, France, Ireland. Cluster 9: Serbia, Switzerland). Additionally,

the total link strength scores showing the collaborative power of the 50 countries were calculated and according to these scores the international collaboration density map is shown in **Figure 3b** (top 20 countries with highest scores USA=1055, Germany=366, England (in UK)=308, Sweden=282, Australia=267, Italy=246, France=236, Canada=215, Japan=191, Switzerland=164, Netherlands=137, Norway=133, Austria=130, Brazil=114, Greece=84, China=83, South Korea=78, Belgium=74, Luxembourg=72, Denmark=60).

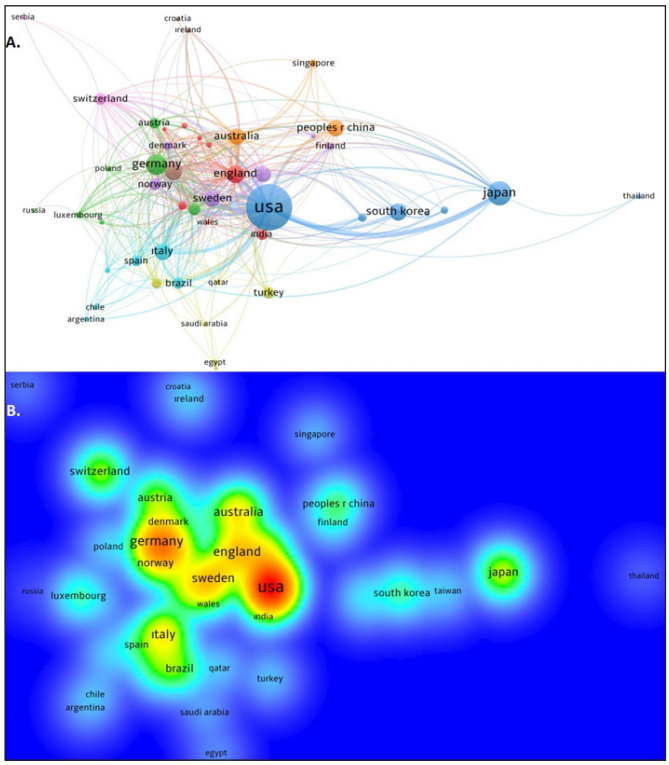

Figure 3. a. Network visualization map of cluster analysis showing cooperation between countries about ACL. Footnote: The color of the circle represents the cluster. The size of the circle indicates the number of articles. The larger the size of the circle, the more articles the country publishes. b. Density map showing the intensity of international cooperation between countries about ACL. Footnote: The strength of international cooperation score increases from blue to red (blue-green-yellow-red)

Correlation Analysis

Positive high level correlations were identified between the number of articles produced by countries with the GDP and HDI values, while there was a moderate level of statistically significant correlation with GDP per capita ($r=0.713$, $p<0.001$; $r=0.719$, $p<0.001$, $r=0.594$, $p<0.001$, respectively).

Active Authors

The top 15 authors actively publishing about ACL were identified to be Fu F.H. (n=278), Hewett T.E. (104), Spindler K.P. (102), Zaffagnini S. (98), Musahl V. (95), Bach B.R. (93), Engebretsen L. (92), Snyder-mackler L. (91), Fleming B.C. (84), Webster K.E. (81), Shino K. (76), Karlsson J. (75), Irrgang J.J. (74), Feller J.A. (73), and Yasuda K. (73)

Active Organizations

The top 20 most active organizations producing most articles about ACL were Pennsylvania Commonwealth System of Higher Education (n=468), University of Pittsburgh (440), University of California System (279), Harvard University (248), Hospital Special Surgery (238), Ohio State University (170), Mayo Clinic (134), Rush University (130), Cleveland Clinic Foundation (122), La Trobe University (121), Boston Children's Hospital (116), University of Vermont (107), Karolinska Institutet (106), Sahlgrenska University Hospital (105), University of Delaware (105), University of Oslo (105), Brown University (104), University of Michigan (102), University of Michigan System (102), and Vanderbilt University (102).

Active Journals

The 9101 articles about ACL were published in 119 different journals. The top 54 journals publishing 20 or more articles about the topic, the total citation number received by journals and the mean citation number per article are presented in **Table 1**.

Citation Analysis

The top 25 articles with most citations according to total citation number among the 9101 articles published about ACL are presented in **Table 2**. The final column in **Table 2** gives the mean citation number per year for the articles.

Co-citation Analysis

A total of 57,115 studies were identified in the reference sections of all 9101 articles published about ACL. Among these studies, the 9 studies with most co-citations and more than 350 citations were Tegner Lysholm (19) (Number of citations (NC):649), Lysholm Gillquist (20) (NC:510), Hefti et al. (21) (NC:484), Yagi et al. (22) (NC:454), Daniel et al. (23) (NC:445), Irrgang et al. (24) (NC:405), Lohmander et al. (25) (NC: 399), Noyes et al. (26) (NC:359), and Loh et al. (27) (NC: 353).

Trend topics

All of the 9101 articles about ACL used 7738 different keywords. **Table 3** shows 100 different keywords used in at least 33 different articles from among these keywords. The cluster network visualization map showing the cluster analysis results for these keywords is shown in **Figure 4**. The trend network visualization map completed to identify trend topics is shown in **Figure 5** and the citation network visualization map completed to reveal the topics receiving most citations is shown in **Figure 6**.

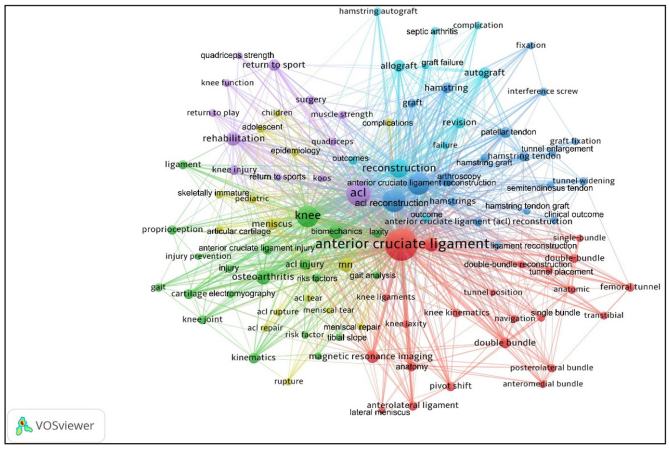

Figure 4. Network visualization map for cluster analysis based on keyword analysis performed to identify clustering of ACL topics from past to present. Footnote: The color of the circle represents the cluster. Keywords in the same cluster have the same color. The size of the circle indicates the number of uses of the keyword.

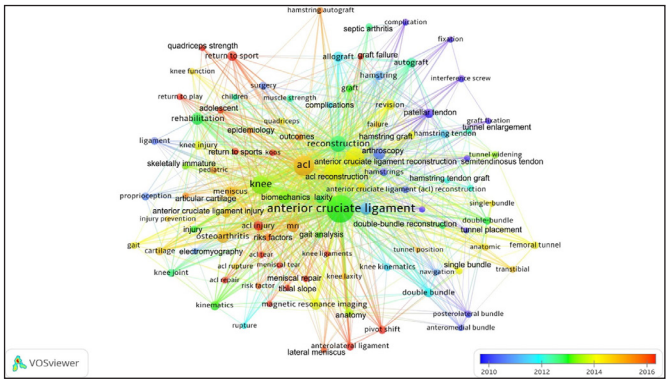

Figure 5. Network visualization map based on keyword analysis to identify past and current trends in ACL. Footnote: In the indicator given in the lower right corner of the figure, the topicality of the subject increases from blue to red (blue-green-yellow-red) over the years. The size of the circle indicates the number of uses of the keyword.

Table 1. The 54 most active journals that published more than 20 articles about anterior cruciate ligament (ACL)

Journals	NA	C	AC	Journals	NA	C	AC
American Journal of Sports Medicine	1614	108284	67.1	Journal of Pediatric Orthopaedics	51	1603	31.4
Knee Surgery Sports Traumatology Arthroscopy	1418	37836	26.7	Techniques in Orthopaedics	49	134	2.7
Arthroscopy: The Journal of Arthroscopic and Related Surgery	915	36671	40.1	Physician and Sports medicine	45	433	9.6
Knee	426	6478	15.2	Asia-Pacific Journal of Sport Medicine Arthroscopy Rehabilitation and Technology	43	108	2.5
Orthopaedic Journal of Sports Medicine	415	3482	8.4	Operative Techniques in Orthopaedics	43	417	9.7
Journal of Orthopaedic Research	357	14124	39.6	Orthopedic Clinics of North America	43	1611	37.5
Arthroscopy Techniques	235	1316	5.6	Journal of Orthopaedic Surgery and Research	42	230	5.5
Clinical Orthopaedics and Related Research	228	10871	47.7	European Journal of Orthopaedic Surgery and Traumatology	40	78	2.0
Archives of Orthopaedic and Trauma Surgery	217	3513	16.2	Journal of Orthopaedic Surgery	37	204	5.5
Journal of Bone and Joint Surgery (American Volume)	211	17030	80.7	Acta Orthopaedica et Traumatologica Turcica	36	319	8.9
Journal of Knee Surgery	185	1320	7.1	Muscles Ligaments and Tendons Journal	36	130	3.6
Arthroscopy	177	8100	45.8	International Journal of the Care of the Injured	30	491	16.4
Clinical Biomechanics	170	4566	26.9	Acta Chirurgiae Orthopaedicae et Traumatologiae Cechoslovaca	29	101	3.5
International Orthopaedics	156	3772	24.2	Journal of Experimental Orthopaedics	28	55	2.0
Orthopedics	135	2605	19.3	Journal of Orthopaedics	28	48	1.7
Journal of Orthopaedic & Sports Physical Therapy	129	6182	47.9	Acta Orthopaedica Belgica	27	252	9.3
Orthopaedics & Traumatology: Surgery & Research	100	1193	11.9	Clinics in Orthopedic Surgery	27	239	8.9
BMC Musculoskeletal Disorders	97	907	9.4	Physical Therapy	27	1960	72.6
Journal of Bone and Joint Surgery (British Volume)	97	6741	69.5	Current Reviews in Musculoskeletal Medicine	26	366	14.1
Osteoarthritis and Cartilage	90	3304	36.7	Current Orthopaedic Practice	25	40	1.6
Revue de Chirurgie Orthopedique et Reparatrice de l'Appareil Moteur	89	785	8.8	Journal of Orthopaedics and Traumatology	25	242	9.7
Clinical Journal of Sport Medicine	67	2697	40.3	Connective Tissue Research	24	326	13.6
Acta Orthopaedica Scandinavica	62	2071	33.4	Zeitschrift für Orthopädie und Unfallchirurgie	23	139	6.0
Gait & Posture	59	1172	19.9	Orthopade	22	182	8.3
Journal of Orthopaedic Science	54	822	15.2	Sportverletzung-Sportschaden	22	111	5.0
Indian Journal of Orthopaedics	54	250	4.6	Acta Ortopedica Brasileira	21	70	3.3
Skeletal Radiology	53	831	15.7	Bone & Joint Journal	20	449	22.5

NA: Number of articles, C: Number of citation, AC: Average citation per document

Table 2. The top 25 most cited articles about ACL by total number of citations

No	Article	Author	Journal	PY	TC	AC
1	Biomechanical measures of neuromuscular control and valgus loading of the knee predict anterior cruciate ligament injury risk in female athletes	Hewett TE. et al.	American Journal of Sports Medicine	2005	1899	105.5
2	Mechanisms of anterior cruciate ligament injury	Boden BP. et al.	Orthopedics	2000	923	40.13
3	Fate of the ACL-injured patient: A prospective outcome study	Daniel DM. et al.	American Journal of Sports Medicine	1994	912	31.45
4	Injury mechanisms for anterior cruciate ligament injuries in team handball a systematic video analysis	Olsen OE. et al.	American Journal of Sports Medicine	2004	760	40
5	Tensile properties of the human femur-anterior cruciate ligament-tibia complex: the effects of specimen age and orientation	Woo SLY. et al.	American Journal of Sports Medicine	1991	700	21.88
6	Accelerated rehabilitation after anterior cruciate ligament reconstruction	Shelbourne KD. and Nitz P.	American Journal of Sports Medicine	1990	697	21.12
7	Biomechanical measures during landing and postural stability predict second anterior cruciate ligament injury after anterior cruciate ligament reconstruction and return to sport	Paterno MV. et al.	American Journal of Sports Medicine	2010	693	53.31
8	Biomechanical analysis of an anatomic anterior cruciate ligament reconstruction	Yagi M. et al.	American Journal of Sports Medicine	2002	657	31.29
9	Effectiveness of a neuromuscular and proprioceptive training program in preventing anterior cruciate ligament injuries in female athletes: 2-year follow-up	Mandelbaum BR. et al.	American Journal of Sports Medicine	2005	655	36.39
10	Mechanisms of anterior cruciate ligament injury in basketball: video analysis of 39 cases	Krosshaug T. et al.	American Journal of Sports Medicine	2007	647	40.44
11	Combined knee loading states that generate high anterior cruciate ligament forces	Markolf KL. et al.	Journal of Orthopaedic Research	1995	629	22.46
12	Abnormal lower-limb symmetry determined by function hop tests after anterior cruciate ligament rupture	Noyes FR. et al.	American Journal of Sports Medicine	1991	585	18.28
13	The synergistic action of the anterior cruciate ligament and thigh muscles in maintaining joint stability	Solomonow M. et al.	American Journal of Sports Medicine	1987	547	15.19
14	Prevention of anterior cruciate ligament injuries in female team handball players: A prospective intervention study over three seasons	Myklebust G. et al.	Clinical Journal of Sport Medicine	2003	523	26.15
15	Knee stability and graft function following anterior cruciate ligament reconstruction: Comparison between 11 o'clock and 10 o'clock femoral tunnel placement	Loh JC. et al.	Arthroscopy: The Journal of Arthroscopic & Related Surgery	2003	494	24.7
16	Abnormal rotational knee motion during running after anterior cruciate ligament reconstruction	Tashman S. et al.	American Journal of Sports Medicine	2004	492	25.89
17	Incidence and trends of anterior cruciate ligament reconstruction in the United States	Mall NA. et al.	American Journal of Sports Medicine	2014	472	52.44
18	Arthroscopic anterior cruciate ligament reconstruction: A metaanalysis comparing patellar tendon and hamstring tendon autografts	Freedman KB. et al.	American Journal of Sports Medicine	2003	467	23.35
19	A biomechanical comparison of different surgical techniques of graft fixation in anterior cruciate ligament reconstruction	Kurosaka M. et al.	American Journal of Sports Medicine	1987	461	12.81
20	Patellofemoral problems after anterior cruciate ligament reconstruction	Sachs RA. et al.	American Journal of Sports Medicine	1989	458	13.47
21	Functional anatomy of the anterior cruciate ligament. Fibre bundle actions related to ligament replacements and injuries	Amis AA. and Dawkins GP.	Journal of Bone and Joint Surgery: British Volume	1991	451	14.09
22	Instrumented measurement of anterior knee laxity in patients with acute anterior cruciate ligament disruption	Daniel DM. et al.	American Journal of Sports Medicine	1985	450	11.84
23	Mechanisms for noncontact anterior cruciate ligament injuries: knee joint kinematics in 10 injury situations from female team handball and basketball	Koga H. et al.	American Journal of Sports Medicine	2010	440	33.85
24	Distribution of in situ forces in the anterior cruciate ligament in response to rotatory loads	Gabriel MT. et al.	Journal of Orthopaedic Research	2004	430	22.63
25	A 10-year comparison of anterior cruciate ligament reconstructions with hamstring tendon and patellar tendon autograft: a controlled, prospective trial	Pinczewski LA. et al.	American Journal of Sports Medicine	2007	429	26.81

PY: Publication year. TC: Total citation. AC: Average citations per year

Table 3. The 100 most frequently used keywords in articles about ACL

Keywords	Number of uses	Keywords	Number of uses	Keywords	Number of uses
anterior cruciate ligament	2522	outcomes	67	navigation	43
ACL	1037	double-bundle	66	return to play	43
ACL reconstruction	948	knee kinematics	66	ACL repair	42
Knee	824	anterior cruciate ligament (ACL) reconstruction	65	anteromedial bundle	42
anterior cruciate ligament reconstruction	820	hamstrings	65	complications	42
reconstruction	529	outcome	64	epidemiology	42
biomechanics	267	hamstring graft	62	failure	42
osteoarthritis	251	laxity	62	septic arthritis	42
anterior cruciate ligament (ACL)	243	ligament	61	single bundle	42
rehabilitation	230	risk factors	61	children	41
Arthroscopy	225	surgery	60	articular cartilage	40
MRI	205	gait	56	clinical outcome	40
magnetic resonance imaging	177	posterolateral bundle	55	tunnel enlargement	40
Meniscus	155	injury	54	ACL rupture	38
Allograft	145	tunnel widening	53	graft fixation	38
Revision	139	anatomic	51	rupture	38
return to sport	135	interference screw	51	risk factor	37
Autograft	125	muscle strength	51	fixation	36
ACL injury	123	pediatric	51	graft failure	36
Hamstring	123	KOOS	49	ligament reconstruction	36
patellar tendon	117	return to sports	49	tunnel placement	36
double bundle	110	double-bundle reconstruction	48	hamstring tendon graft	35
Kinematics	108	electromyography	48	meniscal tear	35
Anatomy	94	knee laxity	48	posterior tibial slope	35
anterior cruciate ligament injury	94	ACL tear	47	semitendinosus tendon	35
Cartilage	90	skeletally immature	47	lateral meniscus	34
hamstring tendon	86	gait analysis	46	quadriceps strength	34
knee injury	82	hamstring autograft	46	single-bundle	34
anterolateral ligament	79	adolescent	45	tibial slope	34
pivot shift	78	complication	45	injury prevention	33
proprioception	72	meniscal repair	44	knee ligaments	33
Graft	68	quadriceps	44	tunnel position	33
femoral tunnel	67	transtibial	44		
knee joint	67	knee function	43		

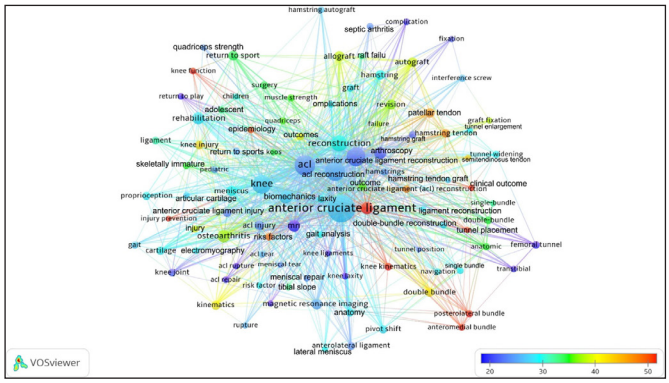

Figure 6. Network visualization map based on keyword analysis performed to identify the most cited topics about ACL. Footnote: In the indicator given in the lower right corner of the figure, the number of citations received by the topic increases from blue to red (blue-green-yellow-red). The size of the circle indicates the number of uses of the keyword.

DISCUSSION

When the article distribution about ACL between 1980 to 2021 is investigated, from 4-179 articles (mean 79 articles) were published from 1980 to 2004. From 2005-2014, from 226 to 394 articles were published (mean 302 articles). From 2015-2021, from 448-727 articles were published (mean 583 articles). The notable increasing trend beginning from 2010-2011 continued until 2021 and the number of articles published reached 727 in 2021. When prediction results for the next 5 years are assessed, it can be said the increasing trend for article numbers will continue.

When the publication distribution for global countries is investigated, 17 of the top 20 most active countries contributing to the literature for article productivity

about ACL were developed countries. Only 3 of the top 20 active countries (China, Brazil, Turkey) were developing countries, though all have large economies. There were high level positive correlations between the number of articles about ACL produced by countries with the GDP and HDI of the countries and a moderate statistically significant correlation with GDP per capita. When active countries are assessed along with development levels, article productivity in the literature about ACL is primarily affected by the economic size of countries and their development level.

When the density map created according to total collaboration between countries is assessed, the countries with highest collaboration were identified to be USA, Germany, England (in UK), Sweden, Australia, Italy, France, Canada, Japan, Switzerland, Netherlands, Norway, Austria and Brazil. When common author collaboration about ACL in countries is investigated, it appears that geographical adjacency affects international cooperation. Collaborations mainly occur between countries located in the same region (international collaboration clusters: (Croatia, France, Ireland), (Serbia, Switzerland), (Argentina, Brazil, Chile), (Italy, Portugal, Spain), (Canada, Denmark, Finland, Norway, Sweden), (Egypt, Greece, Kuwait, Qatar, Saudi Arabia, Turkey), (Japan, Malaysia, South Korea, Taiwan, Thailand), (Austria, Germany, Luxembourg, Netherlands, Poland), and (Belgium, Czech Republic, England (in UK), Scotland, Wales)).

We can recommend that authors who research and want to publish ACL should first pay attention to the top 14 journals in **Table 1** that publish the most articles on ACL. When citation analysis of the journals is assessed, the most effective journals according to mean citation numbers per article published were identified to be Journal of Bone and Joint Surgery (American Volume), Physical Therapy, Journal of Bone and Joint Surgery (British Volume), American Journal of Sports Medicine, Journal of Orthopaedic & Sports Physical Therapy, Clinical Orthopaedics and Related Research, Arthroscopy, Clinical Journal of Sport Medicine, Arthroscopy: The Journal of Arthroscopic and Related Surgery, Journal of Orthopaedic Research, Orthopedic Clinics of North America, Osteoarthritis and Cartilage, Acta Orthopaedica Scandinavica, Journal of Pediatric Orthopaedics and Acta Orthopaedica, in that order. Researchers who wish to publish studies receiving more citations are recommended to prioritize these journals.

When the analyzed articles are assessed according to total citation numbers, the study receiving most citations was identified as the study entitled "Biomechanical measures of neuromuscular control and valgus loading of the knee predict anterior cruciate ligament injury risk in female athletes" published by Hewett et al. (5) in the American Journal of Sports Medicine. The second most effective study was entitled "Mechanisms of anterior cruciate ligament injury", published by Boden et al. (28) in Orthopedics. The third most effective paper was published by Daniel et al. (23) in the American Journal of Sports Medicine entitled "Fate of the ACL-injured patient: A prospective outcome study". The fourth most effective study was published by Olsen et al. (29) in the American Journal of Sports Medicine entitled "Injury mechanisms for anterior cruciate ligament injuries in team handball a systematic video analysis". The fifth most effective study was entitled "Tensile properties of the human femur-anterior cruciate ligament-tibia complex: the effects of specimen age and orientation", published by Woo et al. (30) in the American Journal of Sports Medicine. When articles are assessed according to mean number of citations per year, the most effective study was the one by Hewett et al. (5). The second most effective study was by Paterno et al. (31) published in the American Journal of Sports Medicine and entitled "Biomechanical measures during landing and postural stability predict second anterior cruciate ligament injury after anterior cruciate ligament reconstruction and return to sport" . The third, fourth and fifth most effective studies were by Mall et al. (3), Sanders et al. (32) and Paterno et al. (33) related to the incidence of ACL reconstruction . According to the co-citation numbers for all articles analyzed, the top articles were Tegner and Lysholm (19), Lysholm and Gillquist (20), Hefti et al. (21), Yagi et al. (22), Daniel et al. (23), Irrgang et al. (24), Lohmander et al. (25), Noyes et al. (26) and Loh et al. (27) We recommend that orthopedists interested in this topic firstly read these publications.

When analysis findings about keywords are assessed, the results of cluster analysis identified 6 clusters with different colors about ACL. The keywords receiving most citations were identified as knee kinematics, knee function, posterolateral bundle, anteromedial bundle, tunnel placement, clinical outcome, epidemiology, injury prevention, risk factors, anterior cruciate ligament (ACL) reconstruction, hamstring tendon, and patellar tendon. According to analysis results to identify trend topics, keywords studied in recent years were identified as return to sport, ACL injury, anterolateral ligament, pivot shift, quadriceps strength, KOOS, ACL tear, ACL repair, meniscal repair, knee ligaments, tibial slope, posterior tibial slope, return to play, adolescent, graft failure and lateral meniscus.

We did not encounter any bibliometric study as a result of literature screening about ACL. This comprehensive study is the first bibliometric research related to this topic, which is a strong point of this study. A limitation of the research is that only the WoS database was used for literature screening. Our reason for not choosing the

PubMed database is that citation and co-citation analyses cannot be performed in PubMed. The Scopus database was not chosen due to indexing journals with low impact factor. The WoS database indexes articles published in journals with higher impact factor compared to other databases (13-15).

CONCLUSION

This comprehensive bibliometric research about ACL, a topic with an increasing trend in article numbers in recent years, shares summary information about 9101 articles published from 1980-2021. The trend in the number of articles about ACL increasing every day will continue. Nearly half of the articles originated in the USA. According to analysis results to identify trend topics, the trend keywords studied in recent years were return to sport, ACL injury, anterolateral ligament, pivot shift, quadriceps strength, KOOS, ACL tear, ACL repair, meniscal repair, knee ligaments, tibial slope, posterior tibial slope, return to play, adolescent, graft failure and lateral meniscus. This article may provide better understanding about the historical literature about ACL for clinicians, scientist and surgeons and ideas for new studies to be designed by investigating research trends.

ETHICAL DECLARATIONS

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent: For this type of study formal consent is not required.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article

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Anxiety of parents and children undergoing gastrointestinal endoscopy correlates with sedative doses

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ABSTRACT

Aim: Sedation is a fundamental component of the pediatric gastrointestinal endoscopy (GIE). The dosing of drugs to be used for sedating the child is an important aspect of the efficacy and safety of procedural sedation. Besides, outpatient procedures are stressful situations for pediatric patients and also their families, and therefore, parental anxiety may affect children indirectly. The first aim of the study was to assess the association between parental anxiety and required sedative dose in children undergoing GIE. The second aim was to assess the factors associated with children's preoperative anxiety.

Material and Method: This study was a prospective, observational, and single-center study performed by the same fellowship-trained pediatric gastroenterology specialist and the same anesthesiology specialist. Parental anxiety was evaluated with the State-Trait-Anxiety-Scale (STAI) and children's anxiety was evaluated with the Modified Yale Preoperative Anxiety Scale (mYPAS). Midazolam, ketamine, propofol, and fentanyl were administered for the children's sedation. There were 2 comparisons in this study, the anxiety of parents according to mean STAI scores, and anxiety of children according to mYPAS scores.

Results: Of 120 children and parents, 87 parents (73%) and 57 children (48%) had high anxiety. Of 120 parents, 111 parents (92%) were mothers of the children. Younger children had higher anxiety levels. Before and the start of the GIE heart rates of children were higher both in the high anxiety group of parents and children. In sedatives, high anxiety parents' children and high anxiety children were required more ketamine dosages. ($p<0,05$)

Conclusion: Parental anxiety affects anxiety in children having GIE, and this increases the required sedative doses. Children's younger age, lower weight and high ASA scores were associated with children's preoperative anxiety.

Keywords: sedation, pediatrics, parent, endoscopy, preoperative anxiety

INTRODUCTION

Gastrointestinal endoscopy (GIE) is a diagnostic and therapeutic procedure used to examine the gastrointestinal tract in the pediatric population by pediatric gastroenterologists. Sedation, which is a fundamental component of pediatric GIE, is a safe and cost-effective alternative to general anesthesia (1). The two primary types of sedation for children undergoing GIE is general anesthesia in the operating room, and intravenous (iv) sedation in the outpatient endoscopy suite. The number of pediatric endoscopies performed in outpatient settings with sedation has increased over the past few decades (2). Children's sedation is different from the adult's, particularly in preschool-aged (3). Even though sedation seems safe in children, it is associated with serious adverse events like; apnea, bradycardia, laryngospasm, pulmonary aspiration, airway obstruction, or even death. An important aspect of the efficacy and safety of procedural sedation is the dosing of drugs to be used for sedating the child. Regardless of the procedure, technical advances in patient monitoring increase patient safety. In particular, the use of pulse oximetry, microstream capnography, and bispectral index (BIS) monitoring is highly reliable measurements for the detection of abnormal ventilation and anesthesia depth during procedures.

Ketamine and propofol are both highly effective and safe in children undergoing both upper and lower endoscopy. Ketamine has its anesthetic, analgesic, and amnestic properties, and propofol is a hypnotic agent for short procedures as it is short-acting and does not accumulate with multiple doses. Ketamine-propofol drug combination is usually used in procedural sedation for children (4).

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These procedures are stressful situations for pediatric patients and also their families. Parents of children undergoing outpatient surgery stay with their children both preoperatively and postoperatively, and therefore, parental anxiety may affect children indirectly (5, 6). This can result in decreased pain threshold and more anesthetic requirements in children during the procedure.

As to former, the literature includes studies on the association between preoperative children's anxiety with parent's occupation, educational background, and anxiety (7-9).

Until now, it has not been possible to identify the association between parental anxiety and the required anesthetic dose in children undergoing GIE. The first aim of this study was to determine the association between parental anxiety and required anesthetic dose in children undergoing GIE. The second aim was to assess the factors associated with children preoperative anxiety.

MATERIAL AND METHOD

This study was a prospective, observational, and single center study conducted between February 1, 2022 and May 1, 2022. The study was carried out with the permission of Umraniye Training and Research Hospital Ethics Committee (Date: 17/06/2022, Decision No:54132726-000-1757). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was registered to the Clinical Trials, NCT05210829. Children aged between 2-17 years with American Society of Anesthesiology (ASA) Physical Status I and II, who were scheduled to undergo elective outpatient GIE under sedation by the same fellowship-trained pediatric gastroenterology specialist and the same anesthesiology specialist, and their parents were considered for enrollment in this study. Study participation consent was obtained from parents before starting the procedure. An anesthesiology specialist examined all patients before the day of the procedure. The anesthesiology consent form was given by the family.

The patient's age, gender, height, weight, ASA score, the procedure to be performed (upper or upper and lower GIE), parent's educational status, occupations, children's anxiety scale, and separation scale were recorded by an anesthesia technician in the waiting room. Parental anxiety scale assessments were done by parents and collected by the anesthesia technician. The anesthesiology specialist did not see the children or parents in the waiting room.

Children's anxiety was evaluated with the Modified Yale Preoperative Anxiety Scale (mYPAS) in the presence of their parents 15 minutes before the procedure. The mYPAS is an observational measurement of children's anxiety with a cutoff score of 30, which is commonly used to define probable anxiety. It has 27 items divided into 5 categories: Activity, Vocalizations, Emotional Expressivity, State of Arousal, and Use of Parent. Higher scores indicate greater anxiety. The mYPAS was adapted for the Turkish population by Hatipoğlu et al. (10). The agitation of the child that occurred when the child separated from their parents was evaluated with the "Parental Separation Anxiety Scale". This four-point scale includes; 1- easy to separate, 2- sobbing but easy to cease, 3- crying loudly and difficult to stop but without holding the parents and not letting them go, and 4- crying loudly and holding the parents and not willing to let them go. Parental anxiety was evaluated with the State-Trait Anxiety Scale (STAI) by parents during the child was in the procedure. This self-report anxiety assessment contains two 20-item rating scales for measuring state (STAI-S) and trait (STAI-T) anxiety. Total scores range from 20 to 80, and higher scores indicate higher levels of anxiety with a cutoff score of 40, which is commonly used to define probable anxiety. The STAI was adapted for the Turkish population by Oner and Le Compte (11).

After recording the children's anxiety and separation scale, a 22G or 24G intravenous line was secured. Cardiac, respiratory, and BIS monitoring for sedation levels were performed. Nasal oxygen administration with end-tidal carbon dioxide ($etCO_2$) monitoring was started. All medications were given according to the protocol in the clinic. For the premedication, iv 0.05 mg/kg midazolam was administered to each patient. For sedation, the initial dose of ketamine was 1 mg/kg and, if necessary, up to a maximum of 2 mg/kg was administered. For moderate sedation, anesthesia will be applied with a BIS value of 60-70. Propofol 0.1 mg/kg, maximum 3 mg/kg sedation was administered if adequate sedation cannot be achieved or if wakefulness occurs during the procedure. It was multimodal sedation, that included both midazolam, ketamine, and propofol. Fentanyl was administered only in colonoscopies. The sedation level was monitored with both Ramsay Sedation Scale (RSS) and BIS. The procedure was not started before the patient had RSS of 5 and BIS between 60-70. Before starting the procedure, the BIS value, the amount of drug administered, the patient's oxygen saturation (SpO_2), heart rate (HR), and $etCO_2$ value were recorded. After the start of the procedure, the same data were recorded again. At the end of the procedure, the duration of the procedure and the total amount of drug administered were recorded, and the patient was transferred to the recovery unit. Nasal oxygen was provided for 30 minutes in the recovery unit, and SpO_2 and HR were monitored. Adverse effects such as laryngospasm, desaturation (SpO_2 <90%), respiratory depression, bradycardia, allergies, hiccups, nystagmus, nausea, and vomiting were recorded. Patients with a Modified Stewart Scale ≥ 6 were discharged from the unit.

Statistical Methods: Power analysis was run in order to evaluate the adequate size of the sample. In order to obtain a statistical power of 80 percent with effect size of 0,71 in the study, we needed to enroll a minimum of 2 × 31 subjects to detect significant differences between groups.

Mean, standard deviation, median, minimum, maximum value frequency, and percentage were used for descriptive statistics. The distribution of variables was checked with Kolmogorov-Simirnov test. Independent Samples t-test and Mann-Whitney U test were used for the comparison of quantitative data. Chi-Square test was used for the comparison of qualitative data. SPSS 28.0 was used for statistical analyses.

Results

Participants were 124 children aged between 2 to 17 years, who were scheduled to undergo GIE, between February 1, 2022, and May 1, 2022 by the same fellowship trained pediatrics gastroenterology specialist and the same anesthesiologist, and their parents. Two patients were excluded due to flu, which was recognized at the endoscopy unit, and two patients were excluded due to being coronavirus positive. One hundred and twenty patients were enrolled in the study. (**Figure 1**) Demographic variables of children and parents were presented in **Table 1**. Of 120 patients, the median age was 12 (7, 16) years with 57% female patients, and 18 patients were ASA II. (ulcerative colitis n= 10, asthma n= 3, diabetes mellitus n= 3, coeliac disease n=2) One hundred and one patients (84%) underwent upper GIE and 19 patients (16%) underwent lower GIE. Of 120 parents, 111 parents (92%) were mothers and 9 parents (8%) were fathers of the children.

Table 1. Demographic variables of patients

Variables	Total (n=120)
Age, yr	12 (7, 16)
Preschool (1-5 years)	20 (17)
School-aged (6-17 years)	100 (83)
Child gender Female	69 (57)
Weight, kg	42 (21, 53)
ASA	
I	102 (85)
II	18 (15)
Endoscopy	
Upper	101 (84)
Upper and lower	19 (16)
Parent	
Mother	111 (92)
Father	9 (8)
Parent education level, years	8 (8, 12)
Parent occupation status None	91 (75)

Data are presented as medians (interquartile ranges) or absolute numbers (percentages).

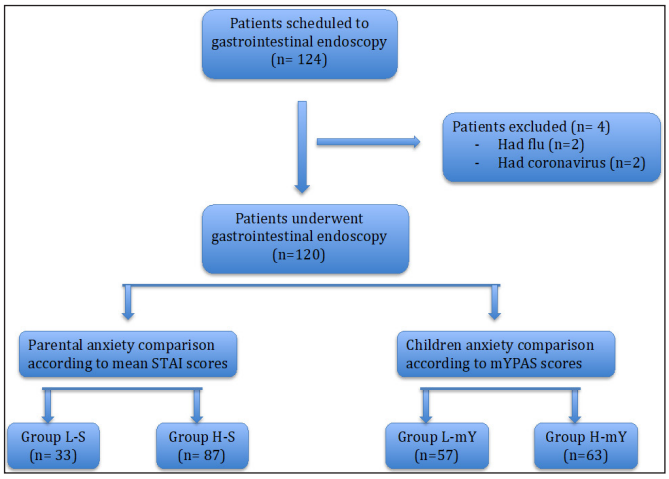

Figure 1. Flow chart

There were 2 comparisons in the current study, the anxiety of parents according to mean STAI scores, and anxiety of children according to mYPAS scores. According to mean STAI scores 87 parents (73%) had higher than 40 points, which indicated high anxiety (Group H-S). Thirty-three parents (27%) had 40 and lower than 40 points in mean STAI score, which indicated low anxiety (Group L-S). Parental education level and occupation status were not significantly different between groups. Mean STAI, STAI-S, and STAI-T scores were significantly different between groups. (p<0,001) There were no significant differences between groups in children's anxiety and separation levels. Before GIE heart rates of children in Group H-S were significantly higher than in Group L-S. (p<0,05) The start of the GIE heart rates of children in Group H-S was not significantly but higher than in Group L-S. (p=0,055) In anesthetic sedatives of children, ketamine dosage was significantly higher (p<0,05) and propofol dosage was not significantly but higher in Group H-S. Group H-S, which parents had more anxiety, children required more ketamine dosage than Group L-S. (p<0,05) There was no serious adverse event in the current study. Nausea and vomiting occurred in 29 patients; 8 (25%) patients in Group L-S, 21 (24%) in Group H-S, and there was no significant difference between groups. (**Table 2**)

In mYPAS score comparison; 57 children (48%) had higher than 30 points, which indicated high anxiety (Group H-mY). All high anxious 57 children's parents were in high anxiety group. Sixty-three children (52%) had 30 and lower than 30 points in mYPAS score, which indicated low anxiety (Group L-mY). Age, weight, and ASA of children were significantly different between groups. (p<0,05) Mean mYPAS scores were significantly different between groups. (p<0,001) Children separation scale, before and the start of GIE heart rates were significantly higher in Group H-mY. In anesthetic sedatives, ketamine dosage was significantly higher (p<0,05) and propofol dosage was not significantly but higher in Group H-mY. (**Table 3**)

Table 2. Parental anxiety comparison according to mean STAI scores

Variables	Group L-S (n=33)	Group H-S (n=87)	p value
Age, yr	13 (7, 16)	12 (7, 16)	0,846[m]
Preschool (1-5 years)	7 (22)	13 (15)	0,356[x2]
School-aged (6-17 years)	25 (78)	75 (85)	
Child gender			
Female	15 (47)	54 (61)	0,156[x2]
Weight, kg	46 (26, 53)	40 (20, 53)	0,381[m]
ASA			0,106[x2]
I	31 (94)	71 (82)	
II	2 (6)	16 (18)	
Endoscopy			0,970[x2]
Upper	28 (85)	73 (84)	
Upper and lower	5 (15)	14 (16)	
Parent			0,210[x2]
Mother	28 (85)	83 (95)	
Father	5 (15)	4 (5)	
Parent education level, years	8 (8, 12)	8 (8,12)	0,158[m]
Parent occupation status			0,115[x2]
None	21 (66)	70 (80)	
Parental STAI scores			
STAI-S	32 (26, 39)	49 (45, 54)	**<0,001[m]**
STAI-T	36 (31, 39)	45 (43, 50)	**<0,001[m]**
Mean	34 (31, 37)	48 (44, 51)	**<0,001[m]**
Children mYPAS	28 (28, 42)	28 (28, 46)	0,426[m]
Children separation scale			0,596[x2]
I	27 (82)	60 (69)	
II	2 (6)	13 (15)	
III	2 (6)	7 (8)	
IV	2 (6)	7 (8)	
Children before GIE			
HR	99 (81, 111)	107 (90, 120)	**0,034[m]**
SpO_2	100 (100, 100)	100 (100, 100)	0,273[m]
$EtCO_2$	36 (35, 40)	37 (26, 39)	0,855[m]
Children start of the GIE			
HR	100 (82, 112)	102 (93, 117)	0,055t
SpO_2	100 (100, 100)	100 (100, 100)	0,419[m]
$EtCO_2$	40 (26, 44)	38 (36, 40)	0,339[m]
Ketamine, mg/kg	1 (1, 1.4)	1.2 (1, 2)	**0,008[m]**
Propofol, mg/kg	0.3 (0, 0.5)	0.5 (0.1, 0.8)	0,127[m]
Fentanyl, mcg/kg	0 (0, 1)	0 (0, 1)	0,516[m]
GIE time, min	7 (6, 10)	8 (7, 12)	0,248[m]
Nausea and vomiting	8 (25)	21 (24)	0,898[x2]

Data are presented as medians (interquartile ranges) or absolute numbers (percentages). P-values in bold represent statistically significant results (P < 0.05). t: independent sample t-test, m: Mann-Whitney U test, X^2: Chi-square test, STAI: state trait anxiety scale, mYPAS: modified yale pediatrics anxiety scale, GIE: gastrointestinal endoscopy, HR: heart rate, SpO_2: oxygen saturation, $EtCO_2$: end-tidal carbon dioxide

Table 3. Children anxiety comparison according to mYPAS scores

Variables	Group L-mY (n=63)	Group H-mY (n=57)	p value
Age, yr	14 (11, 17)	8 (5, 13)	**<0,001[m]**
Preschool (1-5 years)	3 (5)	17 (30)	
School-aged (6-17 years)	60 (95)	40 (70)	
Child gender			
Female	33 (52)	36 (63)	0,233[x2]
Weight, kg	48 (39, 56)	23 (18, 45)	**<0,001[m]**
ASA			**0,005[x2]**
I	59 (94)	43 (75)	
II	4 (6)	14 (25)	
Endoscopy			0,625[x2]
Upper	54 (86)	47 (82)	
Upper and lower	9 (14)	10 (18)	
Parent			0,849[x2]
Mother	58 (92)	53 (93)	
Parent education level, years	8 (8, 12)	8 (8,12)	0,401[m]
Parent occupation status			0,601[x2]
None	49 (78)	42 (74)	
Children mYPAS	28 (28, 28)	45 (36, 65)	**<0,001[m]**
Children separation scale			**<0,001[x2]**
I	62 (98)	24 (42)	
II	1 (2)	15 (26)	
III	0 (0)	9 (16)	
IV	0 (0)	9 (16)	
Parental STAI scores			
STAI>40	45 (71)	43 (75)	0,620[x2]
STAI-S	45 (37, 51)	47 (41, 52)	0,185[m]
STAI-T	44 (37, 48)	44 (38, 48)	0,877[m]
Mean	44 (36, 49)	45 (40, 50)	0,351[m]
Children before the GIE			
HR	98 (85, 110)	110 (92, 121)	**<0,001[m]**
SpO_2	100 (100, 100)	100 (100, 100)	0,176[m]
$EtCO_2$	37 (36, 39)	37 (35, 39)	0,886[m]
Children start of the GIE			
HR	98 (85, 109)	113 (94, 123)	**<0,001[m]**
SpO_2	100 (100, 100)	100 (100, 100)	0,612[m]
$EtCO_2$	38 (36, 40)	38 (35, 40)	0,563[m]
Ketamine, mg/kg	1 (1, 1.5)	1.5 (1, 2)	**0,008[m]**
Propofol, mg/kg	0.3 (0, 0.7)	0.5 (0, 0.9)	0,631[m]
Fentanyl, mcg/kg	0 (0, 0)	0 (0, 0)	0,313[m]
GIE time, min	8 (7, 12)	8 (6, 11)	0,614[m]
Nausea and vomiting	11 (17)	18 (32)	0,071[x2]

Data are presented as medians (interquartile ranges) or absolute numbers (percentages). P-values in bold represent statistically significant results (P < 0.05). t: independent sample t-test, m: Mann-Whitney U test, X^2: Chi-square test, STAI: state trait anxiety scale, mYPAS: modified yale pediatrics anxiety scale, GIE: gastrointestinal endoscopy, HR: heart rate, SpO_2: oxygen saturation, $EtCO_2$: end-tidal carbon dioxide

DISCUSSION

The results of this study indicate that parental anxiety was associated with children's required anesthetic doses for sedation in GIE. All high anxious children (n=57) had high anxious parents. In 87 high anxious parents, 30 parents had low anxiety children. In our study, Group H-S required more ketamine and propofol than Group L-S. Likewise our study, other studies administered both ketamine and propofol with or without premedication to children in procedural sedations [4, 12, 13]. In a study with 125 children, who had a procedure in the emergency department, only ketamine was administered as a sedative agent and required more doses (1.5- 2 mg/kg) than in our study, in which we used multimodal sedatives (14). In addition, there was a formulation for the estimated dose of propofol to induce sedation in children, but it was hard to use in daily practice (15). This formulation included lots of calculations including body surface area. However, the optimal level of sedation differs according to the procedure. For example, in upper endoscopy, the major goal of sedation is to avoid gagging, and in colonoscopy, the goal of sedation is to avoid visceral pain (16).

In our study, we did not see any serious adverse effects of sedation like; desaturation, bradycardia. We believe that using multimodal sedation in outpatient settings protects children from serious adverse events. In one study, they used only ketamine sedation in children undergoing upper GIE and recorded 9.5% laryngospasm (17). Another study showed 20% of transient apnea in the use of only propofol for upper GIE (18). In adverse events, nausea

and vomiting were occurred in 29 children. Children with high anxiety showed higher incidence of nausea and vomiting without a significant difference (32% vs. 17%, p=0,071). In the literature there are conflicted results; Li et al. (19) showed no association between preoperative anxiety and postoperative nausea and vomiting, and Kallar and Jones (20) presented an increased preoperative anxiety results with a postoperative nausea and vomiting.

We did not find any significant difference in mYPAS scores in the comparison of parental anxiety. Similar to our results, Bumin and Uyar (21) showed that maternal anxiety levels did not have a significant association with children's anxiety. In contrast to our results, Cui et al. (9) a found positive correlation between mYPAS of the children and STAI-S score of parents in the younger aged group, but no significant difference in STAI-T scores of groups.

Before and the start of the GIE heart rates were higher in both Group H-S and Group H-mY. Supporting our results, previous literature showed that children's heart rate was positively associated with children's anxiety (22).

We showed that younger ages in children had more preoperative anxiety levels. This finding was consistent with other studies in the literature, which showed younger age was associated with higher preoperative anxiety in children (9, 22, 23). In addition, the current study showed that higher preoperative children anxiety, which included younger ages, was associated with higher preoperative separation levels. Previous literature proved that there was a correlation between age and the separation level of children. This finding might be a result of the older ages being more independent and they might have more prior experience of separation anxiety (24, 25).

The current study showed ASA II children were significantly higher preoperative anxiety levels in the comparison of children's anxiety. Similar to our results, Facco et al. (26) showed the level of anxiety was significantly related to the ASA physical status in adults. Patients belonging to ASA II and III had significantly higher anxiety levels than ASA I patients.

There are some limitations in the current study. One limitation was that we did not examine other factors that could affect the anxiety of the parents, such as parents' cognitive ability, children's or their sibling's previous surgery history. Another limitation was we did not record postoperative children's recovery time or parents' postoperative anxiety levels.

In conclusion, parental anxiety affects anxiety in children having GIE, and this increases the required sedative doses. Multimodal sedative administration might protect children from serious adverse events. These findings encourage further studies to investigate sedative doses and anxiety in both children and their parents in outpatient procedures.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Umraniye Training and Research Hospital Ethics Committee (Date: 17/06/2022, Decision No:54132726-000-1757).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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The usefulness of arylesterase in predicting contrast-induced nephropathy in ST-segment elevation myocardial infarction patients undergoing percutaneous coronary intervention

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ABSTRACT

Aim: Oxidative stress is one of the causes of contrast-induced nephropathy (CIN). Paraoxonase1 (PON1), is one of the oxidative stress markers. The most sensitive method that has been in use to measure PON1 enzyme activity is the measurement of arylesterase (AREase) activity. To explore relationship between AREase activity and CIN development.

Material and Method: A total of 58 STEMI patients were included in our study. The patients were divided into two groups as CIN (+) and CIN (-). The success of AREase activity level in predicting the development of CIN was also examined by using ROC analysis.

Results: Out of the study patients, 13 were CIN (+) and 45 were CIN (-). AREase activity was found to be statistically significantly lower in the CIN (+) group (875 U/L vs 819 U/L, p= 0.004). In the regression analysis, diabetes mellitus, contrast volume and AREase activity were determined as independent risk factors in the development of CIN. As a result of the ROC analysis, we concluded that the AREase activity level <824.1 U/L predicted the development of CIN with 61.5% sensitivity and 86.7% specificity (AUC= 0.768, 95% CI= 0.638-0.868, p=0.001).

Conclusion: AREase level is an independent risk factor for the development of CIN and can be used for the prediction of CIN development.

Keywords: Acute myocardial infarction/STEMI, angiography, coronary, coronary artery disease, percutaneous coronary Intervention (PCI), renal disease, acute

INTRODUCTION

Contrast-induced nephropathy (CIN) is an iatrogenic acute kidney injury that develops after the intravascular administration of the contrast agent for diagnostic or therapeutic purposes and is associated with increased mortality (1). The three pathophysiological mechanisms most frequently accused in the development of CIN are direct tubular damage, intra-renal vasoconstriction, and increased production of reactive oxygen species (ROS) (2). In most patients, CIN can be cured spontaneously and renal replacement therapy is not being required. However, 15% of patients who develop CIN may need temporary haemodialysis, and end-stage renal disease may develop in 4% of patients whose renal functions do not improve (3). Chronic kidney disease, diabetes mellitus, congestive heart failure, intra-arterial interventions, high contrast volume, advanced age, hypertension, hyperuricemia, and multiple myeloma are the conditions that increase the prevalence of CIN (4).

Compared with fibrinolytic therapy, percutaneous coronary intervention (PCI) is the most selective treatment in ST-segment elevation myocardial infarction (STEMI) patients because of the presence of less ischemic complications, higher preserved myocardial mass, and lower mortality rates (5). However, one of the most important complications of PCI is CIN. The frequency of CIN is higher in STEMI patients than the other patients with acute coronary syndromes (6). The risk of CIN can be minimized by hydration during and after primary PCI, keeping the volume of contrast agent limited, and also by choosing a low-osmolar contrast agent (7).

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Various biomarkers have been in use to detect the elevated amount of ROS production that has been considered as one of the most important mechanisms responsible for the development of CIN. Paraoxonase-1 (PON-1) is the enzyme that binds to high density lipoprotein (HDL) and protects it from oxidative modification and hydrolysis by hydrogen peroxide (8). It is known that PON-1 activity decreases in systemic oxidative stress and atherosclerosis (9). One of the two substrates used for the measurement of PON-1 activity is arylesterase (AREase). It has been previously shown that oxidative stress increases in CIN and coronary artery disease (4, 10). However, the relationship between CIN and AREase activity in STEMI patients has not been studied before. In our study, we investigated whether there is a relationship between AREase, a marker of oxidative stress, and the development of CIN in STEMI patients undergoing primary percutaneous intervention and whether this relationship can be used for the prediction of CIN in STEMI.

MATERIAL AND METHOD

Study Population

This is a single centre, retrospective, cross-sectional study. Between October 2019 and January 2020, a total of 58 patients who met the study criteria were included in the study. The exclusion criteria of the study were determined as the presence of acute or chronic infection, malignancy, autoimmune disease, pregnancy, breastfeeding, known systolic heart failure and being under 18 years of age. Patients taking drugs with antioxidant effects were excluded from the study. Individuals who refused to be part of the study were also excluded.

STEMI was defined as chest pain together with the detection of new or presumed new ST segment elevation in ≥ 2 adjacent leads in 12-lead electrocardiography. Emergency coronary angiography was performed to all patients in this group, and as a standard, acetylsalicylic acid, clopidogrel or ticagrelor and heparin were given before angiography, also, if not contraindicated, beta-blockers, angiotensin-converting enzyme inhibitors, and statins were prescribed during hospitalization. Contrast-induced nephropathy has been characterized by an increase in serum creatinine level (≥ 0.5 mg/dL or ≥ 25%), within 48–72 hours after the administration of a contrast agent (11). According to this definition, patients were divided into two groups as CIN (+) and CIN (-). To all of the groups, iohexol, a low osmolar contrast agent, was administered during coronary angiography.

This study was retropesctively designed as a part of entitled "Oxidative stress parameters in patients with ST segment elevation myocardial infarction and the effects on in-hospital prognosis" which was a prospective study supported by Scientific Research Project Unit of Zonguldak Bülent Ecevit (BAP 2019-21664500-01). The study was carried out with the permission of Zonguldak Bülent Ecevit University Non-interventional Clinical Researches Ethics Committee (Date: 11.05.2022, Decision No: 2022/09-8). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data Collection & Blood Sample Preparation

Demographic information, heart rate, systolic blood pressure, body mass index, smoking status, presence of hyperlipidaemia, hypertension and diabetes mellitus, as well as the medications of the patients were recorded for all patients included in the study. Hypertension was defined if an individual had systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg in more than two measurements in the hospital, previously diagnosed as hypertensive or if an individual was under the usage of any antihypertensive medications. Hyperlipidaemia was defined if an individual had serum triglyceride levels ≥200 mg / dl, low-density lipoprotein cholesterol levels ≥130 mg / dl, serum total cholesterol levels ≥240 mg / dl, previously diagnosed as hyperlipidemic, or if an individual was under the usage of lipid-lowering medication. Diabetes mellitus was defined as having fasting plasma glucose levels more than 126 mg / dL in multiple measurements or if an individual was already diagnosed as diabetic, or if a person was under the usage of antidiabetic medications. Both the active smokers and ex-smokers were included in the study as smokers.

Detection of infarct related artery (IRA) as spontaneous complete recanalized in coronary angiography performed before primary percutaneous coronary intervention (PCI) in patients with STEMI was defined as Thrombolysis in Myocardial Infarction (TIMI) flow grade 3.

Transthoracic echocardiography was performed to the patients in the patient group within 24-48 hours after admission to the hospital, and to the patients in the control group at the outpatient admissions clinic. Left ventricular ejection fraction (LVEF) was measured and recorded with biplane images, and patients with LVEF < 50% was regarded as having early left ventricular systolic dysfunction. In-hospital mortality was also recorded in the patient group.

Blood samples of the study patients were taken from the antecubital veins while preparing the patients for coronary angiography and collected into the biochemistry tubes with K2EDTA. Hemogram analysis was performed with

LH 780 Analyser (Beckman Coulter, Miami, USA). Lipid parameters and routine biochemistry parameters were immediately measured with the ADVIA 2400 (Siemens, NY, USA) device. The blood samples were centrifuged at 3000 rpm for 10 minutes and the sera were separated. Separated sera were stored in eppendorf tubes at -80 degrees Celsius until AREase activities were measured.

Arylesterase (AREase) Activities

ELISA kits were used to determine serum PON-1 and AREase activities (Relassay, Turkey). PON-1 activity was measured spectrophotometrically at 37°C and 412 nm and AREase activity was measured at 37°C and 270 nm PON-1 activity was expressed as international units per 1 litre of sera (U/L) and AREase activity was expressed as kilo units per 1 litre of sera (KU/L) (12, 13).

Statistical Analysis

Statistical analyses were performed with SPSS 19.0 software. Distribution of data was determined by Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum) and categorical variables as frequency and percent. Categorical variables were compared using Pearson Chi-square test. Continuous variables were compared with independent sample t test or the Mann-Whitney U test for two groups. The variables of age, hypertension, diabetes mellitus (DM), contrast volume, AREase value and LDL-C were used in Multivariate Binary logistic regression analysis with the backward elimination method to determine risk factors according to the presence of CIN. MedCalc 19.6.4 was used to calculate receiver operating characteristic (ROC) analyses, to determine the optimal cut-off value of AREase to predict the development of CIN. P value of less than 0.05 was considered as statistically significant for all tests.

RESULTS

Among 45 patients, 13 were CIN (+). The frequency of CIN was 22.4%. Both groups were similar in terms of age and sex. Not only diabetes mellitus but also hyperlipidaemia occurred more in CIN (+) patients and this was statistically significant (p= 0.043 and p= 0.038). Demographic and clinical characteristics of the study patients were shown in **Table 1**. No difference was recorded in terms of echocardiography parameters and the patient medications. Contrast volume used was significantly elevated (222 ± 25 ml vs 197 ± 8 ml, p= 0.004) in the CIN (+) group.

Routine biochemical and hemogram values as well as AREase activity levels were shown in **Table 2**. LDL-C was significantly decreased in CIN (+) patients (124 ± 38 mg/dL vs 103 ± 34 mg/dL, p= 0.043). AREase activity was also significantly decreased in CIN (+) group (875 [252-1007] U/L vs 819 [371-939] U/L, p= 0.004) as shown in **Figure 1**.

Table 1. Demographic properties and clinical characteristics of the study patients.

Variables	CIN (-) n= 45	CIN (+) n= 13	P
Age (years), mean±SD	59±12	61±12	0.608
Male, n (%)	32 (76)	14 (87)	0.346
Diabetes mellitus, n(%)	12 (26)	8 (61)	0.043
Hypertension, n(%)	15 (35)	8 (50)	0.324
Smoking, n(%)	30 (71)	11 (68)	0.843
Hyperlipidemia, n(%)	26 (61)	5 (31)	0.038
Body mass index (kg/m2)	26.1 [17-52]	26.9 [23-35]	0.300
Systolic blood pressure (mmHg)	128 ± 20	139 ± 22	0.070
Admission heart rate (beats/min)	79 ± 13	86 ± 12	0.093
Anterior MI presentation	23 (54)	5 (31)	0.101
TIMI 3 flow	13 (30)	3 (18)	0.357
Stent length (mm)	20 [12-41]	22 [9-42]	0.483
Contrast volume (ml)	222 ± 25	197 ± 8	0.004
Infarct related coronary artery (n,%)			0.673
LAD	23 (51)	5 (38)	
CX	7 (15)	2 (16)	
RCA	15 (33)	6 (46)	
Echocardiography parameters			
LA (mm)	37 [30-50]	36 [32-48]	0.588
IVS (mm)	12 [9-15]	12 [9-17]	0.879
PW (mm)	11 [9-14]	11.5 [9-16]	0.555
EDD (mm)	48 [42-65]	47.5 [42-61]	0.787
ESD (mm)	31 [25-40]	30 [26-41]	0.587
EF (%)	45 [30-60]	45 [30-60]	0.860
Drug use			
RAS blocker	14 (33)	5 (31)	0.881
Diuretic	6 (14)	2 (12)	0.861
Beta blocker	7 (16)	3 (18)	0.852
Alfa blocker	0 (0)	1 (16)	0.105
CCB	6 (14)	4 (25)	0.339
Anti platelet	8 (19)	1 (6)	0.233
Combine antihypertensive	10 (23)	5 (31)	0.566
Statin use	11(26)	2 (12)	0.268

Abbreviations: CCB: Calcium channel blockers, CIN: Contrast induced nephropathy, CX: Circumflex, EDD: End diastolic diameter, EF: Ejection fraction, ESD: End systolic diameter, IVS: Inter ventricular septum, LA: Left atrium, LAD:Left anterior descending, PW: Posterior wall, RAS: Renin angiotensin system, RCA: Right Coronary artery, TIMI: Thrombolysis in Myocardial Infarction.

Table 2. Laboratory findings and the studied oxidative stress markers.

Variables	CIN (-) n= 45	CIN (+) n= 13	P value
Urea (mg/dL)	33 [12-83]	40 [23-87]	0.085
Creatinin (mg/dL)	0.9 [0.6-1.2]	0.9 [0.5- 4.6]	0.724
TC (mg/dL)	190 [88-360]	155 [115-241]	0.059
LDL-C (mg/dL)	124 ± 38	103 ± 34	0.043
HDL-C (mg/dL)	39 ± 8.4	39 ± 5.2	0.778
Triglyceride (mg/dL)	151 [56-465]	136 [52-233]	0.100
Peak troponin-T (ng/mL)	5.5 [0.26-131]	2.5 [0.3-10]	0.263
Peak CK-MB (ng/mL)	142 [1.3-300]	116 [21-300]	0.807
WBC count (103/μL)	10.4 6-19	10 (7.9-22)	0.986
Hemoglobin (g/dL)	13.8 ± 2.0	14.1 ± 2.4	0.595
Platelet (103/μL)	245 (140-563)	213 (79-379)	0.409
AREase (U/L)	875 [252-1007]	819 [371-939]	0.004

Abbreviations: AREase: Arylesterase, AU: Arbitrary Unit, CIN: Contrast induced nephropathy, CK-M: Creatine kinase MB, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, OSI: oxidative stress index, TAS: Total antioxidant status, TOS: Total oxidant status, TC: Total cholesterol, U/L: Unit/ Liter, WBC: White blood cell.

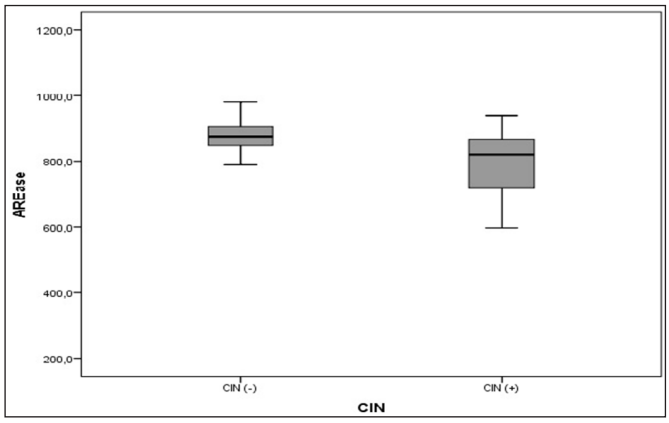

Figure 1. Box plot presentation comparison of arylesterase activity among CIN (+) and CIN (-) groups

In order to determine the independent risk factors in the development of CIN, a Multivariate Binary Logistic Regression analysis was performed by modelling age, LDL-C, hypertension, AREase activity, contrast volume and diabetes mellitus (**Table 3**). As a result of this analysis, diabetes mellitus, contrast volume and AREase activity were determined as independent risk factors for the development of CIN. With the ROC analysis, we concluded that the AREase activity level <824.1 U/L predicted the development of CIN with a sensitivity of 61.5% and a specificity of 86.7% (AUC= 0.768, CI= 0.638-0.868, p=0.001) (**Figure 2**).

Table 3. Multivariate binary logistic regression analysis of independent risk factors for the presence of contrast induced nephropathy in all study patients

Indicators*	Rank**	OR	%95 CI	P value
Hypertension	1	1.417	0.187-10.762	0.736
LDL-C	2	1.013	0.985-1.041	0.372
Age	3	0.937	0.853-1.029	0.171
AREase	4	0.992	0.986-0.998	0.015
DM	4	6.723	1.133-39.882	0.036
Contrast volume	4	1.078	1.025-1.134	0.002

*Abbreviations: ARE: Arylesterase, DM: Diabetes Mellitus, LDL-C: Low-density lipoprotein cholesterol. **Indicates the rank of elimination in stepwise backward LR method.

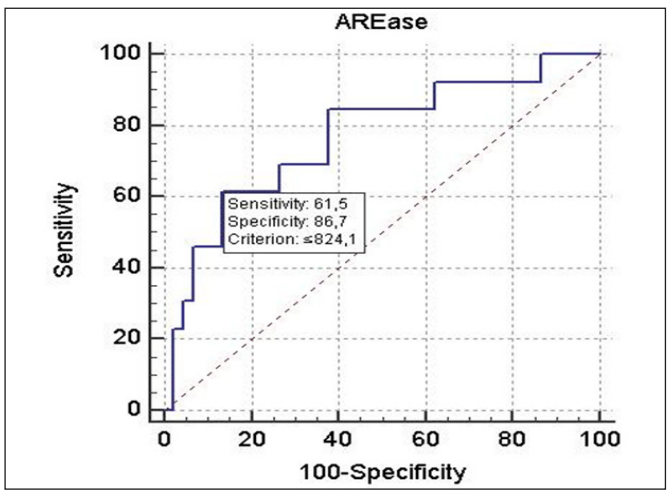

Figure 2. ROC curve analysis of the arylesterase activity level for the evaluation of CIN presence.

DISCUSSION

In this study, we found a significant relationship between AREase level and the development of CIN in STEMI patients who underwent percutaneous intervention. AREase level was significantly lower in patients with CIN (+), and we found a moderate negative correlation in the correlation analysis. After adjusting the other parameters, the presence of diabetes mellitus, contrast volume and AREase activity were found as independent predictors to determine of the development of CIN.

Paraoxonase-1 (PON-1) is an HDL-related enzyme ester with antioxidant and antiatherosclerotic properties. Paraoxonase activity (PONase) and AREase activity are used to measure PON-1 activity (14). AREase is defined as calcium dependent esterase/ lactonase like paraoxonase. However, AREase seems to be more sensitive than PONase in determining PON-1 activity as AREase activity is minimally affected by PON-1 polymorphisms and had lower inter-individual variability (15). For this reason, we decided to study AREase for the measurement of PON-1 activity. To our knowledge, there has been no previous study investigating the relationship between CIN and AREase activity. However, in one study, PON-1 activity was measured in STEMI patients by evaluating PONase, paraoxon hydrolysis (diethyl-p-nitrophenylphosphate), and it was found to be associated with CIN (16). In this study, the rate of diabetes mellitus patients was higher in the CIN (+) group, but no sub-analysis was performed. Similarly, also in our study, AREase activity values reflecting PON-1 activity were found to be associated with the presence of CIN.

AREase activity values reflecting PON-1 activity were found to be significantly lower in people with angiographic coronary artery disease than those with normal coronary arteries, and the low enzyme activities were also shown to be more pronounced in those with occlusion in all three coronary arteries (17). In a study performed by Tang et al. (14) it was found that the low serum AREase and paraoxonase activities in patients with stabile coronary artery disease were both associated with increased risk for major cardiovascular events. However, in this study, the prognostic value of AREase activity were reported to be much higher than the paraoxonase activity (hazard ratio 2.63; 95% CI, 1.97–3.50; P<0.01). In addition to this, it is known that PON-1 activity decreases in patients with chronic kidney disease (15).

In a meta-analysis study, the incidence of CIN in STEMI patients was reported to be closely related with hypertension, diabetes, presence of previous myocardial infarction, age, damaged left anterior descending artery, Killip class 2, decreased left ventricular ejection fraction, lower estimated glomerular filtration rate and

left ventricular ejection fraction <40% (18). In our study, no relationship was found between the responsible coronary artery or stent length and CIN. However, we concluded that the presence of diabetes, contrast volume and AREase activity are independent risk factors for the development of CIN.

Large randomized studies have demonstrated the relationship between high LDL-C and cardiovascular diseases as well as mortality (19). However, major adverse cardiovascular events (MACE) have been found to be associated with low LDL-C at admission stage in STEMI patients, and this situation has been expressed as lipid paradox (20). Although the underlying mechanism is unclear, low LDL-C levels at the admission stage was found to be associated with CD14++CD18+ monocytes in STEMI patients, moreover LDL-C levels less than 85 mg/dL at the admission stage was found to be associated with increased risk for MACE during a median follow-up of 2.7 years. (21). In our study, the LDL-C level was found to be lower in the patient group with CIN (+) than in the group with CIN (-). However, regression analysis failed to demonstrate LDL-C as an independent risk factor for CIN.

There is only one study evaluating the development of CIN and oxidative stress parameters in anterior STEMI patients who underwent percutaneous intervention. In this study, total antioxidant status (TAS), total oxidative status (TOS), and oxidative stress index (OSI) and paraoxon were used to evaluate PON-1 activity as oxidative stress markers (16). A significant correlation was found between all oxidative stress markers and CIN, and according to the regression analysis, PON-1 activity and OSI values were found to be the independent predictors. In our study, AREase, which was shown to be more sensitive to PON-1 activity, was used, and as a result, a significant correlation was found between AREase activity and CIN development in all STEMI patients who underwent percutaneous intervention.

Studies have been conducted on the administration of antioxidants to reduce the development of CIN associated with overproduction of reactive oxygen radicals. Meta-analyses have also shown that the administration of N-acetylcysteine along with hydration reduces the development of CIN (22, 23). Positive effects of ascorbic acid, another antioxidant, on coronary angiography-related nephropathy have also been demonstrated (24). On the other hand, in another study, prophylaxis administration with oral a- or g-tocopherol (vitamin E) was found beneficial in addition to hydration to reduce the development of CIN in patients with chronic kidney disease undergoing coronary angiography (25). It has been previously shown that statins prevent the development of CIN by reducing inflammation and oxidative stress with their pleiotropic effects (26).

Study Limitations

Our study had some limitations. Smoking and statin usage are conditions that affect oxidative stress. However, in our study, the two groups were similar in terms of smoking and statin usage. Therefore, no additional analysis was performed. Also, the patients taking antioxidant drugs such as zofenopril, captopril, and nebivolol were excluded from the study. The most important limitation of our study was the small sample size. In future, our knowledge on this subject will increase with prospective studies that will be conducted in a larger population by grouping and separating diabetic patients. Another limitation may be the seasonal period in which the study was conducted. The design of our study was cross-sectional and included patients over a three-month period, so the results may have been affected by seasonal differences.

CONCLUSION

Inspection of AREase activity in STEMI patients undergoing percutaneous intervention is an independent risk factor for the development of CIN and can be used for prediction. In summary, we can say that AREase activity measurement provides very valuable information in terms of CIN risk in STEMI patients who underwent percutaneous intervention.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Zonguldak Bülent Ecevit University Non-interventional Clinical Researches Ethics Committee (Date: 11.05.2022, Decision No: 2022/09-8).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Evaluation of osteoporosis knowledge level of women who applied to the family medicine outpatient clinics of a university hospital

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ABSTRACT

Aim: This study aimed to assess the knowledge, attitude, and behavior of women aged 18–45 years toward osteoporosis.

Material and Method: A total of 368 females (average age:32.59±7.58) who applied to the family medicine outpatient clinics between 15 May 2016 and 15 August 2016 participated in this study. Participants completed the revised osteoporosis knowledge test, which contained 12 socio-demographic questions.

Results: The average score for participants in the exercise subgroup was found to be 9.56±3.62 out of 20; the average score for the nutrition subgroup was 12.86±4.17 out of 26, and the average total score was 15.08 ± 4.82 out of 32. In general, the average score of participants was found to be 50% percent or less of the maximum scores of each subgroup of the questionnaire. This result suggests that women have inadequate knowledge about osteoporosis. Participants' level of knowledge of osteoporosis was related to their education levels, occupational groups, and smoking status. High educational levels of participants correlated with high average scores ($p<0.05$). Cigarette smoking correlated with low average scores ($p<0.05$). Healthcare workers had higher average scores than non–healthcare workers ($p<0.05$) but the scores were generally considered to be low for both groups.

Conclusion: We can infer that the osteoporosis knowledge level of our study participants is low. Education of whole communities, especially women, should be embarked on. The main focus of this activity should be on the risk factors that engender osteoporosis and basic preventive measures before the disease develops. Exercise and nutrition should be adopted as a lifestyle. Although this duty concerns all healthcare providers, it mostly relies on primary care physicians.

Keywords: Osteoporosis, osteoporosis knowledge test, women, patient education

INTRODUCTION

Osteoporosis (OP) is a metabolic bone disease that worsens over time, leading to decreased bone mineral density and strength, increased bone fragility, and an increased risk of fracture, resulting from deterioration in bone microarchitecture (1). OP should be considered a severe public health issue in climes where life expectancy is rising. Due to the increase in the average life expectancy in our country and because Turkish women possess many risk factors, osteoporosis poses a significant health issue that requires prompt diagnosis and preventive measures (2).

Since 80% of OP patients are women, it is considered a women's health issue in many climes (3). OP is a disease that can be prevented and its development can be delayed by decreasing the risk factors (4). There is a need to raise awareness about osteoporosis in every period of life. However, raising awareness, especially at young ages and in the pre-menopausal period, will have a greater impact on the preservation of bone health and the prevention of disease development (5). The most important approaches in prevention are the gaining of optimal bone mass during childhood and adolescence and the preservation of the gained bone mass afterward. Therefore, screening for osteoporosis risk factors in women and the creation of awareness regarding proper diet and exercise at an early age should be done regularly. These measures are seen as the most effective ways to lower the burden of osteoporosis on the health system (6,7).

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The key, according to modern public health Philosophy, is to safe guard and enhance one's health while still being healthy. Prevention is the primary line of defense against osteoporosis. Nutrition is crucial, especially in the developmental age. Adequate intake of calcium and vitamin D contributes to bone metabolism. Also, performing exercises such as aerobics, weight training, and walking protects one from osteoporosis. Exercise is very important in maintaining and restoring the structural adequacy of bone mass. Physical activities and exercises reduce the loss of bone mass (8).

Since preventing osteoporosis is the main goal, education about nutrition, lifestyles, and risk factors is required for the entire population, especially risk groups. Within the context of preventive health services, it has become imperative to provide training on bone health and awareness–raising initiatives by family physicians. Raising awareness is one of the core competencies of family medicine, an inclusive approach, health promotion, and disease prevention strategies. Primary prevention practices are constantly emphasized and supported by family medicine.

This study aims to assess the knowledge and awareness of osteoporosis among women between the ages of 18 and 45 years, who applied to our outpatient clinics. Following the questionnaire, it is planned to increase the knowledge level of people by providing individualized instruction on exercise and calcium-rich nutrition in the study universe.

MATERIAL AND METHOD

Before commencing the study, approval was obtained from the Ankara University Scientific Research and Publication Ethics Committee (Date: 28.03.2016, Decision No: 06-226-16). In addition, informed consent was obtained from all participants.

Our study is cross-sectional and descriptive. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Our study was conducted at the family medicine outpatient clinics of our hospital, which is a university hospital (tertiary center), between May 15, 2016, and August 15, 2016. The study comprised 368 female volunteers between the ages of 18–45, who applied to our outpatient clinics for any reason and consented to participate in the study. Those who declined to participate in the study were excluded from the study.

39 female patients who applied to the family medicine outpatient clinic underwent a pilot study since the revised 2011 osteoporosis knowledge test (OKT) had never been applied for the study. The sample size we required was at least 340 persons as established by the findings of the pilot study, which showed that the average in the groups was calculated as 14.3 and the standard deviation as 4.7, based on factors, and when the margin of error was taken as α=0.005 and power=0.95.

The study, a questionnaire study aimed to compare the osteoporosis knowledge levels of the participants in subgroups. The original scales in the test were created in 1991 by Kim KK, Horan ML, and Gendler P (9,10). It was translated into Turkish by Kılıç D et al. (11) in 2004 and its validity and reliability study was performed. Later, it was revised by adding eight questions questioning the risk factors in 2011 and translated into Turkish by Şimşir Atalay et al. (12) in 2015 and its validity and reliability study was conducted.

The questionnaire has two parts and a total of 44 questions. The first part consists of 12 questions assessing socio-demographic characteristics, the second part consists of the revised 2011 OKT. The revised 2011 OKT has two subsections. Section 1, the nutrition subgroup, contains 26 questions (1–11 and 18–32). Section 2, the exercise subgroup, includes 20 questions (1–17 and 30–32). 14 questions of these two subgroups are common (1–11 and 30–32). This was factored into the overall score, which has a range from 0 to 32.

Questions 1–11 assessed knowledge of the risk factors for osteoporosis and the answers are considered valid if one of the options is ticked. A sample of one the options are: “There is a high probability of osteoporosis”, “There is a low probability of osteoporosis”, “It has nothing to do with the development of osteoporosis” and “I do not know.” The answers "It has nothing to do with the development of osteoporosis" and "I do not know" are assessed as wrong and given 0 points. The answers "There is a high probability of osteoporosis" and "There is a low probability of osteoporosis" are considered correct and 1 point is given. Other questions contain four optional answers and 1 point is given when correct answers are marked.

The overall average score in the questionnaire is ranked between 0 and 32. The total score of the exercise scale part is between 0 and 20, and the total score of the nutrition scale part is between 0 and 26. A high score indicates that the participant's knowledge of osteoporosis is at a good level.

Statistical Analysis

Data analysis was done with the Statistical Package for Social Sciences (SPSS) 11.5 package program.

Shapiro–Wilk tests were performed to determine whether the numerical variables conformed to anormal distribution. Descriptive statistics were shown as average and standard deviation for normal distribution, median

(min-max) for non–normal distribution, and several cases (%) for nominal variables. The significance of the difference between the groups in terms of averages was assessed by t-test and one-way analysis of variance. The significance of the difference in terms of median values was assessed with the Mann–Whitney–U test and the Kruskal–Wallis test. Nominal variables were assessed with the Pearson Chi-Square or Fisher Exact test. While investigating the relationship between continuous variables, the distribution was assessed with the Spearman Correlation test when it was not normal and with the Pearson Correlation test when it was normal.

$p<0.05$ was considered statistically significant.

RESULTS

The average age of 368 volunteers participating in the study was 32.56 ± 7.58.

When the educational levels of the participants were examined, there was no illiteracy. Characteristics of the study population are given in **Table 1**.

While 83 participants (22.6%) had a chronic disease, 285 participants (77.4%) did not. In 47% (n=39) of patients with chronic illness, disorders were causing secondary osteoporosis. The most prevalent diseases in this group included 23.07% (n=9) rheumatological conditions (Rheumatoid arthritis, Ankylosing spondylitis, Systemic Lupus Erythematosus) and 20.51% (n=8) diseases that are capable of causing malabsorption (Crohn's disease, Irritable bowel syndrome, and Gastroesophageal reflux).

There was chronic drug use in 20.4% (n=75) of the participants in the study. 50.7% (n=38) of the drug users were taking a drug that increased the risk of osteoporosis. Drugs containing levothyroxine sodium constituted 50% (n=19) of drugs in this group.

359 (97.6%) participants were in the pre-menopausal period.

When the responses given by the participants to the OKT questions were analyzed, the average score they got from the nutrition group was 12.86±4.17, and this average score was 49.46% of the maximum score that could be obtained for the nutrition group in the test. The average score of the exercise subgroup was 9.56±3.62, constituting 47.8% of the maximum score that can be obtained for the exercise group in the test. The average of the total score points was 15.08 ± 4.82 and this average constituted 47.1% of the maximum score that can be obtained for the total score of the test.

There was no correlation between the average OKT score and age ($p>0.05$).

There was a significant correlation between the educational status of the participants and their OKT average score ($p=0.010$). The average score of university graduates was higher than what was obtained by primary school and high school graduates. Also, there was a significant relationship between the place where the participants lived and their OKT scores (**Table 2**).

When the OKT scores of the participants were assessed based on whether or not they were health workers, both the total and subgroup average scores of health workers were noticeably higher. Considering the subgroups of health workers; the OKT scores of the doctors in all three departments were also significantly higher than the other healthcare worker groups. There was no significant difference between nurses and medical faculty students (**Table 2**).

When the OKT scores of the participants were analyzed based on whether they smoked or not; the scores of non–smokers were significantly higher ($p<0.001$) (**Table 2**).

Table 2. Comparison of OKT scores according to the variables

Variables	Exercise subgroup scores	p value	Nutrition subgroup scores	p value	Total scores	p value
Educational level		0.01		0.003		0.007
Primary school	5.68±0.74		8.41±0.85		9.77±1.11	
High school	8.25±0.96		11.20±1.42		12.96±1.36	
University	10.24±1.21		13.69±2.01		16.10±3.24	
Place of residence		0.005		0.001		0.003
City center	9.77±1.82		13.12±2.44		15.36±4.23	
District center	7.85±0.85		10.73±1.78		12.75±3.24	
Occupation		<0.001		<0.001		<0.001
Health worker	10.60±1.96		14.19±3.12		16.54±4.12	
Not health worker	8.53±1.34		11.55±2.08		13,63±3.02	
Health care professionals		<0.001		<0.001		<0.001
Doctors	13.58±2.94		18.38±5.04		21.08±6.01	
Nurses	10.77±1.98		14.16±3.15		16.65±4.23	
Auxiliary health personnel	8.74±1.42		12.17±2.23		14.15±3.12	
Medical faculty students	11.78±2.02		15.22±3.42		17.75±4.38	
Smoking status		0.001		0.001		0.001
Smokers	8.51±2.36		11.78±2.12		13.77±3.90	
Non-smokers	9.97±2.94		13.29±3.22		15.60±4.56	

Table 1. Basic characteristics of the study population

Variables	n (%)
Educational level	
Primary school	22 (6%)
High school	76 (20.7%)
University	270 (73.3%)
Place of residence	
City center	328 (89.1%)
District center	40 (10.9%)
Occupation	
Health worker	183 (49.7%)
Doctors	24 (13.1%)
Nurses	62 (33.9%)
Auxiliary health personnel	65 (35.5%)
Medical faculty students	32 (17.5%)
Not health worker	185 (50.3%)
Number of pregnancies	
No pregnancy history	172 (46.7%)
1 pregnancy	87 (23.6%)
2 pregnancies	73 (19.8%)
3 pregnancies	23 (6.3%)
4 and more pregnancies	13 (3.5%)
Smoker	105 (28.5%)
Alcohol user	28 (7.6%)
History of previous fractures	58 (15.8%)
Family history of osteoporosis	106 (28.8%)

There was no significant relationship between the participants' alcohol use, chronic disease, chronic drug use, and OKT scores (p>0.05). In addition, no significant difference was found between the scores of those with chronic diseases that can cause secondary osteoporosis and those with chronic diseases that do not cause secondary osteoporosis (p>0.05). Again, when the participants with chronic drug use were grouped as those who use drugs that cause secondary osteoporosis and those who do not, no statistically significant difference was found between them in terms of OKT scores (p>0.05).

When the participants were assessed according to their menopausal status (pre-menopausal or post-menopausal), family history (family history of osteoporosis), and bone fracture history; the scores of the groups were similar (p>0.05).

Among the 20 questions in the exercise subgroup, the most incorrectly answered question was about whether weight-bearing exercise is a better way to reduce the risk of osteoporosis than cycling and yoga. The correct answer rate for this question was 6.5% (n=24). Among the 26 questions that make up the nutrition group, the most incorrectly answered question was the amount of milk that should be drunk per day for the recommended amount of calcium intake. The rate of answering this question correctly was 6.8% (n=25).

Among the 11 questions in which the risk of developing osteoporosis is assessed, the most incorrectly answered question is the one that assesses the possibility of the occurrence of osteoporosis in overweight people. The correct answer rate for this question was 12% (n=44). In the three questions asked about diagnosis and treatment, more than half of the participants answered wrongly. This is the question that questions the best time for the formation of strong bones. The correct answer rate for this question was 14.1% (n=52).

DISCUSSION

In our study, the average total score of the OKT was 15.08±4.82, and this average constituted only 47.1% of the maximum score that can be obtained for the total score of the test. Although the total score of health workers was significantly higher than non–health workers, it comprised only 51.6% of the maximum score that was obtainable. Thus, in our study, we determined that the level of OP knowledge and awareness was not at the desired level, even among healthcare workers. However, the level of knowledge about osteoporosis increased significantly as the education level increased.

In our study, we found that the level of OP knowledge was not sufficient in women who were at greater risk for OP. This result once again indicated the necessity of providing counseling and education on OP to enhance the bone health of all women, whether or not they have an additional risk factor other than gender. Ungan M and Tümer M (13) in the Mediterranean Osteoporosis Study used the scale they created from available information on hip fractures and risk factors. Also, during the study they conducted with women in rural areas, they used the scale created by Gemalmaz et al. (14). It has been observed that Turkish women lack sufficient awareness of risk factors and it has been emphasized that women should be educated by family physicians or primary care physicians (14). Therefore, family physicians have important duties. Family medicine has been termed the cornerstone of preventive medicine. Primary protection takes the lead in primary health care services. With the precautions and education to be undertaken, the health expenses caused by osteoporosis can also be abated. This is due to the high cost of managing osteoporosis.

Our study was conducted in the family medicine outpatient clinics on the campus of a university hospital. Since almost half of the patients who applied to our outpatient clinics were health workers, it was possible to examine the knowledge levels of the health workers. This gave us the advantage of examining the OP knowledge level from a different perspective than other similar studies.

In our study, the exercise, nutritional, and total knowledge scores of the women were found to be only 50% or less than the maximum scores of the questionnaire. When

other studies conducted in Turkey are examined; In the study conducted by Altın et al. (15), when the answers given by the participants to the knowledge test were assessed, it was observed that the subgroup (nutrition and exercise) and total score averages remained at 50% of the maximum scores of the questionnaire. Similarly, in the study of Öztürk et al. (16) it was observed that the subgroups and total score averages were less than 50% of the maximum scores of the questionnaire. In the study of Okumuş et al.(17) on 100 women, it was found that the level of knowledge about osteoporosis was insufficient. Considering the studies abroad; In the study of Janistewska et al. (18) with 300 women aged 45–65, the average score of the participants in the OKT nutrition group was found to be 9.27, which was below the average we obtained in our study. However, the average score of the exercise group (13.93) and the average score of the total score (15.71) were higher than our study.

When the education levels of the participants in our study were examined; It was determined that 73.4% (n=270) had a university or higher education. We envisaged that this high rate was because the majority of the participants in the study consisted of civil servants and health workers working in the hospital, and the age range of the participants was from the young age group. We, therefore, realized from our study that as the level of education increased, the level of OP knowledge also increased. In a similar study conducted by Aksu et al. (2), more than half of the participants are university graduates and when the education level and osteoporosis knowledge level are examined, it is seen that the level of knowledge increases as the education level increases. Another study by Koç et al. (4) supports this situation. In a different study conducted by Magnus et al. (19) on 1,514 individuals between the ages of 16 and 79, knowledge of osteoporosis was found to be directly related to education level. All these data create the idea that people with low education levels should be given more training on OP.

As expected, there was a significant difference in favor of health workers in the exercise group, nutrition group, and total score averages between health workers and non–health workers. On the other hand, the scores of the health workers constituted only 50% of the maximum scores on the test. This situation shows that the OP knowledge level of health workers is insufficient. In occupational subgroups, the highest scores for all three groups were among physicians. This was highly expected. However, it was observed that the physicians could not answer all the questions correctly, although they answered approximately 70% of the questions correctly. In a different study conducted in England by mailing a questionnaire to 2,515 physicians, mostly general practitioners, they stated that they could not obtain sufficient information about osteoporosis during medical education (20). In a study conducted by Eyigör et al. (21) with medical students, it was observed that medical students had insufficient knowledge about osteoporosis prevention and complications. This situation shows that medical students, who will undertake the primary task of informing the public during their medical school education, do not get enough information about ways to prevent osteoporosis and risk factors. We, therefore, suggest that health personnel, who should be the main source of information for society, should be thoroughly informed about this issue.

In our study, 22.6% (n=83) of the women participating had at least one chronic disease. 47% of these chronic diseases were diseases that could cause secondary osteoporosis. In our study, no significant difference was found between the presence of chronic disease and the average score of all three groups. In a study by Selçuk et al. (22), people with and without chronic disease were asked whether they knew the ways to prevent osteoporosis and treatment methods, and it was seen that those with chronic diseases answered both questions at higher rates. This is because people with chronic diseases are more concerned and sensitive about their health. In our study, on the other hand, it was observed that the presence of the chronic disease did not affect the level of knowledge of the individuals.

In our study, 28.8% of the women participating had a family history of osteoporosis. However, there was no significant relationship between family history and OKT scores. In the study of Koç et al. (4), the average scores of those with a family history of osteoporosis were found to be higher than the average scores of those without. In our study, the reason why we could not find a difference in terms of knowledge level between those with and without a family history of osteoporosis may be due to the much smaller sample size of women with a family history of osteoporosis.

In the study conducted by Umay et al. (23), it was found that a history of fractures under 50 years of age was not a risk factor for osteoporosis. However, in the study of Nayak et al. (24), fracture history was fingered among the important risk factors for osteoporosis. In another study conducted by Pınar et al. (3), it was stated that osteoporosis was seen at a higher rate in individuals with a history of fractures due to falling and impact. In our study, there was no significant difference between the OKT scores of those with and without a history of fracture. It was also observed that those with a history of fractures answered only 50% of the questions correctly. These data suggest that people with a history of fractures are not sufficiently aware of osteoporosis and its prevention methods, even after their fractures.

The most important limitation of our study —our research population— consists only of participants who applied to the family medicine outpatient clinic in a single center for any reason. A significant part of the participants were health workers and their education level was above the general population average. This situation reduces the likelihood that the data obtained will reflect the general population. Therefore, more comprehensive and multi-center studies may be required for more detailed information about the general population. It would not be surprising to find a lower level of osteoporosis knowledge in population-based studies than we did. The fact that approximately five years have passed since the study data were collected can also be considered as a limitation. However, when the current literature is evaluated, it is seen that there are not many studies on this subject in this process and this study is one of the most comprehensive studies in the literature with this scale. In addition to these, an important aspect of our study is that it provides important data about the osteoporosis knowledge levels of health workers. Therefore, we think that our study will contribute to the literature.

CONCLUSION

Therefore, it is necessary to raise awareness about the risk factors, prevention, diagnosis, and treatment of osteoporosis, which is an important public health issue. Along with the elderly population, the OP knowledge level of young women should also be increased. In this way, it will be possible to take protective measures. It should be ensured that factors, such as exercise and nutrition, which are among the preventive measures, are adopted as a lifestyle. It is known that family physicians have an important role in the education of individuals, considering that physicians working in primary care provide continuous service to the same population.

According to the results obtained from this study, we can make the following recommendations;

- All societies, especially women, should be made aware of osteoporosis.
- Women should be informed about the need to reduce the risk factors that cause osteoporosis. Regular physical activity and a healthy and balanced diet should be encouraged.
- The knowledge of health workers who play the most important role in reaching society should be supported by continuous training. During health education, adequate and society-adaptive information should be provided regarding osteoporosis risk factors and preventive approaches.
- Public service announcements should be prepared for public information, and the masses should be reached through visual and written media. With all these measures, we think that awareness of osteoporosis can be increased and that the frequency of the disease can be reduced.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara University Scientific Research and Publication Ethics Committee (Date: 28.03.2016, Decision No: 06-226-16).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article

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The effect of parenteral nutrition products on infection parameters in patients receiving long-term mechanical ventilation support

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ABSTRACT

Aim: Malnutrition can increase the frequency of infections by reducing the immune system response. Parenteral nutrition (PN) is considered an important treatment for patients who cannot receive adequate oral or enteral nutrition. The contents of nutritional products may be different. In this study, we aimed to investigate the effects of soy-based and olive oil-based parenteral nutrition products on infection parameters.

Material and Method: A total of 82 patients were included in the study, 50 of which were soy (Group 2) and 32 were olive-based (Group 1) parenteral nutrition. Patient files and laboratory results were reviewed. Age, gender, 1st, 7th, 14th and 21st days in intensive care, leukocyte and platelet counts, Neutrophil lymphocyte ratio (NLR), C-Reactive Protein (CRP) values, Acute Physiology and Chronic Health Evaluation (Apache II) score and first blood culture results after hospitalization were recorded.

Results: The 7th and 21st day CRP values in Group 1 were statistically significantly lower than the 7th and 21st days CRP values in Group 2. In Group 1, growth in blood culture was statistically significantly lower and in Group 2 there was a statistically significant early growth.

Conclusion: As a result, it was found that olive oil-based lipid-containing nutritional solutions were more advantageous in terms of infection on intensıve care than soy-based nutrition products. It was concluded that patients who received postoperative mechanical ventilator support fed with olive oil-based parenteral nutrition products had less infectious growth.

Keywords: Inflammation, immunity, intensive care unit, parenteral nutrition, parenteral nutrition solutions

INTRODUCTION

Nutritional support is one of the most important routine treatments in intensive care units (ICU). Malnutrition can increase the frequency of infections by decreasing the immune system response. Consequently, it may cause increased mortality, longer hospital stay and higher costs (1,2). Parenteral nutrition (PN) is considered an important treatment for patients who can't receive adequate oral or enteral nutrition (3).

In cases where the gastrointestinal tract is functional, it is recommended that patients be fed enterally as soon as possible (4). Parenteral nutrition is recommended for patients who cannot be given enteral nutrition within 24 hours after hospitalization in the ICU (5). Parenteral nutrition should include a balance between glucose, amino acids and lipids and vitamins, minerals and trace elements for the individual nutritional needs of patients. There are many types of parenteral nutrition products such as soy-based and olive oil-based. Although soy-based products are used extensively, olive oil-based products have also been used in recent years.

Adequate nutrition must be provided in the ICU to support immune functions. Nutrition with products containing arginine, nucleotides, ω-3 polyunsaturated fatty acids (PUFA), glutamine, and products that have been shown to increase the cellular immune response to infection in-vivo and in-vitro have been defined as immunonutrition (6). In the studies conducted, it was observed that acute phase reactants such as serum C-Reactive Protein (CRP) were at lower levels in immunonutrition groups. Nutritional products in the market can contain different amounts of amino acids, lipids, vitamins, minerals and trace elements.The amount of oleic acid 24 65 and the oleic acid-linoleic acid ratio was higher in the olive oil-based nutrition product we used in our study. In comparison, the amount of linoleic

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acid in the soy-based nutrition product was higher. We aimed to investigate the effects of soy-based and olive oil-based parenteral nutrition products used in ICU on infection parameters.

MATERIAL AND METHOD

Pursuant to obtaining ethical clearance from the institutional review board (IRB) on December 14th, 2020 (Protocol Number: KAEK-143-09), a retrospective analysis was conducted on the medical records of 868 patients who were admitted to the ICU for various pathologies during the time frame of September 2019 through September 2020. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

As the inclusion criteria;

- were admitted to the ICU with mechanical ventilator support or who received support for the mechanical ventilator on the first day of admission to the intensive care unit
- needed mechanical ventilator support for 21 days
- only parenteral nutrition in the first 24 hours 21 days of only parenteral nutrition
- being a patient of postoperative surgery due to ileus or intestinal ischemia
- nutritional administration with central venous catheter were accepted. Use of only central venous catheter as parenteral feeding route

As exclusion criteria;

- having a history of immunosuppression
- being diagnosed with malignancy
- staying in ICU for less than 21 days or weaning from mechanical ventilation before 21 days
- peripheral vascular access was used as a parenteral nutrition route.
- having any growth in cultures taken on the day of admission
- patients using steroids
- patients whose culture results indicate contamination or colonization

Patients with a history of immunosuppression, a history of cancer, patients who were treated for less than 21 days in the ICU, patients with peripheral vascular access to the feeding tract, patients with growth in cultures taken on the day of hospitalization or in cultures other than blood cultures taken later were excluded from the study. Central catheters were not routinely replaced, only reproductive ones. The patients' energy needs were calculated by applying the Harris Benedict formula, Eighty-two (82) patients were enrolled in the study. Patients fed with olive oil-based emulsions used at different times according to their presence in the hospital pharmacy were named Group 1 (n: 32) and the patients fed with soybean oil-based emulsions were divided into two groups, named Group 2 (n: 50). A retrospective chart review was conducted to analyze the medical records of patients admitted to the intensive care unit (ICU). Demographic data, including age and gender, as well as laboratory results including leukocyte and platelet count, Neutrophil lymphocyte ratio (NLR), C-reactive protein (CRP) values, Acute Physiology and Chronic Health Evaluation (APACHE) II score and first blood culture results obtained at the 1st, 7th, 14th and 21st days of ICU admission were recorded.

Calculation of Energy Need

The energy need was calculated with the Harris Benedict formula[(for women; 655.1 + (9.56 x weight kg) + (1.85 x height cm) – (4.68 x age) kcal/day for men; 66.5 + (13.75 x weight kg) + (5.03 x height cm) – (6.75 x age)] kcal/day.

Parenteral Nutrition Ingredients

Soy-based and olive oil-based parenteral nutrition ingredients used with central catheter are shown in **Table 1**.

Table 1. Composition of lipid emulsions used in the study.

	Soyabean oil-based Emulsion	Olive oil-based emulsion
Composition (g/100 ml):		
Soyabean oil	20	0.8
Olive oil	-	3.2
Glycerol	2.20	2.25
Egg phospholipids	1.2	1.2
Sodium oleate	-	0.03
Fatty acid content (%)		
Palmitic acid	11	12
Stearic acid	4	3
Oleic acid 24 65	24	65
Linoleic acid	53	17
a-Linolenic acid	8	3
Oleic:linoleic ratio	0.4	3.8

Statistical Analysis

We based our sample size calculation on data from a study comparing the effects of olive oil-based and soybean oil-based emulsions on infection rate and leukocyte count in critically ill patients receiving parenteral nutrition (7). In the same study, soy-based 16 and olive oil-based 23 patients were compared and no significant difference was found in terms of CRP and Leukocyte values. When α risk was accepted as 0.05 and Power (1-B err probe) as 0.95, 22 participants receiving soy-based nutrition and 32 participants receiving olive oil-based nutrition were statistically required. G * Power 3.1.9.4 program was used for these calculations (8).

Statistical analyzes were performed using the SPSS 26.0 software program (SPSS Inc., Chicago, IL, USA).

After Kolmogorov - Simirnov test was applied to all data, one-way analysis of variance test was used for normally distributed data in intergroup evaluation, and Mann Whitney U test was used for data with skewed distribution. One-way analysis of variance test of repeated measures was used for normally distributed data and Wilcoxon signed rank test was used for data showing skewed distribution. Binary logistic regression analysis was performed to understand whether soy-based and olive-oil-based nutrition has an effect on growth in blood culture. Chi-square test was used for the comparison of nominal values between groups. $p<0.05$ was considered significant.

RESULTS

The majority of the patients included in the study were patients in whom enteral nutrition was not possible due to surgical reasons. Parenteral nutrition was initiated in the first 24 hours of hospitalization in the intensive care unit. No statistically significant difference was observed between the two groups in terms of demographic data. 25 of the Group 1 patients were male and the mean age was 76.56 ± 10.31 years. 36 of the group 2 patients were male and the mean age was 72.92 ± 16.72 (**Table 2**).

When the CRP, Leukocyte, Platelet and Neutrophil Lymphocyte Ratio (NLR) values were compared between and within the groups, no statistically significant change was observed between the four measurement values in terms of leukocyte, platelet and neutrophil lymphocyte ratio (NLR) values among the groups. Leukocyte values on the 7th and 21st days in Group 1 and on the 7th and 14th days in Group 2 were found to be statistically significantly lower than the leukocyte values on the 1st day. The 7th day platelet value in Group 1 and Group 2 was found to be statistically significantly lower than the 1st day platelet value. While the NLR value on the 21st day in Group 1 was found to be statistically significantly lower than the NLR value on the 1st day, there was no statistically significant difference between the four measurement values in Group 2. 14th and 21st days in Group 1, 7th, 14th in Group 2. and 21st day CRP values were found to be statistically significantly higher than the 1st day. The 7th and 21st day CRP values in Group 1 were found to be statistically significantly lower than the 7th and 21st day CRP values in Group 2 (**Table 3**, **Figure 1**).

Table 2. Demographic data of the cases. (Values are expressed as mean ± SD)

	Group 1		Group 2		P
	Mean	SD	Mean	SD	
Age (Year)	76.56	10.31	72.92	16.72	0.27
Gender(M/F)	25/7		36/14		0.53

SD: Standart deviation, F: Female, M; Male

Table 3. Comparison of CRP, Leukocyte, Platelet and values of the groups

		1st Day			7th Day			14th Day			21th Day	
		Mean	SD	P 1-7th Day	Mean	SD	P 1-14th Day	Mean	SD	P 1-21th Day	Mean	SD
Crp (mg/l)												
	Group 1	93.36	89.91	0.48	92.38	54.35	0.03*	127.49*	71.50	0.004€	131.54£	58.84
	Group 2	98.95	89.10	0.004†	139.76†	84.42	0.008ß	150.18ß	92.76	0.001^	190.88^	102.20
	P	0.75			0.009			0.25			0.010	
Leukocyte 10^3/µl												
	Group 1	13.78	5.45	0.002**	10.24**	4.26	0.09	11.73	11.39	0.001≠	10.42≠	5.00
	Group 2	13.74	7.62	0.03††	11.32††	4.27	0.02η	11.39η	6.57	0.43	12.43	6.79
	P	0.64			0.17			0.86			0.19	
Platelet 10^3/µl												
	Group 1	267.53	122.93	0.010^^	217.22^^	108.78	0.13	230.22	130.30	0.06	215.28	150.55
	Group 2	258.26	108.01	0.001ǂ	206.84ǂ	123.22	0.65	285.58	291.85	0.08	233.42	197.52
	P	0.87			0.38			0.52			0.93	
NLR												
	Group 1	24.08	49.30	0.13	11.48	8.88	0.56	15.95	19.99	0.007µ	11.08µ	19.66
	Group 2	18.98	18.84	0.14	11.78	7.97	0.12	12.45	9.90	0.25	13.83	13.88
	P	0.85			0.54			0.96			0.76	

*: p 0.03=When day 1 and day 14 are compared, day 14 was found to be significantly higher.
£: p 0.01=When the 1st day and the 21st day are compared, the 21st day was found to be significantly higher.
+: P 0.04=When the 1st day and the 7th day were compared, the 7th day was found to be significantly higher.
B: p 0.01=When day 1 is compared with day 14, day 14 was found to be significantly higher.
^: p 0.01=When day 1 and day 21 are compared, day 21 was found to be significantly higher.
**: p 0.01=When the 1st day and the 7th day are compared, the 7th day was found to be significantly lower.
≠: p 0.01=When day 1 and day 21 are compared, day 21 was found to be significantly lower.
††: p 0.03=When the 1st day and the 7th day were compared, the 7th day was found to be significantly lower.
η: p 0.02=When day 1 and day 14 are compared, day 14 was found to be significantly lower.
^^: p 0.01=When the 1st day and the 7th day are compared, the 7th day was found to be significantly lower.
ǂ: p 0.01=When the 1st day and the 7th day were compared, the 7th day was found to be significantly lower.
µ: p 0.01=When day 1 and day 21 are compared, day 21 was found to be significantly lower.

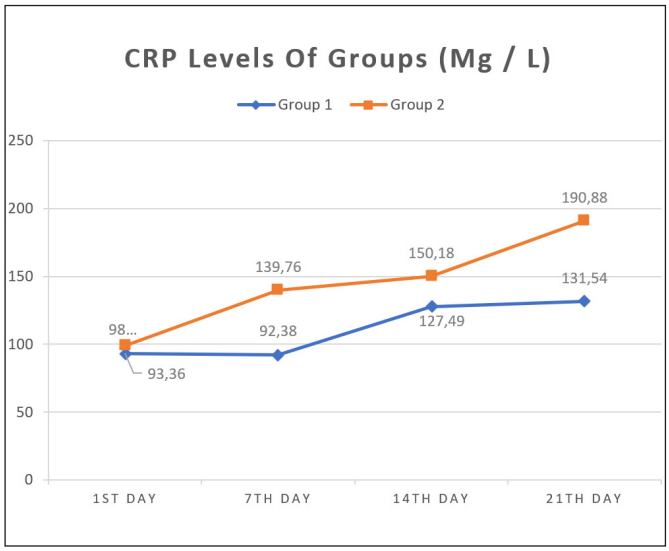

Figure 1. CRP Levels Of Groups

When the blood culture reproduction of the groups were compared, the growth in blood culture was found to be statistically significantly lower in Group 1 (p =0.03). Reproduction was detected in 6 of 32 patients in Group 1, while growth was detected in 20 of 50 patients in Group 2. The most reproductive microorganism in Group 1 was Enterococcus Faecium, in Group 2 Acinetobacter Baumannii and Klebsiella Pneumoniae were the most reproducing microorganisms. When the first blood culture reproduction days of the groups were compared, it was found that there was statistically significantly earlier growth in Group 2 (p =0.03, **Figure 2**).

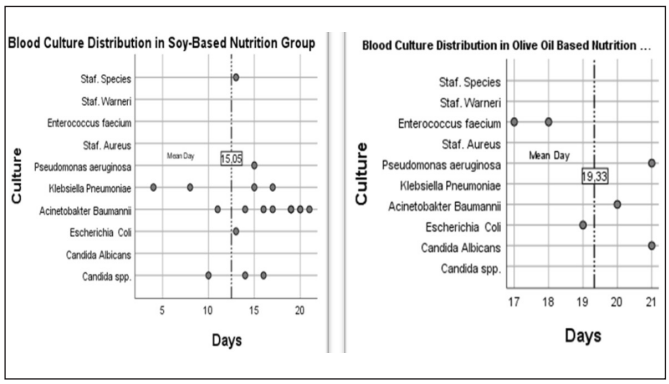

Figure 2. First Blood Culture Breeding Days of Groups

When the APACHE II scores calculated within and between the groups on the 1st, 7th, 14th and 21st days were compared, no statistically significant difference was found between the groups.

In the logistic regression analysis, it was found that age and gender had no effect on blood culture growth and that there was 3 times more growth in blood culture in patients who received soy-based nutrition compared to patients who received olive oil-based nutrition (**Table 4**).

Table 4. Coefficient Estimates of the Logistic Regression Model

Variables	β	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Gender	0.497	0.607	0.670	1	0.413	1.643	0.500	5.394
Age	0.022	0.019	1.413	1	0.235	1.022	0.986	1.060
Group (1)	1.192	0.555	4.618	1	0.032	3.293	1.111	9.762
Constant	-2.735	1.499	3.328	1	0.068	0.065		
Cox & Snell R2 =.071, Nagelkerke R2=.100, -2 Log Likelihood = 96.394								

DISCUSSION

As a result of this study, it is seen that olive oil-based emulsions are more advantageous in terms of CRP, growth in blood culture and breeding day in mean blood culture among the patient groups who received parenteral nutrition products containing two different lipids. There was no significant difference between the groups in terms of leukocyte, platelet, NLR and APACHE II Scores.

Nutritional support is an important part of intensive care treatments. Nutrition has been found to have positive effects on immunological functions, helps wound healing, and reduces mortality and morbidity. As in all patients, the first choice in intensive care patients is oral nutrition, which is a natural diet. Oral nutrition is often not possible in intensive care patients. This has led clinicians to find different ways of nutrition. As a result, enteral and parenteral nutrition types have been developed (9).

Parenteral nutrition is the administration of high concentrations of hypertonic solutions that meet the nutritional needs of patients with a limited absorption capacity of the gastrointestinal system and a problem that prevents nonfunctional or enteral nutrition, via central catheter or peripheral venous route.In our study, all of the patients were patients whose gastrointestinal tract was unsuitable for enteral nutrition due to the operation.

Hyperglycemia, electrolyte inbalance, hypertriglyceridemia, kidney and liver function disorders are frequently encountered metabolic complications of parenteral nutrition (10). These complications that develop in addition to the disease cause an increase in inflammatory response (11).

One of the most important treatments in the ICU is to support immune functions, and adequate nutritional support must be provided for this. Since products containing arginine, nucleotides, ω-3 polyunsaturated fatty acids (PUFA), glutamine have been shown to increase the cellular immune response to infection in-vivo and in-vitro, the term 'immunonutrition' is used for feeding with these products. Studies have shown that acute phase reactants such as serum CRP and fibrinogen have a lower course in patient groups

receiving immunonutrition (6). Arginine, nucleotides and PUFA are found in different proportions in the nutritional products used in our study.

Linoleic acid forms a large part of PUFA in soy-based lipid emulsions (12). Linoleic acid reduces the release of proinflammatory cytokines, impairs reticuloendothelial functions, and inhibits macrophage and lymphocyte functions (7). Cury-Boaventura et al. (13) showed that soy-based lipid emulsion decreased lymphocyte proliferation and even caused death of neutrophils and lymphocytes. In the light of this information, soy-based lipid emulsions negatively affect immune functions (7).

Olive oil-based emulsions contain monounsaturated fatty acids (Monounsaturated fatty acids: MUFA) rich in oleic acid (14). MUFA is thought to be ineffective on immune functions (7,15).In the study of Ockenga et al. (16) on patients with acute pancreatitis, it was reported that parenteral nutrition was associated with CRP, which is an inflammation marker. There are other similar studies in the literature (17,18). Gürsoy et al. (10) reported that soy-based and olive-oil-based nutritional products lower CRP, but there was no statistically significant difference between them. Mateu-de Antonio et al. (7) reported that soy-based lipid-containing emulsion had more suppressive properties on the amount of leukocytes than olive-oil-based lipid-containing emulsions. In our study, the leukocyte, platelet and NLR values between the groups were similar. CRP was found to be close on the 1st and 14th days, and significantly lower in the olive oil-based nutrition group on the 7th and 21st days. When the blood culture results and mean reproduction days of the groups were compared, it was found that the growth was statistically significantly less and later in the olive oil-based nutrition group. No significant difference was observed between the APACHE II scores of the groups.

The limitations of our study can be seen as the different diagnoses of the patients in hospitalization, the absence of additional diseases, the different central catheterization sites, and the limited number of patients.Negative cultures can be false-negative and need to be repeated, which is a limitation of our study.

CONCLUSION

As a result, it was found that olive oil-based lipid-containing nutritional solutions were more advantageous in terms of immune response than soy-based nutrition products. It was concluded that patients who received postoperative mechanical ventilator support fed with olive oil-based parenteral nutrition products had less infectious growth.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Medical Faculty Clinical Researches Ethics Committee (Date: 14.12.2020, Decision No: KAEK-143-09).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

HEALTH SCIENCES
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Comparison of subjective and objective accommodation amplitude values

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ABSTRACT

Aim: Comparison of accommodation amplitude values measured using autorefractometer, push up and minus lens technique.

Material and Method: In this randomized, prospective study, both eyes of 75 healthy individuals between the ages of 15 and 40 were included in the study. They were divided into 5 groups as 15-20 age group 1, 21-25 age group 2, 26-30 age group 3, 31-35 age group 4, 36-40 age group 5 To measure the accommodation amplitude, the minus lens and push up technique were used as subjective methods, and the autorefractometer Tonoref III was used as the objective. The correlation between the measurement methods and the reproducibility of the autorefractory measurements were evaluated. In addition, changes in accommodation measurements with age, gender and pupil diameter changes were investigated.

Results: The mean accommodation amplitude values were 4.86±1.73 D in the minus lens technique, 8.79±4.58 D in the push up technique, and 2.77±1.93 D in the autorefractometer measurement. Autorefractometer accommodation amplitude values were found to decrease significantly with age (p=0.000). It was seen that the correlation between autorefractometry and subjective methods, minus lens and push up was significant and correlated (p=0.000, r=0.47, p=0.001, r=0.28, respectively). Intraclass correlation coefficients of Tonoref III accommodation amplitude were found to be 0.935.

Conclusion: Objective accommodation amplitude measurements made using Tonoref III were found to be correlated with subjective methods, but lower values were detected compared to subjective methods.

Keywords: Minus lens technique, push up technique, amplitude of accommodation

INTRODUCTION

Accommodation is a natural optical mechanism that improves the retinal image quality of nearby objects. In accommodation, the refractive power changes due to the shape change of the crystalline lens caused by contraction of the ciliary muscles (1). The research of accommodation dates back to the 1800s with the subjective push up technique. Hofstetter (2) argued that accommodation amplitude (AA) decreases linearly with age. For clinical purposes, Hofstetter combined the data to give clinicians an estimate of what the norms should be for each age group (age range, 8 to 80 years).

Based on these classical studies, many clinicians have concluded that humans have the greatest amount of AA at birth, then steadily decline until there is none.

Objective and subjective methods are used in the measurement of AA. Among the objective methods, there are dynamic retinoscopy (DR), aberrometers and autorefractometers that can be used in the clinic (3,4). Subjective techniques include push up (PU), push down (PD) and "minus lens (ML)" methods (5,6). However, the subjective methods used are not suitable for the definitive evaluation of AA. Objective accommodation tests can distinguish true accommodation in the optical power of the eye from pseudoaccommodation or other possible confounding factors. Subjective testing may result in a different measurement than it is due to ocular aberration, small pupil diameter, and active accommodation (7).

With this study, we aimed to evaluate the reproducibility and compatibility with age and gender in the use of Tonoref III (NIDEK Co., Ltd.). The use of methods in measuring AA was evaluated. In addition, we investigated comparing Tonoref III with ML and PU methods and the relationship between changes in pupil diameter.

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MATERIAL AND METHOD

The study was carried out with the permission of Tokat Gaziosmanpaşa University Medical Faculty Clinical Researches Ethics Committee (Date: 01.10.2020, Decision No: 20-KAEK-244). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A signed informed consent was obtained from all participants before the study. Between January 2022 and June 2022, eye examination was applied to 75 healthy volunteers. Both eyes of volunteers aged between 15 and 40 were included in the study.

Participants were divided into five groups according to their age. The 1st group was 15-20 years old, 2nd group was 21-25 years old, 3rd group was 26-30 years old, 4th group was 31-35 years old, 5 groups was 36-40 years old. AA measurements made with objective and subjective methods were recorded.

A detailed ophthalmological examination including best corrected visual acuity with Snellen chart, anterior segment and fundus examination with slit lamp biomicroscopy, and intraocular pressure determination with Goldmann applanation tonometry was performed for each patient. AA was measured and recorded with a minus lens, pull-up technique, and autorefractometer Tonoref III. All measurements were made in the same time period (between 09.00-12.00 hours) and under the same environmental condition. Two consecutive measurements were made and the average of the measurements was recorded as AA.

Patients with a visual acuity of less than 20/25, refractive error with a spherical refractive error of more than ±5.0 diopters or a cylindrical value of more than 2.0 diopters, anisometropia, amblyopia, a history of significant ocular trauma, surgery or disease were excluded from the study (8). In addition, patients using drugs that may affect accommodation such as topical cycloplegics, phenothiazines, tricyclic antidepressants and antivertigo drugs were excluded from the study.

Objective Method

The Tonoref III autorefractometer device was used to objectively measure the AA. The device measures the change in pupil diameter from 3 to 8 mm with 1 mm increments. It also measures AA between 0-10 D. Only the central area is used in accommodation. The measurement ends when there is no change in accommodation for more than 6 seconds, or when the measurement time reaches 30 seconds.

During the measurement, the participants were asked to place their chin and forehead on the device and not move their heads. In addition, they were informed about carefully looking at and following the target inside the device. The measurement key was pressed for AA measurements. AA and maximum and minimum pupil diameter were analyzed. The measurement was repeated after a 10-minute rest period.

Subjective Method

ML and PU techniques were used to evaluate the accommodation amplitude subjectively. Refractive errors of all participants were corrected. They were asked to fixate on the N8 target, which consists of the letters Snellen at a distance of 40 cm.

In the ML technique, minus lenses were added at intervals of 10 seconds in increments of 0.25 D. The value at which the clarity of the participants deteriorated was recorded. All measurements were made monocular in both eyes. Total AA was determined as the sum of +2.50 D (dioptric equivalent of working distance) plus minus lens power added to the total.

In the PU technique, the letters that were focused at 40 cm were zoomed in slowly. And at the point where the participants started to see blurred, the distance from the target to the plane of the glasses was measured with a millimeter ruler and converted to diopters.

Statistical Analysis

Statistical evaluation of the data was performed using the Statistical Package for Social Sciences (SPSS) version 20.0. Descriptive statistics were presented as mean±standard deviation or n (%). The conformity of the data to the normal distribution was evaluated with histogram, Q-Q plots and Shapiro-Wilk test. Since all the data were not normally distributed, Mann-Whitney U was used for paired group comparisons and Kruskal Wallis H tests were used for multiple group comparisons. Correlation coefficients of fit were calculated with 95% confidence interval. The relationship between quantitative data was evaluated with Spearman correlation analysis. Significance level was accepted as $p<0.05$.

RESULTS

This study included a total of 150 eyes of the 75 patients. Of the 75 patients, 43 (57.3%) were female and 32 (42.7%) were male. The mean age of women was 26.7±8.0 and the mean age of men was 29.0±7.1 (p=0.07) (15-40 years). Best corrected visual acuity of all participants was 20/20 or better. The mean axial length was 22.18±0.45 mm and its mean spherical equivalent was -1.06±1.3 D.

Mean AA was found to be 2.77±1.93 D (0.31- 9.56 D) in measurements performed with Tonoref III. There was a linear decrease from group 1 to 5. There was a significant difference between the groups (p=0.000) (**Table 1**) (**Figure**). As age increased, the accommodation value

decreased. In the measurements made using Tonoref III, it was seen that the AA value of men was 1.88±1.33 and the AA value of women was 3.47±2.05. There was a significant difference between the two genders (p≤0.000). The mean pupil diameter values were found to be 5.50±1.04. In addition, it was determined that the pupil diameter decreased proportionally as the AA increased. However, no significant difference was observed between the groups (p=0.063) (**Table 1**).

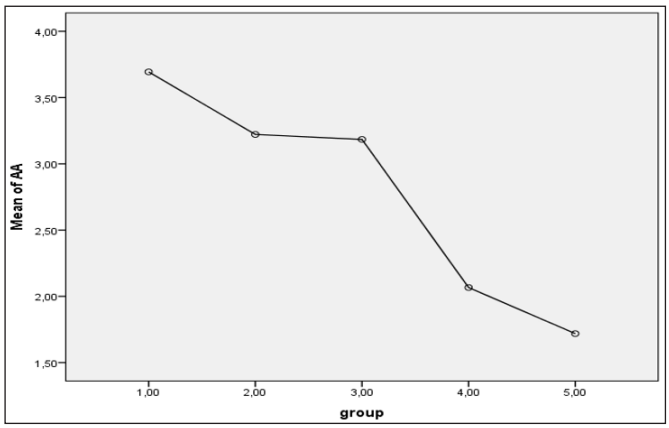

Figure. Change of mean accommodative amplitude value in groups with Tonoref III

Table 1. The mean accommodation amplitude values and pupil size in groups

	Tonoref III (D)	Pupil Size (mm)	ML	PU
Group 1	3.69±1.89	5.81±1.05	5.00±1.87	9.49±3.89
Group 2	3.22±2.35	5.65±1.29	4.81±1.40	10.25±3.61
Group 3	3.18±2.01	5.64±0.94	5.50±1.46	9.71±3.77
Group 4	2.06±1.40	5.14±0.99	4.80±1.99	7.54±5.52
Group 5	1.71±1.10	5.27±0.79	3.97±1.51	7.68±5.14
Total	2.77±1.93	5.50±1.04	4.86±1.73	8.79±4.58
P	0.00*	0.063	0.005*	0.003*

*Statistically significant, AA= accommodation amplitude, D=Diopri, ML=minus lens, PU=push up

While the mean AA value measured with the minus lens technique was 4.86±1.73 D, the AA value measured with the push up method was 8.79±4.58 Subjectively measured AA values were higher than the objectively measured autorefractometer AA values (**Table 1**). When the correlation between the ML, PU technique and the AA values measured with the autorefractometer was examined, it was seen that the difference was statistically significant, but there was a moderate correlation with ML and a weak correlation with the PU method (respectively p=0.000, r=0,43; p=0.001, r=0,28). It was found that there was a significant relationship between pupil diameter change and tonoref AA, but the correlation was moderate (p=0.00, r=3.91). In the Tonoref III AA method, the intraclass correlation coefficient (ICC) value between the two measurements was 0.935 (0.909-0.953).

DISCUSSION

The most important factor affecting AA is age (7). Decreased with age, AA presents with blurry vision and eye fatigue when looking at near objects around the age of 40. In addition, diabetes mellitus, Down syndrome, drug use such as topiramate may cause early deterioration in AA and trigger early presbyopia (9-12).

Presbyopia is a global problem and affects millions of people around the world. Near vision can be clarified with glasses or contact lenses. In recent years, surgical methods have been added to treatment options. In addition, studies using electrostimulation of the ciliary muscle to restore accommodation and studies on medical treatments are continuing (13). Accurate measurement of AA is required in order to reach the correct conclusion about the effectiveness of surgical methods and medical treatments. And it is important to determine whether accommodation and true diopter of AA decrease in early presbyopia.

For the evaluation of accommodation in clinical practice, the most frequently used methods are ML technique, PU and push down methods. Hofstetter (2) published data for the linearly decreasing estimated AA between the ages of 8 and 80 years for use by clinicians in the clinic with the PU method. Large dioptric errors can occur when measuring at close working distances in the push up method. In particular, moving the target too fast or not understanding the concept of the initial blur endpoint can cause errors (14). In the ML technique, inaccurate measurements can be obtained when there is a rapid transition between measurements or when the ambient light is not clear and high refractive errors.

There are various studies in the literature comparing objective and subjective methods. In a study comparing the AA values measured by using dynamic retinoscopy, subjective ML technique and push down method as an objective method, it was seen that the AA values measured with the objective method, as in our study, were lower than other methods. In addition, when the correlation coefficients of agreement between the objective method and both subjective methods were evaluated, it was observed that there was a significant weak agreement (4). Kurt et al. (15) used ML, focus meter, pilocarpine and Hartinger refractometer to compare objective and subjective AA methods. It has been stated that AA measured by subjective methods is higher than by objective methods. The reason for this is that subjectively measured AA measures the best near vision capacity instead of actual accommodation. But with objective measurements, changes in optical power can be measured directly. When we compared Tonoref III and subjective tests in our study, it was seen that Tonoref III had lower values.

The AA values of the genders were compared in our study. It was seen that there was significant difference. When the effect of gender adjustment on AA was considered in previous studies, it is seen that it is a controversial factor. In our study, mean AA in women was significantly higher than in men. Although there was no significant age difference between men and women, the ages of women were lower. There may be a difference due to this. In other studies, it is argued that many factors such as education and nutrition may have led to the difference between genders (16,17).

When the objective AA measurement is compared with the subjective AA measurement, one of the differences is that the pupil diameter cannot be measured in the subjective method. Pupil diameter is one of the important parameters in accommodation. Accommodation occurs together with convergence and miosis. With the reduction of the pupillary diameter, a decrease in optical aberration is observed and image clarity is provided (18). In our study, there was a significant difference between pupil diameter change and AA measurement. In addition, the pupil diameter decreases with age. In the study by Ozulken et al. (19), it was reported that the pupil diameter decreased with age, as in our study.

Intraclass correlation coefficient greater than 0.9 means excellent reproducibility (20). When comparing repeat measurements of AA values, Weng et al. (21) argued that Tonoref III is reproducible and reliable. In our study, the high intraclass correlation coefficient supports that it is a reproducible and reliable test.

Our study has some limitations. We could not compare our results with other objective methods. And our study was done on healthy patients who do not have presbyopia. Patients with presbyopia could be included in the study.

CONCLUSION

As a result, Tonoref III was found to be lower in AA measurements compared to the subjective methods. It was found to have good repeatability. Our results showed that AA was significantly associated with age, changes in pupil size during accommodation and gender.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Tokat Gaziosmanpaşa University Medical Faculty Clinical Researches Ethics Committee (Date: 01.10.2020, Decision No: 20-KAEK-244).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

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Horizontal bone augmentation using a mixture of cortico-cancellous allograft and bovine bone mineral with a collagen membrane: a retrospective study

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ABSTRACT

Aim: The study aimed to evaluate the clinical outcomes of bone augmentation with a mixture of cortico-cancellous allograft and xenograft with a collagen membrane in horizontal augmentation of knife-edge alveolar crests.

Material and Method: Patients with a ridge thickness of less than 4 mm by preoperative tomography were included in the study. Twelve patients (10 Female, 2 Male) were treated with a mixture of Cortico-Cancellous Allograft and Bovine Bone Mineral with a collagen membrane.

Results: Thirty-nine implants were placed in twelve patients. The initial bone thickness is between 1 and 4 cm (mean: 3±0.89440). Nine months after horizontal augmentation, bone thickness varies between 4.53 and 9.15 cm (mean: 4.62±1.16782). The gained bone thickness varies between 1.27 and 7.72 cm (mean 3.66±1.21041).

Conclusion: Augmentation of alveolar bones knife-edge crestal margins with a mixture of Cortico-Cancellous Allograft and Bovine Bone Mineral with a collagen membrane is simple, successful, and feasible.

Keywords: Alveolar bone grafting, bone regeneration, bone substitutes, guided tissue regeneration

INTRODUCTION

Dental implant treatment in atrophic jaws is becoming more prevalent. Periodontal disease, trauma, and bone resorption cause bone insufficiency in the alveolar crest. This insufficient bone causes aesthetic or functional problems; therefore, bone augmentation is recommended (1).

Autogenous bone is the gold standard in bone augmentation due to its osteogenic and osteoinductive properties (2). Although autogenous bone (AB) is the gold standard, the problem in the donor area and the limited amount of bone collection are the disadvantages of the technique. As an alternative to autogenous bones, bone grafts such as alloplasts, xenografts and allografts have been used successfully in alveolar bone augmentation (3,4). Xenografts are preferred in bone regeneration because they preserve tissue volume with their osteoconductive properties and have a slow resorption rate (5,6).

One of the most used techniques in alveolar augmentation is mixing xenograft and autogenous bone. The high biological features of autogenous bone and the slow resorption feature of xenograft are utilized with this technique (7,8). In Several clinical studies, bone defects were treated with a ratio of 1:1 xenograft and autogenous bone chips. It shows successful results both clinically and histologically (9). The disadvantage of the technique is the need for autogenous grafts. It causes prolongation of the operation time and the occurrence of postoperative complaints in the donor area.

Another possibility is using a mixture of allograft, an osteoinductive material, with xenograft (10). There are few publications about the usage of allograft and xenograft combinations in implantology (11,12).

The study aimed to evaluate the clinical outcomes of bone augmentation with a mixture of allograft and xenograft.

MATERIAL AND METHOD

This study was conducted with the data obtained from the files of patients who underwent horizontal bone augmentation with a mixture of allograft and xenograft, and collagen membrane. The study was carried out with

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the permission of Zonguldak Bülent Ecevit University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 26/01/2022. Decision No: 2022/02-22). All procedures were performed in accordance with ethical rules and the principles of the Declaration of Helsinki.

This study includes the patient group who required horizontal bone augmentation for dental implant placement. It includes patients with knife edge alveolar bone (Cawood-Howell Class IV) who applied for dental implant treatment at the Department of Oral and Maxillofacial Surgery of the Faculty of Dentistry of Bülent Ecevit University between 2018-2021. Patients with a ridge thickness of less than 4 mm by preoperative cone beam computed tomography (CBCT) were included in the study (**Figure 1**). Patients who did not smoke, had no systemic disease, and had good periodontal health were included in the study

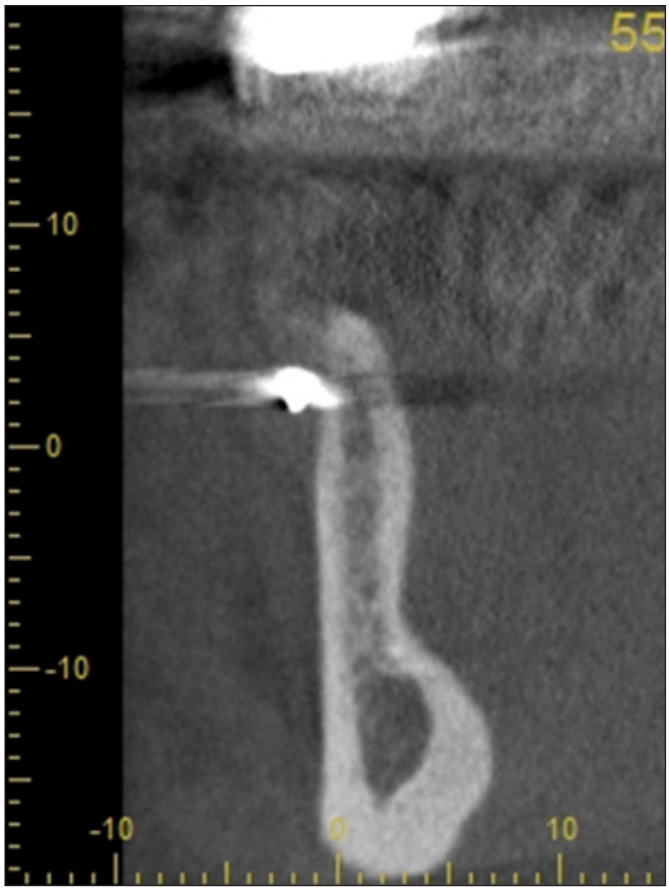

Figure 1. Preoperative CBCT image

Under local anesthesia, a horizontal incision was first made from the crest. In cases with a defect in the palatal aspect of the maxilla, a vestibular shifting incision was performed. Afterward, mesial and distal relaxing incisions were made. After flap dissection, a periosteal relaxing incision was made to stretch the flap. In the mandible, in addition to the buccal relaxing incision, the flap in the lingual region was dissected from the mylohyoid muscle with the help of a periosteal elevator, and the lingual flap was relieved. To adhere the graft particles and ensure easy manipulation, blood was taken from the patient with an additive-free plastic vacuum type 10 ml tube and centrifuged at 800rpm for 3 minutes in the Process for PRF centrifuge device. Injectable platelet-rich fibrin (iPRF) was obtained. For augmentation, xenograft (Nobel Biocare Creos, Chungcheongbuk-do, Korea) and cortico-cancellous freeze-dried bone allograft (Botiss Maxxgraft, Zossen/Germany) were mixed with injectable platelet-rich fibrin (iPRF) at a ratio of 1:1 and applied on the alveolar crest. A long-lasting membrane (Nobel Biocare Xeno Project, Herzogenrath, Germany) was used over the graft mixture. The membrane is fixed with titanium fixation pins. The flap was closed with 5.0 and 6.0 polyamide sutures without tension. Two weeks after the operation, the sutures were removed.

Antibacterial treatment was started in all patients 24 hours before the operation, including amoxicillin-clavulanate 1gr twice daily (7 days) or azithromycin 500mg once daily (3 days). Diclofenac potassium-containing analgesic and Chlorhexidine gluconate mouthwash were prescribed three times a day.

Nine months after augmentation, CBCT was retaken from the patients, and the newly formed bone thickness was evaluated (**Figure 2**). Implants were placed nine months after augmentation (**Figure 3**).

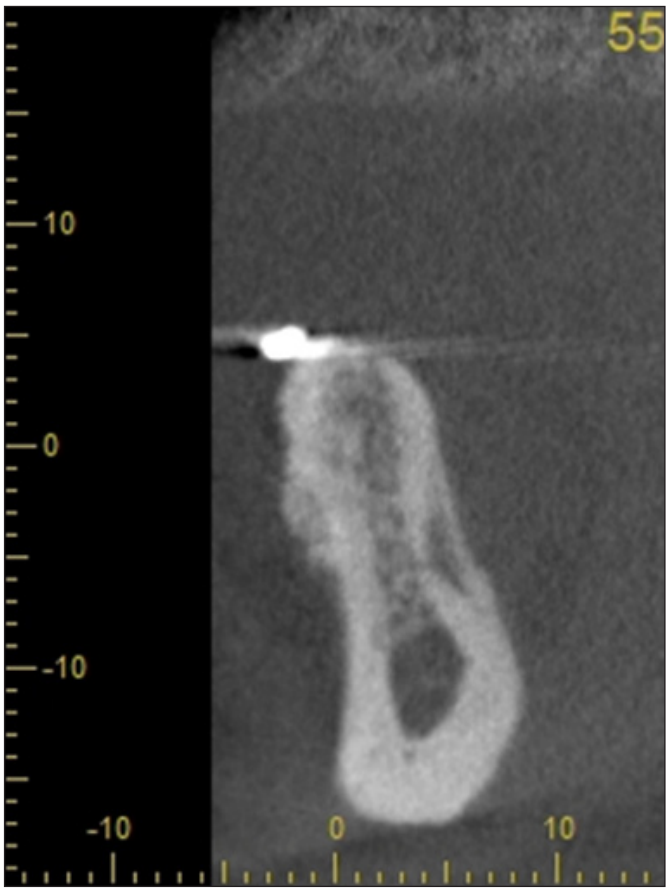

Figure 2. CBCT image of augmentation site nine months after augmentation.

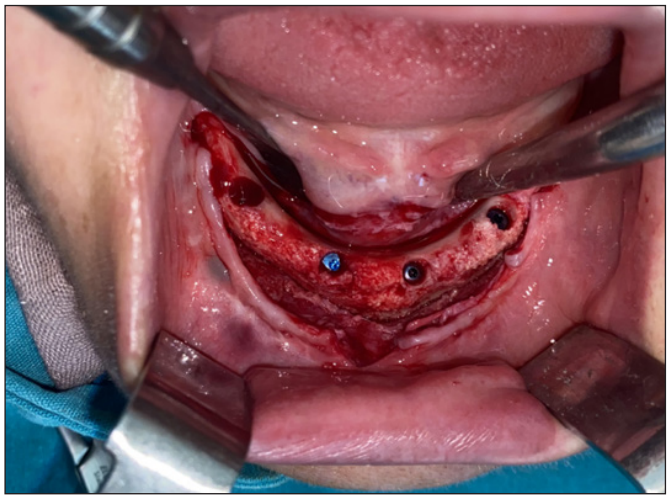

Figure 3. Intraoral view of augmented bone during implant placement.

Statistical analysis was done with SPSS 23.0 for Windows (IBM, Chicago, USA) software. For all the analyzed data, the mean values, standard deviation values for each group were calculated. Normality tests showed a different distribution than normal and Wilcoxon test was used to compare study groups. P values<0.05 were considered sufficient to indicate statistical significance.

RESULTS

All patients recovered without problems after bone grafting, and complications such as post-op infection and membrane exposure were not observed. Thirty-nine implants with SLA surface TiPurePluss (Bego Semados RSX, BEGO Bremen,Germany) were placed in 12 patients (10 Female, 2 Male with a mean age of 50.9) nine months after augmentation (**Figure 3**). Implant placement sites are shown in **Table 2**. The healing cap was placed four months after the implants had been replaced. There was no implant loss during the healing phase. There was no loss of implant after prosthetic treatment. The initial bone thickness is between 1 and 4 cm (mean: 2,6395±0.89440). Nine months after horizontal augmentation, bone thickness varies between 4.53 and 9.15 cm (mean: 6,3997±1.16782). The gained bone thickness varies between 1.27 and 7.72 cm (mean 3,7574±1.21041). The Post-op thickness median value was significantly higher than the pre-op value (p<0.05) (**Table 3**). When the bone changes in the maxilla and mandible are compared, the average residual bone thickness is 2.69±0.89 mm in the mandible and 2.60±0.92 mm in the maxilla. The newly formed bone thickness is 3.73±0.36 mm in the mandible and 3.77±0.21 mm in the maxilla. There were no significant statistical differences in bone width gain between maxillary and mandibular regions (P=0.901).

Table 1. Wilcoxon Signed Rank Test

	Augmented Bone With – Initial Bone Width
Z	-5.442[a]
P-value	.000

a. Based on negative ranks.

Table 2. Implant sites

Implant Site	n:39
Incisors	8 (20.5%)
Canines	5 (12.8%)
Premolars	22 (56.5%)
Molars	4 (10.2%)
Lower jaw	22 (56.4%)
Upper jaw	17 (43.6%)

DISCUSSION

Horizontal augmentation with AB and deproteinized bovine bone mineral (DBBM) mixture is one of the most popular techniques. Mordenfeld et al. (13) evaluated the effects of different ratios of DBBM and autogenous bone mixtures on graft healing and volumetric changes in horizontal bone augmentation. They found the gained crest width as 3.5 (±1.3) mm in the 60:40 group and 2.9 (±1.3) mm in the 90:10 group. It was reported that a thicker crest was obtained in the 60:40 group, but there was no histological difference between the two groups. According to the systematic review and meta-analysis by Elnayef et al. (14), the estimated overall mean horizontal bone gain at the time of regeneration was 3.61±0.27 mm for guided bone regeneration (GBR). The present study demonstrated an average bone gain of 3.75±1.2 mm.

Hashemipoor et al. (15) evaluated the histological and radiological effects of a cortico-cancellous freeze-dried bone allograft (FDBA) with and without autogenous bone in horizontal ridge augmentation. They found that including autogenous bone in the allograft particles does not significantly increase the quality and quantity of regenerated bone. Song et al. (16) compared the outcomes after wide horizontal guided bone regeneration using DBBM with or without autogenous bone chips in a canine model of chronic horizontal alveolar ridge defect. The author stated that including autogenous bone chips to DBBM for horizontal ridge augmentation

Table 3. Analyses of patients' age and bone thickness

	Patients age	Initial bone width	Augmented bone width	Gained bone width
Mean(SD)	50.91 (15.06)	2.6395 (0.89440)	6.3997 (1.16782)	3.7574 (1.21041)
Median	54.00	2.6700	6.1100	3.6600
Interquantile range	26.25	1.47	1.40	1.54
Range	48.00	3.00	4.62	6.45

has no advantage. Kloss et al. (17) evaluated the three-dimensional volumetric changes in autogenous and allogenic onlay graft augmentation in single tooth defects. They found that the rate of graft remodeling volume of freeze-dried cancellous bone blocks was similar to autogenous bone. Therefore, we preferred allograft with osteoinductive properties instead of autogenous bone. We thought to shorten the operation time and have a more comfortable post-operative period by not using an autogenous bone graft.

Wang et al. (18) defined major biological principles "PASS" for predictable bone regeneration; Primary wound closure, angiogenesis, space creation/maintenance, and stability. Initial clot stabilization and wound stabilization are essential in guided bone regeneration. Once the bone grafts are mixed with i-PRF, their consistency transforms into a plastic form within 3-4 minutes, making it easier to apply to the defect area and providing stability to the graft (19). To stabilize the bone grafts, i-PRF was used, and titanium fixation pins were used to prevent membrane micro-movements for optimum wound stability.

Although many studies are showing favourable effects of i-PRF on early bone healing, its effects on long-term bone healing are controversial (20,21). Mu et al. (21) evaluated the effects of i-PRF on bone in sinus augmentations by applying DBBM alone and DBBM combined with i-PRF to rabbit sinuses. They concluded that despite increased vascular formation and bone remodelling in the early stages of healing using i-PRF, bone volume did not change significantly in the long term. İrdem et al. (22) evaluated the effectiveness of DBBM combined with i-PRF on new bone formation in patients with bilateral maxillary sinus atrophy requiring maxillary sinus augmentation. The combination of DBBM with i-PRF did not significantly affect new bone formation. Since xenograft healing takes a long time, we think that the effects of i-PRF on the bone formation are limited, but we think that i-PRF has a great effect on the preservation of bone volume by fixing the graft particles and preventing the movement of the particles.

Primary wound closure and soft tissue primary wound healing seem to be key factors for successful outcomes. Soft tissue dehissence in the early period after augmentation surgery may have a negative effect on the new bone formation process. To minimize the risk of soft tissue dehiscence, flap elongation and passivation must have extremely low residual tension at the flap suture line. While the lingual flap can be easily stretched in the mandible, the palatal flap cannot be stretched in the maxilla due to its dense fibrous structure (23). In our study, mid-crestal incision was used for augmentation in the mandible. Mid-crestal incision was preferred if the defect was in the buccal side of the maxilla. If the defect was on the palatal side we preferred a vestibular shifted flap for preventing soft tissue dehiscence.

In guided bone regeneration, resorbable (human, porcine, and bovine pericardium membranes, human amnion, chorion tissue, human acellular freeze-dried dermal matrix) and non-resorbable membranes (titanium mesh, titanium-reinforced polytetrafluoroethylene) are used as barrier membranes. Non-resorbable membranes are more rigid than non-resorbable membranes. They provide less micro-movement of the graft and have better space-maintaining properties. Some disadvantages include increased exposure risk, the necessary second surgery to remove it, and the technique-sensitive approach (24). Because of these disadvantages, we preferred resorbable membranes in our study. The collagen membrane showed good soft tissue compatibility, and no membrane exposures occurred in our research.

The limitations of the study are the non-homogeneous gender distribution, the absence of a histological evaluation, and the lack of long-term follow-up of the implants. Future studies should include homogeneous sex distribution, histological assessment, and long-term follow-up.

CONCLUSION

Allograft and DBBM combination with a collagen membrane can be safely and effectively used for horizontal augmentation of knife-edge ridges. Further studies will be necessary to confirm these results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Zonguldak Bülent Ecevit University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 26/01/2022. Decision No: 2022/02-22).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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How readable are antihypertensive drug inserts?

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ABSTRACT

Aim: Patients can be protected against possible complications when antihypertensive drugs are regularly and properly used for the treatment of hypertension. The readability of package inserts increases treatment compliance. In the present study, the purpose was to determine the readability level of antihypertensive package inserts.

Materials and Method: A total of 64 commonly used antihypertensive drugs were selected for this study. The readability scores of the package inserts for the selected drugs were calculated according to the Readability Scales developed by Atesman and Bezirci-Yılmaz.

Results: The readability level for the selected package inserts were found to be suitable for an average of 11-12 years of education and high school education level according to the Atesman and Bezirci-Yılmaz Readability Scales, respectively.

Conclusion: When it is considered that the average schooling year in Turkey is 6.5 years, the readability level of antihypertensive package inserts is highly above this level. It is recommended to simplify the package inserts to increase readability and drug compliance and prevent incorrect drug use.

Keywords: Hypertension, package insert, readability level

INTRODUCTION

Hypertension is an important public healthcare issue with increasing prevalence around the world. If untreated, this disease can cause significant mortality and morbidity rates due to heart, brain, kidney, and retina problems (1,2). In terms of first-line treatment, lifestyle changes are recommended to the patients (3,4). The ongoing high blood pressure despite lifestyle changes or due to risk factors (diabetes mellitus (DM), chronic kidney disease (CKD), coronary artery disease (CAD), etc.), antihypertensive treatment is initiated (5). Patients who start the drug treament may desire to learn more about drug-related side effects, drug use, and dosage by reading the package inserts. As the education level of the patients increases, the rate of reading the prospectus increases (6,7). Some patients stop using the drug or change the drug dose regardless of the physician's knowledge after reading the drug inserts. Therefore, these package inserts must be at an adequate level for patients to understand.

Readability levels are the main evaluation criteria to assess whether the package inserts are understood by the patients (8). The readability level of a text is determined by adopting certain scales proven and reported by scientific studies(9). These scales calculate the readability score by using various parameters such as the number of sentences in the text, the number of words, and the number of syllables. Accordingly, Atesman(10) and Bezirci-Yılmaz(11) Readability Scales are frequently used for Turkish texts.

In the present study, the purpose was to measure the readability level of antihypertensive package inserts, which are frequently used by patients in Turkey and to determine which age and education level the texts on the package inserts are suitable for.

MATERIAL AND METHOD

The study was conducted according to the decision of the Afyonkarahisar Health Sciences University Clinical Researches Ethics Committee (Date: 05.08.2022, Decision No: 2022/40). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 64 antihypertensive drugs frequently used by the patients were randomly selected for the study. The readability scores of the package inserts of these drugs were calculated. These drugs were divided into 6 groups which were angiotensin converting enzyme (ACE)

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inhibitors/angiotensin receptor blockers (ARB), calcium channel blockers (CCB), beta-blockers, alpha-blockers, diuretics, and combined drugs (drugs that contain more than one antihypertensive group). The mean readability level of these drug groups was evaluated independently and comparatively. When evaluating the readability levels of the package inserts, the titles and the license information at the end were evaluated based on the text on the inserts.

When determining the readability levels, various scales can be used. These scales provide an average score based on parameters such as the number of words in the text, the number of sentences, and the number of letters. The readability levels of the drugs in our study were evaluated by using Ateşman (10) Readability Scale and Bezirci-Yılmaz (11) Readability Scale.

The readability score calculated on the Atesman Readability Scale ranges from "0" to "100". The scores means that as the score approaches "100", the readability increased as the score decreases toward "0", the readability decreases. When calculating Atesmen readability points, the following formula was used.

$$RS=198.825-(40.175 \times X1)-(2.610 \times X2)$$

RS: Readability Score
X1: Total number of syllables/ Total number of words
X2: Total number of words/Total number of sentences

The comparison of Atesman Readability Scores according to educational levels is shown in **Table 1**.

Table 1: The educational status equivalent of the readability score calculated with the Atesman Readability Scale

Readability score	Educational status
90–100	It can be read by anyone who is in the 4th grade of primary school and below.
80–89	It can be read by anyone studying at the 5th or 6th grade level.
70–79	It can be read by anyone studying at the 7th or 8th grade level.
60–69	It can be read by anyone studying at the 9th or 10th grade level.
50–59.	It can be read by anyone studying at the 11th or 12th grade level.
40–49	It can be read by anyone studying at the 13th or 15th grade level.
30–39	It can be read by anyone with an undergraduate degree.
≤29	It can be read by anyone with a graduate degree

For the Bezirci-Yılmaz Readability Scale, a higher score corresponds to a text that is harder read while a lower score corresponds to a text that is easier to read. In calculating the Bezirci-Yılmaz readability score, the following formula was used;

$$RS= \sqrt{AWC} \times ((S3 \times 0.84) + (H4 \times 1.5) + (H5 \times 3.5) + (H6 \times 26.25))$$

RS: Readability Score
AWC: average word count
S3: average number of 3-syllable words
H4: average number of 4-syllable words
H5: Average number of 5-syllable words
H6: Average number of words with 6 or more syllables

The comparison of Bezirci-Yılmaz Readability Scores according to educational levels is shown in **Table 2**.

Table 2: The educational levels equivalent of the readability score calculated with the Bezirci-Yılmaz Readability Scale

Readability score	Educational status
1-8	Primary School
9-12	Secondary School (High School)
13-16	Undergraduate
16+	Academic level education

The computer program that was developed by Bezirci-Yılmaz was used in calculating the readability scores by using these formulas.

Statistical Analysis

The categorical variables were presented as percentage and frequency and the continuous variables were expressed as mean and standard deviation. The ANOVA Test was used for continuous variable comparison between groups. Statistical analyzes were performed with the SPSS 26.0 package program. All presented p values were bidirectional, and $p<0.05$ values were considered statistically significant.

RESULTS

A total of 64 package inserts were evaluated in the study. The average readability level of these drugs was found 52.58±7.84 according to Atesman Readability Scale and on average, it required 11-12 years of education. According to the Bezirci-Yılmaz Readability Scale, the average readability level was found 11.99±2.35. The corresponding education level was secondary (high school) level on average (**Table-3**)

Table 3: The mean scores of antihypertensive drugs calculated according to the Atesman and Bezirci-Yılmaz Readability Scales and the corresponding education levels

	Number	Minimum	Maximum	Mean (standart deviation)	Educatonal status
Ateşman	64	37,17	79,61	52,5823±7,84	11-12 years
Bezirci Yılmaz	64	5,14	17,24	11,9905±2,35	Secondary School (High School)

Package inserts were divided into 6 groups which were ACE inhibitors/ARB (n:23), CCB (n:10), beta-blockers (n:10), alpha-blockers (n:3), diuretics (n:4), combined drugs (n:14). Among these drug groups, diuretic group drug inserts were found to be the group that required the highest education level for both Readability Scales. It was found that an undergraduate level of education was required on average for the readability of the drugs in the diuretic drug group.

The average scores and comparisons of the drug groups that were calculated according to the Atesman and Bezirci-Yılmaz Readability Scale are shown in **Figures 1** and **2**. The educational levels corresponding to the mean scores of the drug groups are shown in **Table 4**.

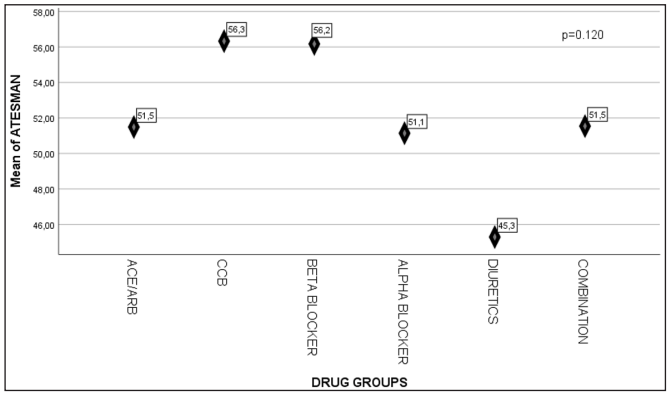

Figure 1: The mean scores of the drug groups according to the Atesman Readability Scale

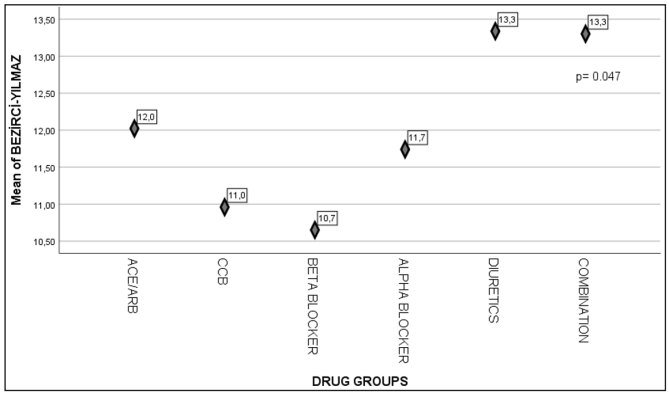

Figure 2: The mean scores of the drug groups according to the Bezirci-Yılmaz Readability Scale

Table 4: The educational status corresponding to the mean scores of the antihypertensive drug groups

	Bezirci-yilmaz	Atesman
ACE/ARB	Secondary schoool (high schoool)	At 11th or 12th grade level
CCB	Secondary schoool (high schoool)	At 11th or 12th grade level
Beta blocker	Secondary schoool (high schoool)	At 11th or 12th grade level
Alpha blocker	Secondary schoool (high schoool)	At 11th or 12th grade level
Diuretics	Undergraduate	13th or 15th grade level
Combined drugs	Undergraduate	At 11th or 12th grade level

DISCUSSION

In this study, the aim was to determine the readability levels of antihypertensive package inserts. According to the Bezirci-Yılmaz and Atesman readability scales, an average high school education is required for the readability of the package inserts. This level is above the schooling level in Turkey. Therefore, we recommend that these drug inserts should be edited in accordance with the schooling year in Turkey. In addition to the text content, the value of a text is also related to how much a text is understandable by the individual who reads the text. The value of the text is determined based on the comprehension level of the individual. Throughout the historical process, various Readability Scales were developed in the world since the 1950s to determine the readability of texts. The Flesch Reading Ease Score (FRES) and the Gunning Fog Index are some of the important readability scales (12,13). These scales determined the readability level by using the number of sentences in the text, the number of words, the number of syllables in the words, and their ratios in the given text.

The dynamics and structure of each language are unique and different. Readability studies for Turkish texts have been developed since the 1990s. The most commonly used Readability Scales for Turkish texts are the Atesman (10) and Bezirci-Yılmaz (11) Readability ScalesAtesman defined readability as the ease or difficulty of a text to understand and comprehend the content of the text.

Package inserts are the most detailed texts that provide sufficient information to the patients regarding the drugs. Patients may increase or decrease the recommended dose by the physician or terminate the treatment due to misunderstanding the information on the package inserts. Incorrect or insufficient understanding of the drugs might lead to significant mortality and morbidity rates for serious diseases such as hypertension. Kasar et al. (14) examined antihypertensive drug use errors in elderly individuals and found that 57% of the patients had followed an incorrect drug use. It was also found that the rate of making mistakes was 7.2 times higher in those who read the drug inserts than in those who did not and 32% of those who did not read drug inserts stated that they did not read drug inserts because they could not understand the text. Solmaz et al. (15) conducted a study on the use of drugs by elderly people living at home and found that 77.7% of the elderly who did not read the package insert indicated that the reason for not reading the package inserts was the inability to understand the texts. These studies show that one of the important reasons for not reading package inserts is the difficulty of understanding of the text.

Ay et al. (16) evaluated the readability levels of eye drop drug inserts and found that the readability level of the package inserts was 46.8 based on the Atesman Readability Scale and 12.8 for the Bezirci-Yılmaz Readability Scale. The education required to be able to read drugs was an average of 13 years, i.e., undergraduate level. Another study evaluating the readability of consent forms used for advanced invasive procedures in cardiology clinics in Turkey reported that patients must have received at least 11 years of education to be able to read and understand the consent forms easily (17). Various studies examining the readability levels of other consent forms have yielded similar results (18–20). In our study, the readability level of antihypertensive package inserts was calculated as 52 according to the Atesman Readability Scale and 11.9 according to the Bezirci-Yılmaz Readability Scale. In other words, an average of 11-12 years of high school education is required to read these package inserts.

The average schooling year and the expected schooling year provide an idea about the education level of countries and regions. Yesilyurt et al. (21) conducted a study in 2016 and reported that the average schooling year in Turkey was 6.51 years, and the expected schooling year was 11.03. In other words, the readability level of antihypertensive package inserts was above the average schooling year in Turkey. This level must be considered when determining the texts that address different members of the society.

CONCLUSION

It was determined in the present study that an average of 11-12 years of high school education is required for antihypertensive package inserts to be readable. Considering that the average year of schooling in Turkey is 6.51 years, this level is found to be at high level. It would be more appropriate if the readability levels of the package inserts were suitable for 6 years of education. In this respect, we recommend that medication errors will decrease and treatment compliance will increase by making the package inserts easier to read and comprehend. Further, more comprehensive studies must be conducted with more comprehensive scales covering the patients' cognitive functions and vision problems.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Afyonkarahisar Health Sciences University Scientific Research and Publication Ethics Committee (Date: 05.08.2022, Decision No: 2022/545)

Informed Consent: There were no patients in our study.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article

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Evaluation of factors related to taste function in type 2 diabetics

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ABSTRACT

Aim: The sense is an important driver of diet choice, which can lead to the development of chronic diseases such as diabetes. Although factors affecting differences in taste function between individuals have been evaluated in healthy individuals, there are limited studies investigating them in patients with type 2 diabetes. The aim of the present study was to analyse the factors affecting taste function in individuals with type 2 diabetes.

Material and Method: Sixty-one participants with a history of type 2 diabetes lasting at least one year and aged 19 to 75 years were enrolled. The taste function was tested using impregnated filter paper strips.

Results: The mean taste strip scores of the participants for sweet, salty, bitter, sour, and overall were 2.38±0.88, 1.91±0.92, 2.28±0.76, 2.18±1.01, 8.7±1.81, respectively. Age was significantly associated with the taste score for salty (r= -0.225 p= 0.041) and sour (r= -0.252 p= 0.040). It was determined that there was no effect of other confounders (gender, body mass index, fasting plasma glucose, glycosylated hemoglobin and duration of diabetes), except age, on the overall taste score in participants.

Conclusion: Future studies with a larger number of patients may help better investigate the factors affecting taste function in type 2 diabetics.

Keywords: Type 2 diabetes mellitus, sweet taste, sour taste, salty taste, bitter taste

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) has increased rapidly worldwide over the past few decades, and is expected to rise by more than 50% by 2045 (1). T2DM is a chronic metabolic disease that requires continuous medical care in which the body cannot benefit adequately from carbohydrates, fats, and proteins due to insulin deficiency or impaired insulin action. Although T2DM is a polygenic illness, environmental and behavioural variables play a role in its incidence (2).

When the chemical concentration of a tastant exceeds a threshold level, taste receptors are activated, resulting in action potentials in fibers of taste nerve strong enough to produce taste perception (3). Previous studies (4,5) reported that activation of sensory receptors induces oral and gastrointestinal secretion, contributing to the metabolic and digestive process. Multiple factors affect the taste threshold, including genetics, age, body weight, consumption, smoking, acute and chronic diseases (6). Taste sensation and food preferences have been shown to be significant in dietary and food consumption. A loss of taste sensation, which could lead to an increase in unhealthy eating habits, could have severe health consequences. It may increase the likelihood of metabolic disorders such as obesity, diabetes, and metabolic syndrome (7,8).

To date, there are very few reports that describe factors linked to taste function in type 2 diabetics. The results of these studies are contradictory in some aspects, suggesting the need for more evaluative studies. The aim of this current study was to determine the factors associated with taste function in type 2 diabetics.

MATERIAL AND METHOD

Study Population

The sample consisted of 61 individuals who had been diagnosed with type 2 diabetes for at least one year. Diabetic patients admitted to internal outpatient clinic. Participants who agreed to participate in this study were asked to sign an informed consent form in accordance with the Declaration of Helsinki. The study was carried out with

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the permission of Gaziantep Islam Science and Technology University Non-interventional Clinical Researches Ethics Committee (Date: 27.09.2022, Decision No: 2022/148). Patients were subjected to preliminary interviews and their suitability for the study was evaluated. The inclusion criteria were age between 19 and 75 years, body mass index (BMI)<40 kg/m². Exclusion criteria were: smoking or history of smoking; chronic use of alcohol or substance abuse in the past 6 months; presence of comorbidity that affects taste (i.e., renal or liver diseases, presence or previous treatment with history of cancer, previous head and neck radiation, hypothyroidism, neurodegenerative diseases, depression, acute infections in the previous 2 weeks, respiratory diseases, periodontitis, anosmia and denture carriers), usage of antibiotics, antihistamines, antidepressants, anticonvulsants, antineoplastic drugs or environmental toxins; pregnancy and breastfeeding.

Data Collection

Face-to-face interviews were used to obtain data on demographic variables and diabetes information using a questionnaire form. Anthropometric measurements of the individuals (body weight, height) were taken. Blood samples were taken to test the fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c). Taste assessments were performed through taste strips.

Anthropometric Measurements

An trained dietitian took anthropometric measurements (weight, height) using standard measurements procedures (9).Body weight was determined using an electronic scale to the nearest 0.1 kilogram. Stadiometer was used to measure height to the nearest 0.1 cm. Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m²).

Laboratory Assays

FPG and HbA1c were measured in blood samples taken after 12 hours of fasting. FPG was measured by the glucose oxidase method. HbA1c levels were measured in the same laboratory by high-performance liquid chromatography.

Taste Test

Taste function tests was performed using the taste strips which are basically tastant impregnated filter paper strip (10). Each of the 16 taste stimuli was impregnated with one of these four tastes: sweet, sour, salty, and bitter. The following concentrations were used for taste stimuli: sweet: 0.4, 0.2, 0.1, 0.05 g/mL sucrose; salty: 0.25, 0.1, 0.04, 0.016 g/mL sodium chloride; bitter: 0.006, 0.0024, 0.0009, 0.0004 g/mL quinine hydrochloride; sour: 0.3, 0.165, 0.09, 0.05 g/mL citric acid. Tastants were solved in distilled water. During the test, participants washed their mouths with a sip of water before each taste strip. The strip was placed in one third of the tongue. With their tongue still extended, the patients had to identify the taste from a list of four descriptors, sweet, sour, salty and bitter (multiple forced choice). The tastes were delivered with increasing concentrations in a random order. Each correct answer was given as 1 point (maximum 4 points for each taste quality score and 16 points for the overall test score). A taste score was calculated based on the number of accurately identified tastes. Taste strips provide various advantages, including a short testing period and good consistency of result (10).

Statistics

The data was analysed using SPSS version 22.0 (SPSS Inc. Chicago, IL, USA). Continuous variables were reported as mean ($\overline{x}$), with and standard deviation (SD), and categorical variables were expressed as number with and percentage. The normality of the variable distribution was checked with the Shapiro–Wilk test. Quantitative data was compared using the independent samples t-test. The spearman correlation coefficient was used to analyse the correlations among taste scores and variables. Multiple linear analysis was used to determine the factors related to overall taste scores. The value of $p < 0.05$ was set as statistically significant.

RESULTS

Table 1 describes the demographic characteristics and baseline measurements of the participants. The current study included 61 adults (33 men and 28 women) with a mean age of 52.39 14.33 years (range from 20 to 74 years). The mean BMI of the participants was 25.38±3.86 kg/m² and mean duration of type 2 diabetes was approximately 4 years. When it comes to biochemical parameters, the mean fasting blood glucose level was 171.64±41.31 mg/dL and the mean HbA1c concentration was 7.59±1.38%.

Table 1. Demographic, anthropometric, and biochemical parameters of participants

	Total (n=61) $\overline{x}$±SD	Men (n=33) $\overline{x}$±SD	Women (n=28) $\overline{x}$±SD	p
Age (years)	52.39±14.33	49.52±14.18	55.79±14.00	0.089
Weight (kg)	71.56±12.25	78.43±9.48	63.47±10.06	<0.001
BMI (kg/m²)	25.38±3.86	26.50±3.52	24.05±3.88	0.012
Duration of diabet (years)	3.77±1.56	3.62±1.42	3.92±1.74	0.817
FPG	171.64±41.31	174.45±43.43	168.32±39.19	0.568
HbA1c (%)	7.59±1.38	7.26±1.34	7.98±1.36	0.043

BMI: Body mass index, FPG: Fasting plasma glucose, HbA1c: hemoglobin A1c

The mean taste strip scores of the participants for sweet, salty, bitter, sour and overall were 2.38±0.88, 1.91±0.92, 2.28±0.76, 2.18±1.01, 8.7±1.81, respectively. Additionally, there were no statistically significant differences between taste scores and gender (all $p > 0.05$). **Table 2** displays the mean taste scores.

Table 2. Taste Scores of Participants

	Total $\bar{x}$±SD	Men $\bar{x}$±SD	Women $\bar{x}$±SD	p
Taste scores				
Sweet	2.38±0.88	2.45±0.87	2.29±0.90	0.459
Salty	1.91±0.92	2.09±0.77	1.79±1.03	0.520
Bitter	2.28±0.76	2.24±0.71	2.32±0.82	0.775
Sour	2.18±1.01	2.33±1.08	2.00±0.90	0.201
Overall	8.70±1.81	9.12±1.88	8.21±1.62	0.068

The correlation between taste scores and investigated parameters are shown in **Table 3**. Age was significantly associated with taste score for salty (r= -0.225, p= 0.041) and sour (r=-0.252,p= 0.040). FPG and HbA1cwere not associated with taste scores. Additionally, we also found that the duration of diabetes and BMI were not related to taste scores for any of the tastes.

Table 3. Correlation between taste scores and investigated parameters

		Sweet	Salty	Bitter	Sour
Age	r	-0.174	-0.225*	0.096	-0.252*
	p	0.180	0.041	0.463	0.040
BMI	r	0.256	0.014	-0.010	0.243
	p	0.066	0.916	0.940	0.059
FBG	r	-0.019	0.082	-0.118	0.209
	p	0.885	0.531	0.367	0.106
HbA1c	r	-0.041	-0.004	-0.105	-0.176
	p	0.751	0.978	0.419	0.175
Duration of diabetes	r	0.174	0.097	0.040	0.010
	P	0.179	0.457	0.758	0.938

BMI: Body mass index, FPG: Fasting plasma glucose, HbA1c: hemoglobin A1c

The multiple linear regression model was significant and could explain8.2%of the variation in the overall taste score among the participants (**Table 4**). This analysis shows that only age had p-values smaller than 0.05, suggesting that age had a significant effect on the overall score of taste. Furthermore, the standardized β coefficients indicated that age was the independent variable with the highest explanatory power in the model (-0.280). Moreover, higher overall taste score was associated with lower age.

DISCUSSION

In the present investigation, the taste scores of 61 patients with T2DM were also examined taking into account gender, age, duration of diabetes, anthropometric measurements and biochemical parameters (FPG, HbA1c).

It has been extensively shown that the sense of taste plays a crucial role in the regulation of nutrient ingestion, the control of the digestive process, and the release of neuroendocrine hunger and satiety hormones. Although factors related to taste sensitivity have been studied in healthy people, patients with type 2 diabetes have reported less of these parameters. The ageing process can also lead to alterations in the sense of taste. It is generally assumed that a decrease in taste sensitivity occurs after the age of 60 years (11).In a study carried out by Pugnaloni et al. (12), it was shown that people with diabetes display a reduced overall taste discrimination, and the researchers also observed that the odds of success decreased by 6.5% for every additional 5 years of age. In this study, we found that age was negatively correlated with salty, sour and overall taste scores. Our findings are consistent with those of Pugnaloni et al. (12), who found that taste function in type decreases with age.

There is no obvious association between gender and taste sensitivity in the literature. Although many studies have reported that men were less sensitive compared to women in taste function in healthy people or cancer patients (13-15).The outcomes of studies on type 2 diabetes are contradictory. According to a study by Yu et al. (16), diabetic men are less sensitive to sweet taste than diabetic women. Some studies found that there was no significant effect of gender on differences in taste function in patients (12, 17, 18).In our study, we did not find significant differences in taste scores according to gender.

The current evidence for a relationship between BMI and taste in healthy adults is inconsistent, with some researches (19-21) finding no association, and others (22-24) suggesting a link between taste sensitivity and BMI. In a study of individuals with type 2 diabetes, it was found that there was no relationship between sucrose

Table 4. Multiple linear regression model explaining variations in overall taste score

	β1 (%95 CI)	SE	β2	t	p	Zero	Partial
Constant	8.478 (3.297 - 13.659)	2.584		3.281	0.002		
Age	-0.035 (-0.069 - -0.002)	0.017	-0.280	-2.107	0.040	-0.394	-0.276
Gender	-0.456 (-1.415 - 0.503)	0.478	-0.127	-0.954	0.345	-0.252	-0.129
BMI	0.065 (-0.07 - 0.200)	0.067	0.138	0.960	0.341	0.301	0.130
FBG	0.004 (-0.007 - 0.015)	0.006	0.090	0.694	0.491	0.208	0.094
HbA1c	-0.087 (-0.418 - 0.245)	0.165	-0.066	-0.524	0.603	-0.096	-0.071
Duration of diabetes	0.166 (-0.118 - 0.451)	0.142	0.144	1.173	0.246	0.135	0.158

F=2.658; p=0.025; Adj. R2= 0,082; β1: unstandardized coefficient; β2: standardized coefficient, BMI: Body mass index, FPG: Fasting plasma glucose, HbA1c: hemoglobin A1c

supra-threshold and BMI (18). In this study, we also found that there was no association between taste scores and BMI.

Some researchers found a direct relationship between blood glucose concentration and taste (25, 26). However, according to other studies, there was no association between taste scores and HbA1c levels (12, 18, 25, 27, 28). In addition to this study, several studies (16, 18, 29, 30) revealed no association between taste and either plasma glucose or glycosylated haemoglobin concentration, confirming the findings of this study. Although the pathophysiology of taste change remains unclear in diabetic patients. In accordance with the literature (18, 28, 31, 32), although the pathogenesis of diabetic patients' taste changes is unknown, the present data demonstrate that taste sensation in type 2 diabetics is not correlated with disease duration. This may be related to additional benefit of antidiabetic drugs in reducing the progression of underling disorders of altered taste sensitivity.

The exact underlying cause of diabetes-related taste impairment is uncertain. However, studies that examine taste function in T2DM have provided a variety of explanations for the decreased taste sensation in type 2 diabetics. First, taste impairment may be a degenerative complication of DM; due to neuropathy of the taste nerves. Increased intracellular glucose in diabetics leads to the formation of advanced glycosylation end products (AGEs), which bind to a cell surface receptor. AGEs have been shown to cross-link proteins (e.g. collagen and extracellular matrix proteins), accelerate atherosclerosis, promote glomerular dysfunction, reduce nitric oxide synthesis, induce endothelial dysfunction, and alter the composition and structure (33). Second, peripheral neuropathy affecting taste nerves or microangiopathy affecting taste buds may be responsible for taste impairment , but this is unlikely in newly diagnosed diabetic patients with clinical signs of microvascular problems (34). Third, the altered taste in T2DM may be associated with a slower rate of receptor turnover (35). In addition, the possible involvement of reduced salivary flow and zinc deficiency in these individuals may be associated with reduced taste function (36). Further, an inherent or acquired defect of the taste receptor or an abnormality in the mechanism underlying the central appreciation of taste in the brain may represent additional involved mechanisms (29).

The limitations of the current study must be taken into account when interpreting its findings. In this case, the inherent limitations of the cross-sectional design cannot be overcome because causality cannot be established from an observational design. Also, the sample size is relatively small. Other limitations relate to medication use; it is essential to point out that the medications of the participants were not documented in this study. Some studies (37-39) showed that diabetes medications (including metformin and losartan) have been linked to taste impairment. Despite limitations, the findings of this study are worthy; as it is one of the first studies to investigate effects of demographic, anthropometric, and clinical factors on taste alterations in type 2 diabetics.

CONCLUSION

The taste score for four basic taste modalities as well as the overall taste score were analysed in patients with Type 2 diabetes. It was discovered that the overall taste score of these individuals was not affected by any other confounding factors, with the exception of age. Future studies in a larger number of patients may help to better investigate the complex link between taste changes, diabetes, and related factors.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gaziantep Islam Science and Technology University Non-interventional Clinical Researches Ethics Committee (Date: 27.09.2022, Decision No: 2022/148).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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The utility of apparent diffusion coefficient values in predicting liver fibrosis in chronic hepatitis B

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ABSTRACT

Aim: We aimed to determine the relationship between apparent diffusion coefficient (ADC) values obtained from diffusion-weighted images, histopathological fibrosis, and activity stages in patients with chronic hepatitis B infection.

Material and Method: A total of 30 patients with chronic hepatitis B admitted to our hospital between September 2012 and June 2014 were included in the study. All patients underwent biopsy and abdomen MRI examination before the treatment. Diffusion examinations at five different b-values (50, 300, 500, 700, and 1000 s/mm²) were added to the abdominal MRI examination.

Results: The hepatic ADC values at all b-values were negatively correlated with fibrosis stages ($p<0.001$ for all b-values). The ADC values at b-values 300 and 1000 were significantly lower in patient groups with histological activity indices 1 and higher compared to the patient group whose activity index was 0 (at b-value 300 $p<0.034$, and at b-value 1000 $p<0.027$). The ADC values at b-values 50, 500 and 700 were not significantly in patient groups with histological activity indices 1 and higher compared to the patient group whose activity index was 0. Hepatic ADC was a significant predictor of stage 2 or greater and stage 3 or greater fibrosis, with sensitivity of 81%-100% and 81%-96% , and specificity of 84,2%-100% and 100% (ADC with all b values).

Conclusion: The ADC values have high sensitivity and specificity in indicating liver fibrosis in chronic hepatitis B infection. We suggest that the addition of diffusion-weighted MR images into liver MRI examination might reduce the requirement for liver biopsies in patients with chronic hepatitis B.

Keywords: Apparent diffusion coefficient, diffusion MRI, hepatitis B, fibrosis, liver, histological activity index

INTRODUCTION

Approximately 400 million people worldwide have chronic hepatitis B infection (1). Hepatitis B infection poses a high risk in terms of the development of liver fibrosis, cirrhosis, and hepatocellular cancer. The early diagnosis and treatment of liver fibrosis in patients with chronic hepatitis B can prevent the progression to cirrhosis (2). The liver biopsy is used as the indicator of the severity of the disease and to detect signs of antiviral therapy in chronic viral hepatitis. However, liver biopsies have some drawbacks, including the invasiveness of the procedure, complications resulting from the procedure, and inadequate sample amounts on some occasions. Therefore, there is a need for a non-invasive method for the detection of liver fibrosis and inflammatory activity in patients with chronic viral hepatitis. In the literature, numerous non-invasive tests that predict the degree of liver fibrosis in chronic hepatitis B have been proposed, but the tests are not as highly sensitive and specific as histopathological examination and have various limitations. Ultrasonography, computed tomography, and conventional MR imaging do not have sufficient sensitivity to show liver fibrosis and early cirrhosis (3).

In diffusion-weighted MR imaging (DWI), signal intensity is inversely related to the degree of diffusion of water molecules. The apparent diffusion coefficient (ADC) is a numerical value for quantitative measurement of proton diffusion given as square millimeter/second. Low ADC shows restricted diffusion of protons. DWI is affected by tissue perfusion, but using high b-values reduces the effect of perfusion on ADC values while fibrosis restricts the diffusion of water. Taouli et al. (3,4) have reported that reduced ADC values were associated with cirrhosis.

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The aim of our study was to quantitatively assess the relationship between ADC values obtained from diffusion-weighted images, histopathological findings, and activity stages of the liver in patients with chronic hepatitis B.

MATERIAL AND METHOD

The study was conducted with the permission of the Noninvasive Clinical Education Planning Board of 3rd step Training and Research Hospital in Ankara (Date: 09.01.2014, Decision No: 2014/352). All procedures were carried out in accordance with the ethical rules and principles of the Declaration of Helsinki.

Patients

A total of 30 patients who were diagnosed with chronic hepatitis B and admitted to our hospital between September 2012 and June 2014 and whose ultrasound examinations were insufficient, causing dynamic liver MR images to be taken were included in our study. Patients with a clinical diagnosis of cirrhosis were not able to undergo liver biopsy and were excluded from the study. In addition, patients that had comorbid malignant diseases and patients with non-hepatitis B diseases that could lead to viral and non-viral chronic hepatitis, such as hepatitis C and autoimmune hepatitis were excluded. Moreover, patients that had more than 10% histopathologically detected steatosis were also excluded from the study. Patients were diagnosed with chronic hepatitis B based on the clinical findings and results of laboratory evaluations. All of the patients were HBs Ag positive, anti-HBc Ig G positive, anti-HBe positive and HBV DNA levels were higher than 2000 UI/ml. Serological tests for hepatitis D and hepatitis C were negative in all of the patients. All patients underwent a biopsy and pre-treatment abdominal MRI examination. Patients that were scheduled to undergo additional diffusion examinations were asked to sign an informed consent form.

MR Imaging

The diffusion-weighted images were obtained by using 1.5 tesla MRI device (GE Medical System, Milwaukee, WI). A body coil was used for all experiments with participants in the supine position. Diffusion-weighted MR imaging at five different b-values was added to the abdominal MRI examination. Ten slices in the middle portion of the liver were taken (with 7-mm thickness and spacing of 1.5 mm). The following were the acquisition parameters of DW-MRI: non-breath hold single-shot spin-echo echo-planar DW-MRI, repetition time 1300, echo time minimum, matrix size 192-256, field of view 40, number of excitation 4. Parallel imaging technique using the generalized auto-calibrating partially parallel acquisition (ASSET) was used with a two fold acceleration factor.

A single radiologist who was blinded to the histology results placed a region of interest (ROI) in each lobe of the liver. Analysis of DW-MRI data was performed with the GE FUNCTOOL software (GE Medical Systems) to obtain ADC maps at each b value (50, 300, 500, 700, and 1000 s/mm²). One-cm² regions of interest (ROI) on the right and left lobes of the liver were measured from three different places, and average values were calculated. The axial echo-planar diffusion-weighted images of patients with stage 0 and stage 4 fibrosis of chronic hepatitis b at b-values 1000 s/mm² are demonstrated in **Figure 1** and **Figure 2**.

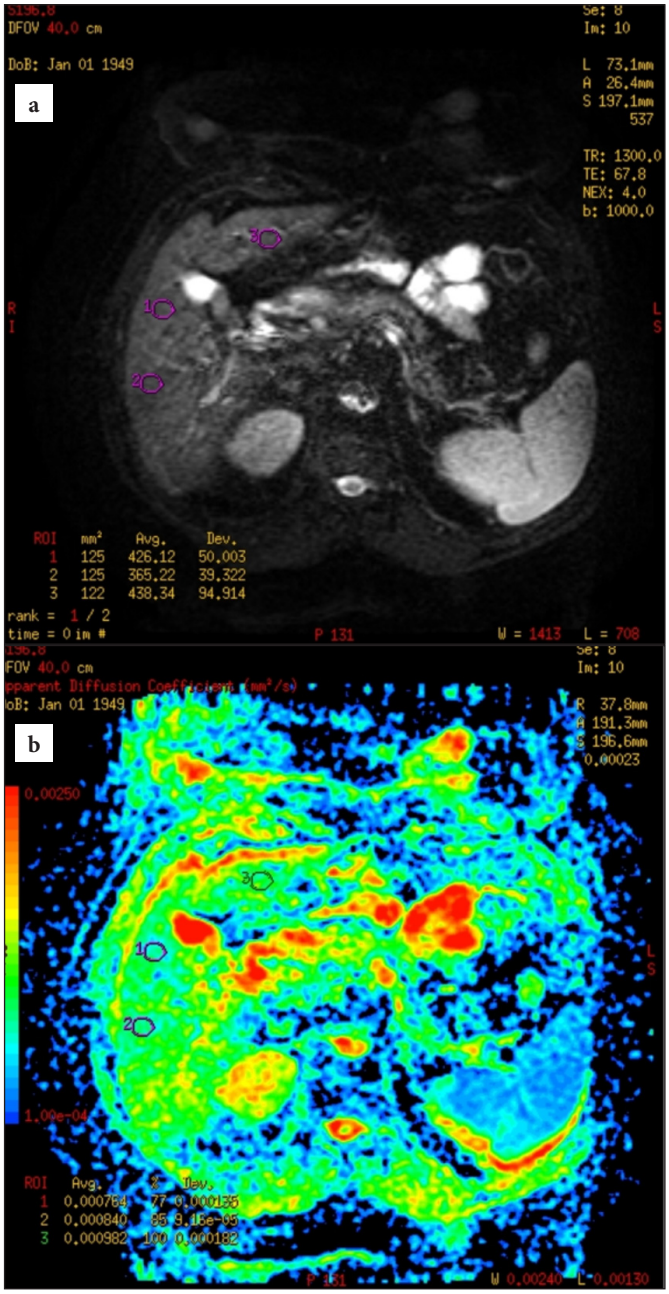

Figure 1. The axial diffusion-weighted images (a) and ADC map (b) of 46-year-old patients with stage 4 fibrosis. The mean ADC value of measurements taken from the right and left lobes of the liver was found as 0.86 x 10-3.

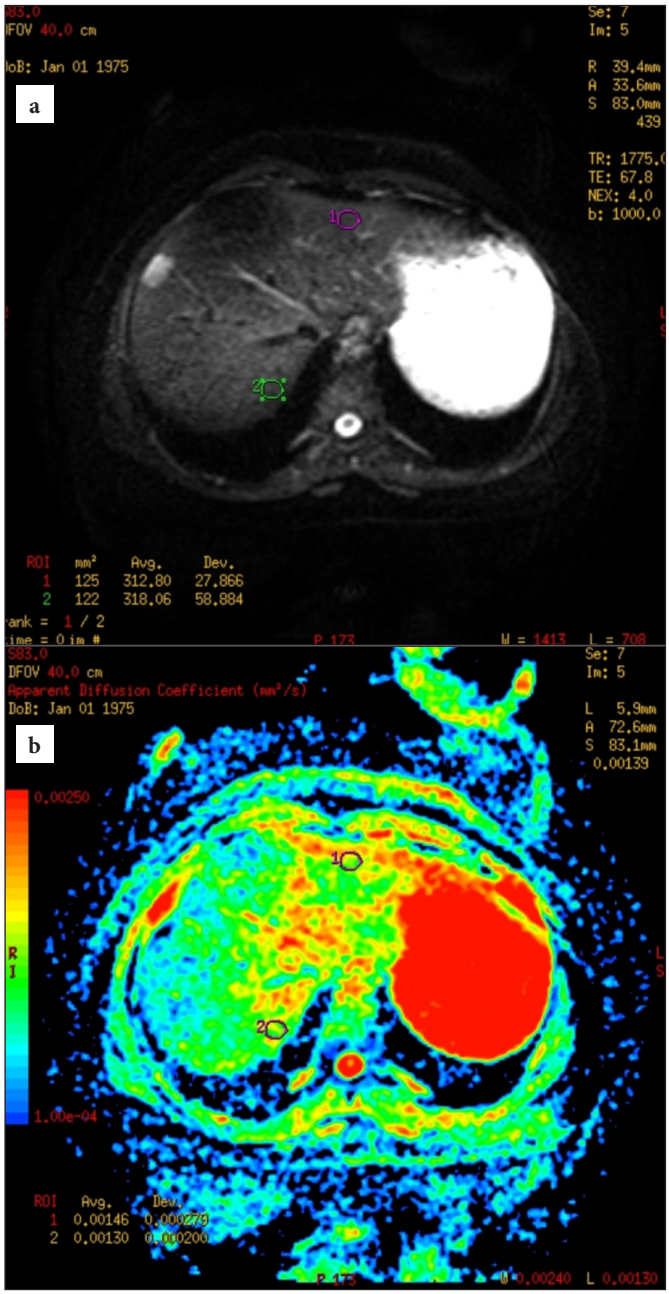

Figure 2. The diffusion-weighted images (a) and ADC map (b) of 32-year-old hepatitis B patient with stage 0 fibrosis. The mean ADC value was 1.38 x10-3.

Liver Biopsies

All our patients underwent percutaneous liver biopsy after MRI examination. A liver biopsy was carried out under ultrasound guidance using an 18-gauge needle by a hepatologist with five years of experience. Pathology slides from all patients were evaluated retrospectively by the same pathologist who then had eight years of experience. Fibrosis staging and inflammatory activity were interpreted according to the scoring system developed by the METAVIR group. The METAVIR stages F0, F1 was termed "no/minimal fibrosis," whereas the presence of METAVIR stages F2, F3, or F4 indicated "significant fibrosis," METAVIR stage F3 or F4 were termed "advanced fibrosis," and METAVIR stage F4 was termed "cirrhosis." For histological activity, grade 0 was termed "no histologic necroinflammatory activity," grade 1 was termed "minimal activity," grade 2 was termed "mild activity," grade 3 was termed "moderate activity," and grade 4 was termed "severe activity." The activity was assessed using a combination of severity and intensity of periportal and lobular necrosis (5).

Statistical Analysis

Statistical Analysis SPSS version 17.0 was used for analysis. A nonparametric Mann-Whitney test was used to compare hepatic ADC between patients stratified according to individual fibrosis stages and patients grouped as stage 1 or lower versus stage 2 or higher and stage 2 or lower versus stage 3 or higher, as well as between patients stratified by inflammation grade (grade 0 vs grade 1 or higher). The Spearman's rank correlation test was used to assess the correlation between hepatic ADC, stage of fibrosis, and grade of inflammation. Receiver operating characteristic (ROC) curve analyses were conducted to evaluate the utility of the ADC measures for prediction of stage 2 or higher and stage 3 or higher fibrosis and for prediction of grade 1 or higher inflammation. A value of $p<0.05$ was considered statistically significant.

RESULTS

Seventeen of our patients were male (56.6%) and 13 were female (43.3%). The mean age of our patients was 50.9±8.5 (35-72). The patients distribution according to stages of fibrosis and activity grade is summarized in **Table 1**. At all b-values, the hepatic fibrosis stages were negatively correlated with ADC values ($p<0.001$). At stage 0 the mean ADC value was 2.17±0.25; at stage 1 it was 1.96±0.37; at stage 2 it was 1.72±0.39; at stage 3 it was 1.48±0.14; and at stage 4 it was 1.13± 0.21 $x10^{-3}mm^2/s$. The distribution of liver ADC values according to the stage of fibrosis is shown in **Table 2**. When patient group whose liver fibrosis stages were 2 or higher (significant fibrosis) were compared with patient groups whose fibrosis stages were 1 or lower (no / minimal fibrosis), the ADC values were significantly lower in patients with significant fibrosis at all b-values. Moreover, when patient groups whose liver fibrosis stages were 3 or higher (advanced fibrosis) were compared with patient groups whose fibrosis stages were 2 or lower (significant fibrosis), the ADC values of advanced fibrosis patients were significantly lower at all b-values ($p<0.001$, for all b-values) (**Table 3**). The evaluation of receiver operating characteristic (ROC) analysis revealed that hepatic ADC values were statistically significant in determining significant and advanced fibrosis (**Table 4**). Furthermore, we detected a negative correlation between ADC values and activity

index. At b-values 300 and 1000, the ADC values were significantly lower in the groups whose histological activity indexes were 1 or higher when compared to the group whose activity index was 0 (at b-value 300 p<0.034, and at b-value 1000 p<0.027) (**Table 5**). ROC analysis revealed that ADC values might be used as an important marker in patients with activity indexes of grade 1 or higher (**Table 6**). In addition, Spearman's correlation test showed that there was a moderate positive correlation between ADC values, inflammation, and stages of fibrosis (r=0.418, p=0.021)

Table 1. Distribution of Fibrosis Stage and Inflammation Grade Among Patients with Chronic Hepatitis B(n: 30)

State or Grade	Fibrosis	Inflammation
0	5	2
1	6	7
2	5	7
3	8	7
4	6	7
Total	30	30

*Fibrosis staging and inflammatory activity were interpreted according to scoring system developed by the METAVIR group

Table 2. Distribution of liver apparent diffusion coefficients (value × 10^{-3} mm²/s) stratified by fibrosis stage (n = 30)

Fibrosis Stage	b Value (s/mm²)				
	50	300	500	700	1,000
0	3.35±0.35	2.62±0.29	1.96±0.17	1.55±0.26	1.38±0.18
1	3.10±0.55	2.24±0.25	1.82±0.14	1.40±0.55	1.23±0.40
2	2.50±0.24	2.04 ±0.11	1.59±0.74	1.36±0.65	1.13±0.21
3	2.23±0.14	1.62±0.12	1.35±0.12	1.20±0.17	1.00±0.16
4	1.57±0.23	1.22±0.26	1.06±0.28	0.95±0.16	0.86±0.12

Table 3. Comparison of liver apparent diffusion coefficients (value × 10–^{3} mm²/s) stratified by fibrosis stage ≤ 1 versus ≥ 2 and fibrosis stage ≤ 2 versus ≥ 3 (n = 30)

Fibrosis Stage	b Value (s/mm²)				
	50	300	500	700	1,000
≤ 1	3.21±0.46	2.41±0.25	1.88±0.16	1.47±0.10	1.30±0.10
≥ 2	2.09±0.42	1.60±0.35	1.32±0.26	1.16±0.19	0.99±0.12
p	<0.001	<0.001	<0.001	<0.001	<0.001
≤ 2	2.99±0.52	2.29±0.27	1.79±0.19	1.43±0.10	1.24±0.11
≥ 3	1.95±0.38	1.45±0.27	1.22±0.24	1.09±0.18	0.94±0.10
p	<0.001	<0.001	<0.001	<0.001	<0.001

Note—Liver apparent diffusion coefficient is significantly decreased in patients with moderate and advanced fibrosis at b values of 500 s/mm² or greater or a combination of all b values (0, 50, 300, 500, 700, and 1,000 s/mm²).
Statistically significant values are displayed in boldface.

Table 5: Distribution of Liver Apparent Diffusion Coefficients (value × 10^{-3}mm²/s) Stratified by Inflammation Grade (n = 30)

Inflamation grade	b Value (s/mm²)				
	50	300	500	700	1,000
0	3.32±0.24	2.62±0.03	1.95±0.07	1.50±0.14	1.43±0.02
≥ 1	2.45±0.68	1.85±0.48	1.50±0.35	1.26±0.22	1.08±0.17
p	0.088	0.034	0.067	0.133	0.027

Note—Statistically significant values are displayed in boldface.

Table 6: The Performance of ADC for Determining of Liver Inflammation in Different b-values (n = 30)

b value (s/mm²)	ADC (Value x 10^{-3}mm²/s)	AUC	Sensitivity (%)	Specifity (%)
50	≤ 3.07	0.866	100	85.7
300	≤ 2.55	0.955	100	92.9
500	≤ 1.85	0.893	100	89.3
700	≤ 1.37	0.821	100	60.7
1,000	≤ 1.38	0.973	100	93.4

Note—Sensitivity and specificity are calculated when hepatic apparent diffusion coefficient is used to diagnose grade 1 or greater inflammation. AUC: Area under the receiver operating characteristics curve, ADC: Apparent Diffusion Coefficient

DISCUSSION

In our study, we determined a significant negative correlation between hepatic ADC values and stages of fibrosis in patients with chronic hepatitis B. Liver diffusion ADC values were highly sensitive and specific in predicting stages of liver fibrosis.

Most of the studies in the literature were based on hepatitis C patients and cirrhosis patients with different etiologies. Our study is based on patients with hepatitis B disease. In our study, sensitivity and the specificity of the ADC values to determine the fibrosis was found to be much higher than in most of the other studies.

Histopathological data is needed to determine the prognosis in patients with chronic viral hepatitis B in order to start antiviral therapy and to evaluate the efficacy of treatment. However, due to possible complications and limitation of sampling sizes of biopsy, there is a need for a more non-invasive examination method (6,7). Basar et al. (8) investigated the relationship of pre-treatment aspartate aminotransferase to platelet ratio index (APRI), Forn's index, FIB-4, S-index, Shanghai Liver Fibrosis Group's index (SLFG), and

Table 4: The Performance of ADC for Determining Liver Fibrosis in Different b-values (n = 30)

b- values (s/mm²)	Prediction of Stage 2 or Greater Fibrosis				Prediction of Stage 3 or Greater Fibrosis			
	ADC (Value ×10^{-3}mm²/s)	AUC	Sensitivity (%)	Specifity (%)	ADC (Value × 10^{-3}mm²/s)	AUC	Sensitivity (%)	Specifity (%)
50	≤ 2.72	0.967	90.9	94.7	≤ 2.47	0.962	81.3	100
300	≤ 2.20	0.974	81.8	100	≤ 1.85	1.000	94.1	100
500	≤ 1.65	0.995	100	94.7	≤ 1.52	0.998	93.8	100
700	≤ 1.37	0.959	90.9	84.2	≤ 1.37	0.980	81.3	100
1,000	≤ 1.17	1.000	100	96.1	≤ 1.11	1.000	96.4	100

HepascoreR with fibrosis in patients with chronic hepatitis B. The authors emphasized that non-invasive serum tests might be useful in indicating the stages of liver fibrosis, monitoring the effectiveness of treatment, and may reducing the need for biopsy. The specificity and sensitivity values of conventional MRI in patients with chronic liver disease and liver fibrosis are low (9). Currently, diffusion-weighted imaging, MR elastography and sonoelastography are used for the detection of fibrosis (10).

Fujimato et al. (11) evaluated 43 patients with hepatitis C, compared the mean and entropy ADC values with fibrosis and activity indices, and reported that mean ADC values decreased with increasing fibrosis stage and activity index, while entropy ADC values increased with increasing fibrosis stage and activity index. In addition, they reported that the combined evaluation of mean ADC and entropy ADC values was more accurate and more successful in indicating the early stages of fibrosis and inflammation compared to the evaluation of ADC values alone. Their ROC analysis determined that sensitivity and specificity for prediction of the activity of stage 1 and higher were 81% and 83%, respectively, and that the cut-off ADC value was 1.35 x 10^{-3}. Bozorg et al. (12) in their study with 33 patients with chronic hepatitis B used three different b-values and reported that the specificity and sensitivity of ADC values at b500 were higher. In our study, the ADC values at b500 and b1000 had higher sensitivity in indicating fibrosis. The reason for this might be that at high b values the influence of perfusion on ADC values is reduced. With the development of fibrosis, the levels of extracellular collagen, glycosaminoglycan, and proteoglycan increase and the diffusion of water molecules become limited. This situation is more prominent at high b-values. Some studies reported that the ADC measurements at low b-values were not indicative of fibrosis (3, 13). In an experimental study, Annet et al. (14) showed that in live mice decreased ADC values were consistent with increased liver fibrosis. However, once the mice were sacrificed the relationship between ADC values and fibrosis was not detectable. As a result, they reported that rather than reflecting restricted diffusion, which developed secondary to fibrosis, the ADC values reflect changes in the perfusion associated with fibrosis. Extracellular collagen deposition and changes in perfusion are seen in liver fibrosis. Changes in body temperature and the location of ROI may affect the ADC values (3, 4, 14). In our study the ROIs were placed away from the vascular areas and the average of three different measurements was taken.

In a study with 54 chronic HCV-infected patients, Lewin et al. (15) compared non-invasive tests such as diffusion-weighted MRI and transient elastography in terms of hepatic fibrosis prediction values and reported that diffusion-weighted MR imaging was as effective as other non-invasive tests in predicting fibrosis in patients with chronic HCV infection.

Taouli et al. (3) used five different b-values in evaluating 23 patients with chronic liver disease and reported that b-values of b500 and higher are more sensitive in showing fibrosis at stages 3 and above. The necroinflammatory activity evaluation in the same study indicated that the hepatic ADC values were lower in the group with mild-to-moderate inflammation (grades 1 and above) compared to the group without inflammation (at b700 the cutoff of ADC=1.35 x 10^{-3}, the sensitivity and specificity of this cutoff value at stages 1 and above was 85.7% and 75%, respectively). We found hepatic ADC in all b values to have high sensitivity and specificity of hepatic fibrosis. The sensitivity and specificity of ADC cutoff value 1.38 at b1000 in determining inflammatory activity of grades 1 or higher were 100% and 93.4%, respectively. In the literature, there is no correlation or low correlation between inflammatory activity score and ADC. ADC was found to be more successful in predicting the stage of fibrosis.(3, 16) In the comparison of inflammatory activity with ADC, we found low ADC in all b values, but b500 and b700 ADC were not statistically significant. Differences in the accompanying fibrosis stage, parenchymal heterogeneous distribution of fibrosis, technical and patient-related factors may cause this statistical difference. Our findings are consistent with the findings of both aforementioned studies.

For chronic active hepatitis B, pegylated interferon and the oral antiviral agents such as entecavir, tenofovir are the choice of treatment. Especially for the oral antiviral agents, apart from the resistance development and different side effect profiles, none of them is superior to the other, in terms of their effects on the liver parenchyma. In chronic active hepatitis B patients, the histopathological analysis which is used for the determination of the efficacy of the antiviral treatment cannot be performed due to ethical issues and invasive procedure complications. Few studies (17, 18) have shown the histopathological recovery of the liver fibrosis in chronic hepatitis B with oral antiviral agents. As the diffusion ADC can detect the stage of the liver fibrosis in chronic hepatitis B patients with a reliability closed to histopathological analysis, studies related to diffusion ADC can be guide the clinicians about evaluating the efficacy of oral antiviral agents and their superiority to each other.

The examinations with diffusion-weighted imaging for assessment of fibrosis have been frequently conducted in patients with chronic hepatitis C, but there are only few reports of this kind of study in patients with chronic hepatitis B (10, 19).

Biexponential, and stretched-exponential diffusion-weighted imaging models, fat and iron corrected ADC evaluation, diffusion curtosis, MR elastography and whole liver histogram diffusion analysis have performed for staging hepatic fibrosis and grading inflammatory activity in patients with chronic hepatitis and recently studies showed that these diffusion methods have good diagnostic performance (20-26).

The limitations of our study are small sample size, lack of ADC values in the post-treatment follow-up. Current diffusion ADC techniques were not used in our study because of the time period in which the patient group is selected.

CONCLUSION

ADC in all b values have high sensitivity in demonstrating liver fibrosis in patients with chronic hepatitis B. We suggest that the addition of diffusion-weighted MR images into liver MRI examination might reduce the requirement for liver biopsies in patients with chronic hepatitis B.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted with the permission of the Non-invasive Clinical Researches Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital (Date: 09.01.2014, Decision No: 2014/352).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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Exploring the discoloration potential of *Propolis* extract and *Morus nigra* syrup on restorative dental composites: an in vitro study

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ABSTRACT

Aim: The aim of this study was to analyse color stability of dental composites immersed in *Propolis* extract and *Morus nigra* syrup at in-vitro conditions simulating clinical usage time intervals and to explore the relationship between discoloration potential and phenolic contents.

Material and Method: A total of 126 composite discs of nanohybrid (n=42), microfilled (n=42) and microhybrid (n=42) were prepared using a Teflon mold with a diameter/thickness of 6 mm/2 mm. After polishing procedures, composites were subdivided into three and immersed into %15 *Propolis* extract with total phenolic content=53 mg GAE/ml (B'eeo, İstanbul) and *Morus nigra* syrup with total phenolic content=25 mg GAE/100 g dw (Hünnap, İstanbul) and distilled water for 12 hours(T1) and 24 hours (T2) simulating 1-year and 2-year time spans respectively. Color measurements were performed by Vita easy Shade Compact (Vita Zahnfabrik, Bad Sackingen, Germany) prior to immersion and analysed by CIEDE2000 formula.

Result: Between T0 and T2, minimum/maximum color change values (ΔE) of nanohybrid, microfilled and microhybrid composites immersed in *Propolis* and *Morus nigra* syrup were 1,24/5,29 and 0,97/2,65 respectively. Nanohybrid composite discs were discolored within clinically acceptable limits in all test solutions. Microfilled and microhybrid composite discs showed clinically unacceptable discoloration at T1 and T2 periods in *Propolis* extract solution.

Conclusion: The phenolic and flavonoid components of herbal formulations can be considered as one of the major determinants in discoloring potential.

Keywords: *Morus nigra*, phenolic content, *Propolis*, discoloration

INTRODUCTION

Dental composites are widely used in dental restorations in daily clinical dental practice, consist of three major chemical content: organic polymeric matrix, inorganic fillers and silane/coupling agent to adhere the fillers to the organic resin. Composite resin materials, simulating the physical features of the hard dental tissues and have excellent aesthetic Of these features, color stability plays a major role in patient satisfaction and long-term survival (1). However multiple factors including inadequate polymerization, water absorption, chemical reactivity, oral hygiene, and surface roughness of the restoration result in discoloration on dental composites (2).

Color changes in composite resins may arise extrinsically or intrinsically. The intrinsic discoloration of resin composites is highly correlated with filler particle size, type, amount, polymeric properties, the presence of tertiary amines due to oxidation of the residual monomers, and the water permeability of the resin (3,4).

The etiology of discoloration associated with adsorption or dye absorption exogenous sources, especially discoloring agents/solutions. *Morus nigra* syrup and *Propolis* extracts are widely used in complementary supportive care of oral lesions due to anti-inflammatory, antimicrobial and antioxidant properties owing to their phenolic contents and flavonoid components (5,6).

Since they are over-the-counter (OTC) products and there is no restriction on the duration of use, the side effects of colorants should definitely be examined. Some

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beverages and oral hygiene products consisting phenolic contents, may affect negatively the color stability of composite resins because of their chemical and physical degrading elements (2, 7-10).

The present study has two hypothesis: (1) Nanohybrid aesthetic dental composite materials would show less discoloration beyond clinically acceptable limits after immersion into tested solution (2). *Morus nigra* syrup would cause more color change in all composites due to its darker and viscous nature.

The aim of this study was to investigate the discoloration potential of *Propolis* extract and *Morus nigra* syrup on dental restorative composites.

MATERIAL AND METHOD

This study does not require ethics committee approval as it is not within the scope of clinical and experimental studies on humans and animals (including data& material).

Sample Preparation

A total of 126 adhesive restorative resins consists of nanohybrid (n=42), microfilled (n=42) and microhybrid (n=42) composite (**Table 1**) discs of shade A1 (manufacturer prescription) were prepared with a diameter/thickness of 6 mm/ 2 mm. Composite samples were placed in Teflon molds as a single layer, and their upper and lower surfaces were stripped and polymerized with a LED light device for 20 sec. (VALO Ultradent , South Jordan, UT) in standard mode (1000 mW /cm 2). After sample preparation, they were kept at 37°C for 24 hours, then polishing with polishing discs 600-, 800- and 1200-grit size (Sof-Lex , 3M ESPE Dental Products, St Paul, MN, USA) for surface standardization. The samples were then washed with distilled water and gently dried.

Immersion into Solutions

Each composite group were subdivided into three subgroups of 14 discs according to immersing solutions (*Propolis* extract / *Morus nigra* syrup) given in **Table 1**. and distilled water. Every subgroup of composite resin was immersed in discoloring and control solutions at room temperature for 12 hours (T1) and 24 hours (T2). Reference time intervals were considered according to Ertürk-Avunduk et al. (11), keeping the samples in solutions for 12 hours in vitro would be simulate 1 year in vivo (2 times a day-1 minute), and keeping them in solution for 24 hours was accepted as a cumulative indicator of exposure for 2 years (11).

Spectrophotometric Analysis

Composite color change in resins were measured by Vita easy Shade Compact (Vita Zahnfabrik, Bad Sackingen, Germany) before and after immersions. Before the measurements, the spectrophotometer was calibrated according to the manufacturer's instructions. Measurements were performed under D65 standard light illumination on a standard white background, with the probe tip standardized perpendicular to the tooth sample surfaces, and 3 measurements were taken from each sample. Following the measurements, color changes calculated according to the CIEDE2000 formula (12):

$$\Delta E_{00} = \left[\left(\frac{\Delta L'}{K_L S_L}\right)^2 + \left(\frac{\Delta C'}{K_C S_C}\right)^2 + \left(\frac{\Delta H'}{K_H S_H}\right)^2 + R_T\left(\frac{\Delta C'}{K_C S_C}\right)\left(\frac{\Delta H'}{K_H S_H}\right)\right]^{1/2}$$

In this study, each of KL, KC, KH were set into 1.0. The value of ΔE00 < 2.25 was considered as a clinically acceptable threshold level for color changes (13).

Statistical Analysis

Statistical analysis of data was performed using IBM SPSS 28.0 statistical package program (IBM SPSS Statistics for Windows 2021, Armonk, NY: IBM Corp). The data showed normal distribution confirmed by the Shapiro-Wilk test. The inter-group comparisons by solutions were analyzed using one-way Anova and Bonferroni Post-Hoc tests. Intra-group comparisons by time interval were analyzed using the paired t-test. Significance level was determined as α= 0.05.

Table 1. Materials tested in this study and their contents

	Characterization	Total phenolic content	Total flavonoid	Manufacturer
Solutions				
*Propolis**	%15 aqueous extract	53 mg GAE/ml	35 mg CE/ml	B'eeo, İstanbul
*Morus nigra***	Cold infusion / syrup	25 mg GAE/100 g dw	4.7 mg CE/100 g dw	Hünnap, İstanbul
Composite resins				
Type/Shade	**Matrix**	**Filler**	**Total filler content w/w**	**Manufacturer**
Nanohybrid/A1	Bis - GMA, hydrophobic aromatic aliphatic dimethacrylate	Silane barium glass filler	78%	Kuraray, Japan
Micro-filled hybrid/A1	UDMA, dimethacrylate co-monomers	Silica glass filler	76%	GC Corporation, Japan
Microhybrid /A1	Bis-GMA, Bis-EMA, TEGDMA, UDMA	Silica-Zirconia filler	78%	3M ESPE, USA

*Folin-Ciocalteu method by Scientific Bio Solutions Laboratory, **Kamiloglu et al. (14)
Bis-GMA: bisphenol A diglycidylmethacrylate; TEGDMA: triethyleneglycol dimethacrylate, UDMA: urethane dimethacrylate; BIS-EMA: Bisphenol-A-Ethyl methacrylate

Table 2. The means (± SD) of ΔE00 values of restorative materials at T1 and T2 time intervals in the study.

	Propolis extract		*Morus nigra* syrup		Distilled water	
	T1 (mean±SD)	T2 (mean±SD)	T1 (mean±SD)	T2 (mean±SD)	T1 (mean±SD)	T2 (mean±SD)
Nanohybrid	1.24±0.65	2.04±1.29	1.32±0.63	1.11±0.45	0.98±0.14	1.01±0.3
Microfilled	3.59±0.47	5.29±0.58	0.97±0.49	1.72±0.25	1.07±0.29	1.28±0.73
Microhybrid	4.24±0.65	4.25±0.65	1.23±0.78	2.65±0.95	0.91±0.34	1.93±0.71

RESULTS

The means and standard deviations of ΔE00 values at T1 and T2 time intervals are shown in **Table 2**.

Between T0 and T2, minimum/maximum color change values (ΔE00) of nanohybrid, microfilled and microhybrid composites immersed in *Propolis* and *Morus nigra* syrup were 1,24/5,29 and 0,97/2,65 respectively. Nanohybrid composite discs were discolored within clinically acceptable limits (ΔE00<2.25) in all test solutions (**Figure 1**). Microfilled and microhybrid composite discs showed clinically unacceptable discoloration at the end of T1 and T2 periods in *Propolis* solution. Microhybrid composite discs immersed in *Morus nigra* solution showed clinically unacceptable discoloration only at T2.

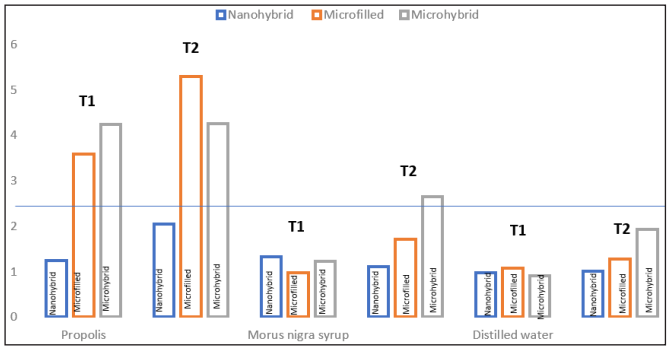

Figure 1. Discoloration of dental composites immersed in test/control solutions regarding clinical acceptable limit.

There was a statistically significant difference between T 1 and T 2 time periods in samples of microfilled composites kept in *Propolis* solutions (p<0.001). More color changes were observed in the T2 time frame for all composites immersed into *Propolis* extract (Figure 1). The greatest discoloration was observed in the end of T1 and T2 time periods in microhybrid (4,24±0,65) and microfilled (5.29 ±0,58) composite samples. There was no statistical difference between T1 and T2 for *Morus nigra* syrup and distilled water (p>0,05). No significant correlation was between filler content of composite materials and degree of a discoloration (p=0.899)

DISCUSSION

Propolis extracts (15) and *Morus nigra* syrup (16) have significant contribution on supportive care of oral lesions. However, there is no study investigating the discoloring effects of these OTC agents on composite resins. The present study is the first to investigate discoloring effects of the commercial products of these OTC solutions on anterior composites. The first hypothesis of this study was confirmed as the nanohybrid composites were more resistant to discoloration for both *Propolis* extract and *Morus nigra* syrup. The second hypothesis of this study was not confirmed that *Morus nigra* syrup would cause more color change in all composites due to its darker more viscous nature as it showed less color changes compared to *Propolis* extract groups.

Phenolic compounds are divided into two groups as phenolic acids and flavonoids. Besides flavonoids and phenolic contents are polyphenolic antioxidants showing antimicrobial activities in oral cavity (17) that also responsible from the sour flavor of fruits and vegetables, and some provide yellow, yellow-brown, red-blue color tones (18).

Keskin and Kolaylı (19) in 2019 reported that the total phenolic substance amount of Anatolian *Propolis* ranged between 16.13-178.34 mg GAE /g. The total phenolic content of the commercial sample of *Propolis* containing %15 aqueous extract used in our study was 53 mg GAE/ml as indicated in manufacturer catalog. In addition, Ozgen et al. (20) stated that the average TP content was 2737 µg GAE/g dw in Türkiye, which was compatible with Kamiloglu et al. (14) ,the reference study for our study. Percentile proportion of an extract, the character of solvent (aqua, ethanol, methanol etc.) and the type of an infusion (cold or hot) closely affect the total phenolic content of a solution. In a present study, *Morus nigra* syrup was obtained by cold infusion which means evaporation process at low temperatures by lowering the boiling point under vacuum and might be the reason low content of phenoic compound. Gonçalves et al. (21) showed the phenolic content of hot infusions were significantly greater than that of cold infusions. Comparing the TPC and TF of test solutions in out study the characterization of *Morus nigra* syrup might be responsible from lower ΔE00 values detected for all types of composites.

Discoloration of composite resins might be multifactorial. Yazici et al. (22) stated that the effect of staining solutions such as tea and coffee on the color changes in composites depends on the immersion time and the content of the resin material. Besides, some studies emphasized the effect polishing procedures ,on color stability of nanocomposites. (23,24). The type of staining solution might also be very decisive in the coloring of

the composite: beverages such as tea, coffee, coke, which are often consumed in daily life, oral hygiene products such as chlorhexidine are investigated by studies (1-3, 10,11,22-25,27) and their discoloring effects on the composites are clearly stated.

Regardless of the solution, the structural properties organic matrix of composites may act in higher susceptibility to water absorption and material disintegration. As indicated on literature (26,27) which are in accordance with our study, the greater proportion of TEGDMA in microhybrid composite might be resulted in an increase in water uptake, herewith increased discoloration (4,24±0,65) compared to nanohybrid (1,24±0,65) and microfilled (3,59±0,47) composite group at the end of the T1 period. In a recent study (28), it was stated that hydrophilic organic matrix elements such as Bis-EMA tends to react less favorably to pigment incorporation comparing UDMA or Bis-GMA. Therefore, hydrophobic aromatic/aliphatic dimethacrylate content of nanohybrid composite tested in this study may be closely associated with the reason lower color changes compared other composite groups.

The amount of inorganic filler might be one of the possible reasons on susceptibility for color changes as the spaces between the filler particles favor pigment deposition (29). However, there were no significant correlation between the degree of a color change and the percentile filler content of composite in our study (p>0,05).

The staining susceptibility of a composite resin may also be attributed to its filler type. Unlike to Poggio et al. (30) which stated nanohybrid absorbs staining substances more easily than microhybrid, the less discolored composite discs were nano-hybrids in our study. On the other hand, Reddy et al. (23) showed that nano-hybrid composites undergo less color change compared to microhybrid composites when exposed to beverages with different phenolic contents, similarly to our study.

Within the limitations of the present study, it can be concluded that the ratio of phenolic and flavonoid components in any herbal formulation played a more important role in its discoloration potential than color or viscosity alone.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study does not require ethics committee approval as it is not within the scope of clinical and experimental studies on humans and animals (including data& material).

Informed Consent: This study does not require informed consent.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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A comparative study of the effects of chronic kidney disease on sonographic arterial stiffness parameters in geriatric and normal population

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ABSTRACT

Aim: Due to its growing incidence rate worldwide, chronic kidney disease is a crucial public health problem which is strongly associated with cardiovascular disease. Cardiovascular disease in chronic kidney disease patients is characterized by arteriosclerosis and increased arterial stiffness, and is the leading cause of morbidity and mortality. A correlation was reported between an increased arterial stiffness and cardiovascular disease in high risk groups such as chronic kidney disease or hypertension as well as general undiagnosed population. Our aim was to show the changes in arterial stiffness parameters in patients with chronic kidney disease in the geriatric population.

Material and Method: 44 chronic kidney disease patients and 44 control group cases of the same age were included in the study. There were 20 female and 24 male cases in each group. Systolic and diastolic diameter were measured for all cases. Intima-media thickness was measured in carotid and femoral arteries. Arterial stiffness parameters were calculated using formulas. Systolic and diastolic arterial blood pressure and body mass index were measured. Their urea and creatinine values were recorded.

Results: There were no differences between two groups in terms of age and sex ($p=0.069$). Body mass index in the patient group was significantly lower compared to the control group ($p=0.025$). Systolic arterial blood pressure was higher in the patient group ($p<0.001$). Arterial stiffness parameters in both arterial systems, particularly in femoral artery, were significantly ($p<0.05$) worse in the patient group compared to the control group.

Conclusion: Intima-media thickness was measured higher, which overlaps with the existing literature. Femoral parameters were more effective in the prediction of atherosclerosis. Chronic kidney disease affects cardiovascular system negatively, and increases atherosclerosis significantly compared to the normal population.

Keywords Arterial stiffness, chronic kidney disease, geriatrics, compliance, diastolic wall stress

This article was presented orally at the 39th National Radiology Congress on 6-11 September 2018 (Abstract/Oral Presentation) (Publication No: 4588257).

INTRODUCTION

Chronic kidney disease (CKD) is a crucial public health problem due to its growing incidence rate worldwide and is strongly associated with cardiovascular disease (CVD) (1). CVD in CKD patients is characterized by arteriosclerosis and increased arterial stiffness (AS), and is the leading cause of morbidity and mortality. In fact, the risk of death from CVD is higher for CKD patients compared to progression towards end-stage renal disease (ESRD) or risk of death from renal failure (2). More than half of deaths in patients with ESRD is associated with cardiovascular causes (3). Apart from ESRD, patients with low-grade kidney diseases are more prone to cardiovascular events. Based on potential population-based studies, it is reported that mild-to-moderate kidney disease can predict cardiovascular morbidity and mortality. However, the increased cardiovascular risk cannot be explained by traditional atherosclerotic risk factors, and it probably results from non-atherosclerotic arterial and heart diseases processes (4).

The evaluation of AS parameters is a replicable, reliable and non-invasive method for the diagnosis of subclinical atherosclerosis. IMT measured in main carotid artery and the degree of subclinical atherosclerosis are associated with cardiovascular

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events and mortality in both general population and CKD patients. Sectional studies on groups without CKD indicated the correlation between carotid IMT and cardiovascular risk factors and presence of CVD (5). Several large observational studies also reported that carotid IMT was a precursor to coronary heart disease events for which it remained statistically significant following the adjustment of traditional risk factors. The correlation between IMT and cardiovascular event risk was also analyzed in terms of a dominant risk factor such as CKD (6).

Even though patient populations in previous studies included geriatric population samples, no studies have so far been carried out on peer patient groups. To this end, the present study analyzes the difference between CKD patients and a geriatric control group of the same age in order to evaluate the correlation between subclinical atherosclerosis and negative clinical results.

Similarly, although existing studies in the literature dealt with arterial stiffness in CKD, they partially focused on functional and quantitative markers such as compliance, diastolic wall stress, distensibility and elastic modulus. The present study concentrates more on these parameters.

MATERIAL AND METHOD

Ethics Approval

The study was carried out with the permission of Elazığ Training and Research Hospital, Noninvasive Clinical Researches Ethics Committee (Date: 18/01/2008 Decision No: Bl04ISM04230045 /21). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Population

After obtaining an ethical committee approval, the present study was conducted on geriatric individuals. It was a monocentral, prospective and observational cohort study on CKD patients and a control group. While the patient group included 20 female and 24 male patients, the control group, similarly, included the same number of males and females. The average age was 70.09 in the patient group, whereas it was 67.98 in the control group.

Measurement List

The following parameters were determined and defined before the study: BMI, systolic and diastolic arterial blood pressure levels, urea and creatinine values, carotid and femoral artery systolic and diastolic diameters, and AS values were calculated using IMT. US measurements were performed by the same radiologist on the same US device. AS values (compliance, diastolic wall stress, distensibility and elastic modulus) were calculated using relevant formulas.

Body mass index was calculated by dividing body weight (kilogram; kg) by the square (m^2) of height (meter; m).

Blood pressure was measured using a sphygmomanometer three times with an interval of 5 minutes. The mean value obtained from three different measurements was calculated unless their difference was higher than 10 mmHg, and, if so, the mean value of two closest measurements was used.

IMT Measurement

A high resolution broadband linear array (multiple frequency: 4-12 MHz) B-mode ultrasound transduser was used to evaluate right main carotid artery, carotid bulbus and internal carotid artery for carotid system and right main femoral artery for femoral system. Main carotid artery located about 1 cm in front of bulbus was standardized for measurement in the carotid system, while main femoral artery located about 1 cm in front of bifurcation was selected for the femoral system. The screen image was enlarged to increase measurement accuracy. Electronic calipers were used for IMT measurement. It was ensured that caliper lines were in parallel with arterial walls. Three different measurements were recorded, and a mean value was calculated for each group.

Systolic and Diastolic Diameter Measurement

For IMT, systolic and diastolic diameters were measured on standardized locations in both systems using the same US device and M-mode US. For a healthier measurement process, a screen image on which the same ultrasonic waves could be monitored without any artifacts was selected. In addition, the image was enlarged for a higher accuracy.

Exclusion Criteria

Smokers and diabetic patients were not included in the study. In addition, cases with a radiological kidney pathology was not included in the control group even if their clinical and laboratory results were not evaluated.

Statistical Analysis

Mean±standard deviation was used to explain the obtained data. An IBM SPSS for Windows (IBM statistics for Windows version 25, IBM Corporation, Armonk, New York, United States) was used or statistical analysis. Student T test was used to compare the parameters.

RESULTS

There were not any differences between two sexes in each group.

No statistically significant differences can be found between two geriatric populations in terms of their age.

Body mass index was calculated as 26.48±3.89 in the patient group, whereas it was 28.46±4.19 in the control group. BMI was significantly lower in CKD patient group compared to the control group.

Arterial blood pressure levels were measured as 162.55±25.60 and 86.64±17.12 mm/hg for systolic and diastolic blood pressure in the patient group, respectively. However, the same values were 125.25±6.30 and 77.50±6.04 mm/hg for systolic and diastolic blood pressure in the control group. As a result, it was found that both systolic and diastolic arterial blood pressure levels were higher in the patient group compared to the control group.

Carotid artery IMT (**Figure 1**) was 0.66±0.11 mm and 0.52±0.14 mm in the patient and control group, respectively. Similarly, femoral artery IMT (**Figure 2**) was 0.65±0.13 and 0.44±0.19 mm in the patient and control group, respectively. Being more apparent in femoral artery, IMT values in both carotid and femoral arterial system were higher (worse) in the patient group compared to the control group.

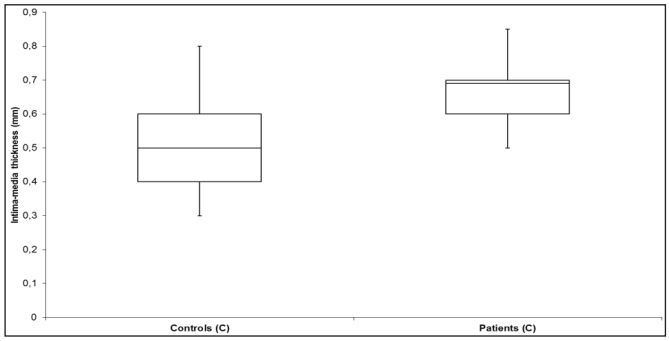

Figure 1. The distribution of carotid artery IMT values in both groups

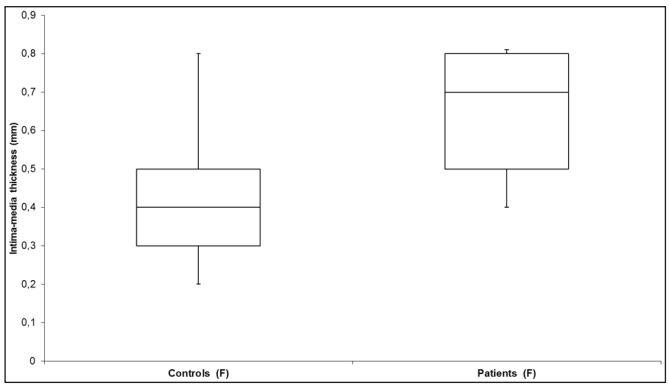

Figure 2. The distribution of femoral artery IMT values in both groups

Compliance: Carotid artery compliance values were statistically higher in the patient group compared to the control group. Although femoral artery compliance values were lower in the patient group compared to the control group, they were statistically insignificant.

Diastolic wall stress: In both carotid and femoral system (albeit being more apparent in femoral system), diastolic wall stress was higher in the patient group compared to the control group, it was still statistically insignificant.

Distensibility: Carotid artery distensibility values were statistically lower in the patient group compared to the control group. However, femoral artery distensibility values were lower and statistically insignificant in the patient group compared to the control group.

Elastic modulus: Carotid artery elastic modulus values (**Figure 3**) were lower in the patient group compared to the control group; however, they were statistically insignificant. On the other hand, femoral artery elastic modulus values (**Figure 4**) were statistically higher in the patient group compared to the control group.

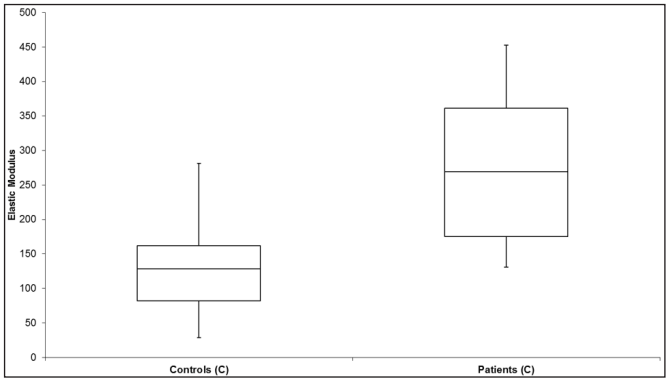

Figure 3. The distribution of carotid artery elastic modulus values in both groups

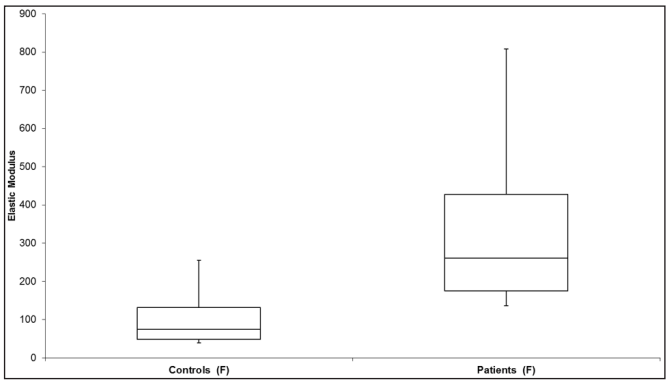

Figure 4. The distribution of femoral artery elastic modulus values in both groups

Urea and creatinine values in the patient group were 95.545±36.575 and 2.393±0.964, respectively.

The results are presented in **Table.**

Table. Collective representation of our findings

	Control		Patient		p
	Mean	Standard deviation	Mean	Standard deviation	
Age	67.982	5.190	70.091	5.531	0.069
Body-mass index	28.455	4.193	26.484	3.890	0.025
Systolic blood pressure	125.250	6.298	162.545	25.596	<0.001
Diastolic blood pressure	77.500	6.044	86.636	17.119	0.042
Pulse	67.500	12.404	74.091	14.079	0.104
Carotid artery intima-media thickness	0.518	0.135	0.664	0.108	<0.001
Carotid artery compliance	0.135	0.249	0.155	0.066	<0.001
Carotid artery diastolic wall stress	663.620	180.102	724.603	204.350	0.614
Carotid artery distensibility	0.004	0.010	0.004	0.002	<0.001
Carotid artery elastic modulus	130.718	96.807	274.069	105.981	0.591
Femoral intima-media thickness	0.436	0.189	0.645	0.132	0.141
Femoral artery compliance	0.249	0.130	0.137	0.097	0.015
Femoral artery diastolic wall stress	752.206	258.070	718.812	184.427	0.013
Femoral artery distensibility	0.009	0.005	0.003	0.002	0.163
Femoral artery elastic modulus	105.188	82.713	379.192	282.456	<0.001
Urea			95.545	36.575	
Creatinine			2.393	0.964	

DISCUSSION

The main innovation of the present study is to include a specific geriatric population and to focus on functional, local and quantitative AS markers, namely compliance, diastolic wall stress, distensibility and elastic modulus.

AS is a term which describes viscoelastic properties of blood vessel wall (8). The elastic structure of large- and medium-sized arteries is a critical factor in determining general cardiovascular health (9). Pulsatile blood flow decreases depending on the elasticity of these arteries. It thus ensures the fixed continuity of bloodstream from the heart at capillary level and its fixed perfusion into vital organs (10). Just as a decreased elasticity leads to such effect in the peripheral system, it may also reduce pulse wave reflection, which results in left ventricular hypertrophy (11). On the other hand, AS, which was defined in the first half of the twentieth century, is an inverse pathological process against this elastic structure (12).

AS measurement is performed non-invasively, and related measurement methods are divided into two groups. The first group benefits from different techniques such as arterial waveform analysis and diameter measurement for qualitative stiffness prediction, while the second group relies on quantitative calculation parameters such as compliance, diastolic wall stress, distensibility and elastic modulus. Compliance is the absolute diameter change based on the increased blood pressure. Diastolic wall stress is the force to which blood vessel wall is exposed during diastole. Distensibility is the proportional change in diameter based on the increased pressure. Elastic modulus offers information about the properties of wall material independently of arterial geometry. Intima-media thickness (IMT) is a structural property. However, compliance, distensibility, diastolic wall stress, elastic modulus and pulse wave velocity (PWV) are functional properties (13). PWV is a local marker of arterial stiffness along an artery. On the other hand, compliance, distensibility, diastolic wall stress and elastic modulus are local markers of arterial elasticity (14).

Increased AS occurs prior to atherosclerosis and is considered as an early marker of systemic atherosclerosis. AS is an independent factor in the prediction of morbidity and mortality in CVD. A correlation was reported between an increased AS and CVD in high risk groups (such as CKD or hypertension) as well as general undiagnosed population (15).

The correlation between CKD and AS is complex. In the field of pathophysiology, many mechanisms including traditional and non-traditional risk factors have been proposed so far. The very first studies demonstrated that an increased AS in CKD was caused by traditional risk factors (hypertension). Pulsatile wall stress increases during hypertension, which leads to the development of elastin degeneration and vascular remodeling. In addition, AS is a vascular biomarker and increases in CKD patients, and it may even become higher in patients with mild kidney disease independently of cardiovascular risk (16). An increased AS in CKD patients cannot be fully explained by traditional risk factors, since many different traditional and non-traditional risk factors such as inflammation, endothelial dysfunction, ageing, vascular calcification, hypertension, uremic toxins and bone-mineral disorders play a certain role in the development of AS in CKD. An increased AS is an important cause for the development of CVD in CKD patients, and it is acknowledged as a non-traditional risk factor for CVD in CKD patients. Additionally, some studies reported that AS itself was likely to contribute to the progress of CKD (17). However, other studies focusing on the correlation between AS and CKD reported contradictory results (18). The prevalence, pathogenesis and clinical importance of AS in patients with early-stage CKD are still unknown (19). On the other hand, it is described as a critical risk factor for all-cause mortality in progressed CKD (20). An increased AS points to an arterial ageing process. Early vascular ageing is already known to occur in early-

stage and progression of CKD. In parallel with increased cardiovascular risk and left ventricular abnormalities, AS is inversely proportional to renal function. Large vessel arteriopathy in CKD causes AS and, consequently, vascular compliance and loss of distensibility (21).

It was reported in the current literature that IMT was higher compared to the normal population at different stages of CKD (22, 23). In a similar vein, it was found in the present study that IMT was measured higher in geriatric age group compared to the normal population in terms of both carotid and femoral arterial system.

Various studies have so far dealt with changes in functional, local and quantitative AS markers in different patient groups such as diabetes (24), schizophrenia (25), and peripherial artery disease (26). In addition, different recovery factors such as treatment and aerobic exercise were analyzed for these parameters (7). Unlike previous studies on arterial stiff in CKD, the present study focuses more on functional, local and quantitative AS markers.

It is known that many different pathophysiological mechanisms contribute to an increased AS in CKD. In addition to a different pathophysiology, multiple and quantitative measurement methods for AS are likely to reveal their correlation in a clearer way. In this respect, similar to the present study, we recommend researchers to draw on functional quantitative parameters in AS studies.

In the present study, there were significant differences between the patient and control group in terms of all functional and quantitative parameters, and they were sometimes statistically significant. It can be thus argued that AS under different pathophysiological conditions may contribute to different parameters, a point which is particularly important for AS studies on CKD patients. Future studies may attempt to explore more correlations among pathophysiology, stiffness parameter and clinical picture.

Similar to the previous study (7), the defined stiffness parameters were more apparent in femoral system.

Limitations

The main limitation of the present study was its reliance on one-shot images, as the obtained data were collected once for the objectives of the present study without any detailed longitudinal evaluation. Additionally, our sectional analysis did not take into account the duration of exposure to risk factors. Even though carotid IMT is independently associated with a risk of cardiovascular event, it is a defective parameter for atherosclerosis and may not necessarily reflect the disease in other vascular beds. The present study aimed to overcome this problem by partially including femoral system in the analysis.

CONCLUSION

CKD affects cardiovascular system negatively and increases atherosclerosis remarkably compared to the normal population. Subclinical atherosclerosis can be diagnosed thanks to IMT and other parameters measured using US, which is a cost-effective, non-invasive and easily accessible imaging method. However, further studies are still needed to analyze clinical practices with IMT and other quantitative parameters for the clinical management and risk classification of CKD patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Elazığ Training and Research Hospital, Noninvasive Clinical Researches Ethics Committee (Date: 18/01/2008 Decision No: Bl04ISM04230045 /21).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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The effect of generalized joint hypermobility on functional capacity, pulmonary function, respiratory muscle strength, and chest expansion in healthy young adults

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ABSTRACT

Aim: Genetic involvement of connective tissue containing elastin, collagen, and fibrils in joint hypermobility determines the tightness and laxity of the ligaments, thereby increasing the possibility of injuries by affecting the stability of joint capsules and the extensibility of tendons. The aim of this study was to investigate the effects of generalized joint hypermobility (GJH) on respiratory function, respiratory muscle strength, chest expansion, and functional capacity in healthy young adults.

Material and Method: Thirty subjects aged between 18-25 years with a four or higher Beighton Score were included as the GJH group, and 30 healthy age-gender volunteers with three or lower scores were included as the control group. Functional capacity was measured with the 6-Minute Walk Test (6MWT), the quadriceps muscle strength with a digital dynamometer, pulmonary function and respiratory muscle strength with a spirometry, and chest expansion with a tapeline.

Results: There were significant differences in the 6MWT distance ($p=0.017$), FVC ($p=0.001$), FEV_1 ($p=0.001$), and MEP ($p<0.001$) while no significant differences were observed in quadriceps muscle strength, FEV_1/FVC, PEF, and MIP ($p>0.05$). There is a significant difference in the xiphoid ($p<0.001$) and subcostal ($p<0.001$) measurement in the chest expansion value, and no difference in the axillary measurement ($p=0.071$).

Conclusion: The results of this study demonstrated that functional capacity, pulmonary functions, respiratory muscle strength, and chest expansion may be affected in young adults with GJH. In this study, it was found that the values that required a forced expiratory maneuver were affected. This suggests that the abdominal muscles, which play an important role in forced expiration, may also be affected by changes in the muscles due to deterioration in the connective tissue.

Keywords: Generalized joint hypermobility, functional capacity, pulmonary function, respiratory muscle strength, chest expansion

INTRODUCTION

Joint hypermobility is a common condition that increases the hyperelasticity of soft tissues and consequently the range of motion of the joint. When systemic disorders are excluded, it is described as increased mobility of the small and large joints in a particular age, sex, and race (1,2). Generalized joint hypermobility (GJH) is defined as hypermobility affecting multiple joints and classified using the Beighton Score, which is based on nine maneuvers tested for hypermobility, and the persons who get four or higher for a maximum total of nine scores as GJH (2-4). The prevalence of GJH in the general population is 20-26% (5,6), and in the child and adolescent population it varies between 2-55% depending on age, gender, or ethnicity (7,8). It is a global health problem that is seen more in women than men and causes symptoms such as pain, fatigue, discomfort, and joint instability (9). Joint hypermobility and GJH may be inherited as a normal trait with no identifiable genetic variant or also be a part of many different genetic syndromes such as Ehlers-Danlos Syndrome and other heritable disorders of connective tissue (10,11). The hypermobility of the joint changes the body biomechanics and causes compensatory mechanisms such as pain or muscle spasms in other body parts (10). The increased range of motion caused by hypermobility and chronic joint laxity may also cause hyperextension injuries to

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the supporting ligaments and soft tissue. Particularly in people who are already hypermobile, forces from repeated muscle contractions can strain the ligaments of the chest wall, leading to fatigue and pain (12).

Exercise capacity or functional capacity refers to the individual's ability to perform submaximal activities that require the pulmonary, cardiovascular, and skeletal muscle systems to work together and in a healthy manner (13). Decreased muscle strength and exercise capacity was reported in children and adolescent with GJH (14,15). Engelbert et al. (14) reported a reduced exercise capacity in children and adolescents with GJH using a maximal exercise test with an electronically braked cycle ergometer. Another study showed a decreased functional capacity as measured with the 6MWT and a decreased jumping capacity in adolescents with asymptomatic GJH (15). One of the important factors affecting exercise capacity and daily activities is muscle strength. In earlier studies, it was found that children and adolescents with GJH had decreased knee extensor and flexor muscle strength (14,16,17).

The chest wall is an elastic structure and follows the displacement of the lung. Chest wall expansion can be used in clinical practice to evaluate rib cage and wall mobility and can be related to lung volumes in healthy subjects (18). Chest wall expansion is related to respiratory muscle strength in healthy individuals (18,19). A study performed by Reychler et al. (20) revealed inspiratory muscle weakness in Ehlers-Danlos Syndrome, but expiratory muscle strength was not evaluated in the study. The effects of joint hypermobility on fatigue, musculoskeletal pain, headaches, postural dizziness, gastrointestinal system, and pelvic floor insufficiency are frequently mentioned in studies (10,21). The respiratory problems in joint hypermobility were also reported in Ehlers-Danlos Syndrome such as dyspnea, asthma, sleep apnea, pneumothorax, and chest wall abnormalities (pectus excavatum, straight back syndrome) (22). However, the effects of hypermobility on the respiratory system remain in the background and have not been well characterized in GJH. So, this study was planned to investigate the effects of joint hypermobility on respiratory function, respiratory muscle strength, chest expansion, and functional capacity in healthy young adults.

MATERIAL AND METHOD

Study Design and Participants

This study is an observational, analytical type of case-controlled study. The study was carried out with the permission of Nuh Naci Yazgan University Scientific Research and Publication Ethics Committee (Date. 16.09.2022, Decision No: 2022/001-001). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects before the study. The study was carried out between September 2022 and December 2022 at Nuh Naci Yazgan University. Thirty subjects aged between 18-25 years with a four or higher Beighton Score were included in the GJH group (23), and 30 healthy age-gender volunteers with a score of three or lower were included in the control group. Exclusion criteria were the presence of any neurological and/or orthopedic problems, chronic and/or acute respiratory disease, and medication use that may affect respiratory functions in the last three months for all subjects.

Outcome Measures

The gender, age, height, weight, Beighton Score, smoking, and physical activity status were recorded. Body mass index was calculated using the weight/height2 formula. Functional capacity was measured with the 6-Minute Walk Test (6MWT), the quadriceps muscle strength with a digital dynamometer (Jtech Commander Muscle Tester, USA), pulmonary function and respiratory muscle strength with a spirometry (Cosmed Pony FX Spirometer, Italy), and chest expansion with a tapeline.

Functional capacity was evaluated with the 6MWT according to the criteria of the American Thoracic Society (24). The test is used to assess aerobic capacity and endurance as a sub-maximal exercise test. The distance that the participants walked at their own walking speed for six minutes in a 30-meter-long straight corridor, as fast as possible but without running, was recorded in meters. In addition, SpO2, heart rate, dyspnea, and fatigue levels were evaluated with a pulse oximeter (Beuer pulse oximeter, Beurer GmbH; Germany) before and after the test. The Modified Borg Scale was used to determine dyspnea and fatigue levels (24,25).

The quadriceps muscle strength was evaluated using a digital hand-held dynamometer (Jtech Commander Muscle Tester, USA). The participant sat on the edge of a bed, their feet not touching the floor and their arms crossed in front of the body. They were asked to keep their pelvis on the bed and to extend the knee joint without a swing movement. The transducer was placed on the anterior distal part of the leg. Measurements were performed three times consecutively and the mean values of the right and left side measurements were recorded as force in Newton (N). All muscle strength tests were performed by the same physiotherapist with the same device (26).

The pulmonary function tests of the subjects participating in the study were performed using a spirometer (Cosmed Pony FX Spirometer, Italy) in accordance with the American Thoracic Society/European Respiratory Society criteria (27). The age, gender, and previously measured

height and weight of the participant were recorded while they were resting for 10 minutes before the test. The test began while the participant's feet were in full contact with the ground in a sitting position. Nasal breathing was prevented with a nose clip, and the subjects were asked to inhale as deeply as possible and then quickly perform a deep expiration. It was important to make sure that the spirometer mouthpiece was closed airtight from the lip, the tongue was not inserted into the mouthpiece, the inspiration was completed, the maneuver started quickly and strongly, there was no pause, no other breathing or coughing occurred during expiration, and the expiration continued until a plateau was seen in the volume-time graph (27). Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC, and peak expiratory flow rate (PEF) were measured.

Respiratory muscle strength was measured (Cosmed Pony FX Spirometer, Italy) in accordance with the American Thoracic Society/European Respiratory Society criteria (28). Before starting the test, the subjects were instructed to close their lips tightly around the mouthpiece to prevent air leaks. The measurement began when the feet were in full contact with the ground in a sitting position. For maximal inspiratory pressure (MIP) measurement, the nasal airway was closed with a latch after the appropriate mouthpiece was fixed. When the subject reached the residual volume, the device's mouthpiece was put in the mouth and maximum inspiration (Müller maneuver) was performed at maximum speed for 1-3 seconds. For maximum expiratory pressure (MEP) measurement, in contrast to the residual volume, it began at total lung capacity and maximal expiration (Valsalva maneuver) was performed at maximum speed for 1-3 seconds. Maximal inspiratory and expiratory performance was put in with one-minute intervals between tests. The measurement was repeated until there was a difference of 10 cmH_2O between the two best measurements and the best result was recorded as cmH_2O (28).

Chest wall expansion was measured using a standard measuring tape at three different levels for chest circumference. With the participant in an upright position, feet shoulder-width apart, arms relaxed at the side of the body, measurements were taken at three sites: Axilla (upper-level), xiphoid (mid-level), and subcostal (lower-level) (29). After placing the tape measure around the chest, the physiotherapist, standing in front of the subject, initially asked them to breathe normally to determine the tidal volume and then to exhale maximally. The difference between the two scales (inhalation-exhalation) was determined as thoracic expansion (chest expansion). Participants were instructed to perform three maneuvers and the average of the obtained values was recorded (18). Measurements were performed by the same physiotherapist to minimize possible errors due to heterogeneity.

Statistical Analysis

Statistical analyses were performed using the SPSS V20.0 statistical program (SPSS, Inc.). The normality of data distribution was determined with the Kolmogorov-Smirnov test. The descriptive data of the demographic variables were expressed as mean-standard deviation, so the data were normally distributed. The differences between the GJH and control groups were tested using an independent sample t-test, and a Chi-square test was used for categorical variables (30).

The G*Power 3.1 (Universitaet Dusseldorf, Germany) software was used for the sample size calculation. In a study performed by Scheper et al. (15), the 6MWT distances of dancers and non-dancers were compared using the Beighton Score ≥ 4 for the classification of GJH. Considering these results, we hypothesized that to obtain a similar difference rate of 90% power and 95% confidence level, a total of 60 participants had to be included in this study.

RESULTS

Thirty young adults with GJH and 30 healthy young adults as the control group were included in the study. The demographic characteristics of the groups are presented in **Table 1**. There were no significant differences between the GJH and the control group in terms of baseline characteristics of the young adults ($p>0.05$), except for the Beighton Score ($p<0.001$).

Table 1. Demographic characteristics of the groups

	GJH group (n=30)	Control group (n=30)	p
Gender (n, %)			0.598
Female	19 (63)	17 (57)	
Male	11 (37)	13 (43)	
Age (years)	22±2.21 [19-25]	22.07±2.32 [18-25]	0.904
Weight (kg)	64.9±13.9 [48-100]	66.8±16.9 [49-120]	0.625
Height (cm)	171.3±8.87 [160-190]	169.5±8.78 [155-186]	0.441
BMI (kg/m^2)	22±3.68 [16.2-32.7]	23±3.8 [18.3-35.1]	0.312
Beighton score	5.57±1.33 [4-8]	0.87±1.2 [0-3]	<0.001
Smokers (n, %)	12 (40)	13 (43)	0.793
Physically active (n, %)	11 (37)	9 (30)	0.584
Infected with COVID-19 (n, %)			0.237
Yes	16 (53)	22 (73)	
No	7 (23)	3 (10)	
Not sure	7 (23)	5 (17)	

Data are presented as mean±SD [min-max], GJH: Generalized joint hypermobility; BMI: Body Mass Index

The mean values of 6MWT distance, quadriceps muscle strength, pulmonary function, respiratory muscle strength, and chest expansion of the two groups, and the comparisons between groups are shown in **Table 2**. There were significant differences in 6MWT distance (p=0.017), FVC (p=0.001), FEV_1 (p=0.001), and MEP (p<0.001) while no significant differences were found in quadriceps muscle strength, FEV_1/FVC, PEF, and MIP (p>0.005). There was a significant difference in the xiphoid (p<0.001) and subcostal (p<0.001) measurement in the chest expansion value, and no difference in the axillary measurement (p=0.071).

Table 2. Comparison of the 6MWT distance, quadriceps muscle strength, pulmonary function, respiratory muscle strength, and chest expansion between groups

	GJH group (n=30)	Control group (n=30)	p
6MWT distance (m)	511.7±69.6	552±56.5	0.017
Quadriceps muscle strength (N)			
Right	298.7±55.6	290.1±72.1	0.638
Left	280.7±57.9	281.4±74.3	0.968
Pulmonary function test			
FVC (L)	3.87±0.6	4.22±0.83	0.064
FVC (% of predicted)	88±6.13	93.4±6.12	0.001
FEV_1 (L)	3.35±0.43	3.87±0.72	0.001
FEV_1 (% of predicted)	89.6±5.07	95.2±7.69	0.001
FEV_1/FVC	87.5±12.4	91.8±4.69	0.076
PEF (L)	6.78±1.94	6.96±2.23	0.736
PEF_%	83.4±18.1	88.2±20.7	0.349
Respiratory muscle strength (cmH_2O)			
MIP	98.88±27.25	105.73±18.99	0.263
MEP	105.87±23.64	135.77±36.23	<0.001
Chest size during inspiration (cm)			
Axillar	68.6±9.78	72.5±12.1	0.175
Xiphoid	77.5±11.8	81.5±12.3	0.211
Subcostal	69.7±11	76.9±12.3	0.021
Chest size during expiration (cm)			
Axillar	80.2±9.03	81.9±9.81	0.471
Xiphoid	71.9±11.2	78±11.5	0.040
Subcostal	68.6±9.78	72.5±12.1	0.175
Chest expansion value (cm)			
Axillar	5.4±3.4	6.7±1.84	0.071
Xiphoid	5.67 ±2.28	3.43±1.81	<0.001
Subcostal	1.17±3.61	4.4±2.11	<0.001

Data are presented as mean±standard deviation, GJH: Generalized joint hypermobility; 6MWT: Six-Minute Walk Test; FVC: forced vital capacity; FEV_1: forced expiratory flow in 1 second; PEF: peak expiratory flow; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure

DISCUSSION

This research aimed to investigate the effects of joint hypermobility on the functional capacity, pulmonary function, respiratory muscle strength, and chest expansion in healthy young adults. As a result of our study, significant differences in 6MWT distance, FVC, FEV_1, MEP, and chest expansion were observed while no differences were found in MIP and knee extensor muscle strength.

Genetic involvement of connective tissue containing elastin, collagen, and fibrils in joint hypermobility determines the tightness and laxity of the ligaments, thereby increasing the potential for injuries by affecting the stability of joint capsules and the extensibility of tendons (1,31). The hypermobility of the joints change the body biomechanics and causes compensatory mechanisms such as pain or muscle spasm in other body parts. For example, anterior pelvic tilt with lumbal hyperlordosis accompanying genu recurvatum and/or flat feet can be observed (10). Joint hypermobility syndrome can also affect daily life activities, especially prolonged standing activities in patients (4). In addition to the impact on daily activities, there is a decrease in functional capacity and cardiorespiratory fitness in joint hypermobility (14,15). Engelbert et al. (14) reported a reduced exercise capacity in children and adolescents with GJH using a maximal exercise test with an electronically braked cycle ergometer. In a study performed by Scheper et. al (15), decreased functional capacity measured by 6MWT and jumping capacity expressed as reduced walking distance and jumping capacity were reported in adolescents with asymptomatic (pain-free) GJH. In our study, we found reduced functional capacity and walking distance in young adults with GJH compared to the healthy control group. The 6MWT is the most common submaximal test used to evaluate the functional capacity including main cardiovascular, pulmonary, and neuro-musculoskeletal performance in chronic lung diseases such as chronic obstructive pulmonary disease, asthma, or cystic fibrosis. The test evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary system (24). Moreover, there is a cut-off value for the 6MWT in chronic obstructive pulmonary disease for identifying patients with high mortality risk (32). The reduced walking distance according to the 6MWT in the GJH group compared to the control group in this study suggested that it may be related to decreased lung functions.

Muscle strength is one of the important factors affecting exercise capacity and daily activities. In earlier studies, it was found that children and adolescents with GJH had decreased knee flexor and extensor muscle strength (14,16,17). In a study, lower muscle activity for quadriceps and hamstrings measured by electromyography was observed during stair climbing, an important daily life activity, in women with symptomatic and asymptomatic GJH (33). In contrast, increased knee extensor muscle strength was reported in healthy adolescents with GJH (7). In the present study, there is no significant difference in quadriceps muscle strength between subjects with and without GJH. This decrease in functional capacity may be due to the decreased lung volumes in individuals with GJH. In addition, a reason why there was no difference

between the groups in terms of quadriceps muscle strength in this study may be that the participants were not classified as symptomatic or asymptomatic. Symptoms such as pain prevent individuals from performing physical activity and cause a decrease in muscle strength (15,17). Schubert-Hjalmarsson et al. (34) showed that pain-free hypermobile children appeared to be more physically active in sports. Muscle strength deficit in hypermobile individuals may be related to pain, either directly or indirectly through inactivity due to pain (35). The presence of both symptomatic and asymptomatic participants in this study may have contributed to the lack of difference in quadriceps muscle strength. Therefore, in future studies, it is important to explain the effects of symptoms on muscle strength in individuals with GJH.

One of the determinants of functional capacity is the state of respiratory functions. Respiratory manifestations such as dyspnea, sleep apnea, and decreased respiratory muscle function have frequently been described in classical or hypermobile Ehlers-Danlos Syndrome (22). Respiratory manifestations in hypermobility spectrum disorders have been noted less often in the literature (22). Soyucen and Esen (36) postulated that benign joint hypermobility syndrome may predispose to childhood asthma. This is the first study to investigate the pulmonary function and respiratory muscle strength in young adults with GJH, to the best of our knowledge. We found significantly reduced lung volume (FEV_1 and FVC) and MEP values. Respiratory muscle strength is associated with lung volume and functional capacity (19). Padkao et al. (19) showed that respiratory muscle strength is associated with functional capacity measured by the 6MWT. In this study, decreased respiratory muscle strength in subjects with GJH may be also one of the reasons for the decrease in the 6MWT distance. However, it was observed that subjects with GJH had lower values in maneuvers requiring forced expiration such as FEV_1 and MEP. This suggests that the abdominal muscles, which play an important role in forced expiration, may also be affected due to deterioration in the connective tissue (37,38). Studies in the literature on functional muscle strength in joint hypermobility generally focus on the lower extremity muscles, but more research is required to investigate trunk muscles including abdominals. In addition, the lower lung capacity observed in both groups can be explained by the fact that more than half of the individuals were exposed to COVID-19 infection, as we showed the long-term effects of covid in a previous study (39).

Muscle strength, fatigue, and pain affect functional capacity in individuals with joint hypermobility (15,17). However, chest wall expansion may be also an important contributor to functional status. The chest wall is an elastic structure and follows the displacement of the lung, and the chest wall expansion can be used in clinical practice to evaluate rib cage mobility and wall mobility and it is related to lung volumes in healthy subjects (18). Chest wall expansion is related to respiratory muscle strength and higher chest mobility reflects the greater MIP and MEP value in healthy individuals (18,19). To the best of our knowledge, there is no study investigating chest wall expansion in GJH. In this study, statistical significance was found in chest expansion value in the measurement of xiphoid and subcostal. Subjects with GJH had more chest wall expansion at the xiphoid level and less at the subcostal level compared to the control group. Individuals may have developed different breathing patterns, potentially due to the structural abnormality of connective tissue. Breathing patterns may also be examined in future studies.

The limitations of the present study include the fact that environmental and psychological factors such as social status were not considered in this study. While this information is beyond the scope of the present article, it should be noted that such information may have an impact on the treatment of individuals diagnosed with symptomatic forms of GJH. The possibility of continuing long-term effects of the COVID-19 infection is also a limitation of the study. However, although the majority of the participants had COVID-19 before, the inability to evaluate the effects of the infection on the respiratory functions of the participants is another limitation. Yet another limitation could be that the potential confounders such as pain were not considered in our study. The last limitation, based on the study design, is that these results offer no causative evidence, but future studies designed as longitudinal observational studies may provide evidence.

CONCLUSION

Functional capacity, pulmonary functions, respiratory muscle strength, chest expansion, and quadriceps muscle strength may be affected in young adults with GJH. In this study, it was found that there was an effect on the values that required a forced expiratory maneuver. This suggests that the abdominal muscles, which play an important role in forced expiration, may also be affected due to deterioration in the connective tissue. Considering the changes in chest expansion, patients with GJH may develop different breathing patterns. It is important to know the symptoms and especially the respiratory management strategies in GJH, which have generally been managed using conservative treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Nuh Naci Yazgan University Scientific Research and Publication Ethics Committee (Date. 16.09.2022, Decision No: 2022/001-001).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Current treatment approaches of newly graduated, intern dentists and dentists in doctoral and specialty training to teeth with excessive substance loss (cross-sectional study)

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ABSTRACT

Aim: New treatment options have been developed as alternative post-retaining restorations and crowns that preserve remaining tooth tissue in endodontically treated teeth with excessive substance loss. This study, current treatment approaches newly graduated, intern and doctoral or specialist dentists in teeth excessive coronal destruction were evaluated.

Material and Method: This cross-sectional study, online questionnaire consisting of 22 questions, 3 parts was applied. First part consists of demographic information participants, second part consists of questions measuring awareness about preferred indirect restorations, last part consists of current treatment approaches newly graduated, intern and doctoral or specialist dentists. Total 234 voluntary participants questionnaires were evaluated. Obtained data were analyzed with IBM SPSS V23.

Results: In restoration of endodontically treated buccal mesial walls (least 2 mm thick) molars, participants all 3 groups preferred posterior adhesive indirect restorations according to their titles. Considering level of awareness, participants high group preferred posterior adhesive indirect restorations more in restorations endodontically treated buccal lingual walled molar teeth. Participants all 3 groups preferred use fiber under composite strengthen teeth in the restoration of teeth with excessive substance loss.

Conclusion: According to the results, it was determined that awareness and knowledge level of dentists who received specialty or doctoral training about new current treatments was higher than other newly graduated and intern dentists. It was observed that participants group with high level awareness mostly preferred posterior region indirect adhesive restorations such as endocrown and onlay.

Keywords: Doctoral student, dentistry student, endocrown, fiber, onlay

INTRODUCTION

Teeth with excessive substance loss can be treated using direct or indirect methods based on the amount of substance loss (1). The composite resins that are applied with the direct method show sufficient strength against forces due to their force absorption and flexibility properties (2). However, because of the polymerization shrinkage that occurs in the composite resins that are applied using the direct method and water absorption after polymerization may lead to deformation and tooth fractures under forces. As in MOD cavities, as the amount of dental tissue that remains decreases, cavity dimensions increase, the problem of polymerization shrinkage is directly proportional to the amount of the composite resin that needs to be used, and the treatment duration is prolonged with the application of the resin in incremental layers, which causes discomfort in the patient and humidity or saliva contamination in the composite resin (3,4).

Indirect methods can be used in the treatment of teeth that are difficult to restore by direct methods or have substance loss to an extent that cannot be restored. While post and core crown treatments used to be the most frequently performed indirect method in the past, with the advancements in adhesive dentistry, conservative approaches in restorative dentistry have allowed the development of new treatment methods for the restoration of teeth with excessive substance loss (5). In decayed or fractured posterior teeth, in cases where direct restorations are inadequate, restorations such as onlay and endocrown

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restorations can be preferred to achieve the ideal proximal contact and an aesthetic morphology and provide abrasion resistance (5,6). During the preparation of a post chamber in conventional post and core systems, the risk of root perforation can be encountered (7). There is no risk of root perforation or fracture in endocrown, which are adhesive restorations. Additionally, as opposed to conventional crowns, because endocrowns and onlays do not require subgingival placement, they do not lead to gingivitis (8). The endocrown was proposed as a "monoblock technique", and it involves micro retention that is obtained by using the micromechanical retention provided by the opposing axial pulp walls and adhesive cementation (9). Thanks to advanced adhesive techniques, as alternatives to direct restorations and post and core crown applications in teeth with excessive coronal tissue loss, indirect restorations such as inlay, onlay, or endocrown restorations are becoming more prevalent today (1).

Based on studies showing that fiber materials that have been used in dentistry in recent years can be used safely in deep cavities along with composites and increase the strength of teeth, using fiber materials along with composites in the restoration of teeth with excessive substance loss has become an alternative treatment option (10-12).

The purpose of this study is to measure the awareness levels of newly graduated and intern dentists regarding the restoration of teeth with excessive coronal tissue loss and evaluate the current restorative treatment methods they prefer.

The hypotheses of this study were determined as follows:

1. The awareness and knowledge levels of newly graduated dentists involved in specialization or doctoral studies (with at most 3 years of professional experience) regarding current treatments are higher in comparison to other newly graduated and intern dentists.
2. Participants with higher levels of awareness and knowledge regarding current treatments prefer newer treatments such as onlay, composite-supported overlay, and endocrown treatments over conventional treatments such as post and core crowns and direct composite restorations.
3. Participants with higher awareness of current methods prefer using fiber materials.

MATERIAL AND METHOD

Before starting this cross-sectional study was carried out with the permission of İstanbul Medipol University Non-Invasive Clinical Studies Ethics Committee (Date: 10.08.2022, Decision No: 697). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants and Design

The sample of this survey study consisted of 234 newly graduated and intern dentists, including 156 female and 78 male participants. Among the participants, 26 were newly graduated dentists, 194 were intern dentists, and 14 were dentists who were involved in specialization or doctoral studies. The inclusion criterion was selected as having at most 3 years of professional experience after graduation. Participation in the survey was voluntary, and the identifying information of the participants was kept confidential. The survey form was created on the Google Forms platform, and the link to the form was shared with the participants via social media.

Survey Design

The survey consisted of 3 parts and a total of 22 questions. The first part included questions on the sociodemographic information of the participants such as gender, age group, and title. The sociodemographic and occupational characteristics of the participants are presented in **Table 1**. The second part of the survey included 6 questions that were prepared to assess the knowledge levels of the participants regarding methods of onlay and endocrown preparations and indirect restorations that are preferred in posterior regions. Each question was worth 1 point for the correct answers and 0 points for the incorrect answers, and a participant providing correct answers to all questions would get 6 points. The third and last part of the survey included questions on the views of the participants towards current treatment approaches in posterior teeth with excessive substance loss. The 13 questions in this part evaluated the preferences of the participants among composite-supported overlay, endocrown, post and core crown, direct composite restoration, and onlay options based on the amount of tissue remaining in molar and premolar teeth and the number of intact walls. The last 2 questions on the survey regarding current treatment approaches assessed whether the participants preferred using fiber materials and which types of fiber materials they used.

Table 1. Demographic characteristics

	Frequency (n) / Mean ± (s. deviation)	Frequency (%) / Median (min. - max.)
Score	4.29 ± 1.53	5 (0 - 6)
Knowledge level		
Low	58	24.8
High	176	75.2
Age	23.26 ± 1.58	23 (21 - 30)
Gender		
Male	78	33.3
Female	156	66.7
Title		
Newly graduated dentist	26	11.1
Intern dentist	194	82.9
Dentist involved in specialization or doctoral studies	14	6

Statistical Analysis

The data were analyzed using IBM SPSS V23. The normal distribution of the data was evaluated using the Kolmogorov-Smirnov test and Shapiro-Wilk test. The Kruskal-Wallis H test was used to compare knowledge scores among 3 or more non-normally distributed groups, and multiple comparisons were examined using Dunn's test.

Pearson's chi-squared and Fisher's exact chi-squared tests were used to compare the categorical variables based on titles and knowledge levels, and the multiple comparisons for these tests were examined using Z-tests with Bonferroni correction. The analysis results are presented with mean ± s. deviation and median (minimum – maximum) values for the quantitative variables and frequency (percentage) values for the categorical variables. The level of statistical significance was taken as $p<0.050$.

RESULTS

The distribution of the knowledge levels of the participants regarding current treatment approaches in the restoration of teeth with excessive substance loss is shown in **Table 2**. The mean, minimum, and maximum scores of the participants were 4.29, 0, and 6, respectively. The median knowledge scores of the newly graduated, intern, and doctorate/specialization groups were 5, 4, and 6, respectively. No statistically significant difference was found in the knowledge levels of the participants based on their titles ($p=0.051$).

The views of the participants towards current approaches in the treatment of teeth with excessive substance loss varied based on their titles and awareness levels. The distribution of the current treatment options preferred by the participants based on their titles is given in **Table 3**. The participants in all 3 title groups mostly preferred direct composite restorations following Class 2 cavity preparations in molar and premolar teeth. Regarding the restorations of molar teeth that have undergone endodontic treatment, have no intact walls, and have margins on the gingival level, while most of the participants in the newly graduated group preferred post and core crown restorations, most of those in the doctorate/specialization group preferred endocrown restorations. Regarding the restorations of molar teeth that have undergone endodontic treatment, have no intact walls, and have margins 2 mm above the gingival level, most of the participants in the doctorate/specialization group preferred endocrown restorations. For the restorations of molar teeth that have undergone endodontic treatment and have only the buccal wall intact (intact and at least 2-mm-thick), while most participants in the newly graduated and intern groups preferred post and core crown restorations, those in the doctorate/specialization group mostly preferred endocrown restorations. In the restorations of molar teeth that have undergone endodontic treatment and have their buccal and lingual walls intact (intact and at least 2-mm-thick), the newly graduated participants mostly preferred endocrown restorations, whereas the intern dentist participants mostly preferred post and core crown restorations. The participants who were involved in specialization or doctoral studies mostly preferred composite-supported overlay restorations, while none of them preferred direct composite restorations. Regarding the restorations of molar teeth that have undergone endodontic treatment and have their buccal and mesial walls intact (intact and at least 2-mm-thick), the participants in all 3 groups preferred onlay, overlay, and endocrown restorations over post and core crown restorations.

For the restorations of premolar teeth that have undergone endodontic treatments, have no intact walls, and have margins 2 mm above the gingival level, most of the newly graduated participants preferred post and core crown restorations, whereas the participants involved in doctoral/specialization studies mostly preferred composite-supported overlay restorations. Regarding the restorations of premolar teeth that have undergone endodontic treatment and have their 2 walls (buccal-lingual or buccal-mesial) intact (at least 2-mm-thick), the participants in all groups mostly preferred posterior adhesive indirect restorations.

The distributions of the preferences of the participants regarding fiber material use and the types of fiber materials they used are presented in **Table 4**. The participants in all 3 groups preferred to use fiber under composites to strengthen the teeth in the restoration of teeth with excessive substance loss. While the newly graduated group preferred everX Posterior, the intern group preferred Ribbond fiber. Those in the doctorate/specialization group had close rates of preference for the two materials.

The distributions of the current treatment approach preferences of the participants based on their awareness and knowledge levels are shown in **Table 5**. In the two groups with low and high levels of awareness, the most frequently preferred type of restoration following Class 2 cavity preparation in molar and premolar teeth was direct composite restoration. Regarding the restorations of molar teeth that have undergone endodontic treatment and have their 2 walls (buccal-lingual or buccal-mesial) intact, while the participants in the group with low levels of awareness mostly preferred direct composite restorations, those in the group with high levels of awareness mostly preferred

posterior adhesive indirect restorations (endocrown, onlay, composite-supported overlay). For the restorations of premolar teeth that have undergone endodontic treatment and have their 2 walls (buccal-lingual or buccal-mesial) intact, the participants in both the groups with low and high levels of awareness preferred posterior adhesive indirect restorations (endocrown, onlay, composite-supported overlay) more. The participants in both groups preferred using fiber material under composite material in the restoration of teeth with excessive substance loss to strengthen the tooth.

Table 2. Comparison of knowledge scores and levels based on titles.

	Newly Graduated	Intern	Doctorate/Specialization	Total	Test stat.	p
Knowledge score	5 (2- 6)[ab]	4 (0- 6)[b]	6 (4- 6)[a]	5 (0- 6)	17.239	<0.001*
Knowledge level					6.814	0.051**
Low	4 (15.4)	54 (27.8)	0 (0)	58 (24.8)		
High	22 (84.6)	140 (72.2)	14 (100)	176 (75.2)		

*Kruskal-Wallis H test, **Pearson's chi-squared test, a-b: There is no significant difference between titles with the same letter.

Table 3. Comparison of treatment preferences based on titles

Treatment preferences: (Assuming that considered walls were intact and at least 2-mm-thick)	Newly Graduated	Intern	Doctorate/ Specialization	Total	Test stat.	p*
Molar with no intact wall, above the gingival level: 1					27.936	0.002
Direct Composite Restoration	1 (3.8)[a]	19 (10.1)[a]	0 (0)	20 (8.8)		
Endocrown	13 (50)[ab]	62 (33)[a]	10 (76.9[b]	85 (37.4)		
Composite-Supported Overlay	3 (11.5)[a]	46 (24.5)[a]	3 (23.1)[a]	52 (22.9)		
Onlay	3 (11.5)[a]	32 (17)[a]	3 (23.1)[a]	38 (16.7)		
Post + Crown	16 (61.5)[a]	92 (48.9)[a]	1 (7.7)[b]	109 (48)		
Molar with intact buccal wall: 1					27.936	0.002
Direct Composite Restoration	1 (3.8)[a]	19 (10.1)[a]	0 (0)	20 (8.8)		
Endocrown	13 (50)[ab]	62 (33)[a]	10 (76.9)[b]	85 (37.4)		
Composite-Supported Overlay	3 (11.5)[a]	46 (24.5)[a]	3 (23.1)[a]	52 (22.9)		
Onlay	3 (11.5)[a]	32 (17)[a]	3 (23.1)[a]	38 (16.7)		
Post + Crown	16 (61.5)[a]	92 (48.9)[a]	1 (7.7)[b]	109 (48)		
Molar with intact buccal and lingual walls: 1					18.052	0.054
Direct Composite Restoration	6 (23.1)	48 (26.2)	0 (0)	54 (24.3)		
Endocrown	10 (38.5)	40 (21.9)	2 (15.4)	52 (23.4)		
Composite-Supported Overlay	5 (19.2)	55 (30.1)	7 (53.8)	67 (30.2)		
Onlay	7 (26.9)	59 (32.2)	5 (385)	71 (32)		
Post + Crown	8 (30.8)	63 (34.4)	1 (7.7)	72 (32.4)		
Molar with intact buccal and mesial walls: 1					6.240	0.795
Direct Composite Restoration	6 (24)	39 (21.3)	2 (15.4)	47 (21.3)		
Endocrown	7 (28)	41 (22.4)	3 (23.1)	51 (23.1)		
Composite-Supported Overlay	5 (20)	42 (23)	4 (30.8)	51 (23.1)		
Onlay	8 (32)	62 (33.9)	5 (38.5)	75 (33.9)		
Post + Crown	8 (32)	68 (37.2)	1 (7.7)	77 (34.8)		
Premolar with intact buccal and lingual walls: 1					16.674	0.082
Direct Composite Restoration	7 (26.9)	57 (30.8)	1 (7.7)	65 (29)		
Endocrown	8 (30.8)	52 (28.1)	1 (7.7)	61 (27.2)		
Composite-Supported Overlay	4 (15.4)	40 (21.6)	7 (53.8)	51 (22.8)		
Onlay	8 (30.8)	47 (25.4)	4 (30.8)	59 (26.3)		
Post + Crown	10 (38.5)	60 (32.4)	2 (15.4)	72 (32.1)		
Premolar with intact buccal and mesial walls: 1					17.424	0.065
Direct Composite Restoration	11 (42.3)	57 (30.6)	2 (15.4)	70 (31.1)		
Endocrown	6 (23.1)	43 (23.1)	1 (7.7)	50 (22.2)		
Composite-Supported Overlay	7 (26.9)	44 (23.7)	7 (53.8)	58 (25.8)		
Onlay	4 (15.4)	53 (28.5)	4 (30.8)	61 (27.1)		
Post + Crown	11 (42.3)	63 (33.9)	1 (7.7)	75 (33.3)		

*Pearson's chi-squared, 1Multiple choices were allowed, a-b: There is no significant difference between titles with the same letter on the same row.

Table 4. Comparison of fiber preferences based on titles

	Newly Graduated	Intern	Doctorate/ Specialization	Total	Test stat.	p*
Prefers using fiber: 1					1.509	0.470
Yes	23 (88.5)	171 (91)	13 (100)	207 (91.2)		
No	3 (11.5)	17 (9)	0 (0)	20 (8.8)		
Types of fiber preferred: 1					8.510	0.075
everX Posterior	16 (64)	81 (46)	6 (46.2)	103 (48.1)		
Ribbond	10 (40)	113 (64.2)	7 (53.8)	130 (60.7)		

*Pearson's chi-squared, 1Multiple choices were allowed, a-b: There is no significant difference between titles with the same letter on the same row.

Table 5. Comparison of treatment preferences based on awareness and knowledge levels

Treatment preferences:	Low	High	Total	Test stat.	p
Molar with no intact wall, above the gingival level: 1				11.264	0.046*
Direct Composite Restoration	9(16.4)[a]	11(6.4)[b]	20(8.8)		
Endocrown	18(32.7)[a]	67(39)[a]	85(37.4)		
Composite-Supported Overlay	11(20)[a]	41(23.8)[a]	52(22.9)		
Onlay	14(25.5)[a]	24(14)[b]	38(16.7)		
Post + Crown	23(41.8)[a]	86(50)[a]	109(48)		
Molar with intact buccal wall: 1				11.264	0.046*
Direct Composite Restoration	9(16.4)[a]	11(6.4)[b]	20(8.8)		
Endocrown	18(32.7)[a]	67(39)[a]	85(37.4)		
Composite-Supported Overlay	11(20)[a]	41(23.8)[a]	52(22.9)		
Onlay	14(25.5)[a]	24(14)[b]	38(16.7)		
Post + Crown	23(41.8)[a]	86(50)[a]	109(48)		
Molar with intact buccal and lingual walls: 1				4.825	0.438*
Direct Composite Restoration	16(29.6)	38(22.6)	54(24.3)		
Endocrown	10(18.5)	42(25)	52(23.4)		
Composite-Supported Overlay	15(27.8)	52(31)	67(30.2)		
Onlay	14(25.9)	57(33.9)	71(32)		
Post + Crown	14(25.9)	58(34.5)	72(32.4)		
Molar with intact buccal and mesial walls: 1				16.847	0.005*
Direct Composite Restoration	19(35.2)[a]	28(16.8)[b]	47(21.3)		
Endocrown	6(11.1)[a]	45(26.9)[b]	51(23.1)		
Composite-Supported Overlay	9(16.7)[a]	42(25.1)[a]	51(23.1)		
Onlay	20(37)[a]	55(32.9)[a]	75(33.9)		
Post + Crown	16(29.6)[a]	61(36.5)[a]	77(34.8)		
Premolar with intact buccal and lingual walls: 1				4.148	0.528*
Direct Composite Restoration	18(33.3)	47(27.6)	65(29)		
Endocrown	11(20.4)	50(29.4)	61(27.2)		
Composite-Supported Overlay	9(16.7)	42(24.7)	51(22.8)		
Onlay	14(25.9)	45(26.5)	59(26.3)		
Post + Crown	19(35.2)	53(31.2)	72(32.1)		
Premolar with intact buccal and mesial walls: 1				1.730	0.885*
Direct Composite Restoration	15(27.3)	55(32.4)	70(31.1)		
Endocrown	10(18.2)	40(23.5)	50(22.2)		
Composite-Supported Overlay	15(27.3)	43(25.3)	58(25.8)		
Onlay	13(23.6)	48(28.2)	61(27.1)		
Post + Crown	18(32.7)	57(33.5)	75(33.3)		
Prefers using fiber: 1				----	0.070**
Yes	46(0.9)	161(0.9)	207(0.9)		
No	8(0.1)	12(0.1)	20(0.1)		
Types of fiber preferred: 1				0.133	0.936*
everX Posterior	25(49)	78(47.9)	103(48.1)		
Ribbond	32(62.7)	98(60.1)	130(60.7)		

*Pearson's chi-squared, **Fisher's exact chi-squared, 1Multiple choices were allowed, a-b: There is no significant difference between knowledge levels with the same letter on the same row

DISCUSSION

There is no single ideal treatment method for the restoration of teeth with excessive substance loss (13). Nowadays, depending on the amount of substance loss in the treatment of teeth with excessive substance loss, in addition to conventional post and core crowns, there has been an increasing usage of onlay, composite-supported overlay, endocrown, and fiber-reinforced direct composite restorations, which are based on a conservative approach, as treatment options (14,15). It was reported that surveys are an effective method for evaluating the awareness levels and education statuses of participants (16). In this survey study, we also measured the education statuses and awareness levels of 234 participants consisting of newly graduated dentists, intern dentists, and dentists involved in doctoral or specialization studies regarding the restoration of teeth with excessive substance loss. A statistically significant difference was found in the median knowledge scores of the participants based on their titles ($p<0.001$). This difference was among all groups.

As a consequence of the developments in materials that are used in dentistry for the restoration of teeth, adhesive procedures, and cementation systems, the prognosis of inlay, onlay, and endocrown restorations has become highly favorable (17). These restorations, which have a monoblock structure, are suitable for conservative treatment because they protect dental tissue, and thus, their long-term prognosis is also positive (18). Fildisi et al. (6) designed overlays applied onto teeth that were build up by composite material and endocrowns that directly reached the pulp chamber. They examined the fracture strength values of the group with the composite-supported overlay and the group with the endocrown. Biacchi et al. (19) compared the fracture strength of conventional post and core crowns and monoblock endocrowns extending up to canal ends in the pulp chamber. In this survey study, for treatment methods that could be preferred in the restorations of posterior teeth, we determined the options of composite-supported overlay, endocrown, onlay, post and core crown, and direct composite restorations.

In our study, it was observed that the participants who were involved with doctoral or specialization studies preferred endocrown restorations more than those who were interns did. In the study in which they designed overlays applied onto teeth that were build up by composite material and endocrowns that directly reached the pulp chamber, Fildisi et al. (6) found higher fracture strength values in the overlay restorations, while both the overlay and endocrown groups showed fractures at force values higher than the maximum chewing forces in the oral environment. Other in vitro studies have also shown that molar teeth restored with endocrowns can endure physiological chewing forces without fractures (20,21). In present study, endocrown restorations reaching the pulp chamber were preferred by both the groups with low and high levels of knowledge regarding the restoration of molar teeth with a history of endodontic treatment, no intact walls, and margins 2 mm above the gingival level. In the study where they compared the fracture strength values of conventional post and core crowns and endocrowns, Biacchi et al. (19) found higher fracture strength values in the endocrowns that had support from the pulp chamber. In our study, for the restorations of molar teeth that have undergone endodontic treatment and have their buccal and lingual walls intact (intact and at least 2-mm-thick), the participants who were involved in doctoral or specialization studies mostly preferred endocrown restorations.

The restoration process for teeth in the posterior area also varies based on the tooth that will be treated (22). It was stated that the performance of endocrown restorations in posterior teeth under axial and lateral forces during functioning is directly proportional to the size of the pulp chamber (23). In our survey study, in the part of questions on the preferred treatment approaches of the participants, there were 6 questions on their preferences in the restoration of molar teeth with excessive substance loss and 5 questions on their preferences in the restoration of premolar teeth with excessive substance loss. This way, the approaches of the participants towards the restorations of premolar and molar teeth with different pulp chamber dimensions were evaluated. In the study where they evaluated the performance of endocrowns in premolars and molars, Bindl et al. (24) observed that premolars showed more failure in comparison to molars due to adhesive breaks. In current study, the participants preferred endocrown restorations more frequently in the context of molar teeth in comparison to premolar teeth regarding the restoration of endodontically treated teeth without any intact walls and with margins 2 mm above the gingival level.

Other factors that are effective in the planning of posterior tooth restorations are the remaining coronal tooth structure and functional requirements. Which tubercle remains and the rate of the remaining tubercle are also important criteria affecting the restoration to be made. While the loss of buccal and lingual tubercles creates both retention and strength problems, the loss of mesial and distal tubercles creates only retention problems (25). In previous studies, it has been recommended to use indirect onlays following at least 1.5-2 mm of cusp reduction to protect the remaining dental structure and increase fracture strength in MOD cavities with excessive substance loss (8,26). In our survey study, we investigated the restoration preferences of the participants based on

different awareness levels with the consideration of intact walls remaining on teeth (thicker than 2 mm). For the restoration of molar and premolar teeth that have undergone endodontic treatment and have their buccal and lingual walls intact (intact and at least 2-mm-thick), both groups with low and high awareness levels preferred posterior adhesive indirect restorations (onlay, endocrown, overlay) more frequently. In the comparisons based on the titles of the participants, while the intern dentist participants mostly preferred post and core crown restorations in the restoration of molar and premolar teeth that have undergone endodontic treatment and have their 2 walls (buccal-lingual or buccal-mesial) intact, the total number for the preference of posterior adhesive indirect restorations was higher than that for post and core crowns.

Garoushi et al. (15) who investigated the effects of fiber materials that are used in dentistry, found that everX Posterior raised fracture strength values. In their studies on the effects of polyethylene fiber use in premolar teeth with MOD cavities on fracture strength and modes of failure, Belli et al. (11) and Hshad et al. (12) reported that Ribbond usage noticeably improved fracture strength values. In our study, in the questions on fiber material preferences, we determined the Ribbond and everX Posterior fiber materials as options. The vast majority of the participants in both the groups with high and low awareness levels preferred using fiber material under composite material in the restoration of teeth with excessive substance loss to strengthen the tooth. While the participants who were intern dentists mostly preferred Ribbond as a fiber material, those who were newly graduated mostly preferred everX Posterior.

CONCLUSION

According to the results of the survey that was conducted in our study, the participants who were involved in doctoral or specialization studies have higher levels of awareness and knowledge regarding current treatment methods in comparison to those who were newly graduated or interns.

In our study, it was observed that posterior adhesive restorations such as endocrown and onlay restorations were preferred more frequently due to the education system in the university environment where each department specialized in its own field, and conservative treatments were preferred, as well as the broad opportunities available to students and practitioners. The newly graduated participants preferred post and core crown restorations more frequently. It is thought that newly graduated dentists and intern dentists will also adopt current treatment approaches such as endocrown and onlay restorations when their participation in training programs, conferences, and seminars focused on current treatments increases. The participants in the group with high awareness levels regarding current treatments in this study were found to prefer using fiber materials. The information in the relevant literature shows that the use of both types of fiber material provides successful outcomes. As a limitation of this study, because the number of dentists who were interns or newly graduated dentists was higher than the number of those who were involved in doctoral or specialization studies, the participants mostly consisted of newly graduated and intern dentists.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Medipol University Non-Invasive Clinical Studies Ethics Committee (Date: 10.08.2022, Decision No: 697).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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Does adolescent pregnancy affect postmenopausal bone mineral density?

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ABSTRACT

Aim: This study aims to investigate the effect of adolescent pregnancies on bone mineral density in the postmenopausal period and to contribute to this controversial issue.

Material and Method: Our study included 70 women at postmenopausal ages. The participants were divided into two groups. Thirty-five women with a history of pregnancy in adolescence were considered group 1, and 35 women without a history of pregnancy were considered group 2. The BMD was measured in the total hip, femoral neck, and lumbar spine. The data were compared using SPSS version 26, and $p<0.05$ was accepted as a statistical significance level.

Results: While there was a statistically significant difference between the femoral neck and total femur T scores measured in BMD in patients with and without a history of adolescent pregnancies, no statistically significant difference was found between the lumbar spine 1, 2, 3, 4 and total L1-L4 spines T scores.

Conclusion: There is no consensus in the literature on the effect of adolescent pregnancy on BMD and bone mass. The results of the studies differ from each other. Our study showed a statistically significant difference between the groups in the femoral T scores measured in BMD, but no difference was found between the lumbar T scores.

Keywords: Adolescent pregnancy, postmenopausal period, osteoporosis

INTRODUCTION

Adolescence is the life stage that begins at age ten and ends at age 19 (1). Adolescent pregnancy (AP) is a critical health problem. Adolescent pregnancies can lead to maternal and fetal complications such as low body mass, maternal anemia, hypertensive disorders, poor fetal growth and low birth weight of newborns worldwide (2).

In addition, there are studies stating that pregnancy and breastfeeding during adolescence may cause a decrease in postmenopausal bone mass (3). There is physiologically increased bone turnover and calcium release during pregnancy (4). Adolescent mothers may be at risk of irreversible bone loss during pregnancy and lactation, especially when calcium intake is low. However, it has been shown that this process can be stopped in pregnant women with calcium intake (5). Although the relationship between pregnancy and maternal bone mass has not been fully understood, it can be thought that, contrary to what is observed in menopause, there is an increase in bone mass due to increased osteoblastic activity during pregnancy (6). AP has a positive effect on peak bone mass. However, there are few research investigating the long-term effects of adolescent pregnancies on bone mass and quality, and their relationship has not been clarified.

Postmenopausal osteoporosis can cause osteoporotic fractures that cause severe mortality and morbidity worldwide (7). In our study, we studied the association between bone density in the postmenopausal period and AP.

MATERIAL AND METHOD

Our study was conducted at a tertiary public hospital, between December 2021 and December 2022. The study was initiated with the approval of the Adana City Training and Research Hospital Ethics Committee (Date: 15.12.2022, Decision No: 2319). All participants provided their written, informed permission. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Our study included 70 women of postmenopausal age who visited the Obstetrics and Gynecology Outpatient Clinic. The participants were separated into two groups. Thirty-five women with a history of pregnancy in adolescence were considered group 1, and 35 women without a history of pregnancy were considered group 2. Patients using drugs that may affect bone mass, such as chemotherapy, heparin, bisphosphonates and lithium, and patients with a history of diseases affecting bone mass, such as chronic kidney, thyroid and parathyroid diseases and cancer, were excluded from the study.

The demographic data, body mass index (BMI), medical history, age of first menstruation, first delivery age, age of menopause, gravidity, parity, levels of serum 25-OH vitamin D and bone mineral densitometry (BMD) (in grams per square centimeter) scores were also recorded.

Using dual-energy x-ray absorptiometry, the BMD was evaluated at central skeletal locations (total hip, femoral neck, and lumbar spine) (DEXA). DEXA scans were conducted utilizing a Lunar Prodigy (GE Healthcare®) device.

The Shapiro-Wilk test was utilized to determine whether or not the continuous data followed a normal distribution. Continuous variables were summarized as mean±standard deviation when it provided the assumption of normal distribution and as median [25%-75%] if it did not. As numbers and percentages, categorical variables were summed up. The Mann-Whitney U test was used when the assumption of normality was not met in the comparison of two independent groups. When available, the Independent Sample t-test was utilized. Utilizing the Chi-square test, the connection between two category variables was examined. A binary ratio comparison was made for the significant relationship. When the expected frequency was less than 5, the Fisher-Exact test was utilized, and a p-value of 0.05 was considered statistically significant.

RESULTS

Thirty-five of the 70 postmenopausal patients included in the study had a history of AP, while the remaining 35 did not. **Table 1** summarizes the sociodemographic and obstetric features of the participants. The mean age (mean ±SD) of patients with a history of AP was 63,51±8,56 years, and the mean age (mean ±SD) of patients without a history of AP was 59±8,23 years. Patients with a history of AP had a mean body mass index (BMI) of 30.34±6.08 kg/m², and those without a history of AP had a mean BMI of 31.35±6.25 kg/m² respectively. Patients having a history of AP and those without a history of AP had median parities of 5 [4-6] and 3 [1-5], respectively. The median [25%-75%] gravida of patients with a history of AP and without a history of AP were 5 [4-6] and 3 [1-5], respectively. The median [25%-75%] age of first menstruation of patients with a history of AP was 13 [13-13] years, and the median [25%-75%] age of first menstruation of patients without a history of AP was 13 [11-17] years. The median [25%-75%] age of onset of menopause of patients with a history of AP was 50 [48-51] years, and the median [25%-75%] age of onset of menopause of patients without a history of AP was 48 [45-65] years. The median [25%-75%] first delivery age of patients with a history of AP was 23 [20-36] years, and the median [25%-75%] first delivery age of patients without a history of AP was 17 [16-18] years. There was no statistical difference between the groups in terms of demographic data such as age, BMI, age at first menstruation and age of onset of menopause. In contrast, education level, parity, gravida and first delivery age values showed statistically significant differences.

Table 1: The Sociodemographic and obstetric characteristics of the study participants

	With history of adolescent pregnancy (n=35)	Without history of adolescent pregnancy (n=35)	P
Maternal age (years) (mean ±SD)	63.51±8.56	59±8.23	0.028
Body mass index (kg/m²) (mean ±SD)	30.34±6.08	31.35±6.25	0.497
Education level (%)			<0.05
Illiterate	18 (51.5%)	6 (17.1%)	
Primary school	12 (34.3%)	14 (40%)	
High school	3 (8.6%)	5 (14.3%)	
University	2 (5.7%)	10 (28.6%)	
Gravida (median [25%-75%])	5 [4-6]	3 [1-5]	<0.001
Parity (median [25%-75%])	5 [4-6]	3 [1-5]	<0.001
Age of first menstruation (years) (median [25%-75%])	13 [13-13]	13 [11-17]	0.775
Age of onset of menopause (years) (median [25%-75%])	50 [48-51]	48 [45-65]	0.200
First delivery age (years) (median [25%-75%])	23 [20-36]	17 [16-18]	<0.001

A statistically significant difference was found between the femoral neck and total femoral T scores measured in BMD in patients with and without a history of AP (p=0.033, p=0.006, respectively). In addition, there was no statistically significant difference between the two groups lumbar spine 1, 2, 3, 4 and total L1-L4 spines T scores (p=0.489, p=0.210, p=0.499, p=0.518, and p=0.324, respectively) (**Table 2**.).

Table 2: BMD scan T-scores and serum vitamin D levels of women during postmenopausal period.

	With history of adolescent pregnancy (n=35)	Without history of adolescent pregnancy (n=35)	P
Lumbar spine 1 (mean±std)	-1.73±1.62	-1.49±1.19	0.489
Lumbar spine 2 (mean±std)	-2.12±1.83	-1.64±1.15	0.210
Lumbar spine 3 (median [25%-75%])	-1.4 [-3.1- -0.65]	-1.75 [2.42- -0.75]	0.499
Lumbar spine 4 (mean±std)	-1.7±1,75	-1.46±1,08	0.518
Lumbar spine 1-4 (median [25%-75%])	-2 [-3.1- -0.8]	-1.8 [-4.4-2]	0.324
Femoral neck (mean±std)	-1,71±1,08	-1,20±0,87	0.033
Total femoral (mean±std)	-1,39±1,11	-0,67±0,95	0.006
Vitamin D (ng/ml) (median [25%-75%])	15.3 [10.3-23.4]	20 [2.9-58]	0.318

DISCUSSION

The effect of pregnancy on bone mass is also unclear in the literature. While some studies report an insignificant loss of BMD during pregnancy (8,9), some studies report a 2-9% loss during pregnancy (10,11). However, another study noted that pregnancy-related changes in bone mass might be reversible (12). In both developed and developing nations, adolescent pregnancies pose a significant public health burden (13). Also, the effect of AP stories on bone mass is still controversial. Our objective is to investigate the association between bone density in the postmenopausal period and AP, gravida, parity, first delivery age, and multiple births and contribute to this controversial topic. Adolescence is a critical period in which about half of peak bone mass is achieved (14). Due to physiological adaptations designed to ensure adequate mineral transfer to the developing fetus and impending lactation, the bone mineral status is significantly altered during pregnancy (15). In a study examining the effect of parity on BMD after menopause, birth and breastfeeding were found to not influence bone density (16).

Numerous studies have demonstrated that AP has either positive or negative effects on BMD (4,6,17,18). One study suggested that AP may affect the physiological processes of bone metabolism and therefore adversely affect peak bone mass (16). Lloyd et al. (6) found that a history of AP had a modest negative effect on femoral bone mass but had no effect on whole-body bone mass. In another investigation, no statistically significant differences were detected when patients with and without AP were compared in terms of lumbar and femoral bone density. It was revealed that patients who gave birth twice throughout puberty had a 6.8-fold increased incidence of osteoporosis (3). In another study conducted in AP, there was no difference in bone mineral densities of the lumbar region. At the same time, there was a difference in bone mineral densities of the femoral neck. In our investigation, there was a statistically significant difference in favour of those with a history of AP between the femoral neck and total femoral T scores evaluated by BMD. In addition, the lumbar spine 1, 2, 3, 4 and total L1-L4 spine T scores did not differ substantially across groups.

Endocrine Society classifies serum 25(OH)D serum levels into three categories: 20 ng/ml indicates a deficiency, 20-29.9 ng/ml indicates insufficiency, and 30 ng/ml indicates appropriate levels (19). Vitamin D deficiency is common among postmenopausal women (20). In a study by Öcal et al. (21), which included pregnant women in the adolescent period, 25(OH)D serum levels were found to be sufficient in only 2% of the patients participating in the study. We did not find a statistically significant difference between the groups' 25(OH)D levels. The median values of both groups were below adequate levels at 15.3 and 20 ng/ml, respectively.

Osteoporosis is a multifactorial disease. Our study is a retrospective clinical study and does not have a study design that can establish a cause-effect relationship. It should be taken into account that other factors may impact postmenopausal BMD levels, such as the nutritional habits, sociocultural level, geographical location, and genetic heritage of the woman, as well as yet unknown. Other limitations of our study are that it is single-centre and the number of patients is relatively low.

CONCLUSION

There is no consensus in the literature on the effect of AP on BMD and bone mass. The fact that the results of the studies differed from each other suggests that the samples of these studies may have resulted from different patient populations and control groups. In our study, there was a statistically significant difference in femoral T scores determined by BMD but no difference in lumbar T scores.

There is no financial backing for the research, and the writers have no vested interests in the subject matter.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Adana City Training and Research Hospital Ethics Committee (Date: 15.12.2022, Decision No: 118/2319).

Informed Consent: All participants provided their written, informed permission.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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A quality analysis of robotic-assisted knee replacement surgery videos on Youtube

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ABSTRACT

Aim: Robotic technology has been used to decrease soft tissue dissection and improve postoperative rehabilitation in several areas and robotic-assisted knee replacement has gained popularity last decades. Youtube has an uncontrolled source, making it difficult to verify the correctness of its process. It is critical to assess what they include. This study aimed to assess the quality of the YouTube video content related to robotic-assisted knee replacement surgeries

Material and Method: We conducted a search on YouTube using the keywords "robotic-assisted knee replacement". The headings of the first 50 videos on YouTube were obtained and simultaneously evaluated by two orthopedic surgeons.. We analyzed the general features and categorized videos according to content. The videos were evaluated by using the DISCERN and JAMA scores.

Results: 37 videos were included. Twenty-three videos contained total knee replacement surgery while fourteen consisted of unicondylar prosthesis system. The content of the videos included 51.4% (n=19) interviews, 16.2% (n=6) live surgery, 13.5% (n=5) patient testimonials, 8.1% (n=3) animation and presentation-lesson, and 2.7% (n=1) model81.1% of the videos were uploaded by hospital accounts. These were followed by health channels (8.1%), firms (5.4%), doctors (2.7%), and patients (2.7%) the average DISCERN score was 40.1±9.4 and the average JAMA score was 2.2±1

Conclusion: The quality of the information in videos on robotic-assisted knee replacement surgery is poor, YouTube is not currently an appropriate source of such information for patients and there appears to be a disproportionate amount of information focusing on robotic-assisted knee replacement surgery.

Keywords: Internet, YouTube, knee, replacement, robotic

INTRODUCTION

Robotic technology has been used to decrease soft tissue dissection and improve postoperative rehabilitation in several areas including, general surgery, cardiology, obstetrics and gynecology, and ophthalmology (1). Over the last decade, robotic-assisted knee replacement has gained popularity for improving templating for preoperative planning, more accuracy in implant positioning, and precision in the execution of the bone cuts during the procedure (2,3).

YouTube is an easily accessible, publically accessible video-based platform serving as a major source of various topics including medical information for both patients and health cares presently. These developments in internet technology illustrate the concept of the 'YouTube generation', with numerous advantages of information sharing and challenges in assuring the quality of the shared videos (4-7). On the other hand, it is an uncontrolled non-peer-reviewed source, making it difficult to verify the correctness of its process. It is critical to assess what they include.

While considering this need, we designed this study and aimed to assess the quality of the YouTube video content related to robotic-assisted knee replacement surgeries.

MATERIAL AND METHOD

Our study was exempted from the ethical review board by our institution, as there was no human or animal participation in the study and the information used is juridically available for the public. The study according to the World Medical Association Declaration of Helsinki, as no patient data or materials were used and all videos used for the study are available on a public

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social media website (YouTube). A YouTube search using the keywords " robotic-assisted knee replacement surgery" was performed on 13 May 2021. Analysis was restricted to the viewed videos more than 10.000 count. Videos were recorded by date of upload, length, number of views, comments, likes and dislikes. Videos were categorized by type of prothesis (total or unicondylar), content (interview, animation, live surgery, patient testimonial, model and presentation-lesson) and upload sources (doctor, hospital, health channel, firm, patient). Non-audio and non- English-language presentations were excluded.

Video reliability was scored by two orthopedic surgeons simultaneously using the Journal of the American Medical Association (JAMA) and Quality Criteria for Consumer Health Information (DISCERN) criterias. The mean scores of JAMA and DISCERN systems were calculated from each scores of surgeons. The data distributions were checked with the Kolmogorov-Smirnov normality test. Continuous variables were reported by the mean and standard deviation (SD). The differences were compared using the independent-samples t-test for normally distributed data and the Mann-Whitney U test for the nonnormally distributed data. Categorical data were represented as numbers and percentages (%). Categorical variables were analyzed with Fisher's exact test and the chi-square test was used to detect differences. Interobserver correlations were calculated with the intraclass correlation coefficient (ICC) (8). An ICC value < 0.40 indicates poor agreement, 0.40–0.59 indicates fair agreement, 0.60–0.75 indicates good agreement, and above 0.75 indicates excellent agreement (9). $p < 0,05$ considered to be statistically significant results. Statistical analysis was performed using SPSS version 25.0 (SPSS Inc, Chicago, IL).

Quality Assessment

Each video with a recorded title was viewed by two orthopaedic surgeons, and evaluated with DISCERN (Quality Criteria for Consumer Health Information) and JAMA (Journal of the American Medical Association) scoring systems.

DISCERN Scoring System

The DISCERN tool was used to analyze quality of the videos on YouTube. The DISCERN scoring system was formed by the Oxford University and British Library employees, and used by healthcare consumers. The DISCERN score includes 15 questions about the content of health information. Users assess the content with a 5-point scale, and total scores differs between 15-75 points. Questions in DISCERN are divided into two sections. The first section (1-8 questions) addresses reliability of the publication, while the second section (9-15 questions) focuses quality of the information about treatment options. DISCERN scores between 63 and 75 points were classified as 'excellent', 51 and 62 as 'good', 39 and 50 as average, 28 and 38 as 'poor', and < 28 as very poor. Higher scores obtained from the scale indicated higher quality of information (10) (**Table 1**).

Table 1. DISCERN scoring system

Section	Questions	No	Partly	Yes
Reliability of the publication				
	1. Explicit aims	1	2 3 4	5
	2. Aims achieved	1	2 3 4	5
	3. Relevance to patients	1	2 3 4	5
	4. Source of information	1	2 3 4	5
	5. Currency (date) of information	1	2 3 4	5
	6. Bias and balance	1	2 3 4	5
	7. Additional sources of information	1	2 3 4	5
	8. Reference to areas of uncertainty	1	2 3 4	5
Quality of information on treatment choices				
	9. How treatment works	1	2 3 4	5
	10. Benefits of treatment	1	2 3 4	5
	11. Risks of treatment	1	2 3 4	5
	12. No treatment options	1	2 3 4	5
	13. Quality of life	1	2 3 4	5
	14. Other treatment options	1	2 3 4	5
	15. Shared decision making	1	2 3 4	5

JAMA Scoring System

This system is a quality scale used for evaluation of information obtained from the healthrelated internet sites. It consists of 4 criteria of "Authorship, Attribution, Disclosure, Currency". Each item is evaluated with 0 (does not meet the desired criteria) or 1 point (meets the desired criteria). The minimum score that can be obtained from these scale is 0 and maximum score is 4 points. Higher scores obtained from the scale shows increased quality of the information, which is assessed (11) (**Table 2**).

Table 2. JAMA scoring system

Section	Questions	No	Yes
Authorship	Authors and contributors, their affiliations, and relevant credentials should be provided	0	1
Attribution	References and sources for all content should be listed clearly, and all relevant copyright information should be noted	0	1
Disclosure	Website "ownership" should be prominently and fully disclosed, as should any sponsorship, advertising, underwriting, commercial funding arrangements or support, or potential conflicts of interest	0	1
Currency	Dates when content was posted and updated should be indicated	0	1

RESULTS

Among the 51 videos assessed, 37 were included. Twenty-three videos contained total knee replacement surgery while fourteen consisted of unicondylar prosthesis system. The mean duration per video was 602±1027 seconds. The mean view count per video was 47.483±44.449. The total view count was 1.756.855. The median number of likes per video was 72 (0-386).

The content of the videos included 51.4% (n=19) interview, 16.2% (n=6) live surgery, 13.5% (n=5) patient testimonial, 8.1% (n=3) animation and presentation-lesson, and 2.7% (n=1) model. The distribution of video contents according to the type of prosthesis were shown in **Table 3**. Although "Live surgery" video contents were more preferred for unicondylar systems than total knee systems, we found no statistically significant difference (p=0.11) while we did not see any "model" and "presentation- lesson" contents in unicondylar system videos.

Table 3. Distribution of video content according to prosthesis type

Category of video content	Prosthesis Type	
	Total n (%)	Unicondylar n (%)
Interview	13 (56.5)	6 (42.9)
Animation	1 (4.3)	2 (14.3)
Live surgery	2 (8.7)	4 (28.6)
Patient testimonial	3 (13)	2 (14.3)
Model	1 (4.3)	0 (0)
Presentation-Lesson	3 (13)	0 (0)

81.1% of the videos were uploaded by hospital accounts. These were followed by health channels (8.1%), firms (5.4%), doctors (2.7%), and patients (2.7%). The distribution of video sources according to the type of prosthesis were shown in **Table 4**. The rate of video sources between two systems were similar. There was no total knee prosthesis videos were uploaded by doctors and patients.

Table 4. Relationship between source of videos according and prosthesis type

Upload Source	Prosthesis Type	
	Total n (%)	Unicondylar n (%)
Doctor	0 (0)	1 (7.1)
Hospital	20 (87)	10 (71.4)
Health channel	2 (8.7)	1 (7.1)
Firm	1 (4.3)	1 (7.1)
Patient	0 (0)	1 (7.1)

The average DISCERN score analysed by the two viewers was 39.4±9.3 and 40.7±9.5 respectively. The average JAMA score of the videos analysed by the two viewers was 1.9±1 and 2.5±1, respectively. Hence, the average DISCERN score was 40.1±9.4 and average JAMA score was 2.2±1. When the DISCERN scores of both viewers were analysed using the Spearman test, we found a strong correlation 0.974. In addition, the JAMA scores of the two viewers using the Spearman test were determine to have a strong correlation 0.803. After analysing the average DISCERN scores of the two viewers, we found that the quality of the videos was very poor in 2.7%, poor in 51.4%, average in 32.4%, good in 5.4% and excellent in 8.1% of the videos contributed to our study.

In the videos with total knee group, the average DISCERN score was 41.5, while the average DISCERN score of videos with unicondylar knee group was 37.7. However there was no statistical difference between the groups (p=0.25). However, the two groups' assessment of JAMA scores were found to be statistically significant (p=0.02).

We compared the DISCERN and JAMA scores of the videos between the hospital and other groups. In terms of DISCERN and JAMA scores, we found insignificant differences between these various groups (p=0.72 and p=0.63, respectively).

"Interview" was the largest subgroup of videos in terms of the content, we compared DISCERN and JAMA scores assessments between the interview videos and others. The average DISCERN scores of the interview videos were lower than those of the others without statistical differences (38.2 vs 42, p=0.21). In addtion that, the average JAMA scores also did not show any significant difference between the interview videos and the others (p=0.9).

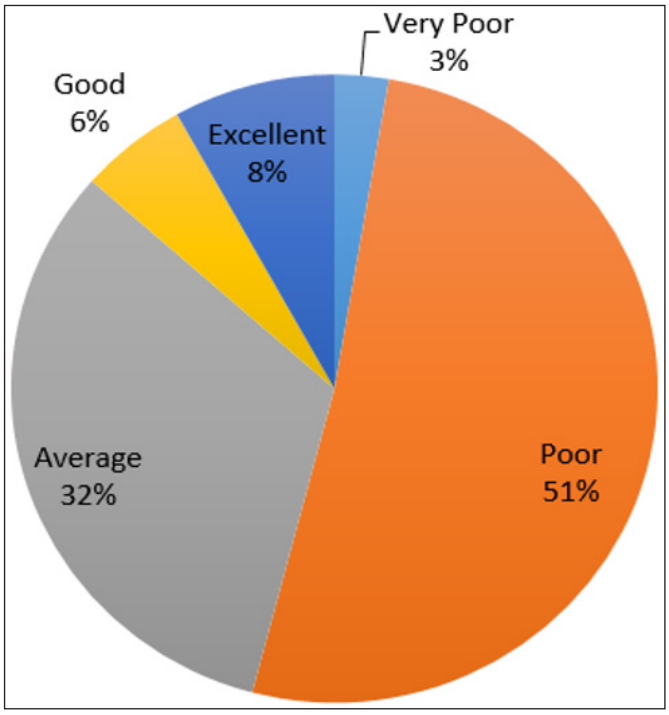

Figure 1. Summary of assessment scores for videos regarding robotic-assisted knee replacement videos

DISCUSSION

This study showed that the quality and reliability of robotic-assisted knee replacement-related information offered on YouTube is low. Approximately 4.5% of all searches on the web include health topics. Health-related queries are performed 6.75 million per day in Google alone (12). On the other hand, most of them are uploaded by nonphysicians and/or institutions. Among these shares, patient testimonials, advertisements, and alternative treatment options become more important. majority of these videos contain misleading and even faulty information. An appropriate video must give accurate information on reasons, treatments, and procedures to viewers, while a video will be misleading if it contains inappropriate information or suggests treatments that have not been proven by competent sources.

Physicians are increasingly being affected by the rapid growth of video-based information. This fact has a negative impact on the patient-physician relationship, and 38% of physicians thought that the patient bringing information decreased the visit efficiency (13). This might be related to the poor educational quality of online videos. In by Koller et al. (14), conducted an analysis of 133 YouTube videos regarding hip arthritis and showed that 84-86% of the videos had poor quality concerning diagnostic or treatment information. Only 2-4% of the videos' quality was excellent. MacLeod et al. (15) evaluated the information quality of 52 femoroacetabular impingement videos and reported that 19.2% of their videos were not useful. In another study, Wong et al. (16) assessed the quality of YouTube videos pertaining to total knee arthroplasty (TKA) and knee osteoarthritis and 64% of videos were of poor educational quality regarding TKA. In our study, 13.5% of the videos regarding robotic-assisted knee replacements were deemed to be of good and excellent quality, with 54.1% of the videos being very poor and poor, 32.4% being of average quality. This study suggests that the majority of videos related to robotic-assisted knee replacements are of poor educational quality. Looking at previous literature, it shows that the lack of high educational quality spreads to other orthopedic topics as well.

In our study, we investigated the quality, and reliability of the videos about robotic-assisted knee replacement surgery on YouTube. In the literature, this study is the first, to investigate this topic. Consistent with the literature, most of the videos were shared by non-physicians (17). Of the 37 videos, 97.3 % were uploaded by non-physicians with 81.1% shared hospital accounts, 8.1% by health channels, 5.4% by firms, and 2.7% by patients. The majority of videos uploaded by non-physicians are not specific to our study, and in the literature review, a considerable part of health-related YouTube videos include anecdotal information and patient experiences. However, in our study, most of the videos shared by hospitals contained interviews with doctors. This difference is due to robotic systems being special and very expensive devices and it is difficult to access them easily. Since hospitals try to put forward their valuable property and they prefer to represent it by interviewing doctors.

The relationship between video characteristics that view, comment, "like" and "dislikes" counts, and educational quality has been previously conducted. There have been different wide-ranging results. MacLeod et al. (15) reported that there was no difference between educational quality and video characteristics. However, Stauton et al. (18) conducted 50 videos regarding scoliosis and reported that high-educational quality videos were related to a lower number of views. They thought that higher quality information may be less "interesting" or "readable" and may reduce popularity. This was also supported by Jones et al. (19) who analyzed Dupuytren's disease videos and found that videos deemed "useful for patients" had the least number of mean views. Additionally, these findings were shown in our study also but we did not detect any statistical differences. It might be because of the small sample size. The total number of views might affect the score of videos regarding robotic-assisted knee replacement videos. We thought that it may be more difficult to represent higher quality information in an attractive or "readable" way, which would therefore directly impact the popularity.

In this study, the mean length of the videos was approximately 10 minutes. Previous studies have shown the mean video length between 6.17-10.35 minutes (20,21). Our results were consistent with the literature.

The current study quantified that the mean number of views was 47,483 and that, collectively, all videos at the time of the analysis had been watched a total of 1.756.855 times. This is compatible with other studies that have sought to analyze the quality and popularity of orthopedic-related YouTube videos. Kunze et al. (22) reported that the mean number of views of the first 50 YouTube videos regarding the posterior cruciate ligament was 50,477 and that the total viewing number was 14,141,285. Staunton et al.(18) found that the mean number of views of the first 50 videos concerning scoliosis was 71,152. Other orthopedic-based YouTube analyses have represented lower mean video-viewing rates as low as 2,651.513 and 34,037 views per video,6 further supporting the idea that robotic-assisted knee replacement is a topic that has a wide range of viewership.

In our study, there was a negative correlation between DISCERN and JAMA scores and like count. These results showed that high-quality videos are not as popular as

low-quality videos. Furthermore, various studies in the literature have reported that low-quality videos are more popular (23-25).

The exclusion and inclusion criteria of the videos and the number of videos included in our study were in accordance with other studies (18,26). Because the aim of our cross-sectional study was to develop an instant search model by seeking the information obtained from the patient's perspective, instead of evaluating all the information about disc herniation on YouTube.

Limitations of this study include a DISCERNE AND JAMA score based on a subjective assessment. In addition, changes in the keywords used to result in the retrieval of different videos would affect the results. Another limitation was the conclusion that different results could be obtained when searches were performed at different times, and alternative evaluation methods could provide different results. Therefore, in our study, we included videos that were found as a result of the search performed on the same day and at the same time for both researchers. The videos analyzed only first 50 videos generated by the search query. Although this limits the generalizability of the findings to all robotic-assisted knee replacement videos currently available on YouTube, viewers rarely explore more than the first few pages of a search for information (27). Finally, different results would be obtained with different sorting schemes, and the video sequence retrieved depended on YouTube's interpretation of our keywords.

CONCLUSION

Our study contributes to a better understanding of the available information about robotic-assisted knee replacement surgery, which is widely viewed on YouTube. The results suggest that the quality of the information in videos on robotic-assisted knee replacement surgery is poor, YouTube is not currently an appropriate source of such information for patients and there appears to be a disproportionate amount of information focusing on robotic-assisted knee replacement surgery. The medical community can improve online patient education by focusing on the topics discussed in these videos. Physicians should be aware of the limitations of YouTube and provide up-to-date and peer-reviewed content.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study has a crosssectional design. Ethics committee approval was not obtained as there was no human or animal participation in the study, and the videos were public. The study according to the World Medical Association Declaration of Helsinki, as no patient data or materials were used and all videos used for the study are available on a public social media website (YouTube).

Informed Consent: Since there was no human or animal participation in the study, and the videos were public, need informed not required.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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Short-term effects of horizontal muscle operations on anterior and posterior segment parameters in strabismus patients

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ABSTRACT

Aim: To evaluate the short-term effects of horizontal muscle resection (Rt) or recession (Rs) surgeries on anterior and posterior segment parameters (ASPs and PSPs) in strabismus patients, using Pentacam HR and optical coherence tomography (OCT) devices.

Material and Method: This prospective study included 21 female and 17 male patients who underwent horizontal muscle surgery (Rt or Rs). ASPs were evaluated with Pentacam HR and PSPs were evaluated with OCT, one day before and one month after surgery.

Results: The mean age of all the patients included in the study was 16.52±7.90 years. Rt surgery was performed on 18 patients and Rs surgery on 20 patients. When the pre- and postoperative measurement values of all patients were compared, statistically significant differences were found in respect of iridocorneal angle (ICA) 90° and anterior chamber depth (ACD) in both the Rt and Rs groups. A significant narrowing was detected in ICA 90° and ACD in Rt patients ($p<0.01$), and significant enlargement was detected in Rs patients ($p<0.01$).

Conclusion: While ACD and ICA 90° may be affected in the short term following Rt and Rs surgeries, no significant changes were seen in the other ASPs and PSPs.

Keywords: Anterior chamber depth, anterior segment parameters, iridocorneal angle, optical coherence tomography, Pentacam HR

INTRODUCTION

Strabismus surgery is currently a frequently applied intervention, especially in pediatric patients. It has been reported that changes occur in anterior and posterior segment parameters (ASPs and PSPs) after strabismus surgeries performed due to ocular or extraocular disorders (1-5). Previous studies have discussed the changes in the anterior segment, especially in the cornea, iris and lens, and it has been concluded that these changes are mostly temporary. (6-8) However, there are also publications reporting that they can be long-term (up to 1 year) or permanent (3, 9, 10). In studies on the posterior segment, changes in the parameters of central retinal thickness (RT), subfoveal choroidal thickness (CT), and retinal nerve fiber layer (RNFL) are predominant (1, 5).

Pentacam® HR (Oculus Inc, Berlin, Germany) is a high-resolution rotating Scheimpflug camera system for anterior segment analysis. It provides clear visualization of the cornea, iris and lens, and measures anteroposterior corneal topography and elevation, corneal refractive power, 360° iridocorneal angle (ICA), anterior chamber depth (ACD), the cornea, and lens optic opacities (11-13). Although it is used especially in the diagnosis and follow-up of corneal diseases, there has been a recent increase in its use in glaucoma, cataract, and strabismus diseases (14-16).

Spectralis optical coherence tomography (OCT) (Heidelberg Engineering, Heidelberg, Germany) is a device widely used in ophthalmology clinics to view posterior segment structures, particularly the retina and choroid. OCT has recently gained importance in the treatment and follow-up of strabismus patients, as it provides valuable information. Especially the changes in ASPs before and after strabismus surgery have started to be a matter of interest in research (1, 5).

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The effect of strabismus surgery on corneal topography and refraction has been extensively studied. However, the number of articles examining the effect on PSPs is limited. Moreover, to the best of our knowledge, there is no study in the literature that has evaluated the effect of strabismus surgery on ASPs and PSPs together. The aim of this study was to determine the effect on ASPs and PSPs of both resection (Rt) or recession (Rs) surgery applied to horizontal muscles through evaluations made using Pentacam HR and Spectralis OCT devices

MATERIAL AND METHOD

This study was conducted in the Ophthalmology Department of Bolu Abant İzzet Baysal University Faculty of Medicine. The study was carried out with the permission of Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee (Date: 22.03.2022, Decision No: 131) and all procedures complied with the tenets of the Helsinki Declaration. Written informed consent was obtained from all patients and/or their parents.

This prospective study included a total of 38 patients, comprising 21 females and 17 males. One day before the operation and one month after the operation, the ASPs, and PSPs of the patients were evaluated with the Pentacam HR (**Figure**) and OCT devices. ACD, central corneal thickness (CCT), anterior and posterior radius of curvature (ARC and PRC), ICA 90° and 180° measurements were automatically calculated and presented as numerical values using Pentacam HR (Figure). The RT and RNFL measurement values were calculated automatically on the the OCT device. The CT measurements were taken manually.

Patients were excluded from the study if the data were insufficient or unreliable, if they did not attend follow-up appointments regularly (n:2), or if the quality of measurements taken with the Pentacam HR or OCT devices was <8/10 (n:3). Patients with secondary strabismus due to any pathological reason, those with eye pathologies other than strabismus, or a history of recent eye surgery were also excluded from the study.

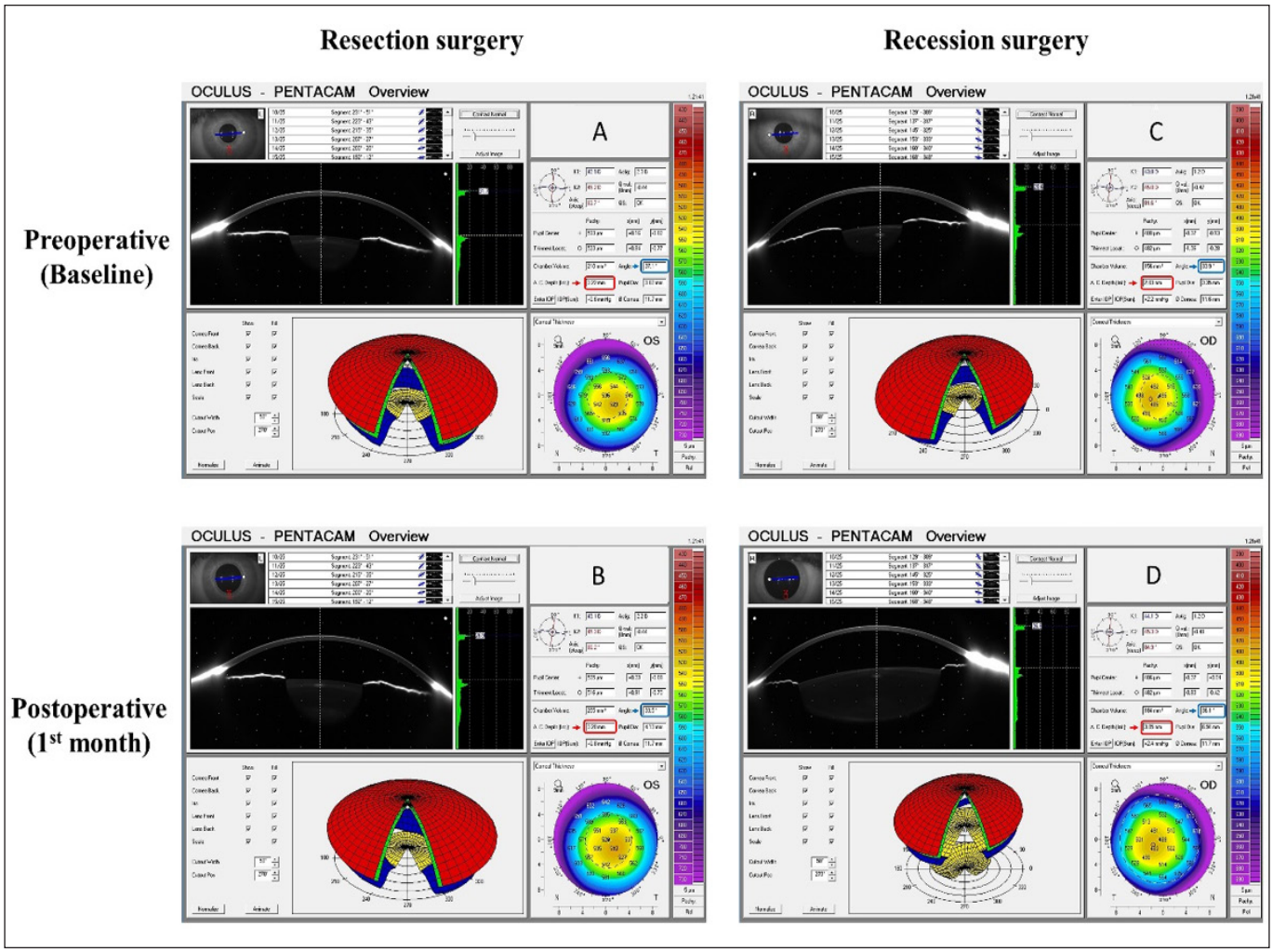

Figure 1. Pentacam HR measurements before and after strabismus surgery.
A-B: Preoperative and postoperative Pentacam HR measurements of a patient undergoing resection surgery. It is observed that there is a decrease in the postoperative ACD and ICA values (Colored arrows).
C-D: Preoperative and postoperative Pentacam HR measurements of another patient undergoing recession surgery. It is observed that there is an increase in the postoperative ACD and ICA values (Colored arrows).
ACD: Anterior Chamber Depth, ICA: Iridocorneal Angle.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS for Windows, vn. 25.0, software. Results were stated as mean±standard deviation (SD) values. The parameters were evaluated with the Paired Samples t-test if they met the assumptions of normal distribution with the one sample Kolmogorov Smirnov test, and homogeneity with the Kaiser-Meyer-Olkin test and Bartlett's Test of Sphericity. If the study data did not meet the parametric test assumptions, statistical evaluation was made using the Wilcoxon signed-rank test. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The mean age of the patients included in the study was 16.52±7.90 years (range, 8-30 years). All the patients were diagnosed with esotropia or exotropia, and interventional surgery was applied to the lateral or medial rectus. Rt surgery was performed on 18 patients and Rs surgery on 20 patients. Postoperative complications were not observed in any of the patients. All the patients received routine topical antibiotics and steroid therapy for approximately 2 weeks postoperatively.

Preoperative and postoperative measurements were taken of the 38 patients who underwent strabismus surgery, and calculations were made to determine whether the difference between the measurements was statistically significant (**Table**). In both the Rt and Rs patients, the differences between the preoperative and postoperative values of CCT, ARC, and PRC were not statistically significant (p range: 0.34-0.71). No statistically significant difference was determined between the Rt and Rs surgery groups in respect of the preoperative and postoperative measurements of ICA 180° (p=0.42, and p=0.66, respectively). The ICA 90° value showed a statistically significant difference from preoperative to postoperative in both Rt and Rs patients ($p<0.01$ and p=0.04, respectively). Mean 3.52±6.84° enlargement was observed in the ICA 90° value in patients who underwent Rs surgery, and mean 5.35±4.76° narrowing was observed in the Rt surgery group. The mean ACD values decreased by 0.08±0.07 mm in the Rt surgery patients ($p<0.01$) and increased by 0.04 ± 0.07 mm in the Rs surgery group (p=0.04); these values were statistically significant in both groups. No statistically significant difference was found between the preoperative and postoperative values of RT, CT, and RNFL measurements made with the OCT device in both the Rt and Rs patient groups (p range: 0.14-0.67).

DISCUSSION

The results of this study demonstrated that while ICA 90° and ACD can be affected in the short term after Rt and Rs surgeries, no significant change was observed in the other ASPs and PSPs. This suggests that the changes in ACD and ICA 90° after strabismus surgeries may have resulted from the mechanical effects caused by changes in the attachment points of the horizontal muscles to the sclera and postoperative wound inflammation. Although the cause of ASP and PSP changes after strabismus surgery is unclear, some of these changes are part of the wound healing mechanism in the re-insertion of the extraocular muscle on the sclera (17). In addition, changing the positions of the extraocular muscle insertions can modify the vector forces exerted on the cornea, resulting in changes in corneal curvature and astigmatic refractive errors (10, 18).

Emre et al. (6) examined changes in ASP in a total of 18 patients who underwent Rs and Rt plus Rs using Pentacam and found that the anterior chamber volume decreased statistically significantly in the Rt plus Rs group. Similarly, Jung et al. (7) evaluated the ASPs of patients who underwent Rs and Rt plus Rs with Pentacam and found that ACD significantly decreased in the Rs group and recovered 3 months after surgery. In another study, it was reported that patients showed statistically significant changes in refractive error, anterior chamber volume and ACD one week after surgery (19). In the present study, while ICA 90° and ACD values decreased postoperatively in Rt patients, they were determined to

Table 1. Measurement values of pre-and postoperative anterior and posterior segment findings with Pentacam HR and OCT devices

	Resection (n: 18)			Recession (n: 20)		
	Preoperative	Postoperative	P*	Preoperative	Postoperative	P*
ICA 90°	39.01±8.08	33.66±5.74	<0.01	36.86±7.58	40.38±10.30	0.04
ICA180°	39.49±7.54	38.42±9.57	0.42	3882±837	39.49±6.87	0.66
ACD (mm)	3.29±0.38	3.21±0.36	<0.01	3.08±0.17	3.12±0.18	0.04
CCT (μm)	534.44±36.61	535.28±34.93	0.64	549.37±43.43	548.68±41.79	0.71
ARC (mm)	7.58±0.34	7.57±0.35	0.59	7.69±0.32	7.64±0.28	0.55
PRC (mm)	6.02±0.36	6.04±0.37	0.47	5.86±0.64	6.01±0.47	0.34
Retinal thickness (μm)	227.22±13.61	227.89±13.13	0.60	221.39±14.44	228.61±22.17	0.14
Choroidal thickness (μm)	344.67±51.96	330.78±43.96	0.25	339.11±69.47	335.06±83.89	0.67
RNFL (μm)	96.94±8.39	96.56±8.52	0.64	102.42±7.46	101.53±6.98	0.20

* $p<0.05$ indicates a statistical significance, ACD: Anterior chamber depth, ARC: Anterior radius of curvature, CCT: Central corneal thickness, ICA: Iridocorneal angle, PRC: Posterior radius of curvature, RNFL: Retinal nerve fiber layer.

have increased in Rs patients. In contrast to Jung et al. (7), the current study results showed that the ACD was enlarged in the Rs group. In the Jung et al. (7) study, a Pentacam device was used and 28 exotropia patients with a mean age of 6.7 years (range: 4 to 13 years) were included in the study. In the current study, an advanced version Pentacam HR device was used, and 38 patients with exotropia or esotropia with a mean age of 16.5 years (range: 8-30 years) were evaluated. Therefore, the different results could be attributed to the differences in the number of patients included in the studies, average age, and diagnoses, and that different devices were used. It can be predicted that after Rs surgery, the muscle tension force from the sclera to the cornea will decrease, and therefore the ACD and ICA 90° values will increase, whereas after Rt surgery, it can be predicted that the muscle tension force from the sclera to the cornea will increase, and the ACD and ICA 90° values will decrease. In the current study, it was observed that there was a widening of the ICA 180° after Rs surgery and narrowing after Rt surgery, but these changes were statistically insignificant.

There are studies in literature in which ASPs have been evaluated after strabismus surgery, and there are also studies that have evaluated PSPs (1, 5, 20). Inan et al. (21) evaluated the CT values of four different groups that underwent Rs surgery with OCT and reported a decrease in the short term. Atalay et al. (1), compared the postoperative CT values of patients who underwent rectus recession or resection (Group 1) with those who underwent oblique muscle myectomy (Group 2) and found that CT increased in Group 1. In a study in which RT and RNFL were evaluated after strabismus surgery, an increase was found in RNFL, but no significant change was found in CT (5). Likewise, in another study in which RT was evaluated on the first day after strabismus surgery, no significant difference was found between pre and postoperative values (20). In the current study, no statistically significant difference was determined between the pre and postoperative CT, RT, and RNFL values of both Rt and Rs patients. It seems that the inclusion of different numbers of patients and groups in the studies, the different interventions made to extraocular muscles, and the use of different devices may lead to different findings. Changes in mechanical forces transmitted through the sclera caused by the changed position of the extraocular muscles or postoperative inflammation and changes in the blood-retinal barrier may partially explain these findings. However, it is difficult to state an exact reason for these different findings.

The major limitations of this study were the relatively low number of patients and short study period. Patients with secondary strabismus and patients who had strabismus surgery other than the medial and lateral rectus muscles were excluded from the study. As only postoperative first month measurements were made and the long-term results were not evaluated, this decreased the impact of the study. However, despite all these limitations, it is important that significant results were obtained. To the best of our knowledge, this is the first study in the literature to have compared the pre-and postoperative values of ASPs and PSPs together after Rt or Rs surgery using Pentacam HR and OCT in patients with strabismus.

CONCLUSION

In conclusion, it should be known that there may be narrowing in the ACD and ICA after Rt surgery, and there may be enlargement after Rs surgery. Especially in patients with amblyopia or glaucoma, the changes in these parameters should be known before the surgery and the patients should be followed up accordingly after the surgery. For better documentation of the changes in ASPs and PSPs, there is a need for further studies with larger groups and longer follow-up periods.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee (Date: 22.03.2022, Decision No: 131).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article

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Comparison of I-Gel insertion conditions with two different induction methods in children: a prospective observational study

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ABSTRACT

Aim: Insufficient depth of anesthesia is one of the important causes of laryngospasm in pediatric patients undergoing surgery. Propofol is a widely used anesthetic agent for induction of anesthesia in children. Its use alone in induction may be insufficient to suppress laryngeal reflexes during laryngeal mask insertion and may lead to complications such as cough, hiccups, and laryngospasm. In this study, the effects of fentanyl-ketamine mixture and remifentanil used as co-induction in anesthesia induction in children on I-gel insertion conditions and hemodynamic stability were compared. In addition, the evaluation of propofol injection pain after the use of coinduction agent was made.

Material and Method: The study included 60 patients aged 2-10 years, of ASA I-III class, who underwent ambulatory surgery. For anesthesia induction, the KF group (n:30) were administered intravenous (iv) 1 mcg/kg fentanyl + 0.5 mg/kg ketamine followed by 3 mg/kg propofol, and the R group (n:30) were administered iv 0.5 mcg/kg remifentanil followed by 3 mg propofol. The I-gel insertion conditions were evaluated by scoring the six variables of mouth opening, ease of insertion, swallowing, coughing, movement, and laryngospasm. Pain during propofol injection was graded using a four-point scale.

Results: No statistically significant difference was determined between the groups in terms of I-gel insertion conditions total score values ($p>0.05$). The pain of the propofol injection was determined at a significantly higher level in Group R ($p<0.05$).

Conclusion: Both induction methods were seen to be easy to apply and provide sufficient success in I-gel insertion. No laryngospasm was observed in either group. More effective relief of propofol injection pain in the fentanyl-ketamine group provided calmer and more stable induction conditions. In this respect, it may be preferable to use fentanyl and low-dose ketamine together as co-induction.

Keywords: Co-induction, ketamine, remifentanil, fentanyl, child

INTRODUCTION

The development of laryngospasm during general anesthesia is known to occur more often in children than adults. One of the important reasons leading to laryngospasm is insufficient depth of anesthesia. A recent study reported that insufficent anesthesia depth in induction increases the risk of laryngospasm development by 7.9-fold (1). Propofol is an anaesthetic agent widely used in the induction and maintenance of anesthesia in paediatric patients. When used alone, the recommended dose of propofol (3 mg/kg) for induction in children may not be sufficient to suppress laryngeal reflexes, and may therefore threaten airway safety by leading to complications such as cough, hiccups, and laryngospasm (2,3). Children require a higher dose of propofol than adults because of the greater distribution volume and higher cardiac flow (4). However, when a higher dose than recommended is used, it may cause hemodynamic instability (5). Recent studies have reported that several co-induction agents used before propofol provide a more stable condition during insertion of the laryngeal mask in the airway (6-8). Co-induction agents administered before propofol in induction may have the advantage of preserving hemodynamic stability by allowing the propofol dose to be reduced while providing sufficient depth of anesthesia. The aim of this study was to compare the hemodynamic data and symptoms by observing the laryngeal mask insertion procedure (I-Gel) and induction with a fentanyl-ketamine mixture

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or remifentanil used as co-induction before propofol, administered by anesthetists in the paediatric operating theatre. Evaluation was also made of the whether or not there was propofol injection pain following co-induction agent administered intravenously.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No: 2 Clinical Researches Ethics Committee (Date: 23.11.2022, Decision No: E2-22-2879). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent for participation in the study was provided by the parents or legal guardians of all the children. The study included 60 patients aged 2-10 years, of ASA I-III classification, who underwent elective surgery as a day patient. The study exclusion criteria were defined as respiratory tract infection within the last 4 weeks, the presence of airway anomaly, hyper-reactive airway disease, or suspected difficult airway. The patients underwent preoperative evaluation, and were admitted to the operating theatre 20 mins after the administration of premedication with 0.5 mg/kg oral midazolam in the premedication unit. A vascular route was opened in the right or left hand with a 24-gauge Intracath and crystalloid fluid was started at 5ml/hour. A 3-way valve was placed between the serum set and the Intracath and the anaesthetic drugs were administered through this 3-way valve. All the patients were monitored with electrocardiography (ECG), pulse oximetry, and non-invasive blood pressure measurements. For anesthesia induction, the KF group (n:30) were administered intravenous (iv) 1 mcg/kg fentanyl + 0.5 mg/kg ketamine (in the same injector) followed by 3 mg/kg propofol, and the R group (n:30) were administered iv 0.5 mcg/kg remifentanil followed by 3 mg propofol. For both groups, the drugs to be given before propofol were prepared as 10ml in a single injector and after slow push in 10 secs, propofol was also administered in 10 secs.

When the eyelash reflex was lost, the lungs were ventilated with 100% oxygen. At 60 secs after the propofol injection, the I-Gel insertion procedure was performed on all patients by an anesthetist of the same seniority. Effective ventilation was confirmed by chest wall movements and the observation of square wave capnograph tracing. In the maintenance of anesthesia, both groups were administered 40/60% oxygen/nitrous oxide together with 3% sevoflurane. The I-Gel insertion conditions were evaluated by scoring the six sub-variables of mouth opening, ease of insertion, swallowing, coughing/gagging, involuntary body movements, and laryngospasm. Pain during the injection was evaluated using the 4-point scale recommended by Cameron et al. (9). During induction, a record was made for each patient of the time to the loss of the eyelash reflex, the time to apnea, jaw slackness, degree of mouth opening, and the occurrence of laryngospasm, cough, swallowing, gagging, and involuntary body movements. Heartbeat rate (HR) and mean arterial pressure (MAP) were recorded for all patients before induction and at 1, 3, 5, and 10 mins after induction.

Statistical Analysis

Data obtained in the study were analyzed statistically using IBM SPSS vn. 25.0 software (IBM Corpn., Armonk, NY, USA). Descriptive statistical methods were used in evaluations with results stated as mean±standard deviation (SD), median, minimum, maximum, and interquartile range (IQR) values, or number (n) and percentage (%). In the comparisons of categorical data, the Chi-square (2) test was used. Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov and Shapiro-Wilk tests, skewness-kurtosis, and graphic methods (histogram, Q-Q Plot, Stem and Leaf, Boxplot). Quantitative data showing normal distribution were compared between the groups using the Independent Samples t-test, and for comparisons of groups of data not showing normal distribution, the Mann Whitney U-test was applied. It was determined necessary to have sample size of 20 patients per group to determine a difference within the group of at least 20% with the Paired Samples t-test (α=0.01, two-sided, power=90%). A value of $p<0.05$ was accepted as statistically significant.

RESULTS

In the comparisons between the groups, no statistically significant difference was determined in respect of age, gender, weight, and ASA values ($p>0.05$). The difference in the duration of anesthesia between the groups was determined to be statistically significant, with a shorter duration of anesthesia in the R group patients ($p<0.05$).

No statistically significant difference was determined between the groups in respect of the total scores of the I-Gel insertion conditions of the time to the loss of the eyelash reflex, the duration of apnea, jaw slackness, degree of mouth opening, the occurrence of laryngospasm, cough, swallowing, gagging, and involuntary body movements, and ease of I-Gel insertion ($p>0.05$). The difference between the groups in respect of propofol injection pain values was statistically significant, with greater levels of propofol injection pain felt in the R group patients ($p<0.05$).

No statistically significant difference was determined between the groups in respect of the HR and MAP values ($p>0.05$).

Table 1. Comparisons of the demographic data of the patient groups

	Group KF (n=30)	Group R (n=30)	P
Gender			0.531[a]
Female	5 (16.7%)	8 (26.7%)	
Male	25 (83.3%)	22 (73.3%)	
Age (years)	4.7±2.3	5.4±2.4	0.251[b]
Weight (kg)	21.1±9.0	21.0±8.3	0.953[b]
ASA classification			0.371[a]
I	26 (86.7%)	23 (76.7%)	
II	3 (10.0%)	3 (10.0%)	
III	1 (3.3%)	4 (13.3%)	
Surgical Intervention			--
Inguinal Hernia	14 (46.7%)	12 (40.0%)	
Hydrocele	4 (13.3%)	3 (10.0%)	
Orchiopexy	4 (13.3%)	2 (6.7%)	
Port Attachment	1 (3.3%)	5 (16.7%)	
Cystoscopy	2 (6.7%)	3 (10.0%)	
Bilateral Inguinal Hernia	2 (6.7%)	1 (3.3%)	
Excision	--	3 (10.0%)	
Epispadias	1 (3.3%)	--	
Hypospadias	1 (3.3%)	--	
Retrograde Intrarenal Surgery	--	1 (3.3%)	
Circumcision	1 (3.3%)	--	
Anesthesia duration (mins)	51.3±15.9	41.5±15.9	0.020[b]

a: Chi-Square Test (n (%)), b: Independent Samples t Test (Mean±SD), KF Group: Ketamine-fentanyl group, R Group: Remifentanil Group, ASA: American Society of Anesthesiologists

DISCUSSION

The results of this study demonstrated that there was no statistically significant difference between the two induction methods in respect of the I-Gel insertion conditions and ease of insertion. Generally, both methods provided sufficient ease of application and success in I-Gel insertion. Laryngospasm was not observed in any patient in either group. Moreover, the hemodynamic and respiratory data were found to be stable and similar before and throughout 10 mins after I-Gel insertion in both groups.

Effective and safe insertion of a laryngeal mask requires sufficient mouth opening and a sufficient depth of anesthesia. Traumatic laryngeal mask insertion can cause postoperative throat pain (2). In a study of adult patients by Güçlü et al. (11) it was reported that the addition of ketamine and remifentanil to propofol showed similar effects in respect of laryngeal mask insertion conditions, and these were both agents that could be selected in induction. Goh et al. (12) compared groups administered ketamine or fentanyl with a placebo group, and while both agents provided similar conditions in laryngeal mask insertion, they were found to be significantly superior to the placebo group. In a study of paediatric patients by Goel et al. (13) it was reported that a combination of ketamine or midazolam with propofol resulted in a lower dose of propofol required together with stable hemodynamics and appropriate laryngeal mask insertion conditions. The

Table 2. Comparisons of the I-Gel insertion conditions, time to loss of eyelash reflex, and time to halting of spontaneous respiration of the groups

	Group KF (n=30)	Group R (n=30)	P
Time to loss of eyelash reflex (secs)	22.2±18.4	25.6±24.8	0.545[a]
Time to halting of spontaneous respiration (secs)	28.8±23.1	28.5±25.7	0.962[a]
Jaw slackness			
Poor	--	1 (3.3%)	0.331[b]
Satisfactory	10 (33.3%)	6 (20.0%)	
Excellent	20 (66.7%)	23 (76.7%)	
Swallowing			
None	28 (93.3%)	27 (90.0%)	1.000[b]
Mild	2 (6.7%)	3 (10.0%)	
Cough/gagging			
None	29 (96.7%)	29 (96.7%)	1.000[b]
Mild	1 (3.3%)	1 (3.3%)	
Involuntary body movements			
None	14 (46.7%)	20 (66.7%)	0.278[b]
Mild	15 (50.0%)	9 (30.0%)	
Laryngospasm			1.000[b]
Severe	1 (3.3%)	1 (3.3%)	
None	30 (100.0%)	30 (100.0%)	
Mouth opening			1.000[b]
Full	28 (93.3%)	28 (93.3%)	
Partial	2 (6.7%)	2 (6.7%)	
I-Gel Insertion			0.536[b]
Easy	20 (66.7%)	21 (70.0%)	
Difficult	10 (33.3%)	8 (26.7%)	
Impossible	--	1 (3.3%)	
I-Gel insertion conditions total score	5.7±0.9	5.6±0.9	0.468[a]
Propofol Injection Pain	0.03±0.18	1.23±1.17	<0.001[a]
None	29 (96.7%)	12 (40.0%)	<0.001[b]
Mild	1 (3.3%)	4 (13.3%)	
Moderate	--	9 (30.0%)	
Severe	--	5 (16.7%)	

a: Independent Samples t Test (Mean±SD). b: Chi-Square Test (n (%)). KF Group: Ketamine-fentanyl group, R Group: Remifentanil Group,

Table 3: Comparisons of the hemodynamic data of the groups

	Group KF (n=30)	Group R (n=30)	P
Heartrate (beats per min)			
Basal	110.4±22.9	112.0±15.6	0.757[a]
After induction	93.4±19.5	99.2±17.9	0.240[a]
After LMA Placement	96.7±20.9	101.5±20.0	0.360[a]
1 min	94.5±18.9	97.7±19.3	0.519[a]
3 mins	96.1±18.1	98.0±18.9	0.703[a]
5 mins	98.0±17.3	100.1±19.0	0.656[a]
10 mins	98.4±16.5	102.2±18.4	0.407[a]
MAP (mmHg)			
Basal	80.4±10.2	83.7±13.0	0.289[a]
After induction	71.8±11.3	71.3±15.5	0.902[a]
After LMA Placement	70.0±11.2	68.5±12.9	0.633[a]
1 min	65.3±10.2	64.3±9.4	0.703[a]
3 mins	63.0±7.8	62.1±7.8	0.657[a]
5 mins	62.5±5.9	60.5±6.9	0.234[a]
10 mins	65.4±7.9	62.8±8.3	0.218[a]

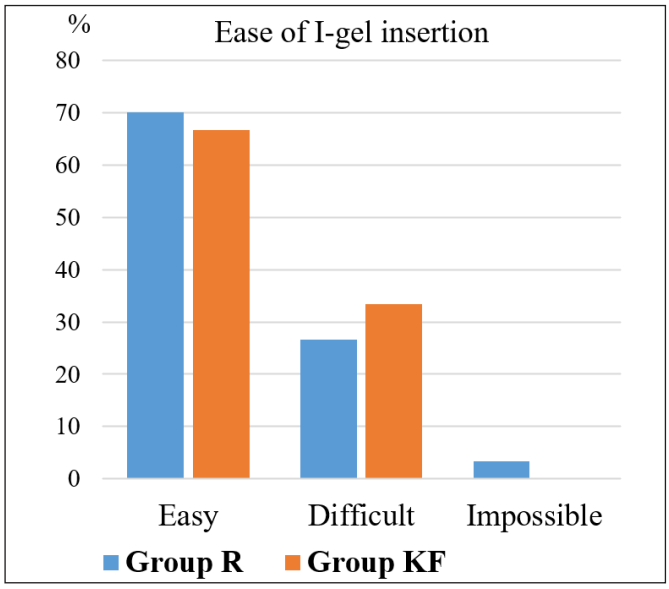

Figure 1.

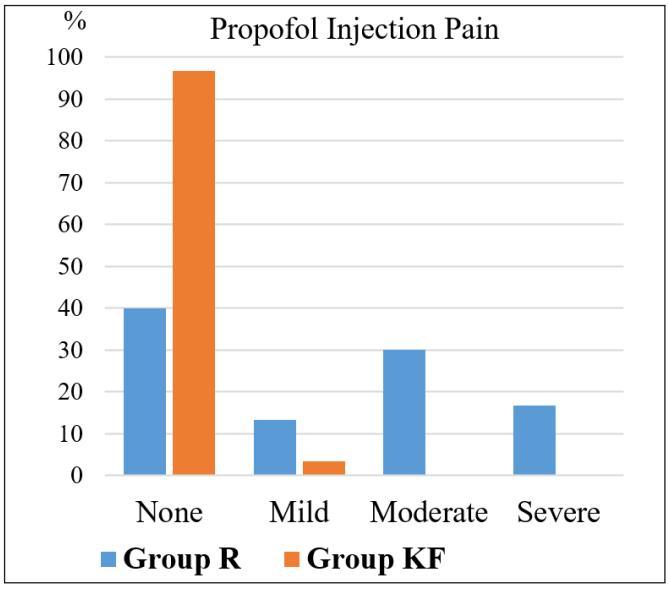

Figure 2.

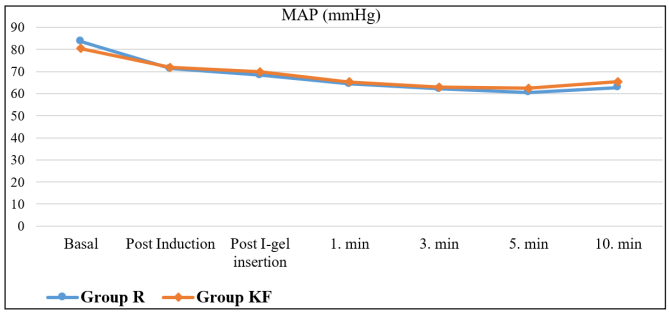

Figure 3.

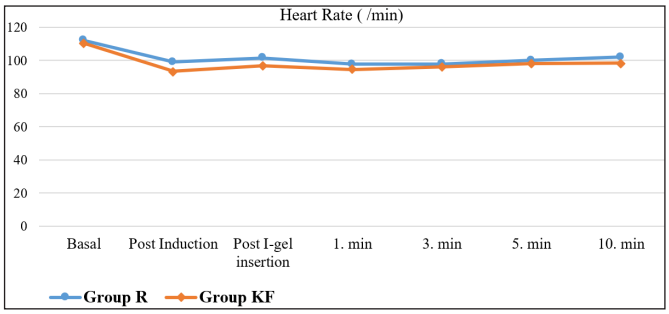

Figure 4.

main concern related to the adddition of ketamine for children is of secretion increase and that this could lead to negative outcomes. However, in the current study, this complication was not observed in the fentanyl-ketamine group during or after the I-Gel insertion procedure. It has been reported that ketamine administered at a sub-anesthetic dose can eliminate the side-effects of propofol.

Previous studies have stated that it is necessary to suppress the swallowing reflex together with cough and gagging to be able to correctly place the LMA in the hypopharynx. In a study by Singh et al. (14) conducted using 3.5 mg/kg propofol in children, comparisons were made of co-induction with 0.2 mcg/kg fentanyl or 0.5 mg/kg ketamine. The results showed that significantly more gagging, coughing and swallowing symptoms were seen in the ketamine group compared to the fentanyl group. There were also observed to be significantly more involuntary body movements in the ketamine group during LMA insertion. In the current study, with fentanyl added to ketamine at the same dose, these findings were observed in fewer patients, but the difference in comparison with the remifentanil group was not statistically significant. Similar findings related to ketamine have been reported in studies by Goh et al. (12) and Sağır et al. (15). These results in the current study suggest that the addition of fentanyl to ketamine provides more suitable conditions for laryngeal mask insertion. To reduce the side-effects associated with induction agents in children, the use of substances such as fentanyl as an induction agent together with ketamine or propofol has been recommended during the LMA insertion procedure. A synergistic interaction between ketamine and opioids has been reported in some studies (16,17). Using lower doses of different anaesthetics and opiods together in the two groups of the current study was observed to provide sufficient depth of anaesthesia and optimal hemodynamic conditions. Remifentanil is an ultra short-effect potent opioid, which is metabolised by non-specific plasma and tissue esterases. It is a slightly more potent agent than fentanyl, and in a similar study it has been shown that when combined with propofol, it is an appropriate agent to improve conditions without the use of a muscle relaxant in laryngeal mask insertion (18). It has also been reported that remifentanil administered before propofol achieves stable hemodynamics and reduces the propofol requirement (19,20). In a study by Kwak et al. (5) the bolus dose of remifentanil was found to be 0.56 mcg/kg in children with 50% probability (ED50)

of successful laryngeal mask insertion with propofol 2.5 mg/kg. In the current study, 0.5 mcg/kg remifentanil was used with 3 mg/kg propofol in induction and successful insertion conditions were observed to be obtained.

The insertion procedure was able to be performed in all the patients in the fentanyl-ketamine group. In one patient in the remifentil group, the I-Gel insertion procedure could not be accomplished at all. In a study of infants by Kayhan et al. (21) 1 mcg/kg remifentanil and 3mg/kg propofol were administered to all the patients in induction, and the insertion procedure was unsuccessful in 1 patient in the group which used I-Gel. In the same study, the I-Gel insertion total score was found to be 6.2±0.5. In the current study, the total score was determined to be similar at 5.7±0.9 in the remifentanil group, and 5.7±0.9 in the fentanyl-ketamine group. Ghatak et al. (22) compared ketamine and fentanyl with a control group, and reported that the LMA insertion total scores were significantly better in the ketamine group (6.33±0.88) and fentanyl group (6.59±0.95), than in the control group (8.12±0.52).

Ketamine creates sympathetic stimulation which leads to an increase in vascular resistance and myocardial contractility, resulting in increased arterial pressure and heart rate (12). When applied together with propofol for anesthesia induction, it can provide hemodynamic stability, even at sub-anesthetic doses. In a study by Begeç et al. (8) the administration of 0.5 mg/kg ketamine with 4 mg/kg propofol was found to preserve hemodynamic stability in LMA insertion. In the current study, it was similarly observed that hemodynamic stability was obtained with the addition of 3 mg/kg propofol and 1 mcg/kg fentanyl to ketamine at the same dose. In Group R, following the slow injection of 0.5 mcg/kg remifentanil, although there was a rapid decrease in heart rate, this was observed to be very short-term. In a similar study, higher heart rate and higher mean arterial pressure were recorded continuously in the ketamine group compared to the fentanyl and saline groups, even in patients administered premedication with clonidine (23). Previously cconducted co-induction studies have shown that the addition of fentanyl to propofol increased depressive effects on blood pressure and heart rate (10, 22). Like fentanyl, remifentanil also shows a vagotonic effect related to a significant increase in sympathetic nerve activity mediated by arterial baroreflex, leading to bradycardia and hypotension. These effects have a rapid onset and short duration (2).

As propofol has rapid onset and short effect duration, it is the preferred drug for anesthesia induction in millions of patients each year. Despite these positive properties, approximately three in five patients experience pain during the propofol injection, and one of these patients reports severe or intolerable pain. Some patients remember anesthesia induction as the most painful part of the perioperative period. Consequently, pain associated with the propofol injection continues to be a problem (24).

In the current observational study, the effect of the drugs used as co-induction before propofol on the pain of the propofol injection was evaluated with a 4-point scoring system. In Group KF, the pain level was zero in 29 of the 30 patients and at a mild level in one patient. In Group R, no pain was reported in 40% of the patients, and severe pain in 16%. In a previous similar study of children, 0.5 mcg/kg remifentanil was administered before propofol, and while no pain was reported by 60% of the children, there was severe pain in approximately 7% (25). Başaranoğlu et al. (26) compared 1mcg/kg fentanyl and 1 mcg/kg remifentanyl with a saline group, and found that both drugs made no significant difference from the saline group in preventing propofol injection pain. In a study by Zhao et al. (27) 0.5 mg/kg ketamine administered before propofol was found to effectively eliminate pain and reduce the amount of propofol used. The similar result obtained in the current study with the addition of ketamine and fentanyl was concluded to have originated from ketamine, and fentanyl made a positive contribution to this.

There were some limitations to this study, primarily that it was observational in design so data could not be collected in a blind manner. Another limitation was that as the cases included were of different types and durations of surgical interventions, the two groups could not be compared in respect of postoperative recovery time, postoperative pain, nausea and vomiting, or hallucinations.

CONCLUSION

The results of this observational study showed that the success of I-Gel insertion and the hemodynamic conditions were similar in the remifentanil group and the ketamine-fentanyl group when those drugs were administered as co-induction before propofol. The effective elimination of propofol injection pain in the ketamine-fentanyl group provided more comfort and stable induction conditions. Therefore, this could constitute a reason to prefer the use of ketamine and fentanyl together as co-induction.

In conclusion; It was observed that I-gel insertion conditions were safe and successful at a similar rate between ketamine-fentanil and remifentanil used as co-induction before propofol, and hemodynamic conditions were stable in both groups. More effective improvement of propofol injection pain in the ketamine-fentanyl group provided calm and comfortable induction conditions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No: 2 Clinical Researches Ethics Committee (Date: 23.11.2022, Decision No: E2-22-2879).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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The association between vitamin D level and ICU mortality in COVID-19 patients: a single center survey

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ABSTRACT

Aim: Vitamin D, an immune modulator, may contribute COVID-19 infection. This study aims to assess the relationship between vitamin D value and clinical outcomes (need for mechanical ventilation (MV) support and intensive care unit (ICU) mortality) in critically ill patients diagnosed with COVID-19.

Material and Method: This study included critically ill adult patients diagnosed with COVID-19 infection. Serum vitamin D level was analyzed using liquid chromatography mass spectrometry. Vitamin D concentration was classified as normal (≥20 ng/mL) and deficiency (<20 ng/mL). The association between serum vitamin D value and the need for MV treatment and ICU mortality was analyzed by logistic regression model.

Results: Ninety-six critically adult COVID-19 patients with were recruited. The mean age of patients was 68.8±12.6 years. The mean APACHE II score of participants was 14.5±6.7. A total of 69.8% of participants had vitamin D deficiency. Patients with deficiency of vitamin D had significantly higher procalcitonin, BUN and creatinine concentrations than patients with normal vitamin D value (p=0.031, p=0.003, and p=0.001, respectively). Serum vitamin D level was negatively weak correlated with SOFA score (Rho=-0.238, p=0.020), serum creatinine (Rho=-0.299, p=0.003) and troponin levels (Rho=-0.330, p=0.004). Serum vitamin D value was not significantly associated with the need for MV support and ICU mortality (p>0.05).

Conclusion: Approximately 70% of our study sample has below the normal range of serum vitamin D value. Low serum vitamin D concentrations were associated with increased SOFA, creatinine, and troponin concentrations in patients with COVID-19 infection. Vitamin D deficiency was not a predictor of need for MV support and ICU mortality in COVID-19 patients.

Keywords: COVID-19, vitamin D, intensive care unit, mortality

INTRODUCTION

COVID-19, a global clinical viral disease, can progress to critical illness and acute respiratory failure, increasing the likelihood for ICU admission and the possibility of subsequent mortality (1–3).Vitamin D acts as an immune modulator through several mechanisms, including modulation of cytokine release, neutrophil activity, ACE-2 receptors, and pulmonary barrier function (4,5).Vitamin D has also been cited as having a possible impact concerning the treatment as well as the prevention of COVID-19 infection (6–9). Achieving normal vitamin D status has become a significant clinical goal in COVID-19 patients, based on the preliminary evidence of ICU admission, more extended ICU stay, and the mortality rate. Research suggests that a deficiency in vitamin D levels leads to worse outcomes in COVID-19 patients than in those with levels reported as average (10–13).Given the inconclusive clinical evidence, further primary studies would be apposite in clarifying how vitamin D status affects disease severity and mortality in COVID-19 patients (4–6,14).

This study aims to determine the relationship between vitamin D status and poor clinical outcomes (need for mechanical ventilation (MV) support and mortality) in critically ill patients receiving ICU treatment for COVID-19.

MATERIAL AND METHOD

The study was carried out with the permission of Kayseri City Training and Research Hospital Clinical Researches Ethics Committee (Date: 15.04.2021; Decision No: 2021/370). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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This study was made retrospectively in a single-center ICU between August 2020 and January 2021. The inclusion criteria of the current study were as follows:

1. ≥18 years of age,
2. Diagnosed with COVID-19 (positive SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) test and thorax CT consistent with COVID-19 infection),
3. Presence of acute respiratory distress syndrome (ARDS) (15),
4. ≥48 hours expect ICU stay.

Pregnant women, patients with rickets and osteomalacia were excluded.

Data were collected from patients' medical record. At ICU admission, demographic characteristics, symptoms related to COVID-19 on ICU admission, presence of comorbidity, the severity of illness scores (Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), Glasgow Coma Scale (GCS), Charlson Comorbidity Index), need for Mechanical Ventilation (MV) support (Invasive) were recorded.

Troponin, C-reactive protein (CRP), procalcitonin, blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), ferritin, D-dimer, PaO_2/FiO_2 ratio, lactate, leukocyte, neutrophil count, lymphocyte count, platelet count of patients was recorded. In addition, the length of ICU/hospital stay, and ICU mortality were noted.

Vitamin D Measurement

The concentrations of vitamin D of the participants were obtained from their medical records. Liquid Chromatography Mass Spectrometry (LC-MS/MS) (SCIEX Model 4500 Q TRAP) was utilized to determine 25(OH)D levels at the ICU admission.

According to vitamin D levels, we classified two groups: normal (Vit D ≥20 ng/mL) and deficiency (Vit D <20 ng/mL).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY). Continuous variables were presented as mean±SD or median (interquartile range, IQR) based on normality distribution. Categorical variables were shown as numbers (%). The difference between categorical variables was analyzed using the Chi-square test. The difference between continuous variables was analyzed with the two independent sample t test. Vitamin D level correlation with other parameters was analyzed using Spearman correlation analysis. The association between vitamin D levels and the need for MV and ICU mortality was assessed using logistic regression analysis adjusted with potential confounders (age and gender). A p-value <0.05 was accepted as statistically significant.

RESULTS

This study included 96 critically ill patients with respiratory failure related to COVID-19 infection in ICU. The mean age of the study sample was 68.8±12.6 years, and 52.1% of the cohorts were male. The mean APACHE II score was 14.5±6.7, and SOFA score was 5.5±2.2 at ICU admission. The most common reason for ICU admission was dyspnea (75.0%). In addition, the most common comorbidities of patients were hypertension (53.1%) and diabetes mellitus (39.7%). **Table 1** shows the patients' demographic and clinical characteristics.

MV support was required in 42.7% of patients. The median length of ICU stay was 10 (6.3-15) days, and the median length of hospital stay was 16 (11-26.5) days. The mortality rate of the participants was 57.3% in ICU (**Table 1**).

A total of 67 (69.8%) patients had vitamin D deficiency (<20 ng/mL). There was no statistically significant difference between groups in terms of age, symptoms on admission, and severity of illness (APACHE II score, SOFA score, GCS, Charlson comorbidity index) (p>0.05 for all). Approximately half of both groups treated with MV support. Patients with deficiency of vitamin D had similar length of ICU and hospital stay to patients with normal vitamin D status (p=0.606 and p=0.903, respectively).

Furthermore, the ICU mortality rates of the patients with deficiency of vitamin D and normal vitamin D status were 56.4%and 46.3%. The ICU mortality rate was similar between two groups (p=0.534) (**Table 1**).

As shown in **Table 2**, patients with deficiency of vitamin D had significantly higher procalcitonin than patients with average vitamin D value (median: 0.35 vs median: 0.15, p=0.031).Compared to patients with normal vitamin D values, patients with deficiency of vitamin D had significantly higher serum BUN (median: 33.0 (24.0-53.0) vs 24.0 (18.0-27.5), p=0.003) and creatinine value (1.2 (0.9-1.9) vs. 0.8 (0.7-1.1) ng/mL, p=0.001). There was no significant difference in serum CRP level and WBC count according to vitamin D classification (p>0.05 for all) (**Table 2**).

There was negatively weak-correlation between vitamin D levels and SOFA score (Rho=-0.238, p=0.020), serum creatinine (Rho=-0.299, p=0.003), and troponin (Rho=-0.330, p=0.004) levels (**Table 3** and **Figure 1**).

Table 1. Patient demographic and clinical parameters

	Total (n=96)	Normal Vitamin D (n=29)	Vitamin D Deficiency (n=67)	p value
Age (year), ±SD	68.8±12.6	68.6±13.46	68.9±12.31	0.925
Gender, n (%)				
Male	50 (52.1)	13 (26.0)	37 (74.0)	0.238
Female	46 (47.9)	32 (69.6)	14 (30.4)	
BMI (kg/m²), ±SD	27.9±4.5	28.3±4.33	27.8±4.53	0.600
Active smoking, n (%)	51 (53.1)	32 (62.7)	19 (37.3)	0.058
Comorbidity, n%)				
Hypertension	51 (53.1)	23 (45.1)	28 (54.9)	0.484
Diabetes mellitus	38 (39.6)	18 (47.4)	20 (52.6)	0.260
CAD	17 (17.7)	6 (35.3)	11 (64.7)	0.509
Asthma	14 (14.6)	7 (50.0)	7 (50.0)	0.423
COPD	11 (11.5)	3 (27.3)	8 (72.7)	0.105
Symptoms on admission, n (%)				
Dyspnea	72 (75.0)	32 (44.4)	40 (55.6)	0.521
Cough	14 (14.6)	5 (35.7)	9 (64.3)	0.160
Weakness	14 (14.6)	4 (28.6)	10 (71.4)	0.627
Fever	12 (12.5)	5 (41.7)	7 (58.3)	0.674
Myalgia	8 (8.3)	3 (37.5)	5 (62.5)	0.738
Indigestion	8 (8.3)	3 (37.5)	5 (62.5)	0.255
Severity of illness scores, ±SD				
APACHE II	14.5±6.7	13.1±7.0	15.1±4.5	0.176
SOFA	5.5±2.2	4.9±2.2	5.7±2.2	0.092
GCS	13.1±3.5	13.4±3.1	13.0±3.7	0.642
Charlson comorbidity index	4.2±2.0	3.9±1.9	4.3±2.0	0.345
MV support, n (%)	41 (42.7)	20 (48.8)	21 (51.2)	0.782
Length of stay, median (min-max)				
At ICU	10.0 (6.3-15.0)	10.0 (7.0-16.0)	10.0 (6.0-15.0)	0.606
In hospital	16.0 (11.0-26.5)	15.0 (9.5-28.0)	16.0 (11.0-24.0)	0.903
Mortality, n (%)				
ICU mortality	55 (57.3)	31 (56.4)	24 (43.6)	0.534
Hospital mortality	57 (59.4)	31 (54.4)	26 (45.6)	0.724

ICU: Intensive care unit, MV: Mechanical ventilation.

Table 2. Laboratory findings according to vitamin D status

	Total (n=96)	Normal Vitamin D (n=29)	Vitamin D Deficiency (n=67)	p value
Troponin (ng/mL)	23.0 (12.3-49.2)	17.5 (10.7-35.1)	27.4 (15.1-56.9)	0.094
CRP (mg/L)	110.7 (59.4-183.9)	88.0 (58.0-179.4)	125.0 (60.4-192.0)	0.346
Procalcitonin (µg/L)	0.29 (0.13-0.85)	0.15 (0.11-0.40)	0.35 (0.15-0.97)	0.031
BUN (mg/dL)	28.0 (21.0-46.0)	24.0 (18.0-27.5)	33.0 (24.0-53.0)	0.003
Creatinine (mg/dL)	1.0 (0.8-1.6)	0.8 (0.7-1.1)	1.2 (0.9-1.9)	0.001
LDH (U/L)	485.5 (373.5-619.0)	535.0 (387.0-620.5)	467.5 (370.8-620.3)	0.500
AST (IU/L)	39.0 (27.3-54.8)	41.0 (27.0-67.0)	38.0 (28.0-51.0)	0.336
Ferritin (µg/L)	742.0 (394.0-1589.0)	853.0 (482.0-1245.5)	716.5 (344.8-1847.5)	0.777
D-dimer (µg/L)	1604.5 (905.0-3604.8)	1630.0 (821.0-3501.5)	1579.0 (924.0-3652.0)	0.612
PaO_2/FiO_2	87.3 (70.3-158.3)	93.0 (68.0-167.0)	86.0 (71.0-143.0)	0.747
Lactate (mmol/L)	1.8 (1.4-2.6)	1.5 (1.3-2.6)	1.9 (1.4-2.6)	0.482
WBC (10^9/L)	11.3 (8.3-14.0)	12.7 (9.2-15.2)	11.2 (7.7-13.6)	0.298
Neutrophil (10^9/L)	10.0 (7.1-12.9)	10.7 (8.4-13.4)	9.8 (6.5-12.4)	0.307
Lymphocyte (10^9/L)	0.67 (0.47-0.97)	0.67 (0.51-0.83)	0.67 (0.45-0.98)	0.971
Platelet (10^9/L)	233.0 (169.3-300.3)	255.0 (174.0-329.0)	225.0 (157.0-283.0)	0.171

CRP: C-reactive protein; BUN: Blood urea nitrogen; LDH: Lactate dehydrogenase; AST: Aspartate aminotransferase; WBC: white blood cell, All data presented as median (IQR)

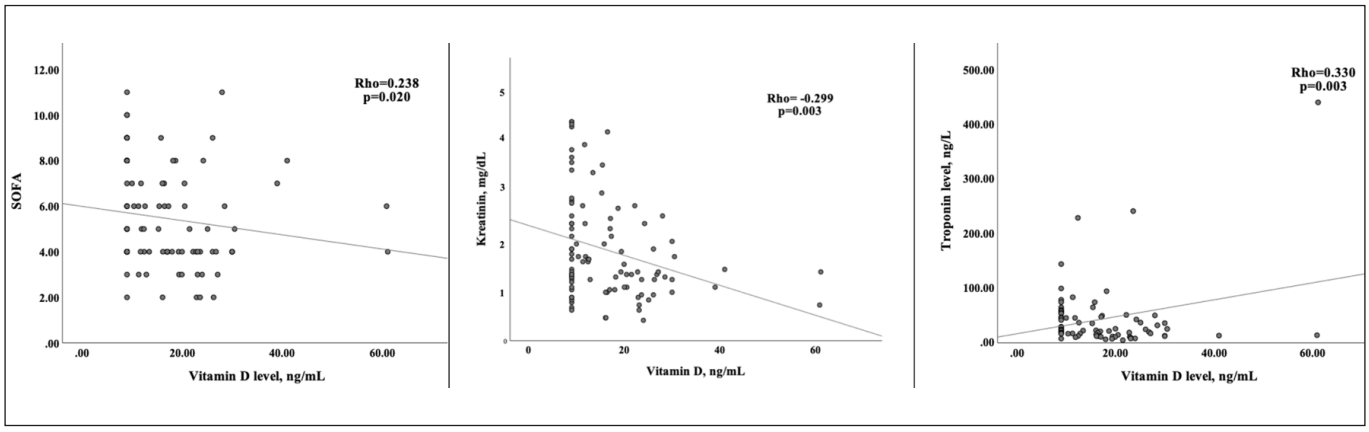

Figure 1. Correlation of vitamin D levels with SOFA score and serum creatinine and troponin levels

There was no statistically significant correlation between PaO_2/FiO_2 ratio and vitamin D level at baseline of the study (Rho= 0.008, p=0.940). Serum vitamin D levels were also not correlated with other severity of illness scores (APACHE II, GCS) and other laboratory findings (**Table 3**).

Table 3. Correlation of vitamin D levels with severity of illness scores and laboratory parameters

Variables	Vitamin D level	
	rho	p value
SOFA	-0.238	0.020
Charlson comorbidity index	-0.010	0.924
GCS	0.127	0.218
Troponin	-0.330	0.004
CRP	-0.140	0.174
Procalcitonin	-0.159	0.121
BUN	-0.177	0.085
Creatinine	-0.299	0.003
LDH	0.107	0.306
Ferritin	0.082	0.430
Ddimer	-0.105	0.308
PaO_2/FiO_2	0.008	0.940
Lactate	-0.060	0.561
Neutrophil	-0.058	0.572
Lymphocyte	-0.075	0.470

GCS: Glasgow Coma scale; CRP: C-reactive protein; BUN: Blood urea nitrogen; LDH: Lactate dehydrogenase, r: correlation coefficient, Pearson correlation analysis

The results of the logistic regression analysis showed that the impact of vitamin D level on the need for MV support or mortality risk was not statistically significant, even after adjusting for age and gender (p>0.05 for both). In addition, there was no association between deficiency of vitamin D (<20 ng/mL) and both needs for MV support and ICU mortality (p>0.05). After adjusting for confounding variables (age and gender), vitamin D status was not associated with both needs for MV support and ICU mortality (p>0.05)(**Table 4**).

Table 4. Logistic regression analysis for vitamin D levels in predicting need for MV support and ICU mortality

	Need for MV support		ICU Mortality	
	OR (95% CI)	p value	OR (95% CI)	p value
Model 1				
Vit D, ng/mL	1.042 (0.972-1.118)	0.243	0.980 (0.914-1.051)	0.573
Vit D<20 ng/mL	1.770 (0.417-7.506)	0.438	0.950 (0.224-4.041)	0.945
Model 2				
Vit D, ng/mL	1.028 (0.960-1.100)	0.427	0.999 (0.931-1.071)	0.967
Vit D < 20 ng/mL	1.269 (0.293-5.501)	0.751	1.422 (0.312-6.475)	0.649

Model 2 adjusted for age and gender, MV: Mechanical ventilation; OR: Odds ratio; CI: Confidence interval

DISCUSSION

The findings revealed patients with a deficiency of 69.8% in our study sample. The vitamin D levels were negatively correlated with SOFA score, serum creatinine, and troponin levels. The level of vitamin D status of COVID-19 patients was not associated with the need for MV treatment and mortality.

Approximately 70% of our study sample had vitamin D deficiency. Bassatne et al. (14) performed a systematic review of 31 observational studies in 18724 patients with COVID-19 infection. It was suggested that 13-82% of COVID-19 patients had vitamin D deficiency. Karahan et al. (16) conducted a retrospective cohort study investigating relationship between vitamin D status and mortality in 149 COVID-19 patients in our country. Similar to our study, vitamin D deficiency was considered as Vit D <20 ng/mL. It was found that 69.1% of study participants had vitamin D deficiency in consistent with our results.

In our study sample, patients with vitamin D deficiency had significantly higher procalcitonin, BUN and creatinine value compared to patients with normal

vitamin D status. In addition, there is a correlation between serum vitamin D levels and serum BUN, creatinine, and troponin in ourpatients. A meta-analysis of 3637 COVID patients by Mohamed Ben-Eltriki et al. (17) indicated that patients with low vitamin D levels had higher troponin levels compared to the patients with average vitamin D levels. Similarly, Tarek M Yosef et al. (18) reported a negative correlation between vitamin D levels and serum BUN, creatinine in a case-control study involving 80 COVID-19 patients. According to a retrospective study of 71 COVID-19 patients, found a significant association between low vitamin D levels (<20 ng/ml) and increased troponin value (19). Similar to our results, Quintana et al. (20) reported that there was relationship between low vitamin D status and higher procalcitonin level in critically ill patients with COVID-19.

A total of 42.7% of study participants were treated with MV support. The mortality rate was 57.3% of the study participants. In our study, serum vitamin D level was not associated with the need for MV treatment and ICU mortality. A retrospective study with 270 patients with COVID-19 revealed that vitamin D levels were <20 ng/mLin 35.2% of patients, along with the need for MV (21.9%), ICU stay (32.2%) and mortality (26.7%) in almost one-third of the patients. Similarly, there was no significant correlation between vitamin D status and mortality, need for MV, or ICU admission in COVID-19 patients (8). Notably, in a meta-analysis of 20 clinical studies in 12.806 COVID-19 patients, low vs. high vitamin D serum levels were reported as having similar mortality rates, ICU admission rate, ventilator support requirement, and length of ICU stay (9). A retrospective multicenter study of 197 patients with COVID-19 revealed that 73.10% of the patients had deficiency levels of vitamin D compatible with our data (21). Multivariate analysis adjusted for demographics and comorbidities showed that the correlation between vitamin D status and COVID-19 severity parameters, including MV support and mortality, was not statistically significant. We think that mortality in patients with COVID-19 infection may be due presence of cerebrovascular disease, thromboembolic events, etc. Contrary to our study findings and the above-mentioned studies, several studies suggest that the vitamin D deficiency has a significant effect on hospital admission, ICU admission, or mortality in patients diagnosed with COVID-19 (10,13,22,23).A meta-analysis of 17 observational studies involving 2756 patients suggests a significant relationship between vitamin D deficiency and higher mortality rates (OR 2.47) compared to patients with normal vitamin D status(10).

Study Limitations

There are several limitations of the study. The study was designed as cross-sectionally and did not include a few time points in ICU. Our study sample was small. A prospective observational study design may improve reliable observation of clinical outcomes of critically ill patients with COVID-19 infection. The retrospective single-center design of this study can be regarded as a notable limitation that prevents generalizing our findings to the overall ICU-hospitalized COVID-19 population. Several studies revealed a correlation between vitamin D supplementation and poor clinical outcomes in COVID-19 patients (11,24). However, we did not follow the vitamin D supplementation of patients.

CONCLUSION

The findings of this study revealed that about 3/4 of patients hospitalized in the ICU diagnosed with COVID-19 had below average range vitamin D status. Moreover, serum vitamin D concentration was related to increased SOFA score, serum creatinine, and serum troponin value. Nonetheless, vitamin D status was not associated with the need for MV treatment and ICU mortality. Randomized controlled studies with long-term study periods involving vitamin D supplementation are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kayseri City Training and Research Hospital Clinical Researches Ethics Committee (Date: 15.04.2021; Decision No: 2021/370).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Evaluation of polysomnography changes in patients using antidepressants

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ABSTRACT

Aim: In patients followed up with sleep disorders and receiving antidepressant treatment, the choice of antidepressant should be appropriate to the characteristics of the patient and the drug. The aim of this study is to show the effects of antidepressant drug selection on polysomnography results.

Material and Method: This study was planned retrospectively and was conducted by scanning patient files. Between 01.06.2018 and 01.06.2022, the files of patients who underwent polysomnography in the sleep laboratory of our hospital and were using antidepressants were scanned. Differences between antidepressant groups and polysomnography results were analyzed with IBM SPSS v23.

Results: 103 patients (43 women/60 men) were included in the study. It was determined that 56 of these patients used selective serotonin reuptake inhibitors and 47 of them used serotonin and norepinephrine reuptake inhibitors. Yates correction was used in the comparison of gender according to the groups, and there was no statistically significant difference between the distributions of gender according to the groups (p=0.248). According to the drug groups, the results of the polysomnography examined in the study do not differ according to the groups.

Conclusion: It was shown that the antidepressant groups examined in the study did not differ in terms of affecting the results of polysomnography. Other clinical characteristics of the patient can be taken into account in the selection of antidepressants in these groups.

Keywords: Polysomnography, antidepressants, serotonin, norepinephrine

INTRODUCTION

Polysomnography, during sleep; It is the process of recording many neurophysiological, respiratory, cardiovascular physiological and physical parameters during the night, at a certain period, simultaneously and continuously. Polysomnography is the gold standard test used in the diagnosis of many sleep disorders, especially sleep breathing disorders (1). With polysomnography, electrical signals produced by different tissues of the human body are recorded and visualized through electrodes and sensors (2).

Sleep is not a homogeneous process. It is divided into two stages, REM and NREM sleep, which show quite different characteristics in terms of neurochemical, electrophysiological and neurobiological aspects. The word REM is formed from the initials of the words "rapid eye movement". The characteristic feature of the REM period is rapid eye movements. NREM sleep is also divided into three substages, N1, N2, and N3. In a healthy adult, sleep begins with NREM (3). The onset of sleep with REM is pathological. An individual who goes to sleep at night passes from awake to Stage N1 within 15-20 minutes at the latest. Stage N1 is a short transitional period and continues with Stage N2. After this stage, sleep deepens and Stage N3 begins. This NREM process, which lasts around 90-100 minutes and gradually deepens, is followed by the first REM period, which lasts no more than 3-5 minutes. NREM and REM then continue in cycles of about 90-110 minutes throughout the night, and there are usually 4-6 NREM-REM cycles per night of sleep. It is pathological that the first REM period occurs earlier than 30 minutes. Another feature of these cycles is the decrease of NREM deep sleep from the first half of sleep to the second half of sleep and the prolongation of REM sleep (4). The first half of sleep is dominated by NREM deep slow sleep, while the second half of sleep is

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dominated by REM sleep. The graph showing the change of sleep stages over time is called a hypnogram. Sleep follows a certain sequence within itself and changes NREM / REM periods as it progresses. (5-6).

The use of antidepressant drugs began in the 1950s with monoamine oxidase inhibitors and tricyclic antidepressants. Since it has been suggested that the beneficial effect of antidepressants may be due to their ability to block noradrenaline and/or serotonin reuptake, pharmaceutical companies are exploring potential antidepressants for neurotransmitter reuptake blocking. Partly as a result of this consideration, agents have been developed that can specifically block noradrenaline reuptake, serotonin reuptake, or both (7).

The choice of antidepressant is based on the person's medical history. Drug safety, side effect profile, tolerability and drug interaction potentials should be considered; because these variables directly affect participation in treatment (8).

The selection of antidepressants in patients with sleep disorders should be in accordance with the characteristics of the patient and the drug. In this study, it was examined whether the antidepressant drugs used by the patients and the results of polysomnography were related by retrospective file scanning.

MATERIAL AND METHOD

This retrospective study was carried out in a tertiary hospital with a total of 1607 beds and also includes 253 intensive care beds. Between 01.06.2018 and 01.06.2022, the patient files who underwent polysomnography in the sleep laboratory of the neurology clinic of our hospital were scanned. This research was approved by the local Ethics Committee (Date: 30.06.2022, Number: 661). No funds were used from any institution. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The files of those using antidepressants were selected from these patients. Patients were divided into 2 groups as those using selective serotonin reuptake inhibitors (SSRI) and those using serotonin and norepinephrine reuptake inhibitors (SNRI). The present study was designed retrospectively and no additional tests or blood tests were performed on the patients. Polysomnography results; Age, Total recording time (min), Total time in bed (min), Sleep period time (min), Total sleep time (min), Sleep activity (%), Sleep onset time (min), Waso (min), Rem latency (min) (after onset of sleep), Rem latency (min) (after lights off), N1(min), N2(min), N3(min), R(min) were recorded. Differences between antidepressant groups and polysomnography results were analyzed.

Exclusion criteria from the study; Patients under the age of 18, insomnia patients, patients using hypnotic and sedatives were determined as patients with irregular sleep due to shift work. Patients aged 18 and over and who had previously undergone polysomnography in the sleep laboratory of the Neurology clinic and who also used antidepressants were included in the study.

Statistical Analysis

Data were analyzed with IBM SPSS V23. Conformity to the normal distribution was evaluated using the Shapiro-Wilk test. Yates correction was used to compare gender by groups. Independent two-sample t-test was used to compare normally distributed data according to paired groups, and Mann-Whitney U test was used to compare non-normally distributed data. Analysis results mean ± s for quantitative data. Categorical data as deviation and median (minimum – maximum) were presented as frequency (percentage). Significance level was taken as $p<0.050$. Significance level was taken as $p<0.050$.

RESULTS

103 patients (43 women/60 men) were included in the study. It was determined that 56 of these patients used SSRI and 47 of them used SNRI (**Table 1**).

Table 1. Comparison of gender by groups

	SSRI	SNRI	Test is.	p*
Gender			1.333	0.248
Women	20 (35.7)	23 (48.9)		
Men	36 (64.3)	24 (51.1)		

* Yates fix

There was no statistically significant difference between the distributions of gender according to the groups. (p=0.248).

The differences between the antidepressant groups and polysomnography results are shown in **Table 2**.

The mean age values did not differ according to the groups (p=0.846). While the mean value was 45.6 in the 2 group, the mean value was 46.1 in the 1 group. The median values of the total recording time did not differ according to the groups (p=0.123). While the median value was 405.0 in the SNRI group, the median value was 396.8 in the SSRI group. The median values of total time in bed did not differ according to the groups (p=0.223). While the median value was 402.9 in the SNRI group, the median value was 396.8 in the SSRI group. The median values of sleep period duration did not differ according to the groups (p=0.253). While the median value was 370.5 in the SNRI group, the median value was 365.5 in the SSRI group. The median values of total sleep time did not differ according to the groups (p=0.431). While the

Table 2. Comparison of quantitative data by groups

	SNRI		SSRI		Test is.	p
	average ± SS	median (Min - Max)	average ± SS	median (Min - Max)		
Age	45.6±12.3	46 (22-71)	46.1±12.2	48 (18-71)	0.195[2]	0.846
Total recording time (min)	471.6±492.9	405 (246.6-3767.1)	394.8±32.2	396.8 (259.4-463.9)	1082.500[1]	0.123
Total time in bed (min)	399.2±41.2	402.9 (246.6-457.1)	394.8±32.2	396.8 (259.4-463.9)	1131.500[1]	0.223
sleep period duration (min)	351.8±73.1	370.5 (74.5-432)	348.7±52.6	365.5 (222.5-458)	1143.000[1]	0.253
Total sleep time (min)	298.6±85	307 (35.5-430.5)	313.4±68.6	325.3 (113-422.5)	1435.500[1]	0.431
sleep activity (%)	78.2±13.4	77.3 (39.1-95.5)	79.4±13.3	82.8 (47.8-99.4)	1370.500[1]	0.721
sleep start time (min)	47.2±69.1	30.5 (3-352.5)	39±34.9	33.5 (1-185.5)	1347.500[1]	0.837
Waso (min)	53±38.8	46.2 (1.2-157.8)	45±42.4	34.5 (1.2-230.1)	1101.500[1]	0.157
REM latency (after sleep onset)	195.9±84.6	198.5 (52.6-345)	245.2±459.5	180.3 (21.5-3253)	879.000[1]	0.470
rem latency (after lights off)	229.3±86.4	229 (76-388)	214.6±79.1	215.5 (66.5-357)	882.500[1]	0.488
N1 (min)	4.7±2.4	4.1 (1.1-12.8)	4.6±3	3.9 (0.7-16.6)	1239.000[1]	0.612
N2 (min)	49±15.3	48.8 (6.9-76.4)	50.3±10.2	51.3 (22.6-71.8)	0.488[2]	0.627
N3 (min)	14.4±10	12 (0-41.4)	15.6±7.9	15.9 (0-37.8)	0.656[2]	0.513
R (min)	11.2±9.1	9.9 (0-37)	9.6±7.6	9.1 (0-31.3)	1217.500[1]	0.516

1Mann Whitney U test, 2Two independent samples t-test, Mean ± s. deviation, median (minimum – maximum)

median value was 307.0 in the SNRI group, the median value was 325.3 in the SSRI group. The median values of sleep efficiency did not differ according to the groups (p=0.721). While the median value was 77.3 in the SNRI group, the median value was 82.8 in the SSRI group. The median values of sleep onset time (min) did not differ according to the groups (p=0.837). While the median value was 30.5 in the SNRI group, the median value was 33.5 in the SSRI group. Waso (min) median values did not differ according to the groups (p=0.157). While the median value was 46.2 in the SNRI group, the median value was 34.5 in the SSRI group. Median values of rem latency (after onset of sleep) did not differ between groups (p=0.47). While the median value was 198.5 in the SNRI group, the median value was 180.3 in the SSRI group. Median values of rem latency (after lights off) did not differ between groups (p=0.488). While the median value was 229.0 in the SNRI group, the median value was 215.5 in the SSRI group. N1 median values did not differ according to the groups (p=0.612). While the median value was 4.1 in the SNRI group, the median value was 3.9 in the SSRI group. N2 mean values did not differ according to the groups (p=0.627). While the mean value was 49.0 in the SNRI group, the mean value was 50.3 in the SSRI group. N3 mean values did not differ according to the groups (p=0.513). While the mean value was 14.4 in the SNRI group, the mean value was 15.6 in the SSRI group. R median values did not differ according to the groups (p=0.516). While the median value was 9.9 in the SNRI group, the median value was 9.1 in the SSRI group.

DISCUSSION

Sleep; It is a state of unconsciousness that can be reversed with various environmental stimuli such as sound, light, and contact. An average of one-third of human life is spent in sleep (9-10). PSG is a test used in the diagnosis of sleep disorders such as respiratory arrest, snoring, and periodic leg movements during sleep (11).

There was no statistically significant difference between the polysomnography results determined in the present study and the antidepressant groups. However, the most different value from the polysomnography results compared to the two antidepressant groups was found in the WASO (wake after sleep onset) value. WASO; It is the sum of the waking hours in the time period from the onset of sleep until the last awakening. It is obtained by subtracting sleep latency from the total wakefulness time. Any technical malfunctions or the time spent by the patient in the toilet are also included in this statement. It is important in terms of showing sleep continuity and divisions. In this study, while the median value was 46.2 in the WASO, SNRI group, the median value was 34.5 in the SSRI group. It is an important finding in terms of showing that the patient group using SNRI has more sleep continuity and fragmentation.

In addition, REM latency after the onset of sleep and REM latency after the lights were turned off, a shorter time (in minutes) was determined in the SSRI group in both parameters. We see that the SSRI group is more effective in terms of sleep efficiency (%). It was determined that the total sleep time was higher in the SSRI group.

Insomnia is a common psychiatric disorder that severely affects the daily lives and quality of work of affected individuals (12). Psychiatric disorders, particularly anxiety and mood disorders, are a common cause of insomnia symptoms (13-14).

It is well known that certain classes of antidepressant drugs can impair sleep quality, mainly due to activation of serotonergic 5-HT2 receptors and increased

noradrenergic and dopaminergic neurotransmission. The most prominent among them are SNRI, norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, SSRI and tricyclic antidepressants. It is important to note that SSRIs in particular can cause disruption of sleep continuity, which is clinically expressed as increased insomnia complaints. Increased amounts of serotonin are likely responsible for the effects on REM sleep. The effect of the SSRI and SNRI group on sleep appears to be related to the increase in noradrenergic neurotransmission and activation of serotonergic 5-HT2 receptors. It significantly suppresses REM sleep, and this effect may decrease in the later stages of treatment (15). Commonly, SSRIs and SNRIs can be used for the clinical treatment of depression and insomnia. However, their role in the treatment of insomnia in patients with anxiety and mood disorders is controversial. It has been shown that SSRI treatment can lead to anxiety and insomnia (16-17).

In contrast, it showed that antidepressant treatment initially resulted in lower sleep quality, but resulted in greater improvement in sleep duration several weeks later and when used at lower doses. In the present study, similar to other studies, patients' sleep efficiency decreased, WASO and rem latency increased, stage 3 and rem sleep decreased (18-19) . However, as a limitation of the study, we should state that the doses and duration of use of antidepressants used by our patients were not specified in our study.

SSRI and SNRI are drugs used to treat depression. Sleep disturbances are an integral feature of depressive disorders. It ranges from hypersomnia to difficulties in maintaining sleep (20-21). Difficulties in maintaining sleep are evaluated as early onset of the first episode of REM sleep and increased phasic REM sleep in polysomnography.

Similarly, the early onset of the first episode of REM sleep was shortened in both groups.

The sleep efficiency of the patients was decreased and it was 77% and 82% in the SSRI and SNRI groups, respectively. Waso and REM latency increased in both groups. The ratio of stage 3 sleep and REM sleep time to total sleep time decreased (22).

CONCLUSION

In this study, which was presented in patients who preferred SSRI or SNRI in their current treatment, no superiority or difference was detected in their negative effects on sleep. Placebo-controlled randomized studies are needed for the labels of SSRI and SNRI group drugs on polysomnography results in order to guide the choice of antidepressants in patients with sleep disorders.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kayseri City Training and Research Hospital Clinical Researches Ethics Committee (Date: 30.06.2022, Number: 661).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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Comparison of anterior midline incision and double incision in the surgical treatment of tibial plateau fractures

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ABSTRACT

Aim: Tibial plateau fractures are complex fractures that often develop after high-energy trauma, often involving intra-articular fractures. They are rarely treated conservatively. Surgical planning and approach are very important in preventing possible complications. In this study, we compared two different incisions in the same fracture types.

Material and Method: A total of 26 patients (20 males-6 females) with tibial plateau fractures were included in the study. Twelve of the patients were selected from those using anterior midline incisions, and 14 from those using double incisions as anterolateral and posteromedial incisions. The mean age of the patients is 50.8 (24-76) years. The distribution of patients according to fracture classification was 9 Schatzker type-6, 17 Schatzker type-5. Average follow-up time is 34.1 months (24.5-42.2). Postoperative complications, union time, joint range of motion, radiological Rasmussen criteria, Medial Proximal Tibial Angle (MPTA) and Posterior Proximal Tibial Angle (PPTA) measurements, Lachman and valgus-varus stress tests for ligament stability evaluation, Hospital for Special Surgery (HSS) and visual analogue scale (VAS) assessments were performed to evaluate the clinical status of the patients. Results were compared between both incision groups.

Results: Union in the anterior midline was 11.07 (±1.68) weeks and bilateral union was 9.96 (±1.35) weeks (p :0.074). Rasmussen scoring was 14.83 (±2.16) in the anterior group and 14.57 (±2.13) in the bilateral group (p:0.760). The MPTA was 85.35 (±3.97) degrees in the anterior group, and the MPTA was 86.40 (±3.74) degrees in the bilateral group (p: 0.492). PPTA was 80.77 (±1.95) degree in the anterior group, and PPTA was 80.85 (±1.78) degree in the bilateral group. HSS score was 70 (±9.02) in the anterior group and HSS score was 71.71 (±1.15) in the bilateral group (p:0.681). Rom was measured as 101.67 (±12.67) degrees in the anterior group and 107.86 (±13.54) degrees in the bilateral group (p: 0.243). The VAS anterior group was 2.83 (±1.64) and the VAS bilateral group was 3.36 (±2.09) (p:0.491).Instability was seen in 1 patient in the anterior group and 1 patient in the bilateral group (p:1). Infection was observed in 1 patient in the anterior group and in 3 patients in the bilateral group (p:0.598).

Conclusion: The anterior incision is as effective a surgical approach as bilateral incision in correct patient preferences. Surgical site visibility in anterior incision is satisfactory. The principal aspect is to perform the correct surgical planning for the correct patient.

Keywords: Tibial plateau fracture, anterior midline incision, visual analogue scale

INTRODUCTION

Tibial plateau fractures occur after high-energy trauma with serious complications (1). They are usually caused by the rotational compression effect of high-energy forces in the valgus or varus position of the fixed extremity, such as a pedestrian's leg being hit by a car bumper (2). The Schatzker classification system is the most common classification of tibial plateau fractures used in the literature: it is based on the location of the fracture, its size and the amount of collapse of the bone (3).

Less invasive techniques and often anterolateral and posteromedial double incision approaches have been used to avoid postoperative wound problems. However, the reduction quality is close to 50%, even when anterolateral and posteromedial approaches are used in the resultant radiological evaluations (4).

In some multicomponent tibial plateau fractures, even two incision techniques are not sufficient to achieve reduction, therefore several incisions are needed. The anterior midline incision method described by Perry may be a suitable alternative for comminuted tibial plateau fractures (5).

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The anterior midline incision, which is an approach that orthopedic surgeons are accustomed to due to total knee arthroplasty, provides adequate visualization of the inside of the joint, either by medial parapatellar incision or by removing the meniscus from the lateral or medial side. The aim of this study was to compare anterior midline and bilateral incisions in the same fracture configurations.

MATERIAL AND METHOD

The study was carried out with the Samsun Training and Research Hospital Clinical Researches Ethics Committee (Date: 02.02.2022, Decision No: 2022/2/9). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The informed consent was waived due to the retrospective nature of the study and the fact that the assessment utilized anonymous research findings.

A total of 137 patients with proximal tibia fractures treated between the 1st of January 2015 and the 1st of December 2022 were evaluated. Patients with Schatzker type 1,2,3,4, limited follow-up, other techniques, open fractures, as well as patients requiring a fasciotomy, were excluded from the study. Twenty-six patients (twenty males and seven females) with Schatzker types 5 and 6 treated with anterior midline and bilateral approach were included in the study. Anterior incision was used in twelve of these patients, and anterolateral and posteromedial double incisions were used in fourteen of them.

Surgical Technique

The patients were placed in the supine position by applying a tourniquet to the extremity to be operated under spinal/epidural anesthesia. The knee was supported below at approximately 75 degrees of flexion. The knee was lifted in the form of a flap by entering through a straight incision from the anterior midline, without detaching the subcutaneous tissue. In some patients, the joint was opened anteriorly with a medial parapatellar incision, and in some patients, the lateral and/or medial menisci were released, making the intra-articular visible without touching the extensor mechanism. The fascia on the muscle was opened and the anterolateral muscles were lifted subperiosteally from the bone as a block. The incision was extended proximal and distally in some patients, depending on how far back it was required to go. Compression fractures involving the joint were removed, the gradations at the joint level were corrected and they were temporarily fixed with neighbours. After the fracture line was reduced under scopy control, fractures were detected with lateral and medial plates and/or screws from anterior to posterior. It was ensured that the skin was not detached during the procedures. The protection of muscle fascia and subcutaneous structures together as a block is aimed at preventing possible tissue nutrition and preventing necrosis (**Figure 1, 2, 3**).

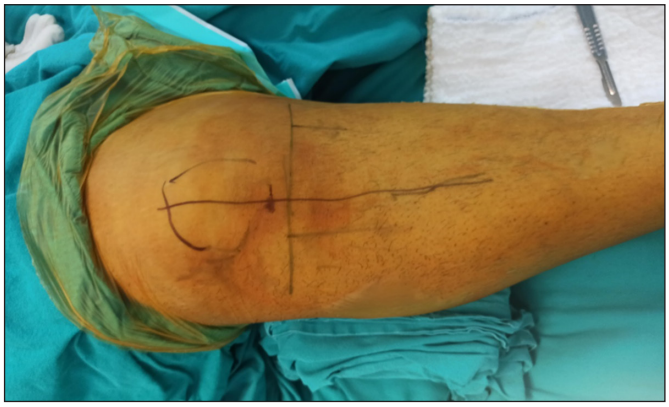

Figure 1. Anterior midline incision

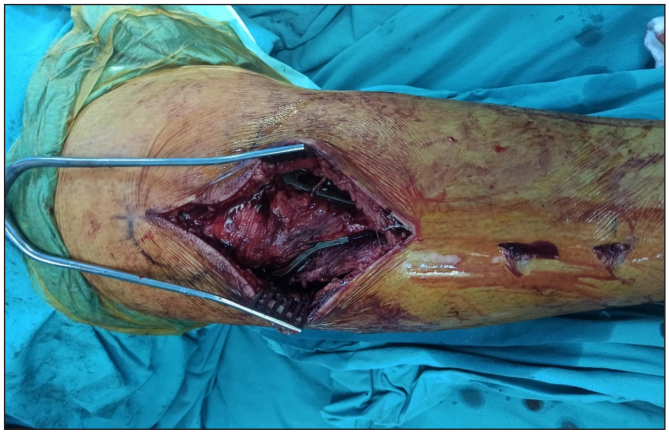

Figure 2. Anterior midline approach dual plate without medial parapateller incision.

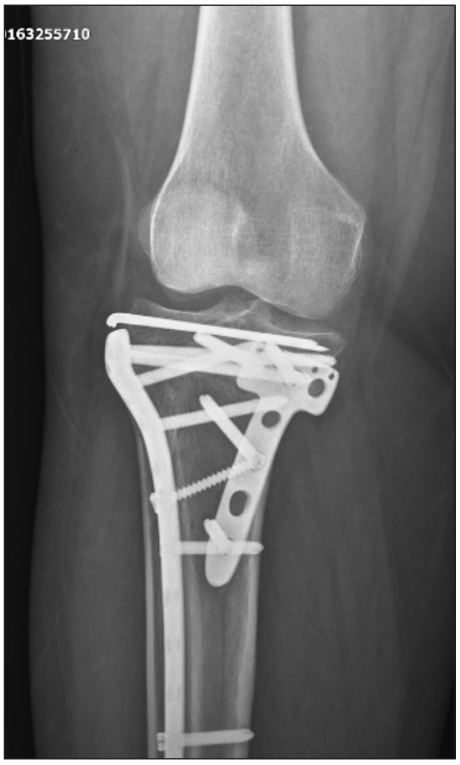

Figure 3. Anterior midline approach with meniscus release without medial parapateller incision dual plate x-ray

In the Anterolateral and Posteromedial approaches, the patients were placed in the supine position by applying a tourniquet to the extremity to be operated under spinal/epidural anesthesia. The knee was supported under approximately 75 degrees of flexion, and the subcutaneous tissues were lifted up to the fascia in the form of a flap by entering through the anterolateral and posteromedial incisions. The fascia was opened and the muscles were lifted subperiosteally from the bone. The joint capsule was opened, and the menisci were released from the places where they were attached to the tibia and the inside of the joint was visualized. The steps in the joint were corrected and supported with grafts and fixed with plates under the control of scopy (**Figure 4**).

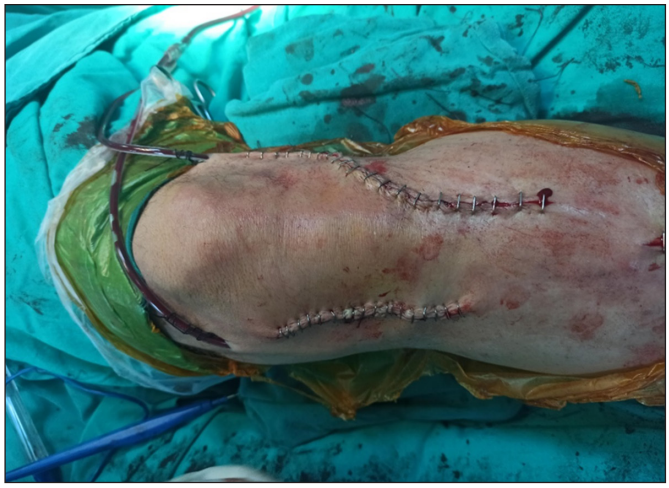

Figure 4. Bilateral incision; anterolateral and medial for dual plating

In both approaches, a drain was placed in the patients and a temporary long leg splint was placed after the operation. The splints of the patients were removed early postoperatively or 10 days later, and Range of Motion (ROM) exercises were started with an angle-adjustable knee brace. Patients who were thought to have adequate fracture union during their follow-up were taught progressive load-increasing exercises and started walking.

The patients were controlled clinically and radiologically every month. After 6 months of follow-up, the patients were evaluated clinically in terms of visual analog scale, Hospital for Special Surgery (HSS) knee score, ROM and Ligament instability. HSS results ≥85 were considered excellent, 70-85 good, 60-69 moderate, and <60 poor.

Pain was assessed on a visual analogue scale (VAS) ranging from 0 to 10 cm. The VAS was performed in two sections. In the first section we asked the patients to score their pain near the fracture site during Daily activity. Anterior group VAS 2,83 (1-7) 1 patient marked who is go on revision 7, Bilateral group 3,35 (1-7), 3 patients marked 7 whose were operating more than one and still unstable knee motion.

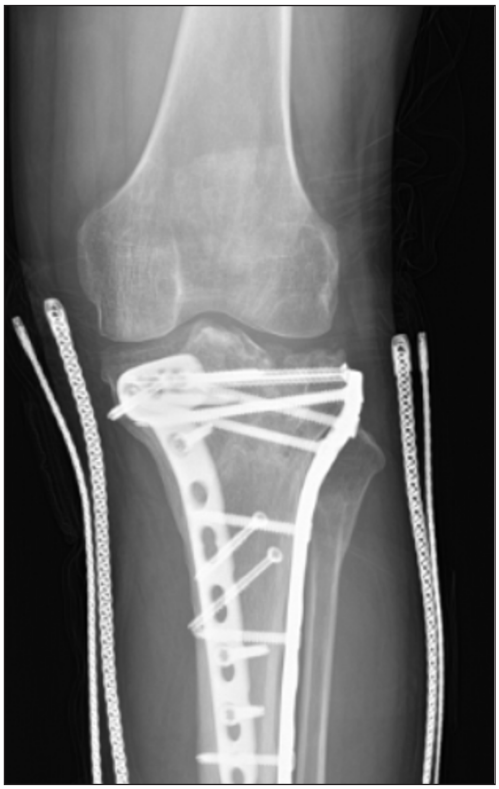

Figure 5. Bilateral approach dual plate x-ray

The Rasmussen radiological criteria, Medial Proximal Tibial Angle (MPTA) and Posterior Proximal Tibial Angle (PPTA) were evaluated radiologically. If the MPTA is between 85° and 90°, PPTA is between 77° and 84° and <3 mm stepping, this is considered as anatomical reduction.

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 15.0 for windows. Categorical variables were expressed as frequencies and continuous variables were expressed as mean and standard deviations. The Shapiro-Wilk test was used to assess normal distribution of the continuous data. The Student t test and chi square test were used to compare continuous variables and categorical variables between anterior and bilateral group. A p value less than 0.05 was indicative of statistical significance for all comparisons.

RESULTS

A total of twenty-six patients (20 males and 6 females) with tibial plateau fractures were included in the study. Twelve of the patients were selected from those using anterior midline incisions, and fourteen from those using double incisions as anterolateral and posteromedial incisions. The mean age of the patients was 50.8 (24-76) years. The distribution of patients according to fracture classification was 9 Schatzker type-6, 17 Schatzker type-5. The average follow-up time was 34,1 months (24.5-42.2).

Union in the anterior midline was 11.07 (±1.68) weeks and bilateral union was 9.96 (±1.35) weeks (p: 0.074). Rasmussen scoring was 14.83 (±2.16) in the anterior group and 14.57 (±2.13) in the bilateral group (p:0.760). The MPTA was 85.35 (±3.97) degrees in the anterior group, and the MPTA was 86.40 (±3.74) degrees in the bilateral group (p: 0.492). PPTA was 80.77 (±1.95) degrees in the anterior group, and PPTA was 80.85 (±1.78) degrees in the bilateral group. HSS score was 70 (±9.02) in the anterior group and HSS score was 71.71 (±1.15) in the bilateral group (p:0,681). Rom was measured as 101.67 (±12.67) degrees in the anterior group and 107.86 (±13.54) degrees in the bilateral group (p: 0.243). The VAS anterior group was 2.83(±1,64) and the VAS bilateral group was 3.36 (±2.09) (p:0.491). Instability was seen in one patient in the anterior group and one patient in the bilateral group (p:1). Infection was observed in one patient in the anterior group and in three patients in the bilateral group (p:0.598) (**Table 1**).

Table 1. Clinical and radiological results of patients with tibial plateau fracture

	Group	N	Mean	Standart deviation
Age	Anterior	12	44.83 years	10.83
	Bilateral	14	55.93 years	11.12
Bony union	Anterior	12	11.07 weeks	1.68
	Bilateral	14	9.96 weeks	1.35
Follow-up time	Anterior	12	34.69 months	5.69
	Bilateral	14	33.62 months	6.13
Rasmussen scoring system	Anterior	12	14.83 points	2.16
	Bilateral	14	14.57 points	2.13
MPTA	Anterior	12	85.35 degrees	3.97
	Bilateral	14	86.40 degrees	3.74
PPTA	Anterior	12	80.77 degrees	1.95
	Bilateral	14	80.850 degrees	1.78
HSS	Anterior	12	70.00 points	9.02
	Bilateral	14	71.71 points	11.55
ROM	Anterior	12	101.67 degrees	12.67
	Bilateral	14	107.86 degrees	13.54
VAS	Anterior	12	2.83 points	1.64
	Bilateral	14	3.36 points	2.09

MPTA: Medial Proximal Tibial Angle, PPTA: Posterior Proximal Tibial Angle, VAS: visual analogue scale, HSS: Hospital for Special Surgery, ROM: Range of Motion.

DISCUSSION

Schatzker Type V and VI plateau fractures, particularly posterior fractures that distort the joint, are often challenging fractures. Therefore, many different treatment strategies such as anterolateral, posteromedial incisions and fibular osteotomy have been developed (4–7). Currently, many new approaches are reported, and the anterior midline approach is one of them.

The need for knee arthroplasty may arise, as the gradation of the joint after these fractures can lead to pain and arthrosis. There are many studies in the literature related to this (8–11). None of our patients needed arthroplasty treatment until this study.

Chakraverty et al. (12) recommend anterior midline incision in patients with tibial tubercle fracture and lateral plate placement. In their study with seventeen patients, Çakar et al. (13) reported that the joint visibility achieved by entering the anterior midline incision in the medial parapatellar was satisfactory for fracture reduction.

In the colon-specific plating method performed by Selvaraj et al. (4), the anterior incision may not be sufficient for the posterior plate only, out of the single plate, double plate and triple plate used, but we suppose that this rosin can be resolved with anterior-posterior screws since the joint can be seen easily.

We believe that fewer incisions will reduce soft tissue complications, in parallel with the study by Kumar et al. (14), in which they published the results of less extensile indirect reduction in 2021, though we believe that reduction by visualizing the joint would be more appropriate since indirect reduction of intra-articular fractures often results in failure.

In the study by Cıtak et al. (15) in which they compared the results of single plate and double plate in bicondylar fractures without posteromedial fractures, they could not find a significant clinical difference. Although the double plate provides a more rigid stability biomechanically, it has not been seen clinically. In our opinion, this is valid for posterior fracture fragments. We believe that if an articular surface that does not have a step with an adequate sagittal plane is provided with screws, it will give clinically sufficient results.

In the study of Wang et al. (7) in 2021, they showed that the combined use of double lacquer and compression screws decreased the rate of reduction loss and increased clinical satisfaction. In our study, we believe that a reduction reinforced with double plate and anterior posterior compression screws, which are used more frequently in anterior incision, is effective on good results.

In a study conducted by Raj et al. (16) on thirty patients with tibial plateau fractures in 2021, they reported good to excellent results with bilateral incision double plate. Various complications were encountered in five patients, but there was no non-union or malunion as a result. They reported radiological results that were close to anatomical results. Similar results were obtained in both groups in our study.

According to Mandal et al. (17), their series of Schatzker V/VI fractures, a single midline incision resulted in a higher rate of postoperative skin necrosis compared to the double incision technique. However, such a result

was not encountered in our study, and we suspect that the possible difficulty is excessive detachment of the skin. In contrast, Barei et al. (4) reported deep wound infection in 8.4% of them after combined anterolateral and posteromedial combined tibia operations for bicondylar tibial plateau fractures.

Guild et al. (18) reported that anterior midline incision is a safe and adequate surgical approach when performed by an experienced surgeon, and there is no difference in terms of infection or reoperation with bilateral incision, as a result of the largest series of retrospective studies using 41 anterior midline incisions in 92 patients and 51 bilateral incisions. Similar results were obtained in our study, and we did not see any difference between the two approaches in terms of postoperative clinical satisfaction.

Lifting the skin as a flap on the muscle fascia without separation is important with regard to possible skin necrosis. In the 2013 study by Cho et al. (19), when the muscle and skin were separated as flaps, it was stated that the functional status of postoperative patients may be different as a result of deltoid and MCL damage in the medial region and LCL and other collateral ligament damage in the lateral region. However, in a complex fracture involving the joint, it is impossible to objectively demonstrate that the functional outcome is impaired.

This study has many limitations. Open fractures were not included because their natural course is prone to infection. Not all surgical operations are performed by the same surgeon, and surgical experience may make a difference between the results. Although the classification of fractures is similar, some surgeons' medial parapatellar incision and some surgeons' access to the joint by removing the lateral and medial meniscus, may result in different results in the same approach, but our number of patients was insufficient to evaluate this. Another shortcoming of the study is that radiological results cannot be made by seeing the articular surface in detail with tomography, because it poses an ethical problem to perform postoperative computed tomography for each patient. None of our patients had had arthrosis leading to knee replacement yet, but we think that if this happens, the anterior midline incision will be a safer approach. The principal question concerning the anterior midline incision is the reduction of posterior fractures. Visual reduction of the knee joint with either the medial parapatellar or lateral or medial approach and fixation of the posterior elements with screws is sufficient in most cases. Although the mechanical superiority of the posterior plate is not discussed, we believe that its necessity should be discussed.

CONCLUSION

The anterior midline incision is an adequate approach for the reduction of many fractures involving the joint. In this approach, it is important not to detach the skin, but to lift it as a flap over the muscle fascia in terms of possible skin necrosis. It is satisfactory in terms of visibility of intra-articular fractures and advantageous in terms of prosthetic surgeries which may be needed in the future.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Samsun Training and Research Hospital Clinical Researches Ethics Committee (Date: 02.02.2022, Decision No: 2022/2/9).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: The authors declare that this study has received no financial support.

Author Contributions: The author declares that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Comparison of diagnostic methods in onychomycosis

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ABSTRACT

Aim: Onychomycosis is a chronic fungal infection of the nail bed, plate, or matrix. This study aimed to compare the sensitivity of three diagnostic methods in the diagnosis of onychomycosis.

Material and Method: This study included 39 patients with a clinical diagnosis of onychomycosis of the toenails, who presented to Medipol Mega University Hospital between May 2019 and August 2022. Using the nail samples taken from the patients, the results of the direct microscopic examination with standard potassium hydroxide (KOH), histopathological examination performed with periodic acid-Schiff (PAS) staining, and fungal agents that grew in fungal culture were noted.

Results: Eleven (28.2%) patients were female, and 28 (71.8%) were male, with the mean age being 43.1±13.9 years. Of the patients, 53.8% had distal subungual onychomycosis and 46.2% had total subungual onychomycosis. The mean disease duration was 38.8±24.5 (12-120) months. Fungal infection was detected on direct microscopic examination with standard KOH in 66.7% of the patients, culture growth in 38.5%, and PAS staining on histopathological examination in 71.8%, and the sensitivities of these methods were determined as 74.3%, 49.2%, and 80%, respectively, with the negative predictive values being 30.8%, 16.7%, and 36.4%, respectively.

Conclusion: Among the investigated methods, histopathological examination with PAS staining was found to have the highest sensitivity and negative predictive value in the diagnosis of onychomycosis.

Keywords: Onychomycosis, potassium hydroxide examination, periodic acid-Schiff staining, fungal culture

INTRODUCTION

Onychomycosis is a fungal infection of the nail that causes the thickening and discoloration of the affected nail plate (1). According to recently published studies, the global prevalence of onychomycosis approximately 5.5% in the general population (2,3). Onychomycosis accounts for 50% of all nail diseases and is the most common disorder affecting the nail unit (1). Predisposing factors for this fungal infection include diabetes, human immunodeficiency virus, immunosuppression, diabetes, obesity, smoking, trauma, tinea pedis, psoriasis, and older age (4). Onychomycosis most commonly involves the toenails, usually affecting the first (great) toenail. It typically presents as the white or yellow-brown discoloration of the nail and often causes the hyperkeratosis of the nail bed, which results in varying degrees of onycholysis (1,4). Organisms that cause onychomycosis include dermatophytes, non-dermatophyte molds (NDMs), and yeasts. Dermatophytes, particularly *Trichophyton mentagrophytes* and *Trichophyton rubrum*, are responsible for approximately 90% of toenail onychomycosis cases, and the remaining dermatophyte infections are caused by *Epidermophyton floccosum*, *Microsporum* species, *Trichophyton verrucosum*, *Trichophyton tonsurans*, *Trichophyton violaceum*, *Trichophyton soudanense*, *Trichophyton krajdenii*, *Trichophyton equinum*, and Arthroderma species (1,5,6). The most common NDM organisms associated with onychomycosis are *Aspergillus* spp., *Scopulariopsis brevicaulis*, *Fusarium* spp., *Acremonium* spp., *Neoscytalidium* spp., and Syncephalastrum spp. (7,8). Yeast-induced onychomycosis is rare. Candida albicans accounts for approximately 70% of yeast-induced onychomycosis cases (9). There is a need for effective and sensitive diagnostic tests that can confirm the diagnosis of onychomycosis before initiating systemic antifungal therapy. Currently, the main diagnostic methods for onychomycosis are direct microscopic examination, histological examination, and culture analysis (10). However, direct microscopic examination with potassium hydroxide (KOH) and histological examination with periodic acid-Schiff (PAS) staining cannot identify fungal species. Therefore, despite the disadvantage of being the slowest

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method, culture analysis has the benefit of identifying the species causing onychomycosis (11). The current study aimed to compare the diagnostic value of direct microscopic examination, histopathological examination, and fungal culture analysis in the clinical diagnosis of onychomycosis.

MATERIAL AND METHOD

The study was carried out with the permission of İstanbul Medipol University Clinical Researches Ethics Committee (Date: 26/08/2022, Decision No: E-10840098-772.02-4808). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study included 39 patients with onychomycosis who presented to the dermatology outpatient clinic of Medipol Mega University Hospital between May 2019 and August 2022. The patients' age, gender, comorbidities, disease duration, and examination findings were recorded from their files. The results of the direct microscopic examination with KOH, histopathological examination with PAS staining, and fungal agents that grew in culture were noted.

Direct Microscopic Examination

For this examination, a 10-20% KOH solution was utilized as the most commonly used material (10). The sample taken from the suspicious nail was placed on a slide, one or two drops of this solution were dropped onto the slide, which was then covered with a coverslip. The slide was left in a petri dish with moist blotting paper for 30-60 minutes and examined under a light microscope.

Histopathological Examination

Sections of 3-µm thickness were taken from paraffin blocks, placed on positively charged slides, and kept in an oven at 60 °C for 30 minutes. Histochemical staining was automatically performed with the Ventana Benchmark® Special Stain device (Ventana, Roche, USA) using the PAS staining kit, BSS deparaffinization, BSS liquid cover slip, and BSS wash solutions. This device has a two-stage operating system, in which the deparaffinization process is performed in the first stage and in the second. PAS, background staining (hematoxylin), and bluing were performed. After the staining was completed, the sections were passed through an increasing alcohol series (80%, 90%, and 96%) and left in xylene for two minutes to remove chemicals. The samples were covered with a film using an automatic closure device (Tissue Single Film, Sakura, Japan). The preparations were analyzed under a light microscope (Eclipse Ni, Nikon, Japan).

Fungal Culture

Specimens were inoculated to Sabouraud agar (Becton Dickenson, USA) and dermatophyte agar (Becton Dickenson, USA) and incubated at 25 °C for 28 days (12). Media were monitored every 24 hours in terms of colony growth. When visible colonies were formed, the microscopic examination was performed. Identification was made based on the presence and shape of microconidia and macroconidia, as well as the shape of the colonies.

Statistical Analysis

SPSS 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses. As descriptive statistics, numbers and percentages were used for categorical variables, and mean, standard deviation, minimum, and maximum values for numerical variables. Differences between the screening tests were examined with the McNemar test. Taking any test positivity as the gold standard, the effectiveness of each screening test was evaluated based on sensitivity defined as the test's ability to produce a positive result in individuals that truly had the disease, selectivity as the negative test rate among the individuals without the disease, positive predictive value as the probability that the individuals with a positive test truly have the disease, negative predictive value as the probability that the individuals with a negative test do not have the disease, accuracy as the rate of correct identification of the individuals with and without the disease, and negative likelihood ratio as the ratio of the probability of an individual with the disease testing negative to the probability of an individual without the disease testing negative. The statistical alpha significance level was accepted as $p < 0.05$.

RESULTS

The study included a total of 39 patients with a diagnosis of onychomycosis, 11 (28.2%) female and 28 (71.8%) male, with a mean age of 43.1±13.9 years. Distal subungual onychomycosis was present in 53.8% of the patients and total dystrophic onychomycosis in 46.2%. The mean disease duration was 38.8±24.5 months, with a minimum value of 12 and a maximum value of 120 months. **Table 1** summarizes the characteristics of the patients participating in the study.

Table 1. General characteristics of the patients

Age, mean±SD (min-max/median)	43.1±13.9 (19-75/41)
Gender, n (%)	
Female	11 (28.2%)
Male	28 (71.8%)
Distal subungual onychomycosis, n (%)	21 (53.8%)
Total dystrophic onychomycosis, n (%)	18 (46.2%)
Disease duration (month), mean±SD (min-max/median)	38.8±24.5 (12-120/36)

SD: Standard deviation

Of the patients, 66.7% tested positive in the direct microscopic examination with KOH, 71.8% in the histopathological examination with PAS staining, and 38.5% in the culture analysis. The rate of positivity detected

in the culture analysis was lower compared to the remaining diagnostic methods. The rates negative test results were 33.3%, 28.2%, and 61.5% for KOH examination, PAS staining, and culture analysis, respectively. **Table 2** presents the rates of positive and negative test results of the cases according to the diagnostic methods.

Table 2. Positivity and negativity rates of the diagnostic methods

Onychomycosis	KOH examination		Culture		PAS staining	
	N	%	n	%	n	%
Positive	26	66.7	15	38.5	28	71.8
Negative	13	33.3	24	61.5	11	28.2

KOH vs. culture, p = 0.02; KOH vs PAS, p = 0.774; culture vs PAS, p = 0.011, KOH: Potassium hydroxide; PAS: Periodic acid-Schiff

The histopathological examination with PAS staining was the method with the highest sensitivity (80%) and negative predictive value (36.4%). The sensitivity of the direct microscopic examination with KOH was 74.3%, and that of the culture analysis was 49.2%. The negative predictive values of the KOH examination and culture analysis were found to be 30.8% and 16.7%, respectively (**Table 3**).

The distribution of the fungal agents that grew in culture was as follows: Trichophyton spp. in nine cases, *Aspergillus* spp. in three, Penicillium spp. in one, and Candida spp. in one. The study data are summarized in **Table 4**.

Table 3. Sensitivity percentages obtained as a result of analyses performed with the diagnostic methods

	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %	Accuracy %
KOH	74.3	100%	100%	30.8	76.9
Culture	49.2	100%	100%	16.7	48.7
PAS	80.0	100%	100%	36.4	82.1

KOH: Potassium hydroxide; PAS: Periodic acid-Schiff

Table 4. Summary of the study data

Patient number	Age	Gender	DSO	TDO	Disease duration (month)	KOH	PAS	Culture	
1	70	M	+	-	24	+	+	+	Trichophyton
2	61	M	-	+	60	-	+	-	-
3	29	M	+	-	24	-	-	+	*Aspergillus*
4	31	M	-	+	60	+	+	-	-
5	48	M	-	+	12	+	+	-	-
6	40	M	-	+	48	+	+	-	-
7	44	M	-	+	48	+	+	-	-
8	26	M	+	-	12	+	+	+	Trichophyton
9	39	F	+	-	36	+	+	-	-
10	34	F	-	+	24	+	+	-	-
11	40	M	-	+	24	+	+	+	Trichophyton
12	19	M	+	-	36	+	+	-	-
13	64	F	-	+	24	+	+	-	-
14	31	M	+	-	24	-	+	-	-
15	46	M	+	-	60	+	+	-	-
16	59	M	+	-	72	+	-	-	-
17	28	M	+	-	12	-	-	+	Candida
18	55	F	+	-	60	-	+	-	-
19	41	M	-	+	36	+	+	-	-
20	30	F	-	+	48	-	-	-	-
21	43	F	-	+	12	-	-	-	-
22	72	M	+	-	60	+	+	-	-
23	27	F	+	-	72	-	-	-	-
24	51	F	+	-	60	+	+	-	-
25	35	M	+	-	24	+	+	-	-
26	25	M	+	-	24	+	-	-	-
27	47	F	+	-	24	-	+	+	*Aspergillus*
28	75	M	-	+	36	+	+	+	Penicillium
29	22	F	-	+	12	-	+	+	Trichophyton
30	40	M	-	+	60	+	+	-	-
31	31	F	+	-	60	+	-	+	Trichophyton
32	50	M	-	+	12	+	+	+	Trichophyton
33	45	M	+	-	24	+	-	+	Trichophyton
34	47	M	-	+	12	-	-	-	-
35	57	M	+	-	12	-	+	+	*Aspergillus*
36	46	M	-	+	60	-	+	-	-
37	51	M	+	-	72	+	-	+	Trichophyton
38	41	M	-	+	120	+	+	+	Trichophyton
39	40	M	+	-	12	+	+	+	Penicillium

KOH: Potassium hydroxide; PAS: Periodic acid-Schiff; F, Female; M, Male; +: Positive result; -: Negative result; DSO: Distal subungual onychomycosis; TDO: Total dystrophic onychomycosis

The microscopic images of fungal hyphae and yeast visualized using the three diagnostic techniques are summarized in **Figure 1**.

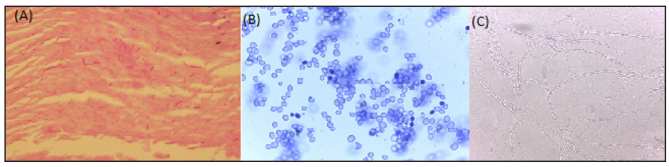

Figure 1. Microscopic images. A: Histochemical examination of fungal hyphae with periodic acid-Schiff staining (x200); B: *Candida* yeast cells stained with methylene blue (x40); C: Direct microscopic examination of fungal hyphae with potassium hydroxide

DISCUSSION

Onychomycosis is one of the most common fungal diseases. Direct microscopic examination with KOH is a fast and inexpensive diagnostic method for onychomycosis. However, when using this method, false negative results may be obtained due to the examination of the infected nail not containing any fungal hyphae, the poor quality of the KOH solution, the presence of a history of topical and systemic treatments, and the insufficient experience of the clinician (13-16). Furthermore, secondary contamination and air bubbles mimicking fungal structures can produce false positive results. In the literature, the positivity rates of the direct microscopic examination with KOH in onychomycosis vary between 32 and 96% (17-22). In many studies, the positivity rate of this diagnostic method was found to be lower compared to the histopathological examination with PAS staining and higher compared to the culture analysis (17,18,23-25); however, there are also researchers reporting that the direct microscopic examination with KOH had the lowest positivity rate (19,20). In contrast, in two studies conducted in Turkey, Aydıngöz et al. (21) and Ceren et al. (22) determined the KOH method to have the highest positivity at 96% and 85%, respectively. In onychomycosis, the sensitivity of this test varies in a wide range from 44 to 92% (17-20,22,26-29). It was found to be the most sensitive method in the diagnosis of onychomycosis by Ceren et al. (22) (92%) and Hsiao et al. (27) (87%). However, Wilsmann-Theis et al. (26) determined that the KOH method had the lowest sensitivity with a rate of 48%. In the current study, the positivity and sensitivity rates of the direct microscopic examination with KOH were 66.7% and 74.3%, respectively. These rates were lower than the histopathological examination with PAS staining and higher than the culture analysis.

In the literature, the positivity and sensitivity rates of the culture analysis are generally found to be lower compared to the histopathological examination with PAS staining and direct microscopic examination with KOH. The culture positivity rate as reported to be low (19%) by Ceren et al. (22), higher (52%) by Gianni et al. (30) and vary between 19 and 52% in other studies (17,21,23-25,28). However, the absence of growth in culture does not exclude the diagnosis of onychomycosis. Among the reasons for negative results are insufficient analysis material, the incorrect placement of samples in the culture medium, material being kept in the culture medium longer than required, contamination with or growth of secondary pathogens, removal of nail material from the distal portion that does not contain live fungi, and the use of topical or systemic antifungals. Therefore, positivity increases in repeat culture analyses. In a study by Gupta (31), when the culture analysis was performed once, the positivity rate was 44.5%, but when it was performed four times, the positivity rate increased to 63.7%. Test results are affected by differences in the sampling and handling of clinical specimens in centers, skill levels, or clinical samples (11). In the literature, the sensitivity of the culture analysis varies between 20 and 70% (17-20,22,26-29). In a study on onychomycosis, Jeelani et al. (19) found the sensitivity of the culture analysis to be as high as 70%; however, this rate was lower compared to other diagnostic methods. Consistent with the literature, in the current study, the positivity and sensitivity rates of the culture analysis were 38.5% and 49.2%, respectively, but it had the lowest sensitivity among the three diagnostic methods. Although this analysis allows for the fungal agent to be classified as a dermatophyte, non-dermatophyte mold, or yeast, it does not provide information on whether the growing agent is a true pathogen or there is any contamination (21,31). Grover et al. (23) detected fungi in 44% of 120 cases, and 70.2% of these positive cases were identified to have Trichophyton spp. Hajar et al. (32) identified Trichophyton spp. in 80% of positive cultures. In another study, Trichophyton spp. were also shown to be the most isolated organisms (33). In the current study, Trichophyton spp. grew in 60% of the positive cultures.

In the literature, it has been shown that the most sensitive method in the diagnosis of onychomycosis is the histopathological examination with PAS staining. In previous studies, the positivity of this test varied between 47 and 90%, and its sensitivity ranged from 80 to 92% (13,19-26,28-30,33). The PAS method was reported to have a high sensitivity rate of 80% by Karimzadegan-Nia et al. (29), 82% by Wilsmann-Theis et al. (26), 90% by Shenoy et al. (18), 91.6% by Jeelani et al. (19), and 92% by Weinberg et al. (20). However, in other studies, despite the high sensitivity rates of this test (80, 81, and 90%), this method still had lower sensitivity values compared to the direct microscopic examination with KOH (21,22,27). In the current study, the histopathological examination with PAS staining had the highest positivity (71.8%) and sensitivity (80%).

The rates of negative predictive values of the direct microscopic examination with KOH, histopathological examination with PAS staining, and culture analysis were previously reported as 53%, 42%, and 10%, respectively by Ceren et al. (22), 58%, 77%, and 43%, respectively by Weinberg et al. (20), and 50%, 40%, and 28%, respectively by Hsiao et al. (27). In the current study, the negative predictive value was 30.8% for the KOH method, 36.4% for the PAS method, and 16.7% for the culture analysis. The histopathological examination with PAS staining had the highest negative predictive value.

CONCLUSION

This study investigated the sensitivity of the direct microscopic examination with KOH, histopathological examination with PAS staining, and culture analysis in the diagnosis of onychomycosis. The histopathological examination with PAS was found to be superior to the remaining two methods in the diagnosis of onychomycosis, with a high negative predictive value and sensitivity. The culture analysis had the lowest sensitivity and negative predictive value.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Medipol University Clinical Researches Ethics Committee (Date: 26/08/2022, Decision No: E-10840098-772.02-4808).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Analysis of perinatal outcomes of pregnancies from consanguineous marriages in a tertiary hospital in Bursa, Turkey

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ABSTRACT

Aim: In this article, we aimed to contribute to the outcomes of the consanguineous marriage literature by analyzing fetal results in this population.

Material and Method: We included 185 patients in this retrospective research. Demographic, clinical, ultrasonographic and delivery data were received from electronic patient records. Also, we recorded the postnatal results, and findings of the infants. By combining all the data, we reported a descriptive analysis of the results of our consanguineous marriage cases with perinatology follow-up.

Results: We had 231 pregnant women in the study, and their mean age was 28.9 years. 117 (50.6%) of the pregnant women had first-degree, and 114 (50.4%) had second-degree consanguineous marriages. Fetal findings were evaluated as usual in 157 (68%) of the pregnant in the ultrasonographic scans performed between prenatal 20-24 weeks of gestation. When we look at the first postnatal examinations of the babies, no abnormal findings were in 134 babies (58.8%). Twenty-two infants (9.6%) were followed up in the neonatal intensive care unit with the diagnosis of transient tachypnea of the newborn, and phototherapy was required in 14 infants (6.1%) due to hyperbilirubinemia. The number of cases requiring surgical intervention after delivery or with significant life-threatening anomalies included 56 findings in 32 infants. There were spina bifida cases in 8 infants and hydrocephalus in 9 infants.

Conclusion: There was an increased level of congenital anomalies associated with consanguineous marriages. Health care centers should educate individuals regarding the negative role of cousin marriages leading to abnormalities in children.

Keywords: Consanguinity, perinatology, congenital abnormalities, down syndrome

INTRODUCTION

Consanguineous marriage (CM) has been traditionally practiced by many societies worldwide since ancient times (1). Consanguinity is a mixture of two Latin words: "con" means similar, and "sanguineus" means blood. It indicates an association between people who have an identical forefather or belong to the same blood. The kindred ship is often referred to as an association shared by two biologically related people (2). In the medical literature, it is generally defined as the union of a second cousin or closer couple (3). The most common form of CM is between first cousins of both mothers and fathers. Consanguinity is a cultural practice in many countries, and around 10% of the population worldwide are married to biological or blood relatives (1).

The prevalence of CM, the union between two people who are related as second cousins or closer, varies globally, with rates as low as 5% in the USA, Western Europe, and Australia and up to 70% in regions such as the Middle East (4).

Marriage between related individuals has resulted in several adverse outcomes among children. Several studies have reported an increased risk of death among the children of consanguineous couples. The most commonly studied and well-known association with CM is congenital anomalies. Offspring of related individuals are more likely to have rare autosomal recessive diseases that are uncommon in children of non-consanguineous couples. Absolute risk changes by population, and the outcome was 1.7–2.8% higher for the children of first cousins than those from non-related couples (4–6).

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Consanguineous marriage is one of the predisposing factors for multifactorial complications, like obesity, cardiovascular disorders, diabetes, and malignancies, which influence reproductive outcomes (7,8). These marriages are associated with higher rates of congenital disabilities, as are several single-gene and multifactorial diseases (9,10).

CM may also result in spontaneous abortion (SAB), a common outcome occurring in 15–20% of all clinically recognized pregnancies. Chromosomal abnormalities are implicated in approximately 50% of early losses (4,11). It is recommended that consanguineous couples be offered genetic counseling to discuss the increased risk of recessive disease in their offspring and the increased risk of stillbirth or perinatal death (5).

In this article, we reported the obstetric analysis of consanguineous marriage cases who applied to our obstetrics outpatient clinics and had perinatology follow-ups with any fetal reason. We aim to contribute to the results of the consanguineous marriage literature by analyzing fetal outcomes in this population.

MATERIAL AND METHOD

The study was carried out with the permission of Bursa Yüksek İhtisas Training and Research Hospital Clinical Researches Ethics Committee (Date: 24.08.2022, Decision No: 2011-KAEK-25 2022/08-15). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this retrospective study, we included 231 pregnancies who applied to our tertiary care hospital between 2019-2022 and were followed up by perinatology due to consanguineous marriage. In our department, in our daily practice, first-trimester drug use, bad obstetric history, excessive first-trimester nuchal translucency, high risk detected in double triple or quadruple test, a major or soft anomaly sign detected on ultrasonography, placental invasion anomaly, consanguineous marriage, or We refer pregnant women with a history of babies with abnormalities in their previous pregnancy to perinatology control. In this study, we evaluated only the patients included in perinatology follow-up due to consanguineous marriage. Thus, we aimed to make a homogeneous contribution to patient standardization.

Demographic, clinical, ultrasonographic, prenatal genetic diagnosis, and delivery data were obtained from electronic patient records. We recorded the postnatal examination findings, gestational week, fetal birth weight, intensive care observations, and diagnoses of the infants. Pathological conditions detected as a result of the examination were divided into groups according to organ systems. All couples were told to receive genetic counseling and to apply to the genetic diseases' diagnosis-screening department.

We also noted the birth findings of the mothers, the birth complications, if any, and the mode of delivery.

Statistical Analysis

For proper statistical analyses, Windows-based SPSS 24.0 statistical analysis program was used (SPSS Inc., USA). To determine whether they were normally distributed or not, variables were examined via visual (histograms, probability plots) and analytical methods (Shapiro-Wilk's test). Variables were descriptively specified as mean±standard deviation (X±SD), mean difference between groups, 95% confidence interval (95%CI), median (minimum-maximum (min-max)), U value, frequency (n) and percentage (%).

RESULTS

In this study, we analyzed the follow-up of consanguineous pregnancies who applied to the perinatology outpatient clinic of our tertiary hospital and whose obstetric and neonatal outcomes are also available. We had 231 pregnant women in the study, and their mean age was 28.9 years. 117 (50.6%) of the pregnant women had first-degree, and 114 (50.4%) had second-degree consanguineous marriages. All pregnancies were singleton pregnancies. While the ethnicity of 191 (82.7%) patients was Turkish, the race of 40 patients (17.3%) was Syrian. One hundred forty-five of the deliveries were by cesarean section (63.6%), and 83 were by vaginal delivery (36.4%). Among the indications for cesarean section, the most common reason was previous uterine surgery (n=70, 48%). Other causes were acute fetal distress (n=43, 29%), cephalopelvic disproportion (n= 18, 1.2%), surmaturation (n=9, 0.6%), other (n=5, 0.3%), respectively. Three pregnancies were terminated after amniocentesis with the diagnosis of Down syndrome (The ages of these pregnant women were 23, 25 and 35.). The mean weight of babies born in the 2nd or 3rd trimester was 2920±565.4 grams. The third trimester birth weight was 2984.9±508.2 grams, while the second trimester was 604±104 grams. The median value of the weeks of birth was 38 weeks (24-40). While 149 (65.4%) babies were given to their mothers after birth, 77 (33.3%) were followed in the neonatal intensive care unit. Only 34 of the pregnant women who were offered genetic counseling were interested in this issue, and this rate remained at 14 percent among all pregnant women. The relevant analysis is summarized in **Table 1**.

Table 1. Descriptive analyses of values regarding the mothers and the babies

Characteristics of mothers and babies	Pregnant women (n= 231) X±SD/Median (min-max)
Age (year)	28.9 ± 6.9
Parity	2 (0-6)
Week of birth	38.3 (24-40)
Birth weight (gr)	2920±565.4
Postpartum with mother, breastfeeding (n;%)	149; 65.4%
Neonatal intensive care (n;%)	77; 33.3%
Intrauterine ex fetus (n;%)	2; 0.8%
Postpartum death in first 24 hour (n;%)	6; 2.6%
Termination (n;%)	3; 1.3%
Degree of kinship (n; %)	
First degree	117 (50.6%)
Second degree	114 (%50.4)
Race	
Turkish	191 (82.7%)
Syrian	40 (17.3%)
Method of delivery	
Ceserean	145 (62.8%)
Vaginal delivery	83 (35.9%)
Termination	3 (1.3%)

gr: gram, n: frequency, %: percentage, X: mean, SD: standard deviation, min: minimum, max: maximum. Descriptive analyses were presented using (X±SD), median (min-max) and (n;%) for normally distributed, non-normally distributed and categorical variables, respectively.

Fetal findings were evaluated as usual in 157 (68%) of the pregnant in the ultrasonographic scans performed between prenatal 20-24 weeks of gestation. Facial defects were observed in 8 (3.4%) of the other fetuses (2 retrognathia, 4 cleft palate-lip, 2 cystic hygroma). There were extremity anomalies in 11 fetuses (4 short limbs, 3 femur bowing) and genitourinary abnormalities in 6 fetuses (4 pelviectasis, 2 polycystic kidneys). In comparison, there were gastrointestinal system findings in 16 (6.9%) fetuses (5 hyperechoic bowels, 4 intestinal atresias, 4 diaphragmatic herniae);and we detected cardiac results (hyperechoic heart in 8 fetuses, vsd in 3 fetuses) in 15 fetuses. The most common finding we noticed in the pregnant women we screened belonged to the central nervous system and these findings were present in 19 fetuses (8.2%). Anomaly involving more than one system was present in ten babies. The entire analysis is summarized in **Table 2.**

While the diagnosis of pregnancy in labor (n=93, 40.8%) constituted the majority of the delivery indications, the number of cases with a history of cesarean section reaching 39 weeks was 51 (22.4%). While delivery was decided due to intrauterine growth retardation in 19 fetuses, 20 pregnant women were subjected to labor induction due to surmaturation (>41 weeks gestational age). The median Apgar values at the 1st minute were 7 (4-9). When we look at the first postnatal examinations of the babies, no abnormal findings were in 134 babies (58.8%). While 22 infants (9.6%) were followed up in the neonatal intensive care unit with the diagnosis of transient tachypnea of the newborn, phototherapy was required in 14 infants (6.1%) due to hyperbilirubinemia. The number of cases requiring surgical intervention after delivery or with significant life-threatening anomalies included 56 findings in 32 infants. More than one anomaly was present in 10 infants. There were spina bifida cases in 8 infants, hydrocephalus in 9 infants, 2 omphaloceles, a cardiac anomaly in 6 infants, intestinal atresia in 4 infants, and 3 diaphragmatic hernia cases. Four babies were born with cleft palate-lip finding. Down syndrome morphology was detected in two babies and both of them were born as intrauterine ex fetuses. One infant had signs of metabolic disease, and one infant had anal atresia. The complete analysis of birth outcomes is available in **Table 3**.

Table 2. Descriptive analysis table of second trimester fetal ultrasonographic screening findings

Findings	Pregnant women (n= 231)
Usual (n; %)	157; 68%
Fascial defects (n; %) Retrognathia (n=2) Cleft palate-lip (n=4) Cystic hygroma (n=2)	8; 3.4%
Extremity anomalies (n; %) Short limbs, achondroplasia (n=4) Bowing of femur (n=3) Claw hand (n=1) Polydactyly (n=1) Rocker bottom feet (n=1) Pes equinovarus (n=1)	11; 4.6%
Genitourinary anomalies (n; %) Pelviectasis (n=4) Polycystic kidney (n=2)	6; 2.6%
Gastrointestinal system findings (n; %) Hyperechoic bowels (n=5) Intestinal atresia (n=4) Diaphragmatic hernia (n=3) Omphalocele (n=2) Anal atresia (n=1) Small gallbladder (n=1)	16; 6.9%
Cardiac findings (n; %) Hyperechoic focus (n=8) Ventricular septal defect (n=3) Cardiomegaly (n=2) Hypoplastic heart (n=1) Hydrothorax (n=1)	15; 6.4%
Nervous system abnormalities (n; %) Hydrocephalus (n=9) Spina bifida (n=8) Cerebellar hypoplasia (n=2) Vermian hypoplasia (n=1) Mega cisterna magna (n=2)	19; 8.1%
Others Kyphoscoliosis (n=2) Hydrops fetalis (n=4)	6; 2.6%
Obstetric findings (n; %) Polyhydramnios (n=6) Oligohydramnios (n=4) Intrauterine growth retardation (n=2) Placenta previa (n=2) Placenta percreata (n=1)	15; 6.4%

n: frequency, %: percentage. Descriptive analyses were presented using (n;%) for categorical variables. There is more than one finding in the same case, and n and percent values were determined according to the total number of volunteers

Table 3. Analysis table according to the findings of the babies in the first 24 hours after birth

Findings	(n= 228) Median (min-max)
Healthy baby (n; %)	134; 58.7%
Transient tachypnea of the newborn (TTN) (n; %)	22; 9.6%
Hyperbilirubinemia (n; %)	14; 6.1%
Sacral dimple (n; %)	16; 7%
Gastrointestinal system findings (n; %) Intestinal atresia (n=4), Diaphragmatic hernia (n=3) Omphalocele (n=2) Anal atresia (n=1)	10; 4.3%
Cardiac findings (n; %) Ventricular septal defect (n=4) Cardiomegaly (n=2) Hypoplastic heart (n=1) Hydrothorax (n=1)	8; 3.5%
Central nervous system abnormalities (n; %) Hydrocephalus (n=9) Spina bifida (n=8) Cerebellar hypoplasia (n=1) Hypotony (n=1)	19; 8.3%
Fascial defects (n; %) Cleft palate-lip (n=4)	4; 1.7%
Extremity anomalies (n; %) Short limbs, achondroplasia (n=4), Bowing of femur (n=3) Polydactyly (n=1) Pes equinovarus (n=1)	9; 4%
Genitourinary anomalies (n; %) Pelviectasis (n=1) Polycystic kidney (n=1)	2; 0.9%
Others Kyphoscoliosis (n=2) Hydrops fetalis (n=2)	4; 1.7
APGAR 1st minute score	7 (4-9)

n: frequency, %: percentage. Descriptive analyses were presented using median (min-max) and (n;%) for non-normally distributed and categorical variables, respectively. There is more than one finding in the same case, and n and percent values were determined according to the total number of volunteers.

DISCUSSION

In this article, we published our research results on the effects of inbreeding on birth outcomes, congenital malformations, and fetal growth/development/health. As genetic and environmental factors can determine such effects, there are dissimilarities among the available reports in the literature.

The concept of kinship is generally defined in clinical usage as a union between two people who are second cousins or more closely related. The most common form of consanguineous marriage worldwide is between first cousins (12,13). The estimation of consanguinity shows that about 10% of the world's population is married to a biological relative (14). However, this estimate is unclear due to the lack of information on consanguineous marriage in many South and Southeast Asian countries and Africa. It is now accepted that variables such as socioeconomic status, maternal age, maternal education, birth order, and birth intervals should be adequately controlled in evaluating the effects of inbreeding on health (6).

Consanguineous marriage is essential due to infant death, miscarriages, and fetal death. Cousin marriage is a significant cause of genetic disorders and congenital disabilities transmitted from parents to children (15). Infant deaths and fetal deaths are some of the consequences of consanguineous marriages (16,17). Cousin marriage can cause congenital heart defects (18). Congenital cardiovascular malformations are common in these associations and affect 2.4 to 8.0 in 1000 infants (19). In our study, prenatal cardiac findings were found in 15 fetuses. In contrast, cardiac pathology was present in 6 (2%) babies after birth (ventricular septal defect in 4 babies, hypoplastic right heart in 1 baby, and cardiomegaly in 2 baby). Six babies who were taken to the neonatal intensive care unit after birth died. Two of these babies had severe hydrocephalus and extremity abnormalities. One baby had a hypoplastic heart, while the other three died with prematurity signs.

The present study showed that 12% of mothers had major congenital abnormalities which required surgical intervention after delivery or had a life-threatening from consanguineous marriages. Mosayebi et al. (20) and Naveed et al. (2) determined this rate to be around 14-15% in their studies. We detected hydrocephalus in 9 infants and spina bifida in 8 infants. Anomaly involving more than one system was present in 10 babies. When we look at the ultrasonographic examination performed in the prenatal period, we found that the pelviectasis findings of 3 babies regressed (75%) after birth, and there was ventricular septal defect in 1 baby who could not be diagnosed prenatally. Naveed et al. detected brain anomalies in 26% of the babies in their study. In their study, Tomatır et al. (21) detected brain anomalies in 12 (31%) cases. In our cases, postnatal brain anomaly constituted 25% of abnormal cases.

One of the interesting parts of our study was the indifference of consanguineous couples to prenatal genetic counseling. Consanguineous couples be offered genetic counseling to discuss the increased risk of recessive disease in their offspring and the increased risk of stillbirth or perinatal death. The fact that only 34 (14%) of 231 couples received genetic counseling during the prenatal period and that other cases did not require it supports the need to increase social awareness of this issue.

There were also some limitations of our study. Some couples who applied with consanguineous marriage did not apply to our department during the follow-up and were excluded from the study, thus reducing the total number of cases. In addition, consanguineous couples were not compared with the average population and there was no control study regarding obstetric outcomes. This study is only descriptive, and we aimed

to contribute to the literature by analyzing the prenatal and postnatal findings and current consanguineous pregnancy outcomes, which we followed up on in our department.

CONCLUSION

There was an increased level of congenital anomalies associated with consanguineous marriages. A wide range of genetic disorders was seen in families having cousin marriages. There should be increased awareness among families regarding the negative impact of cousin marriage. Health care centers should educate individuals regarding the negative role of cousin marriages leading to abnormalities in children.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bursa Yüksek İhtisas Training and Research Hospital Clinical Researches Ethics Committee (Date: 24.08.2022, Decision No: 2011-KAEK-25 2022/08-15).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Quality, reliability and content evaluation of YouTube videos associated monkeypox

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ABSTRACT

Aim :Human monkeypox (HMPX) is a re-emerging infectious disease. YouTube is an effective tool for disseminating health-related information. Considering that dissemination of information about the ways of transmission and prevention of infectious diseases in public is very important. The aim of this study is to evaluate the information content and reliability of the videos about MPX on the popular and widely used video-sharing platform YouTube.

Material and Method: YouTube (http://www.youtube.com) was searched using the keyword 'monkeypox'. The number of views, likes, comments, and duration of the videos were recorded. The videos were analyzed blindly by an infectious diseases and microbiology (virology) specialist. The content was rated out of 10 points. The videos are grouped according to the uploaded source by the news agency and Physicians /Public coorperation.A DISCERN tool and the Global Quality Scale (GQS) were used to evaluate the reliability and quality of the videos.

Results: Of the 100 videos screened, 44 that met the inclusion criteria were included in the study.Our study shows that video reliability (DISCERN) and Quality Scale (GQS) of YouTube videos related to MPX uploaded by physicians and health institutions were statistically significantly higher than news agencies. In terms of content, we are on the aspect that all videos contain useful information. Cohen Kappa scores indicating inter-observer agreement were 0.802, 0.827, and 0.858 for the Content , DISCERN and the GQS scores, respectively (95% confidence interval (CI).

Conclusion: HMPX, especially during the global disease epidemic, the quality and reliable publication of useful YouTube content by Physicians /Public cooperation can help reduce and control the spread of the disease.

Keywords: Monkeypox, quality, content, reliability, YouTube

INTRODUCTION

Human monkeypox (HMPX) is a re-emerging infectious disease. Monkeypox (MPX), is an Orthopoxvirus, a genus that includes camelpox, cowpox, vaccinia, and variola viruses. Clinically, it is difficult to distinguish from smallpox. The most important distinguishing clinical characteristic that distinguishes MPX from smallpox is lymph node enlargement, which usually occurs at the onset of fever. The rash usually appears 1-3 days after the fever and lymphadenopathy have started. Usually, the rash first appears on the peripheral area of the body (face) but can cover the entire body during a serious illness. The lesions often present as first macular, then papular, then vesicular, and pustular (1).

Isolation of the virus from the lesions in the laboratory is the gold standard for the diagnosis of the disease(2). MPX is transmitted through respiratory droplets, direct contact, or fomites (3).

Pneumonia, encephalitis, sight-threatening keratitis, and bacterial infections are all possible complications of HMPX (4). Mortality rates are 1%–10% (5).

Those exposed to MPX, should be monitored for 21 days as this is the accepted upper limit of incubation period. Contagiousness is consistent with symptom onset; therefore, close contacts do not need to be isolated while asymptomatic (6).

MPX was first isolated and described in 1958 in Singapore when monkeys became ill. However, in 1970, the virus was found in a child in the Democratic Republic of the Congo. This was the first confirmed case of the virus in a person.

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Although first described in monkeys, available data suggest that African rodents are natural reservoirs. Infections have occurred in squirrels, rats, mice, monkeys, and humans. Cases outside Africa were detected in post-travel, with sporadic clusters in Ghana in 2003, Nigeria in 2018, Singapore in 2019, and the United Kingdom in 2021 (7).

Until now reported in at least 75 countries outside of Africa. The increasing number of confirmed cases in countries outside of Central and West Africa, where the virus is endemic, and the globalization of MPX are of concern to medical and public health officials (8,12).

A significant portion (if not all) of the cases described were in men who had sexual intercourse with men (MSM), and most of these cases were diagnosed in sexually transmitted infection (STI) clinics. This shows that some of those who carry the virus communicate through certain social networks and this causes the spread (9).

Social media platforms are used as a frequently used information source about health, they have a significant impact on human attitudes, behaviors, and decisions (10).

One of the most frequently used social media platforms, YouTube is an effective tool for disseminating health-related information (11).

Especially in global public health emergencies, It is important to promote accurate and reliable information through such platforms, which may contribute to preventing the spread (13).

Considering that dissemination of information about the ways of transmission and prevention of infectious diseases in public is very important in terms of preventing the spread of the disease and to our knowledge , the quality, reliability and content of MPX videos on YouTube is valuable because it is the first research article in the literature.

The aim of this study is to figure out how accurate and useful the information is in the MPX videos on YouTube, which is a popular site for sharing videos.

MATERIAL AND METHOD

YouTube (http://www.youtube.com) was searched using the keyword ‘‘Monkeypox’ between July 20, 2022 - July 23, 2022. The YouTube "relevance" filter has been applied to the default Search, as most viewers do. All selected videos have been added to the YouTube library database for further analysis .

The videos that met the inclusion criteria were analyzed in more detail (Universal resource locators (URLs), total video time, total number of comments, likes, and upload date).

The videos were analyzed blindly by an infectious diseases andmicrobiology (virology) specialist. Any discrepancies between the authors were resolved by reconsideration and consensus.

The videos are grouped according to the uploaded source by the news agency, health institution/physician. Videos that met the inclusion criteria were evaluated for reliability (DISCERN), quality (GQS), and content.

Video reliability was evaluated using the DISCERN tool. Each question was scored as yes or no, and the score was assigned as 1 or 0 points, with the total DISCERN score ranging from 0 to 5.Higher scores indicate greater reliability. The five-point Global Quality Scale (GQS), which has been used in many YouTube studies, was used to measure the overall quality of the videos. Higher scores indicate better video quality.

The content was rated out of 10 points . (microbiology, epidemiology, forms of transmission, symptoms, clinical, diagnostic testing, complications, treatment, prognosis, prevention methods (vaccine etc) . If a parameter was deemed sufficient, it received one point; if it was deemed insufficient, it received zero points.

Statistical Analysis

Inter-observer agreement was evaluated with Cohen's Kappa coefficient. All statistical tests were performed using IBM SPSS Statistics software (version 26.0). “p” value less than 0.05 was considered statistically significant. Shapiro-Wilk test was performed to assess the normality of the data. Not normally distributed DISCERN, GQS, and content were analyzed with Mann Whitney U.

Ethical Statement

No human participants or animals were included in the study. Publicly available YouTube videos were analyzed, and for that reason, ethical approval was notneeded for other similar YouTube studies (14,15).

RESULTS

Thirty of the 100 videos reviewed were in languages other than English, 14 were irrelevant, six were duplicates, and six were the experiences of patients who had contracted with MPX but were excluded from the study.As a result, 44 videos met the inclusion criteria and were analyzed in more detail. (**Figure 1**)

Cohen Kappa scores indicating inter-observer agreement were 0.802, 0.827, and 0.858 for the Content , DISCERN and the GQS scores, respectively (95% confidence interval (CI).

The authors got the title, upload date, length, number of views, number of views per day, likes, and comments from the video.

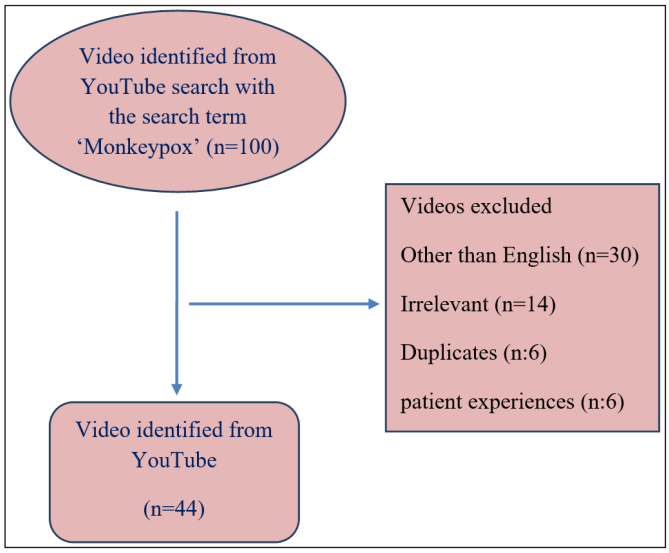

Figure 1. Criteria of including and excluding of YouTube videos

A total of 44 videos were included for analysis. Baseline features of the analyzed .(**Table 1**).

Table 1. Baseline features of the analyzed videos

Variables	Videos (n=44)
Video Content (point)	7* (2-10)
Number of views	51* (1-474)
Number of likes	527* (6-16000)
Screen time (minutes)	229* (13-2329)
Number of comment	646* (13-6868)
Source of upload	
News	n=16 36.3%
Physicians, Public coorperation	n=28 63.7%
Target audience	
Public	n=38 86.3%
Healthcare professionals	n=6 13.7%

*Data presented as median (minimum–maximum) values

The first of the countries with the most uploaded videos was the United States of America (50%).

The videos uploaded by academic Physicians / Public cooperation had higher DISCERN and GQS scores than Newsletter video sources, and the difference was statistically significant ($p < 0.005$ for both) **Table 2**.

Table 2. Quality, Reliability and Content of YouTube videos according to source

	Physician /Public coorperation n:28 63.7%	Newsletter n:16 36.3%	p
Video Content (point)	9(2-10)	7(2-10)	0.073
DISCERN	5(2-5)	4(2-5)	0.030
GQS	5(2-5)	4(2-5)	0.042

*Mann Whitney U, Data presented as median (minimum-maximum), Values of p<0.05 were accepted as signifcant and marked in bold

DISCUSSION

Our study shows that video reliability (DISCERN) and Quality Scale (GQS) of YouTube videos related to MPX uploaded by physicians and health institutions were found to be statistically significantly higher than news agencies. In terms of content, we are on the aspect that all videos contain useful information.

In studies evaluating, Ebola-related internet videos on YouTube, most of the videos were described as helpful. It was emphasized that YouTube appears to be a generally useful source of information about the epidemic and that increased efforts to disseminate scientifically accurate information are needed to avoid unnecessary panic (16,19).

Similar trends in our study were seen in the past during evaluations of YouTube's role as a source of information for H1N1 influenza and Ebola virus outbreak (17,18).

A recent study about information and misinformation on COVID-19 revealed conversely, that social media channels were the most important source of misinformation (20,21).

The production and transmission of information on the health-related topic are increasing at an exponential rate in this age.

Until now the outbreak has continued to grow, and there are now more than 16 thousand reported cases from 75 countries and territories, and five deaths.A public health emergency was declared by the World Health Organization (WHO) on 23 July 2022.

Government organizations and educational institute should recognize and utilize YouTube as a strong platform for sharing health information with public and for educating future health-care providers (22).

This study has a cross-sectional design. It is only available on YouTube and other social media platforms in English. However, we believe that this research article will to contribute the literature highlight the significance of sharing higher-quality education videos, and provide a new perspective for future research.

CONCLOUSION

HMPX, especially during the global disease epidemic, the quality and reliable publication of useful YouTube content by Physicians /Public cooperation can help reduce and control the spread of the disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was conducted as a YouTube research, there is no need for ethics committee approval.

Informed Consent: This study was conducted as a YouTube research, there is no need for informed consent.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Immature granulocyte and other markers in prediction of mortality in spontaneous intracerebral hemorrhage

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ABSTRACT

Aim: This study aims to evaluate immature granulocyte count (IG#) and percentage (IG%) in the prediction of mortality in spontaneous intracerebral hemorrhage (SICH).

Material and Method: Demographic characteristics and laboratory test results of patients diagnosed with SICH and admitted to the neurology clinic in a tertiary hospital between January 1, 2020, and January 1, 2022, were recorded. One hundred ten patients were included in the study. While 80 of these patients constituted the group that recovered after treatment, 30 of them formed the group that died despite treatment. IG and other laboratory and clinic parameters were statistically compared in both groups.

Results: Of 110 patients, 45 (42.7%) were female, and 65 (57.3%) were male. IG counts were higher in the non-survival group than in the survival group (p=0.001). When the patients were divided according to low IG% (<0.6) and high IG% (>=0.6), 30 patients were in the high IG# group, and 80 patients were in the low IG% group. White blood cell (WBC), neutrophil count (NEUT#), monocyte count (MONO#), IG#, neutrophil-lymphocyte ratio (NLR), and hemorrhage volume (HV) values were statistically significantly higher in the high IG% group than in the low IG% group; Glasgow coma score (GCS) and percentage of lymphocytes (LYMPH%) values were significantly lower too. In addition, the mortality rate in the high IG# group was significantly higher than the mortality rate in the low IG% group (53.23% vs. 17.5%).

Conclusion: IG is a new, easily accessible, inexpensive, and promising marker for predicting in-hospital mortality in patients with SICH.

Keywords: Spontaneous intracerebral hemorrhage, inflammation, immature granulocyte, prognosis, mortality

INTRODUCTION

Stroke is one of the leading causes of death worldwide. SICH is an acute brain injury caused by sensitive blood extravasation from a ruptured cerebral blood vessel to the brain parenchyma. It is a common emergency associated with high morbidity and mortality rates. SICH accounts for 10 to 15% of all strokes. Hospitalizations for SICH have increased by 18% over the past decade, possibly due to an increase in the elderly population and increased anticoagulant and antiplatelet therapy (1).

Studies on SICH have been conducted to reduce morbidity and mortality, and some of these studies focus on anti-inflammatory treatments due to the pathophysiology of inflammation. The goal is to minimize neuron damage caused by brain tissue edema and reduce morbidity and mortality by suppressing acute inflammation. The role of inflammation in the pathophysiology of SICH has been well-established in some studies. SICH causes the release of proinflammatory cytokines and an increase of immune cells in brain tissue. Studies have also reported the relationship between NLR, lymphocyte-monocyte ratio (LMR), and platelet-lymphocyte ratio (PLR) obtained from white blood cell count as systemic inflammation markers and poor prognosis in patients (2).

IG is a new inflammatory parameter measured using an automated blood cell analyzer. Recently, it has been discovered that the number and percentage of IG in peripheral blood help to predict complications and mortality in many diseases, such as sepsis, septic shock, local infection, coronary artery disease, acute appendicitis, and pancreatitis (3,4). Moreover, in one study, IG was associated with 30-day mortality in acute ischemic stroke (5). However, there is only one study on

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IG in the literature to predict mortality in patients with SICH, and the relationship between 30-day mortality and IG has been investigated (6). Therefore, in this study, we aimed to investigate the role of IG obtained at admission in predicting in-hospital mortality in patients with SICH.

MATERIAL AND METHOD

The study was carried out with the permission of Kastamonu University Medical Faculty Clinical Researches Ethics Committee (Date: 05.10.2022, Decision No: 2022-KAEK-85). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

Data records from a tertiary hospital's laboratory information system were used for this retrospective study between January 1, 2020, and January 1, 2022. The diagnosis of intracerebral hemorrhage (ICH) was made after obtaining the patient's history, examination, and detecting the hemorrhagic lesion in computed tomography (CT). One hundred ten patients who applied to the emergency department and applied to the neurology clinic with the diagnosis of ICH were included in the study. While 80 individuals formed the post-treatment survival group, 30 died despite the treatment, creating the non-survival group (**Table 1**). Moreover, when the patients were divided (according to the literature, 4-7) low IG% (<0.6) and high IG% (>=0.6) (**Table 2**), 30 patients were in the high IG# group, and 80 patients were in the low IG% group. Patients without hemogram data, those under 18, pregnant women, trauma patients, those with a diagnosis of Covid-19, or those with PCR positivity were excluded from the study.

Materials

Age, gender, comorbidity, hemogram parameters, using drugs, ICH hemorrhage regions, and physical examination findings were compared. In addition, IG and other hemogram parameters routinely measured in the Sysmex XN 1000 (Hematology-Analyzer-Sysmex Corporation, Japan) were statistically compared in both groups. With these parameters, the rate of predicting the death of the patients from the hemogram results on the first day of admission to the hospital was investigated. Ethical rules and the principles of the Declaration of Helsinki carried out all procedures.

We retrospectively reviewed admission head CT scans of SICH patients. We assessed ICH volume on the admission with the ABC/2 method. The ABC/2 method identified the CT image with the largest hemorrhage area. Next, the largest diameter (A) of the hemorrhage on this image was measured. The largest diameter 90° to A on the same image was measured next (B). Finally, the approximate number of 10-mm images on which the ICH was seen was calculated (C)—comparing each CT image with hemorrhage to the CT image with the largest hemorrhage on that scan calculated C. If the hemorrhage area for a particular image was greater than 75% of the size seen on the image where the hemorrhage was most significant, the image was considered one hemorrhage image for determining C. If the area was approximately 25% to 75%, the image was considered half a hemorrhage image; if the area was less than 25% of the largest hemorrhage, the image was not considered a hemorrhage image. These CT hemorrhage image values were then added to determine the value for C. All measurements for A and B were made using the centimeter scale on the CT scan to the nearest 0.5 cm. A, B, and C were then multiplied, and the product was divided by 2, which yielded the volume of hemorrhage in cubic centimeters. The degree of shift and herniation developed in patients didn't measure in the radiological images because these images were admission cranial CT, and herniation was not an expected finding in the first images. In addition, patients who died due to secondary causes were not included in the study.

Statistical Analysis

Statistical Package for Social Sciences 18.0 for Windows (SPSS Inc., Chicago, USA) program was used for statistical analysis of the data. Descriptive statistics of the obtained data were given as percentage (%) and number for categorical variables, and median (25 Percentiles, 75 Percentiles) for numerical variables. When the data between the survival and non-survival groups; high (>=0,6) and low (<0,6) IG% groups were compared, the Student's t-test and the Mann-Whitney U test were used for normally and non-normally distributed variables, respectively. Pearson Chi-square test was performed to determine whether there was a significant difference between conditions with a nominal distribution, such as: gender, diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), atrial fibrillation (AF), coronary artery disease (CAD), prior stroke, GCS, antiplatelet agent (APA) use, oral anticoagulant (OAC) use, antihypertensive (AH) use, statin use, brainstem hemorrhage (BH), lober hemorrhage (LH), basal ganglia hemorrhage (BGH), cerebellum hemorrhage (CH), intraventricular hemorrhage (IVH), and surgical operation. Receiver Operating Characteristic (ROC) analysis was performed and Youden's index was used to determine Area Under Curve (AUC), sensitivity, specificity and cut-off values. A p value of <0.05 was considered statistically significant. For the multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine independent predictors of patient outcome.

RESULTS

A total of 110 SICH patients who met the inclusion criteria were included in the study. 45 (42.7%) patients were female, and 65 (57.3%) were male. The median and interquartile range IQR ages of the patients were 70.5 and 65-77.2, respectively. Some of the patients also had comorbidities. 36 (32.7%) patients with DM, 101 (91.8%) patients with HT, 19 (17.2%) patients with HL, 14 (12.7%) patients with AF, 36 (32.7%) patients with CAD, and 21 (19.1%)) patients with a previous stroke. Some of the patients were using drugs. 22 (20.0%) patients used APA, 16 (14.5%) patients used OAC, 95 (86.4%) patients used AH, and 9 (8.2%) patients used statins. When we classify patients according to ICH regions: 9 (8.3%) patients with bleeding into the brain stem, 39 (35.5%) patients with bleeding into the lober, 57 (51.8%) patients with bleeding into the basal ganglia, 6 (5.5%) patients with bleeding into the cerebellum, 39 (35.5%) patients with IVH, and 9 (8.2%) patients with who had a surgical operation.

When the demographic and hemogram data of non-survival and survival patients were classified according to hospital mortality (**Table 1**), it was observed that 30 patients were in the non-survival group and 80 patients were in the survivor group. There was no statistical difference between the ages of the non-survival and survival groups. Hyperlipidemia was higher in the survival group (p=0.018). On the other hand, atrial fibrillation (p=0.018), oral anticoagulant use (p=0.001), systolic (<0.001), and diastolic blood pressure (0.001) were statistically significantly higher in a non-survival group compared to the survival group. Furthermore, IVH, HV, pulse, WBC, PLT, PCT, NRBC#, NRBC%, NEUT#, IG#, and IG% values of the non-survival group were significantly higher in the non-survival group compared to the survival group. GCS values were substantially lower in the non-survival group compared to the survival group.

When the patients were classified according to low IG% (<0.6) and high IG% (>=0.6), (**Table 2**) 30 patients were in the high IG# group, and 80 patients were in the low IG% group. There was no statistically significant difference between the two groups regarding age and gender (p>0.05). WBC, NEUT#, MONO#, IG#, NLR, and HV values were significantly elevated in the high IG% group compared to the low IG% group; GCS and LYMPH% values were decreased in the high IG% group compared to the low IG% group. In addition, the mortality rate in the high IG# group was significantly increased compared to the mortality rate in the low IG% group (p=<0.001).

Table 1. Comparison of demographic, clinical and hemogram data of deceased and surviving patients with SICH

	Non-Survival (30)	Survival (80)	p
Age (Years)	72 (68;78)	70 (64;77)	0.119
Male Gender n(%)	18 (60.0)	45 (56.3)	0.723
Clinical History			
DM	10 (33.3)	26 (32.5)	0.934
HL	1 (3.3)	18 (22.5)	0.018
HT	29 (96.7)	72 (90.0)	0.256
AF	9 (30.0)	5 (6.3)	0.001
CAD	15 (50.0)	21 (26.3)	0.018
Prior Stroke	7 (23.3)	14 (17.5)	0.488
Vital Signs at ED presentation			
SBP (mmHg)	190 (177; 205)	155 (140; 180)	<0.001
DBP (mmHg)	100 (97;110)	80 (70; 100)	0.001
Heart Rate (BPM)	75 (69; 85)	70 (68; 74)	0.033
GCS	5 (3; 12)	14 (13; 15)	<0.001
Prestroke Medications			
APA	6 (20.0)	16 (20.0)	1.000
OAC	10 (33.3)	6 (7.5)	0.001
AH	28 (93.3)	67 (83.8)	0.192
Statin	1 (3.3)	8 (10.0)	0.256
Brain Imaging ICH Parameters			
HV (mL)	33 (13; 51)	7.5 (1.3; 22.7)	<0.001
Location			
BH	5 (16.7)	4 (5.1)	0.111
LH	8 (26.7)	31 (38.8)	0.238
BGH	15 (50.0)	42 (52.5)	0.815
CH	2 (6.7)	4 (5.0)	0.732
Presence of IVH	17 (56.7)	22 (27.5)	0.005
Surgery	5 (16.7)	4 (5.0)	0.061
Laboratory Features			
WBC ($\times10^9$/L)	11.1 (8.8; 14.5)	9.2 (7.1; 11.3)	0.006
PLT ($\times10^9$/L)	255 (257; 300)	205 (170; 248)	0.002
PCT (%)	0.26 (0.21; 0.30)	0.20 (0.17; 0.25)	0.002
NRBC# ($\times10^9$/L)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.012
NRBC%	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.045
NEUT# ($\times10^9$/L)	8.72 (6.07; 12.5)	7.05 (4.82; 8.97)	0.009
LYMPH% ($\times10^9$/L)	12.8 (6.5; 17.8)	15.4 (10.5; 23.3)	0.044
MONO# ($\times10^9$/L)	0.72 (0.40; 0.88)	0.57 (0.43; 0.69)	0.080
IG# ($\times10^9$/L)	0.06 (0.03; 0.12)	0.04 (0.02; 0.05)	0.001
IG (%)	0.6 (0.4; 0.8)	0.4 (0.2; 0.5)	0.002
NLR	6.4 (4.3; 9.8)	4.6 (2.9; 8.9)	0.116
PLR	169 (109; 292)	146 (97; 206)	0.254

Abbrevations: DM, diabetes mellitus; HL, hyperlipidemia; HT, hypertension; AF, atrial fibrillation; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; GCS, Glasgow coma score; APA, antiplatelet agent; OAC, oral anticoagulant; AH, antihypertensive; HV, hemorrhage volume; BH, brainstem hemorrhage; LH, lober hemorrhage; BGH, basal ganglia hemorrhage; CH, cerebellum hemorrhage; IVH, intraventricular hemorrhage; WBC, white blood cell, PLT, platelet; PCT, Plateletcrit; NRBC#, Nucleated red blood cell count; NRBC%, Nucleated red blood cells percentage; NEUT#, neutrophil count; LYMPH#, lymphocyte percentage; MONO#, monocyte count; IG%, immature granulocyte percentage; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio
Referans Interval: WBC($\times10^9$/L): (3.39 - 8.86), PLT ($\times10^9$/L): (171 – 388), PCT (%): (0.19 - 0.41), NRBC($\times10^9$/L): (0.000 - 0.015), NRBC (%): (0.000 - 0.030), NEUT# ($\times10^9$/L): (1.50 - 5.00), LYMPH (%): (21.6 - 49.0), MONO#($\times10^9$/L): (0.22 - 0.63), IG#($\times10^9$/L): (0.01 - 0.04), IG (%): (0.16 - 0.62)
The Student's t-test and the Mann-Whitney U test were used for normally and non-normally distributed variables respectively.
Pearson Chi-square test was performed to determine whether there was a significant difference between conditions with a nominal distribution.

Table 2. Comparison of demographic, clinical and hemogram data of SICH patients with high (>=0.6) and low (<0.6) IG%

	High IG% Group (30)	Low IG% Group (80)	p
Age (Years)	73 (67;77)	70 (64;78)	0.325
Male Gender n(%)	21 (58.3)	42 (56.8)	0.875
Clinical History			
DM	12 (40)	24 (30)	0.320
HL	5 (16.7)	14 (17.5)	0.918
HT	30 (100)	71 (88.8)	0.055
AF	4 (13.3)	10 (12.5)	0.907
CAD	14 (46.7)	22 (27.5)	0.056
Prior Stroke	8 (26.7)	13 (16.3)	0.216
Vital Signs at ED presentation			
SBP (mmHg)	175 (150; 193)	170 (150; 190)	0.360
DBP (mmHg)	100 (88; 110)	100 (80; 100)	0.166
Heart Rate (BPM)	73 (69; 79)	73 (70; 76)	0.860
GCS	13 (7.7; 14.2)	14 (13;15)	0.021
Prestroke Medications			
APA	9 (30.0)	13 (16.3)	0.108
OAC	4 (13.3)	12 (15.0)	0.825
AH	29 (96.7)	66 (82.5)	0.064
Statin	4 (13.3)	5 (6.3)	0.227
Brain Imaging ICH Parameters			
HV (mL)	17.0 (4.8; 32.3)	5.1 (1.8; 20.7)	0.025
Location			
BV	3 (10.3)	6 (7.5)	0.663
LV	13 (43.3)	26 (32.5)	0.290
BGV	12 (40.0)	45 (56.3)	0.129
CV	2 (6.7)	4 (5.0)	0.663
Presence of IVH	12 (40.0)	27 (33.8)	0.542
Surgery	3 (10.0)	6 (7.5)	0.702
Laboratory Features			
WBC (×10^9/L)	11.1 (8.9; 17.1)	9.1 (7.2; 11.2)	0.002
PLT (×10^9/L)	218 (260; 270)	205 (170; 248)	0.444
PCT (%)	0.23 (0.18; 0.30)	0.22 (0.18; 0.26)	0.164
NRBC# (×10^9/L)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.326
NRBC (%)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.687
NEUT# (×10^9/L)	8.9 (6.1; 14.8)	6.9 (4.8; 8.8)	0.002
MONO# (×10^9/L)	0.73 (0.54; 1.00)	0.56 (0.40; 0.69)	0.001
LYMPH (%)	12.8 (6.5; 17.8)	15.4 (10.5; 23.3)	0.044
IG (%)	0.09 (0.06; 0.15)	0.03 (0.02; 0.05)	<0.001
NLR	6.3 (4.2; 13.1)	5.0 (2.9; 7.6)	0.048
Mortality (%)	16 (53.23)	14 (17.5)	<0.001

Abbrevations: DM, diabetes mellitus; HL, hyperlipidemia; HT, hypertension; AF, atrial fibrillation; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; GCS, Glasgow coma score; APA, antiplatelet agent; OAC, oral anticoagulant; AH, antihypertensive; HV, hemorrhage volume; BH, brainstem hemorrhage; LH, lober hemorrhage; BGH, basal ganglia hemorrhage; CH, cerebellum hemorrhage; IVH, intraventricular hemorrhage; WBC, white blood cell, PLT, platelet; PCT, Plateletcrit; NRBC#, Nucleated red blood cell count; NRBC%, Nucleated red blood cells percentage; NEUT#, neutrophil count; LYMPH#, lymphocyte percentage; MONO#, monocyte count; IG%, immature granulocyte percentage; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio
Referans Interval: WBC(x109/L): (3.39 - 8.86), PLT (x109/L): (171 – 388), PCT (%): (0.19 - 0.41), NRBC(×10^9/L): (0.000 - 0.015), NRBC (%): (0.000 - 0.030), NEUT# (×10^9/L): (1.50 - 5.00), LYMPH (%): (21.6 - 49.0), MONO#(×10^9/L): (0.22 - 0.63), IG#(×10^9/L): (0.01 - 0.04), IG (%): (0.16 - 0.62)
The Student's t-test and the Mann-Whitney U test were used for normally and non-normally distributed variables respectively. Pearson Chi-square test was performed to determine whether there was a significant difference between conditions with a nominal distribution.

In the ROC analysis (**Table 3**), IG# (cut off: 0.055, AUC: 0.703), IG% (cut off: 0.55, AUC: 0.693), HV (cut off: 0.693) off: 12.1, AUC: 0.801), and PCT (cut off: 0.255, AUC: 0.692), tests showed moderate-high predictive properties.

Table 3. ROC analysis values of some hematological data in SICH patients

	Cut-off	AUC	95%CI	p	Sensivite %	Spesifite %
IG#	0.055	0.703	0.59-0.82	0.001	57	77
IG (%)	0.55	0.693	0.58-0.81	0.002	53	84
HV (mL)	12.1	0.801	0.71-0.89	<0.001	80	72

Abbrevations: IG#, immature granulocyte count; IG%, immature granulocyte percentage; HV, hemorrhage volume

In the univariate logistic regression analyses performed, IG% (OR:4.488, 95% CI:1.342-12.017, p=0.020), OAC (OR: 6.167, 95% CI: 2.000-19.018, p=0.002), HV (OR: 1.039, 95% CI: 1.1019-1.059 p<0.001), and IVH (OR: 3.448, 95) %CI: 1.440-8.255 p=0.005) were found to be independent predictors of hospital mortality. In multivariate logistic regression analysis, IG% OR: 11.218, 95% CI: 1.637-76.867, p=0.014), OAC (OR: 9.090, 95% CI: 2.124-38.905, p=0.003), HV (OR: 1.030, 95% CI: 1.1009-1.051 p=0.005), and IVH (OR: 3.922, 95 % CI: 1.180-13.032 p=0.026) were independent predictors of hospital mortality. Interestingly, IG% has a very high OR (**Table 4**).

Table 4. Logistic regression analysis of ındependent markers of hospital mortality in SICH patients

	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Age (Years)	1.030 (0.989-1.073)	0.152	1.066 (0.998-1.138)	0.056
OAC	6.167 (2.000-19.018)	0.002	9.090 (2.124-38.905)	0.003
HV (mL)	1.039 (1.019-1.059)	<0.001	1.030 (1.009-1.051)	0.005
Presence of IVH	3.448 (1.440-8.255)	0.005	3.922 (1.180-13.032)	0.026
PLT (×10^9/L)	1.011 (1.003-1.018)	0.005	1.015 (1.005-1.025)	0.004
IG (%)	6.488 (1.342-12.017)	0.020	11.218 (1.637-76.867)	0.014

Abbrevations: OAC, oral anticoagulant; HV, hemorrhage volume; IVH, intraventricular hemorrhage; PLT, platelet; IG%, immature granulocyte percentage

DISCUSSION

The most important result of our study is that IG is an inexpensive, easily accessible, and important prognostic marker in predicting mortality in patients with SICH. Furthermore, in many studies (3-7) IG, is an important biomarker in predicting mortality and disease severity in patient groups, is also promising in patients with SICH.

Previous studies have associated white blood cells and NEUT#, NLR, PLR, and other inflammatory parameters with poor prognosis in SICH patients. For example, Lattanzi et al. (8) associated higher WBC in peripheral blood with hematoma early deterioration and enlargement. In addition, in previous studies, high WBC were found to be a strong predictor of poor prognosis in the prognosis of SICH and subarachnoid hemorrhage (SAH) patients (9). In a study by Walsh et al. (10), the MONO# was independently associated with the 30-day case fatality rate in 240 adults SICH patients. Another study reported that a high PLR value was a significant predictor for short-term prognosis in SICH patients (11). In our research, WBC, PLT, NEUT#, and were significantly higher in the non-survival group than survival group but for NLR and PLR was no significant difference between groups.

The early mortality of SICH has been reported to be approximately 30% to 40%. In our study, the mortality rate was determined as 37.5%. Consistent with other previously published studies, neither gender nor age was a significant predictor of outcome (10). In addition, for hypertension, diabetes, coronary artery disease, and the use of antiplatelet agents parameters there was not a significant difference between the survival and non-survival groups. However, similar to the literature, the mortality rate was significantly higher in patients with atrial fibrillation and using oral anticoagulants (11). It was thought that it might be due to their bleeding-increasing effects. However, hyperlipidemia was significantly higher in surviving patients. Roquer et al. (12) also found that low lipid serum levels are associated with poor prognosis in SICH. Iso et al. (13) also showed an inverse relationship between serum cholesterol levels and mortality in SICH. Moreover, our study confirmed that initial judgment status and ICH volume, as defined in previous studies, are significant predictors of mortality (14). Initial hemorrhage volume and associated cerebral edema are a sequential delayed effect on the medical course. It causes an increase in intracranial pressure and increases the risk of mortality. In addition, we found intraventricular hemorrhage is significantly associated with mortality, similar to the literature (15). The primary treatment is antiedema and general supportive therapy by keeping the systemic arterial blood pressure at the desired level. In our study, there was no statistical difference in mortality between patients who received and non received surgical treatment. The location of hemorrhage was not identified as a risk factor for mortality. While the infratentorial location was significant for mortality in some studies, it was not consistent in others (16).

IG is an early marker of bone marrow activation that can be easily and quickly measured from peripheral blood without needing additional equipment. In recent years, with technological developments, simple and easily measurable biomarkers such as IG have been used for diagnostic and prognostic purposes in many diseases. Immature granulocytes in the circulation are generally not released into the peripheral blood in healthy individuals, and elevation of immature granulocytes is an essential feature of early inflammation. Studies conducted in recent years have shown that IGC and IG% increase in cases of infection and sepsis (17). In such cases, an increase in the IGC may help indicate the presence of acute inflammation. In addition, studies have revealed that IG are significantly higher in the early period in many inflammatory conditions such as acute appendicitis, acute pancreatitis, and after cardiac surgery (16-20). In addition, it has been shown that IGC at admission can significantly predict mortality in cardiovascular diseases (21). Moreover, one study showed that IG alone effectively predicted 30-day mortality in ischemic stroke. Korkut et al. (6) also showed that a higher IG number at admission in SICH was an independent predictor of 1-month mortality. To the best of our knowledge, there has yet to be a study in the literature examining the relationship between the IG and the in-hospital mortality of SICH. Only one study examined 30-day mortality. Our study found that the IGC and IG% was significantly higher in non-survival group than in survival group. Patients with an IG% of 0.6 and above had a considerably worse prognosis in-hospital mortality. In addition, the high IG% in our study was determined to be an independent risk factor for mortality in SICH patients.

Our study had some limitations. First, it is a single-center and retrospective study. Second, serial IG measurements were kept a secret. Another limitation is the absence of tumor necrosis factor and interleukin-6 levels, which we could not test in the emergency department. Finally, prospective studies of the made larger patient population are needed to understand the mortality relationship between IG and SICH.

CONCLUSION

This study showed that IG is a new, easily accessible, inexpensive, meaningful, and promising marker for predicting mortality in patients with SICH. In addition, in centers where CT is not available, it can be useful and even life-saving in differential diagnosis and early referral of the patient to an advanced center.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Medical Faculty Clinical Researches Ethics Committee (Date: 05.10.2022, Decision No: 2022-KAEK-85).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Evaluation of pancreatic stent and/or suppository indomethacin efficacy in post ERCP pancreatitis prophylaxis: a single center experience

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ABSTRACT

Aim: Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is a serious complication of ERCP. In this study, we aimed to compare the use of rectal indomethacin, pancreatic stenting or both techniques for prevention of PEP.

Material and Method: Patients who underwent ERCP for the first time due to choledocholithiasis between January 2022 and June 2022 were retrospectively reviewed. The clinical findings, demographics, laboratory records, endoscopic intervention characteristics, whether rectal indomethacin was applied before the procedure, whether pancreatic stent was placed or not were evaluated.

Results: A total of 367 patients who underwent ERCP for the first time were included in the study. The mean age was 61 (28-92) years and 53.4% were female. In 124 (33.8%) patients, involuntary guide-wire insertion into the pancreatic duct occurred during canulation. Pancreatic stent was placed in 82 (22.3%) of the patients. Rectal indomethacin was administered to 288 patients (78.5%), while indomethacin could not be administered in 79 patients (21.5%), because they did not give consent. When patients with involuntarily pancreatic canulation were evaluated, the rate of PEP was 3.6% in the stented group, while it was 15.3% in the stent-free group ($p<0001$). The incidence of PEP was 20.3% in 79 patients who could not be administered rectal indomethacin, while this rate was 3.1% in those who received rectal indomethacin ($p<0001$).

Conclusion: The first and most important way to prevent PEP is to avoid unnecessary ERCPs. Rectal indomethacin administration reduces the risk of PEP. All patients with involuntary wires in the pancreatic duct, should be evaluated for pancreatic stent placement.

Keywords: Post-ERCP pancreatitis, rectal indomethacin, pancreatic stent, prophylaxis

INTRODUCTION

Cholelithiasis is quite common in the community and often requires hospitalization and intervention if symptomatic (1). Although the frequency of cholelithiasis varies according to geographical region and age, it can be considered as 10-30% (2-4). Choledocholithiasis is the name given to the condition that occurs when gallstones fall into the main bile duct. About 5-20% of people with gallstones develop choledocholithiasis (5-6). Endoscopic retrograde cholangiopancreatography (ERCP) is the routine treatment method used all over the world in the treatment of choledochal stones (7, 8). Although the most common indication of ERCP is choledochal stones and cholangitis, ERCP is performed with many indications such as drainage of malignant biliary obstructions, treatment of postoperative biliary complications, treatment of acute or chronic pancreatitis complications, PSC and sphincter Oddi dysfunction. ERCP is an advanced endoscopic intervention performed with a side-view endoscope, and it is mostly used for therapeutic rather than diagnostic purposes, as it has complications related to the procedure. Although ERCP is mostly considered a safe procedure, the complication rate related to ERCP has been reported between 7-12% and the mortality rate between 0.1-1.4% (9 – 12). Twenty-one studies were analyzed in a systematic review and 16885 patients were evaluated. ERCP complications were found in 7% (13). Common complications include pancreatitis, bleeding, cholangitis, and perforation.

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Post ERCP pancreatitis (PEP) is a serious complication of ERCP that occurs due to mechanical or thermal damage to the pancreatic orifice, hydrostatic damage of the contrast medium, or manipulation of the guidewire. PEP is defined as abdominal pain that occurs or worsens 24 hours after ERCP with elevation of amylase or lipase to 3 times the upper limit of normal or more (14). Studies have reported the incidence of PEP between 3.5-9.7%, and the mortality due to PEP between 0.3-0.8% (13, 15).

The increase in pressure in the main pancreatic duct due to periampullary inflammation developed during canulation in the ERCP process is blamed in the development mechanism of PEP (16). Difficult canulation, guidewire entrance to the main pancreatic duct, injection of opaque material into the main pancreatic duct, balloon dilation of the biliary sphincter without EST, pancreatic sphincterotomy, and papillectomy are the conditions that increase the risk of procedure-related PEP. Conditions such as young age, female gender, history of ERCP-related pancreatitis, type 1 or 2 Oddi sphincter dysfunction can be considered among the conditions that increase the risk of PEP for the patient.

There are several strategies that can be applied to prevent the development of PEP. The most important of these is to perform the ERCP procedure with the correct indication and to avoid unnecessary procedures. Among the pharmacological prevention methods, the method accepted all over the world and recommended for routine use by the guidelines is administration of 100 mg indomethacin rectally immediately before the procedure (14, 17). In addition to indomethacin, suppository diclofenac can also be used. In addition to pharmacological techniques, there are endoscopic techniques that can be applied during ERCP. These techniques include the use of guide wire-mediated methods as the first canulation method, switching to fistulotomy or conventional pre-incision methods without persistence if conventional canulation is unsuccessful, and guide wire placement in the pancreatic duct in cases of recurrent guide wire into the pancreatic duct. In this study, it was aimed to compare the use of rectal indomethacin, pancreatic stenting or both techniques used for the avoidance of pancreatitis following ERCP.

MATERIAL AND METHOD

The study was carried out with the permission of Kastamonu University Medical Faculty Clinical Researches Ethics Committee (Date: 24.02.2022, Decision No: E1-22-2851). This study was planned as a single-center, retrospective, controlled cohort study. Nevertheless, no patients' written informed consent was acquired because the study was retroactively planned. All procedures were performed in Ankara City Hospital, Gastroenterology Clinic. The Declaration of Helsinki's ethical guidelines and principles were followed during every procedure. Patients over 18 years of age were included in the study.

ERCP naive patients who underwent ERCP for the first time due to choledocholithiasis in our clinic between January 2022 and June 2022 were retrospectively reviewed. The electronic medical records of the patients were reviewed. The clinical findings, demographic characteristics, laboratory records, endoscopic intervention characteristics of the patients, whether rectal indomethacin was applied before the procedure, whether pancreatic stent was placed or not were evaluated. The patients were evaluated in terms of PEP 24 hours after the procedure in accordance with the guidelines.

All patients underwent the procedure after 12 hours of fasting. All patients were sedated with midazolam and/or propofol. If deemed necessary during the procedure, patients were administered 20 mg hyoscine-N-butyl bromide or 1 mg glucagon to ensure duodenal relaxation. Endoscopic procedures were performed with side-view therapeutic duodenoscopes (TJF-260V or TJF-Q180V, Olympus, Japan). In all patients, canulation was attempted with a 0.035-inch standard guidewire-loaded sphincterotome (Boston Scientific Corporation, MA, USA; Micro-Tech, Nanjing, Co, Ltd) as the first canulation method. In cases where standard canulation failed, 3 canulation methods were used depending on the papillary status or whether the guide wire was inserted into the pancreatic duct: fistulotomy, conventional precut or double guide-wire canulation. Cholangiography was taken after canulation. Afterwards, sphincterotomy was performed on the patients and the stones in the common bile duct were removed with a stone removal balloon or dormia basket.

Prophylactic pancreatic stent was placed in patients with a high risk of pancreatitis among patients who had wires to the pancreatic duct during the procedure. Prophylactic stents were removed after 3 days. Rectal indomethacin was administered to all patients who gave consent before the procedure. However, rectal indomethacin was not administered to patients who did not give consent. Ringer's lactate infusion was administered prophylactically to all patients with wire going into the pancreatic duct, at a rate of 1500cc in the first 2 hours and 1500cc in the next 8 hours.

Patients who could not be cannulated with ERCP and required PTC were excluded from the study. Patients

who underwent ERCP due to pancreatic pathologies such as chronic pancreatitis, patients who underwent drainage due to pancreatic malignancy, and patients with altered anatomy were excluded from the study. Patients who had previously undergone ERCP for any reason were excluded from the study. Only patients with proven choledocholithiasis and underwent first-time ERCP were included in the study.

Statistical Analysis

The Kolmogorov-Smirnov test was performed to analyze the normality of the distribution of continuous variables. Continuous variables were expressed as median (interquartile range), and categorical variables were given as frequency (percentage). Continuous variables were analyzed via the Mann-Whitney U test (two groups' comparisons). Categorical variables were analyzed via the Chi-Square test or the Fisher's Exact test, followed by a post hoc test when needed. We used IBM SPSS Statistics for Windows, version 25.0 (IBM Corp, Armonk, N.Y, USA) for analyses and considered a two-tailed p-value < 0.05 as significant.

RESULTS

A total of 367 patients who underwent ERCP for the first time due to choledocholithiasis were included in the study. The mean age of the patients was 61 (28-92) and 53.4% were female. Demographic data of the patients and information about the procedure are given in **Table 1**. In 124 (33.8%) of these 367 patients, involuntary guide wire into the pancreatic duct occurred during canulation. Pancreatic stent was placed in 82 (22.3%) of these patients, who were at high risk (female gender, young age) and had wires to more than one pancreatic duct. Rectal indomethacin was administered to 288 of the patients (78.5%), while indomethacin could not be administered in 79 patients (21.5%), because they did not give consent. In 64 of the patients, both rectal indomethacin was applied and a pancreatic stent was placed.

All of the patients with pancreatic stent placed were patients with wires going into the pancreatic duct during canulation. The mean age of patients with pancreatic stent implantation was statistically significantly younger, and the majority were statistically significantly female. The incidence of PEP was 7.7% in patients without pancreatic stent placement, while this rate was 3.6% in patients with pancreatic stent placement. The difference was statistically significant (p=0.004) (**Table 2**). When patients with wires to the pancreatic duct were evaluated in terms of PEP, the rate of PEP was 3.6% in the stented group, while this rate was 15.3% in the stent-free group (p<0001).

Table 1. Basic demographic data, patient characteristics, data on the ERCP procedure

	Total (n=367)
Age, years	61 (28-92)
Gender, female	196 (53.4)
BMI (kg/m2)	27.55 (23.51-31.51)
Comorbidity	
CAD, n (%)	48 (13.0)
COPD, n (%)	14 (3.8)
CRF, n (%)	3 (0.8)
Cholecystectomy, n (%)	126 (34.3)
Periampullary diverticulum	
Type 1	6 (1.6)
Type 2	22 (5.9)
Type 3	9 (2.5)
Type 4	5 (1.4)
Wire to the pancreatic duct, n (%)	124 (33.8)
Cannulation method	
Standard, n (%)	261 (71.1)
Conventional Precut, n (%)	14 (3.8)
Double guide-wire, n (%)	58 (15.8)
Fistulotomy, n (%)	34 (9.3)
Pancreatic stent, n (%)	82 (22.3)
Rectal indomethacin, n (%)	288 (78.5)
PEP, n (%)	25 (6.8)
Hospital stays, days	2 (2-3)

x Results are expressed as median (interquartile range) or frequency (%). BMI: Body mass index, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure

Table 2. Comparison of the group with pancreatic stent placement and the group without pancreatic stent placement

	Total (n=367)	No pancreatic stent placed (n=285)	Pancreatic stent placed (n=82)	P
Age, years	61 (28-92)	68 (52-92)	47(28-68)	**0.005**
Gender, female	196 (53.4)	141 (49.4)	55 (67.0)	**0.036**
Pancreatic cannulation	124 (33.8)	42 (14.7)	82(100)	**0.001**
PEP	25 (%6.8)	22 (7.7)	3 (3.6)	**0.004**

x Results are expressed as median (interquartile range) or frequency (%). Significant P values are in bold. PEP: Post-ERCP Pancreatitis

The incidence of PEP was found to be 20.3% in 79 of the 367 patients who could not receive rectal indomethacin because they did not give their consent, while this rate was 3.1% in those who received rectal indomethacin, and the difference was statistically significant (p<0001). On the other hand, age and gender were not statistically significantly different between the groups who received and did not receive rectal indomethacin. (**Table 3**).

Table 3. Comparison of rectal indomethacin administered and non-administered groups

	Total (n=367)	Rectal indomethacin administered (n=288)	Rectal indomethacin not administered (n=79)	P
Age, years	61 (28-92)	63 (49-92)	58 (34-74)	0.354
Gender, female	196 (53.4)	154 (53.5)	41 (51.9)	0.436
PEP	25 (6.8)	9 (3.1)	16 (20.3)	0.001

x Results are expressed as median (interquartile range) or frequency (%). Significant P values are in bold. PEP: Post-ERCP Pancreatitis

When all patients were evaluated, post-ERCP pancreatitis developed in 25 (6.8%) of 367 patients. The patients who developed PEP were evaluated in 4 groups according to the techniques applied for the prevention of pancreatitis as those with pancreatic stent placement, those who received rectal indomethacin, those in whom both were applied, and those who did not receive any technique. Of 25 patients who developed PEP, 14 (56.0%) were in the group that did not receive any prophylaxis. On the other hand, 8 patients (32%) were in the rectal indomethacin-only group, 2 patients were in the pancreatic stent-only group, and 1 patient was in both prophylactic group (**Table 4**).

Table 4. Distribution of patients with PEP according to prophylaxis groups

Total PEP	No PEP Protective Measures	Rectal Indomethacin Only	Pancreatic Stent Only	Rectal Indomethacin + Pancreatic Stent
25 (100)	14 (56.0)	8 (32.0)	2 (8.0)	1 (4.0)

x Results are expressed as frequency (%). PEP: Post-ERCP Pancreatitis

When all patients were evaluated, 20 of the 25 patients who had PEP had involuntary wires in the pancreatic duct. Of the 124 patients who were unintentionally inserted wires to the pancreatic duct, 82 (66.1%) had stents placed. 101 (81.5%) of these patients received rectal indomethacin; 23 (18.5%) did not. In the cross-group analyses of these patients, 71 patients received both rectal indomethacin and stenting, and only 1 (1.4%) of these individuals experienced PEP. Of the 30 patients who received rectal indomethacin without a pancreatic stent, PEP appeared in 6 (20.0%) of them. Of the 11 patients who received a pancreatic stent but no rectal indomethacin, PEP developed in 2 (18.2%) of them. Comparatively, PEP was noted in 11 (91.7%) of the 12 patients who did not have a pancreatic stent implanted or receive rectal indomethacin. A statistically significant difference was found between the groups ($p<0.001$).

DISCUSSION

Post ERCP pancreatitis is the most common and significant complication of ERCP, and the most important principle in its prevention is to avoid intervention in patients without a clear indication. In ERCP procedures performed with the correct indication, worldwide accepted methods for the prophylaxis of PEP are pancreatic stent placement in case of pancreatic canulation and rectal indomethacin administration to all patients before the procedure. The patients who developed PEP among the patients included in our study were mostly those who did not receive pancreatitis prophylaxis. Patients with pancreatic stenting as prophylaxis had statistically significantly lower rates of PEP than those without stenting. Similarly, PEP development was found to be statistically significantly lower in patients who received rectal indomethacin.

In a multicenter randomized study conducted by Philip et al. (18), 167 patients who had unintentional wires in the pancreatic duct were randomized, and half of them had pancreatic stent placement and half were followed without stent. While the development of PEP was 12.6% in the stented group, this rate was found to be 25% in the stent-free group. In our study, the rate of PEP was found to be 3.6% in patients who had a stent inserted in the pancreatic duct, while the rate was 15.3% in those who did not have a stent. The low rate of pancreatitis in our patients was thought to be due to the administration of rectal indomethacin to the patients. In this direction, rectal indomethacin administration to all patients at the beginning of the procedure reduces the risk of pancreatitis whether the wire goes into the pancreatic duct or not, and routine application is required.

In a systematic review of Pekgöz et al. (19), 54 articles on reducing the risk of PEP were evaluated and the importance of especially rectal indomethacin and pancreatic stenting was emphasized in the prevention of PEP development. In our study, consistent with the literature, statistical analyzes showed that pancreatic stent placement and routine administration of rectal indomethacin to all patients reduce the risk of pancreatitis in case of involuntary wire insertion into the pancreatic duct.

In a meta-analysis of 15 studies conducted by Masci et al. (20), risk factors for post-ERCP pancreatitis were evaluated, and female gender, Oddi dysfunction, and pancreatic canulation were found to be significant risk factors. In our study, the risk of PEP was found to be higher in young female patients, and these patients were treated more insistently on prophylaxis. In addition, pancreatic stenting was performed in patients with wires to the pancreatic duct, thus providing a lower rate of PEP development.

In a study by Harewood et al. (21) with 19 papillectomy patients, they placed pancreatic stent in 10 patients but did not place it in 9 patients, and found that 3 of the 3 PEPs that developed were in stentless patients. Papillectomy is a high-risk procedure for PEP, and pancreatic stenting is also effective in PEP prophylaxis in these patients. Similarly, in our study, the rate of PEP in patients with pancreatic stent insertion was found to be significantly lower than in the group without insertion.

In a study by Döbrönte et al. (22) with 228 patients, the patients were randomized, and half of the patients were administered rectal indomethacin and half were given placebo. Although the PEP rate was higher in the placebo group, it was not statistically significant. In a study by Elmunzer et al. (23) 602 patients were randomized to rectal indomethacin and placebo, and PEP developed statistically significantly less in the rectal indomethacin group. In a meta-analysis of 61 studies conducted by Yaghoobi et al. (24) it was shown that rectal indomethacin used immediately before ERCP reduced the risk of PEP in both high-risk and low-risk patients. Likewise, in our study, rectal indomethacin was found to reduce the risk of PEP for all patients.

The fact that our study was retrospective, and randomization could not be performed can be considered the weaknesses of our study. On the other hand, the fact that our center is a center with a very high volume (more than 2000 ERCPs are performed annually) prevents operator-dependent false results due to its high level of experience, constituting the strength of our study.

CONCLUSION

Post-ERCP pancreatitis is an important complication of ERCP. The first and most important way of prevention is to prevent unnecessary attempts. Rectal indomethacin administration reduces the risk of PEP in all procedures performed on ERCP naive patients with the correct indication. All patients with involuntary wires in the pancreatic duct, including all high-risk patients, should be evaluated for pancreatic stent placement.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Medical Faculty Clinical Researches Ethics Committee (Date: 24.02.2022, Decision No: E1-22-2851).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Does YouTube™ give us accurate information about bruxism?

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ABSTRACT

Aim: The aim of this study is to evaluate the quality of the information provided by the most watched videos about bruxism on YouTube™.

Material and Method: The results of YouTube™search were examined using the keyword "bruxism". The searching limited to the first 130 videos. DISCERN and the video information and quality index (VIQI) and the criteria were used for evaluating the videos. Also, the interaction index and the viewing rate of the videos were calculated. The Kruskal-Wallis H Test, Pearson's Chi-Square Test, Spearman's rho correlation were used for statistical analyses. Significance level was taken as $p<0.05$.

Results: Thirty-eight percentage of the videos were uploaded by dentist/specialist, 43% of them were uploaded by hospital, 4% of them were uploaded by commercial, 2% of them were uploaded by layperson, and 13% of them were uploaded by other. The average DISCERN score was 36.65 (poor). According to VIQI, 3 of the videos were found to be Scale 5, 15 of them were Scale 4, 35 of them were Scale 3, 39 of them were Scale 2, 8 of them were Scale 1.

Conclusion: The bruxism videos on YouTube™, mainly prepared by health professionals, were found to be insufficient and poor.

Keywords: Bruxism, internet, social media

INTRODUCTION

Bruxism is a condition that concerns clinicians and academics who are interested in dentistry, neurology and sleep medicine (1). The definitions of bruxism have undergone many changes over the years. According to the consensus report in 2013, the bruxism was characterized by a clenching or grinding action of the teeth and/or pushing the lower jaw, repetitive and grouped as nocturnal or awake bruxism depending on the circadian rhythm (1). At the consensus meeting in 2018, the definition of bruxism was re-evaluated and nocturnal bruxism and awake bruxism were completely separated from each other. The nocturnal bruxism is masticatory muscle activity (rhythmic and tonic) during sleep, not a sleep disorder in healthy individuals. The awake bruxism is a chewing muscle activity characterized by repetitious or continuous tooth contact and/or by bracing or thrusting of the mandible while waking, not a sleep disorder in healthy individuals (2).

According to a systematic review, the prevalence of self-reported SB in adults is 12% (3). In children, self-reported SB varies between 3.5 – 40.6% according to different age groups (4). The main conditions caused by nocturnal bruxism are: headache after waking up, temporomandibular disorders, tooth wear, fractures/failures of the tooth or implant (5-8). Before getting help from healthcare professionals, patients with these complaints do research on the internet to get more detailed information about their illness and determine the path they should follow for their treatment.

Today, the active use of social media causes it to be predicted that patients will receive more support from social media and video sharing platforms regarding their health in the future (9). YouTube™, one of the video sharing platforms, has been operating since 2005 and is one of the platforms where health-related videos are shared and watched the most because it is easily accessible by the public (10). After the videos on YouTube™ gained importance in dentistry and medicine, the reliability of this information was investigated with many studies. These studies are related to orthodontics (rapid maxillary expansion, orthodontic elastics, impacted canine, sleep apnea) (9,11-15), oral surgery (16-19), pedodontics (20), endodontics (21), and prosthodontics (22,23). In these studies, the scales with standard parameters were used to determine the reliability of the contents. The most common of these parameters are Journal of American

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Medical Association (JAMA) benchmark Criteria, DISCERN, Global Quality Score (GQS) and Video Information and Quality Index (VIQI).

In the literature search, conducted in Pubmed and Google Scholar databases, no studies on "bruxism" and YouTube™ were found (as of 1st of May 2022). The aim of the current study is to evaluate the quality of the information provided by the most watched videos about bruxism on YouTube™. The research hypothesis of this study was that the videos about bruxism on YouTube™ were misleading or incomplete.

MATERIAL AND METHOD

There was no human or animal participation in the study and the videos reviewed on YouTube™ were open to everyone. Therefore, it was not necessary to obtain ethics committee approval.

The results of YouTube™search were examined using the keyword "bruxism" on 6th of May 2022 to evaluate the information about bruxism. According to the search results, it was evaluated as the first 130 videos. The exclusion criteria were as follows: languages other than Turkish, irrelevant to the title, poor video quality, videos with comments turned off, silent videos, videos longer than 15 minutes (**Table 1**). The results of the search were saved by creating a playlist as search results may vary on separate days. The evaluation of the videos was performed by two authors (H.Y and H.B.) to avoid bias. The DISCERN and the VIQI and the criteria were used for evaluating the videos. Also, the interaction index and the viewing rate of the videos were calculated.

Table 1. Reasons for excluding videos

Exclusion Criteria	Number of videos
Languages other than Turkish	3
Irrelevant to the title	8
Poor video quality	1
Videos with comments turned off	5
Silent videos	4
Videos longer than 15 minutes	9

The DISCERN was first published in 1998 for developing a short instrument, which enables patients and healthcare providers to judge the quality of information about treatment choices (24). It consists of a total of 16 questions, which is scored between 1 and 5 points. The scores of videos were calculated by summing up the points from each question. The videos were divided into 5 categories according to the rating. The range of 16-26 points indicated very poor, 27-38 points indicated poor, 39-50 points indicated fair, 51-62 points indicated good, and above 63 points indicated excellent.

The information accuracy, the flow of information, quality and precision of the videos were evaluated with VIQI scale. While evaluating the videos with VIQI, a 5-point Likert scale was used (1: poor, 5: high quality).

Those who uploaded the videos were grouped as dentist/specialist, hospital/university, commercial, layperson, or other. The view counts, comment counts, the length of the video, time elapsed since the upload date, the likes and dislikes counts were determined. The viewers' interaction was calculated as follows: Subtracting the likes counts from the dislikes counts, dividing by the total view counts and multiplying by 100. The viewing rate was calculated by dividing the view counts by the number of days since upload and multiplying by 100 (25).

Statistical Analysis

Data were analyzed with SPSS software program (version 23, SPSS Inc, Chicago, Ill). Conformity to normal distribution was evaluated using the Shapiro Wilk test. Mann-Whitney U test was used to compare the data that were not normally distributed according to the paired groups. The Kruskal-Wallis H Test was used to compare the data that were not normally distributed, and multiple comparisons were examined with the Dunn test. Pearson's Chi-Square Test was used to compare categorical data. Spearman's rho correlation was used to examine the relationship between data that did not show normal distribution. Analysis results were presented as mean ± standard deviation and median (minimum – maximum) for quantitative data, and frequency (percent) for categorical variables. The significance level was set at $p<0.05$.

RESULTS

A total of 130 videos were analyzed and 30 of them were not included because they did not meet the criteria (languages other than Turkish; n=3, irrelevant to the title; n=8, poor video quality; n=1, videos with comments turned off; n=5, silent videos; n=4, videos longer than 15 minutes; n=9) as mentioned in **Table 1**.

According to DISCERN scores, out of 100 videos, one of them was found to be excellent, 9 of them were good, 33 of them were fair, 38 of them were poor and 19 of them were very poor. The average DISCERN score was 36.65 (poor). The distribution of the scores according to DISCERN were shown at **Table 2**.

Table 2. Distribution according to DISCERN scores

Total DISCERN Score (16-80)	
Score 16-26 – Very poor	19
Score 27-38 – Poor	38
Score 39-50 – Fair	33
Score 51-62 – Good	9
Score 63-80 – Excellent	1
The average DISCERN score	36.65

According to VIQI, out of 100 videos, 3 of them was found to be Scale 5 (high quality), 15 of them were Scale 4, 35 of them were Scale 3, 39 of them were Scale 2, 8 of them were Scale 1. 39% of the total videos were Scale 2. The distribution of the scores according to VIQI were shown at **Table 3**.

Table 3. Distribution of videos according to video information and quality index (VIQI)

Scale 1 (poor quality)	8
Scale 2	39
Scale 3	35
Scale 4	15
Scale 5 (high quality)	3

As seen in **Table 4**, there was a positive correlation between view count and all quantitative observations except DISCERN score. The highest correlation found between view count and likes (r= 0.744; p <0.001). There was a moderate correlation between total video duration and likes (r= 0.392; p<0.001), dislikes (r= 0.324; 0.001), and total DISCERN scores (r= 0.441; p<0.001). There was a moderate correlation between viewer's interaction and likes (r= 0.461; <0.001). There was a moderate correlation between viewing rate and total numbers of comments (r= 0.581; p<0.001), likes (r= 0.696; p<0.001) and dislikes (r= 0.541; p<0.001).

Table 4. Correlation between video features and quantitative observations

	View count	Total video duration (second)	Viewer's interactions	Viewing rate
Total numbers of comments	0.642; <0.001**	0.296; 0.003*	0.144; 0.153	0.581; <0.001**
Likes	0.744; <0.001***	0.392; <0.001**	0.461; <0.001**	0.696; 0.001**
Dislikes	0.591; <0.001**	0.324; 0.001**	-0.166; 0.098	0.541; <0.001**
Number of days since upload	0.274; 0.006*	-0.144; 0.154	-0.179; 0.076	-0.181; 0.073
Total DISCERN	0.075; 0.459	0.441; <0.001**	-0.029; 0.771	0.116; 0.251

Spearman's rho correlation coefficient, (P <0.05), *** High positive correlation, **Moderate positive correlation, *Weak positive correlation

38% of the videos were uploaded by dentist/specialist, 43% of them were uploaded by hospital, 4% of them were uploaded by commercial, 2% of them were uploaded by layperson, and 13% of them were uploaded by other. There was no significant difference between video source and view count (p=0.078), viewing rate (p=0.344). There was statistically significant difference between the video source categorization and the total video duration (p=0.005). The videos in hospital/university category were significantly had shorter time. There is statistically significant difference between video source categorization and viewer's interactions (p=0.016). The videos in dentist/specialist category were significantly had highest viewer's interactions (**Table 5**).

Table 5. Comparison and descriptive statistics of video sources

Video source	View count	Total video duration (second)	Viewer's interactions	Viewing rate
Dentist / specialist	322.5 (15-42683)	142.5 (36-604)[ab]	2.8 (0-27)[a]	45 (1-5265)
Hospital / university	245 (6-11272)	115 (31-810)[b]	0.8 (0-7)[b]	36.2 (1-3900)
Commercial	4428.5 (389-22111)	90.5 (64-127)[ab]	0.6 (0-3)[ab]	513.6 (35-1496)
Layperson	2915.5 (531-5300)	577 (311-843)[ab]	1.9 (1-3)[ab]	368.2 (92-644)
Other	148 (11-44135)	301 (63-619)[a]	2.9 (0-14)[ab]	51.2 (3-13294)
P	0.078	0.005*	0.016*	0.344

Median (Min – Max), *Significant results of Kruskal-Wallis test, (*P <0.05), [ab]There is no difference between groups with the same letter

DISCUSSION

In the current study, the quality of videos about bruxism on the digital content platform YouTube™ was evaluated. The videos rated as low quality according to the DISCERN criteria, and it was evaluated mainly as Scale 2 and Scale 3 in the VIQI criteria with 5 ratings. The research hypothesis of this study was accepted that the videos about bruxism on YouTube™ were misleading or incomplete.

In the present study, videos were evaluated according to VIQI and DISCERN criteria. In recent studies, evaluating the videos about dentistry on YouTube™ used JAMA (22), DISCERN (22), VIQI (14) and GQS (9, 13, 15) criteria. There is no consensus in the literature about which of these scales is more precise. However, in some studies (13, 22), a more objective evaluation was desired by using the two scales together. In this study, two separate evaluation criteria were used, and the results of the evaluations made according to the VIQI and DISCERN criteria were parallel to each other. In the study of Eksi-Ozsoy (22), the evaluation of the JAMA criteria had a higher score than the DISCERN criteria, inconsistent with current study.

It was reported that YouTube™users viewed the first 60 to 200 videos and 90% of YouTube™ users search the first three pages (17, 26). In previous studies (13-16, 18, 21-23), examining video content in the field of dentistry, between 100 and 150 videos were evaluated. In the current study, the first 130 videos were evaluated and 30 of them were not included because they did not meet the evaluation criteria.

In the current study, although the number of commercial videos was less than the dentist/specialist and hospital uploaders, the view counts and the viewing rate were higher than all video uploaders. One reason may be that the videos uploaded by commercial can reach more

viewer because they are often sponsored content. The commercial's total video duration was shorter compared to other videos, as another reason, viewers may have preferred to watch short videos.

Most of the studies evaluating the videos about dentistry in the literature (9,11,13-22) found the videos poor and inadequate, in consistent with this study. In the one of the studies that found the video content sufficient, no standardized evaluation criteria were used (12). The most dangerous part in terms of health-related videos is that there are no rules or restrictions on uploading videos and everyone can easily shoot and upload videos. The videos about "bruxism" were mainly uploaded by the dentist/specialist (38%) and the hospital (43%). The interactions of dentist/specialist videos resulted in more interaction by viewers than all video sources. Although the videos about "bruxism", mostly prepared by professionals, attract the attention of the audience, the evaluation of videos as poor and insufficient in terms of both evaluation criteria (VIQI and DISCERN) shows that health professionals should produce higher quality content.

Many factors (biological, genetic, psychological, and external) play a role in the etiology of bruxism (27-29). The social isolation, which is one of the psychological factors, negatively affects both physical and mental health (30, 31). In the study of Saczuk et al. (32), it was observed that the findings of TMD and bruxism increased with social isolation. One of the important results of the current study was that videos containing bruxism increased with the COVID-19 pandemic process. Based on the date of the first COVID-19 case in Turkey (March 11, 2020), 23% of the videos were uploaded before and 67% after that specific date.

One of the limitations of the study is that many new videos are uploaded to YouTube™ every minute, and the data of the study can evaluate the videos at the time of the evaluation. Another limitation is that patients or non-professionals may search for videos with other words (tooth clenching, tooth grinding) than "bruxism". In future studies, an extensive analysis can be made by adding other social media platforms, for example Instagram.

CONCLUSION

Within the limitations, the following results were obtained from this study:

1. The videos about "bruxism" were found to be poor on the YouTube™ video platform.
2. Most of the videos were prepared by the dentist/specialist and hospital. Due to the insufficient content, health professionals should prepare better quality and informative videos about bruxism.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was not obtained as there was no human or animal participation in the study, and the videos were public. The study according to the World Medical Association Declaration of Helsinki, as no patient data or materials were used and all videos used for the study are available on a public social media website (YouTube™).

Informed Consent: There was no human or animal participation in the study and the videos reviewed on Youtube™ were open to everyone. Therefore, it was not necessary to obtain informed consent.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Can asymptomatic SARS-CoV-2 infection cause spontaneous abortion?

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ABSTRACT

Aim: The probability of spontaneous abortion is known to increase (15%) in the pregnant women who develop symptomatic and even "Severe Acute Respiratory Syndrome (SARS)" due to maternal infections. It is known that the SARS-CoV-2 virus, one of these infectious agents, enters host cells by binding to angiotensin-converting enzyme 2 (ACE2). New literature data have shown the increased ACE2 receptor in the endometrium during the decidualization phase and the ability of SARS-CoV-2 to enter endometrial stromal cells through ACE2 proteins. This shows that the COVID-19 infection can cause many pathologies such as early pregnancy loss. The aim of this study is to investigate the effects of SARS-CoV-2 virus which are positive in the uterine samples on pregnancy loss.

Material and Method: 13 women who had first trimester pregnancy loss were included in this cross-sectional study. None of these pregnant women had any known symptoms of SARS-CoV-2 infection. SARS-CoV-2 infection was screened in uterus and naso-oropharynx samples by real-time polymerase chain reaction (RT-PCR) test in these pregnant women. Women with positive RT-PCR results will be evaluated for pneumonia by lung tomography. It is planned to evaluate the sample taken from the naso-oropharynx in the partners of these women for SARS-CoV-2 infection by RT-PCR. In addition, in positive cases, RT-PCR was planned from the uterus and naso-oropharynx samples at 7-day intervals until the case turned negative.

Results: RT-PCR test for SARS-CoV-2 was positive only in a sample taken from the uterus of one woman (7.6%). The naso-oropharyngeal sample of the same patient was negative, and the patient had no symptoms of COVID-19. No COVID-19-related lesion was observed in the lung tomography of this patient. The results of the RT-PCR test performed 7 days later with samples taken from the uterus and naso-pharynx were also negative. After the patient's positive RT-PCR result, a naso-oropharyngeal sample was taken from his partner. The RT-PCR test result for SARS-CoV-2 in the patient's partner was negative.

Conclusion: The fact that the SARS-CoV-2 virus was negative in the naso-oropharyngeal sample and positive in the uterine sample in a pregnant woman who had a miscarriage suggests that the endometrium may be an entry route for the virus. These data suggest that the virus can lead to adverse pregnancy outcomes, including early pregnancy loss, even without known symptoms. A large number of studies are needed to evaluate the effects of common viruses on pregnancy beyond the expected and defined symptoms.

Keywords: Pregnancy loss, SARS-CoV-2, abortion, intrauterine, COVID-19

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INTRODUCTION

Pregnancy loss, also known as a miscarriage or spontaneous abortion, is generally defined as a nonviable intrauterine pregnancy up to 20 weeks of gestation (1,2). Common risk factors for abortion include advanced maternal age, medical conditions, drug and/or substance abuse, and environmental exposure.

Overall, approximately 15% of abortions are associated with an infectious etiology (3). The cumulative incidence of abortion due to parvovirus B19 infection during pregnancy is approximately 8%, and the risk of abortion due to an infection is 5.6 times higher in the first trimester than in the second trimester (4). Untreated syphilis leads to a 21% increased risk of abortion and stillbirth (5). Maternal cytomegalovirus (CMV) infection increases the abortion rate by 2.5 times (6). However, maternal infection with HIV or toxoplasmosis has not been shown to be associated with abortion risk (7,8).

Coronavirus disease 2019 (COVID-19) was first seen in Wuhan, China in December 2019 as a disease that can progress to acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF) caused by the severe

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acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Due to the ongoing pandemic caused by the infection, new scientific data are rapidly added to the literature. However, the relationship between SARS-CoV-2 and abortion has not yet been clarified (9). On the other hand, there are data suggesting that infection may cause maternal vascular malperfusion and decidual arteriopathy in pregnant women (10-12). SARS-CoV-2 positivity has been shown in tissues such as the placenta or placental membranes of a small number of patients (10,13).

The SARS-CoV-2 virus uses angiotensin-converting enzyme 2 (ACE2) to enter the cell. For this reason, studies have shown that it can replicate not only in the respiratory system but also in other tissues where ACE2 is present (14). The fact that SARS-CoV-2 can enter endometrial stromal cells using ACE2 shows that it can also cause pregnancy loss (15,16).

The aim of this study was to investigate the effects of the SARS-CoV-2 virus on pregnancy loss by showing positivity in uterine samples.

MATERIAL AND METHOD

The study was approved by the Republic of Turkey, Ministry of Health, Scientific Research Studies Evaluation Commission (Date: 16.05.2020, Decision No: 2020-05-15T15_13_17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Women who were evaluated for pregnancy loss in the Department of Obstetrics and Gynaecology, Medicana International İstanbul Hospital, and Esenler Maternity and Children's Hospital between 15 April 2020 and 14 June 2020 were invited to participate in the study. The study included 13 women who agreed to participate. The presence of COVID-19 symptoms during pregnancy, smoking habits, obstetric history, and chronic diseases of these women were questioned.

Vacuum aspiration was planned to be performed under sedation and sterile operating room conditions as a treatment for pregnancy loss. The coagulation and hemogram parameters of all patients were evaluated preoperatively. Before starting the operation, samples were taken from the naso-oropharynx and uterus of all patients under sedation for RT-PCR test.

The RT-PCR method targeting the RdRp (RNA-dependent RNA polymerase) gene was used for the detection of SARS-CoV-2 in naso-oropharyngeal and uterine samples. Specimens were transported to the Molecular Virology Laboratory within 12 hours of collection and tested immediately upon acceptance.

RT-PCR was studied in the naso-oropharyngeal samples of the partners of women with a positive RT-PCR result for the SARS-CoV-2 virus to screen the virus. Chest computed tomography (CT) examinations of these women and their partners were evaluated for the presence of infiltrating areas. Their serum CRP, Ferritin, D-Dimer, LDH levels were also measured. In addition, in positive cases, RT-PCR was planned from the uterus and naso-oropharynx samples at 7-day intervals until the case turned negative.

Data were analyzed using the SPSS software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). A p-value less than 0.05 was considered statistically significant.

RESULTS

The study consisted of a cross-sectional analysis of 13 pregnant women who had pregnancy loss during the SARS-CoV-2 pandemic. Age, gestational age, gravida, parity, abortion, the presence of COVID-19 symptoms during pregnancy, smoking habits, and chronic diseases were determined (**Table 1**).

Table 1: Demographic and laboratory data of 13 women, who had pregnancy loss

	Min	Max<	Mean	Standart Deviation
Age	20	38	29	5.29
Gestatational Age (day)	34	88	52.61	15.22
Gravida	1	5	2.38	1.44
Parite	0	3	1	0.91
Abort	0	2	0.3	0.63
WBC* Count (10^3/uL)	5.15	14.69	8.81	2.59
Hemoglobine Count (g/dL)	10.8	14	12.53	1.02
Platelet Count (10^3/uL)	158	405	260.46	77.96
Lymphocyte Count (10^3/uL)	1.3	4.3	2.28	0.74
aPTT* (second)	26.9	47.8	34.88	4.68
Prothrombin time (INR*)	0.92	1.29	1.04	0.98
	n		**%**	
Chronic Disease	1		7.6	
Smoking Habits	4		30.8	
COVID-19 Symptoms	0		0	

*WBC: White blood cell, aPTT: Activated partial thromboplastin time, INR: International Normalized Ratio

According to their gestational age, all patients were in the first trimester of pregnancy. None of the patients had symptoms that may be caused by COVID-19. Only one woman had controlled hypothyroidism as a chronic disease. The laboratory results of the patients showed no severe anemia, lymphopenia, or coagulation disorder.

Given the RT-PCR results, the SARS-CoV-2 virus was not detected in any of the naso-oropharyngeal samples. The RT-PCR test was positive for the SARS-CoV-2 virus in the uterine sample of only one 38-year-old woman, who was a smoker, pregnant for the first time, and had no additional chronic disease or symptoms (7.69 %) (**Table 2**).

Table 2. Demographic and laboratory data of women who were positive for SARS-CoV-2 in endometrial rt-PCR

Age	38
Gestational Age (day)	57
Gravida	1
Parite	0
Abort	0
WBC Count	8.48 10^3/uL
Hemoglobine Count	13.9 g/dL
Platelet Count	223 10^3/uL
Lymphocyte Count	2.27 10^3/uL
aPTT	26.9 second
Prothrombin time	0.92 INR*
Chronic Disease	no
Smoking Habits	10 cigarettes maximum per day
COVID-19 Symptoms	no
Naso-oropharynx rt-PCR*	negative
Endometrial rt-PCR	positive
LDH*	147 U/L
CRP*	1.3 mg/dL
Ferritin	27.52 ng/mL
D-Dimer	577 ng/mL
Thorax-CT*	no infiltrative lesion
Chromosomal abnormalities in abort material	no

*WBC: White blood cell, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, rt-PCR: Real-time reverse transcriptase-polymerase chain reaction, LDH: Lactate dehydrogenase, CRP: C-reactive protein CT: Computed tomography

The patient was evaluated based on the positive intrauterine RT-PCR result, which was reported four days after the surgical procedure. The asymptomatic patient was also examined for COVID-19 infection. Her chest CT showed no active infiltration. The laboratory evaluation showed normal lymphocyte count and LDH levels. Acute phase reactants (CRP, ferritin, D-dimer) were also studied. The CRP and D-Dimer levels were above the normal range but the ferritin level was normal.

The partner of the patient was considered a suspected COVID-19 patient and was evaluated with RT-PCR of the naso-oropharyngeal sample, which negative for SARS-CoV-2.

The treatment algorithm recommended by the Ministry of Health of the Republic of Turkey for asymptomatic patients was used for the treatment of the patient who was isolated and followed up at home. Seven days after the initiation of the patient's treatment, an intrauterine RT-PCR sample was taken for a follow-up examination and the result was reported negative for this sample. In the later period, the patient and her partner exhibited no symptoms associated with COVID-19.

Only in this case, genetic analysis was ordered for the abortion material upon the patient's own request. No chromosomal abnormalities was detected on the examination of the abortion material.

DISCUSSION

Although many studies have been conducted on the effects of SARS-CoV-2 on pregnancy and fetus, the long-term effects of SARS-CoV-2 are still unclear since it is a quite new infectious agent (17). Most studies have evaluated naso-oropharyngeal swab samples of pregnant women (18). However, the data at the molecular level have shown that the respiratory epithelium is not the only tissue through which the virus enters the cell and becomes effective (16). SARS-CoV-2, which enters the cell via ACE2, also involves other tissues including the lung, heart, intestine, kidney, and placenta (15).

The increased expression of ACE2 during the formation of the decidual endometrium also increases the probability of viral replication (15). It has been reported that SARS-CoV-2 is effective in the decidual endometrium in the early stage of pregnancy, while it is effective in the placental area with the formation of the placenta in the later stage of pregnancy (11, 19). The virus is believed to cause pregnancy complications due to maternal vascular malperfusion and decidual arteriopathy (19). A limited number of meta-analyses in the literature have reported cases of maternal death, neonatal death, preterm birth, preeclampsia, and early pregnancy loss (17,18,20). Among these data, there are only a few case reports evaluating the fetus, placenta, and placental appendages separately for SARS-CoV-2 (10). Despite the small sample size, this study is of importance in terms of filling this gap in the literature.

This study evaluating 13 cases of pregnancy loss demonstrated positive RT-PCR result for the virus in the uterine sample of only 1 patient. No virus was detected in the naso-oropharyngeal sample taken simultaneously from the same patient. Although this data does not provide clear evidence, it suggests sexual transmission of SARS-CoV-2. The absence of known symptoms of COVID-19 and infiltrative lesions on chest CT in the positive case strengthens the suspicion that the virus may also cause disease manifestations beyond the known.

Our study is a prospective study conducted with the special permission obtained by the COVID-19 Ethics Committee from the Ministry of Health at the beginning of the COVID-19 pandemic. Ethics Committee permission of the Ministry of Health, which was obtained at the beginning of the study, was granted for a period of 3 months. In this context, this time has been determined out of necessity for the study. However, studies have also reported that pregnant women increase their protective measures, and therefore, pregnant women are less infected (21). This situation reduces our sample size dramatically.

The long-term complications of the COVID-19 infection in pregnant patients and the asymptomatic illness are still mysterious (22). The indications for the SARS-CoV-2 test

include the presence of predetermined symptoms and a history of suspected contact. Accordingly, there is not sufficient knowledge on the role of SARS-CoV-2 positivity in obstetric complications. The investigation of the relationship between obstetric complications and SARS-CoV-2 positivity will help predict adverse reproductive outcomes. Therefore, there is a need for more comprehensive studies including intrauterine fetal deaths in the later stages of pregnancy.

CONCLUSION

A positive SARS-CoV-2 sample from the uterus indicates that the endometrium can serve as an entry route for the virus. The SARS-CoV-2 virus can enter through the endometrium in pregnant women, potentially leading to adverse pregnancy outcomes, including early pregnancy loss. While our study's sample size was small, it supported this finding. Large-scale studies are needed to investigate the effects of SARS-CoV-2 and other common viral infections during pregnancy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Republic of Turkey, Ministry of Health, Scientific Research Studies Evaluation Commission (Date: 16.05.2020, Decision No: 2020-05-15T15_13_17).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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A biomarker predicting unfavorable prognosis in malignant pleural mesothelioma: systemic immune–inflammation index

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ABSTRACT

Aim: Malignant pleural mesothelioma (MPM) is an extremely mortal condition. Only a few prognostic biomarkers have been described for MPM. Our study looked into the association between patient survival and the Systemic Immune Inflammation Index (SII).

Material and Method: A total of 158 patients who were admitted to our hospital between January 2013 and December 2022, and had a histopathologically confirmed diagnosis of MPM were included in the study. Before treatment, hematological parameters and SII were determined. A Spearman's correlation analysis was performed to analyze the correlation of mean survival with hematological parameters.

Results: The study involved 158 patients in all. 70 patients had a history of smoking, the median age was 63 years, the mean survival time was 15.3 months, and 57.6% of the participants were men. The epithelioid type (84.2%) was the most prevalent histological subtype, and 29 patients had stage 4 illnesses. Of the participants, 84% had received chemotherapy, and 22% had received radiotherapy before. Among the 39 patients who had surgery, 5 had an extrapleural pneumonectomy. SII mean±sd was (1427.2±1207.3). The patients with stage 4 disease had significantly shorter survival (p=0.001). The patients who had surgery survived significantly longer (p=0.01). Hemoglobin (Hb) (r:0.21, p:0.01) and Hematocrit (Hct) (r:0.18, p:0.03) values showed weak positive correlations with mean survival. It was evident that mean survival got shorter as SII (r:-0.17, p:0.04) and neutrophil-lymphocyte ratio (NLR) (r:-0.19, p:0.02) values got higher. On the other hand, there was a strong positive association between mean survival and the lymphocyte-monocyte ratio (LMR) (r:0.21, p:0.01). When the parameters that had statistically significant differences among the groups were taken as control variables and the statistical analysis was re-performed, it was found that Hgb and Hct values as well as NLR and LMR ratios lost their significant correlations with survival. However, the SII ratio was still negatively correlated with survival (r:-0.16, p:0.04).

Conclusion: Pretreatment SII is a noninvasive and easy-to-calculate biomarker that predicts the prognosis of MPM. It is negatively correlated with mean survival regardless of the tumor stage and surgical management.

Keywords: Malignant pleural mesothelioma, systemic immune-inflammation index, prognosis, survival

This study was presented as an oral presentation at the 11th International Congress of Medical and Health Sciences Research (UTSAK) held on 24 - 25 - December 2022.

INTRODUCTION

Malignant mesothelioma (MM) is a fatal and extremely aggressive disease. Malignant pleural mesothelioma, which accounts for 80% of mesotheliomas, develops from the pleura (MPM) (1-3). Due to rising environmental contamination as well as occupational and environmental asbestos exposure, MPM incidence has recently been predicted to rise. Due to its lengthy latent period following exposure, MPM is frequently detected in later life. This period is about 20-40 years (3,4). MPM is an insidious disorder. The diagnosis is difficult due to non-specific symptoms and normal radiological findings early in the course of the illness.

Regardless of the tumor stage, MPM is resistant to treatment and has a median overall survival (OS) of 9–17 months (3). Malignant tumor formation and progression are highly dependent on tissue inflammation (5,6). Serum lymphocyte, monocyte, neutrophil, and platelet counts, are indicators of a systemic inflammatory response. These cell counts are used to determine the lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio, which are all directly associated with the prognosis of various cancers (7,8). The systemic immune-inflammation index (SII) is calculated based on lymphocyte (L), neutrophil (N),

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and platelet (P) values (SII=N×P/L). This parameter is correlated with prognosis in malignant tumors (9).

Very few biomarkers have been identified for MPM. There is no specific algorithm for the management of MPM. There are few prospective and retrospective studies on MPM patients' prognostic variables, as well as the effectiveness and tolerability of antineoplastic therapy. The objective of this study was to retrospectively examine how systemic inflammation affected MPM patients' prognoses.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara Atatürk Sanatoryum Training and Research Hospital Clinical Researches Ethics Committee (Date: 25.01.2023, Decision No: 2012-KAEK-15/2624). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A retrospective analysis was performed on patients who were admitted to our hospital between January 2013 and December 2022 and who had a histological MPM diagnosis. The patients' demographic, laboratory, therapeutic, clinical, and survival information was documented. The readings from the laboratory used for the analysis were those at the time of diagnosis and before therapy. Demographic, clinicopathological, therapeutic, and prognostic data were systematically analyzed. Asbestos exposure, TNM stage, histopathological subtype, SUV max value on PET, chemotherapy and radiotherapy data, surgical treatment history, life expectancy, hemoglobin (Hb), hematocrit (Hct), neutrophil, monocyte, lymphocyte, and platelet (PLT) count, white blood cell count (WBC), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and systemic immune-inflammation index (SII) were determined, calculated, and recorded. NLR was calculated as absolute neutrophil count divided by absolute lymphocyte count and LMR was calculated as absolute lymphocyte count divided by absolute monocyte count. Systemic immune-----inflammation index (SII) (SII=N×P/L), known as systemic immune–inflammation index, is calculated on neutrophil (N), platelet (P), and lymphocyte (L) count. The staging of malignant mesothelioma was performed using the tumor–node–metastasis (TNM)-based on The International Mesothelioma Interest Group (IMIG) Staging System.

Overall survival (OS) and survival were reported (OS was defined as the interval between diagnosis and death or last follow-up). The informed consent of the participants was not obtained due to the retrospective nature of the study.

Study Population

The patients who were admitted to our hospital between January 2013 and December 2022 and histopathologically diagnosed with MPM were reviewed retrospectively.

Inclusion criteria are (1) a histopathological diagnosis of MPM in our hospital between January 2013 and December 2022; (2) age ≥ 18 years; (3) the presence of clinical and follow-up data; and (4) not having received any anti-neoplastic treatment before the definitive diagnosis.

Exclusion criteria are (1) the patients with benign mesothelioma or tumor origin elsewhere other than pleura; (2) having an anti-neoplastic treatment before the definitive diagnosis; (3) the patients with inflammatory or autoimmune disorders (4). In addition, those with any viral infections (HBV, HCV, HIV, etc.), autoimmune disorders, including systemic lupus erythematosus, leukemia, any other hematological disorders, inflammatory disorders, or solid organ (liver, spleen, etc.) conditions.

Statistical Method

The SPSS 23 package application for Windows was used to conduct all statistical analyses. The percentiles in the descriptive data of the variables were calculated using cross-tabs. Mann-Whitney U test was used to compare the means. To analyze the relationship of survival with age and hematologic variables, the Spearman correlation test was employed in the case of continuous data that did not fit the normal distribution. In the comparison of the groups, the stage and the presence of a surgical procedure, which are thought to affect survival, were used as control variables, and the parameters found to be correlated in the Spearman correlation test were re-evaluated with partial correlation analysis. Results were considered statistically significant when the p-value was less than 0.05.

RESULTS

The study involved 158 patients in all. The average lifespan was 15.3 months, with a mean age of 63. Among the participants, 57.6% were men, and 70 patients had a history of smoking. A history of asbestos contact was evident in 123 participants. The most common histopathologically subtype was the epithelioid type (84.2%), 29 patients had stage 4 tumors. 84% of the participants had chemotherapy, and 22% had radiotherapy. While the surgery was performed on 39 patients in total, 5 had an extrapleural pneumonectomy. **Table 1** displays the means for hematological parameters and demographic information. A comparison of the mean survival of the groups showed significantly shorter survival in patients with stage 4 tumors compared to other stages (p=0.001). The mean survival was 6.5

months in stage 4 patients, while this value was 17.3 months in the patients with tumors in other stages. The survival was 20.4 months in the surgery group, it was significantly longer than the no-surgery group, which had 13.6 months of survival (p =0.01). **Table 2** provides a detailed comparison of the groups' survival rates. The correlation of mean survival with hematological parameters was analyzed with the Spearman correlation test. Age and survival did not significantly correlate with one another (p=0.22). Hemoglobin (r:0.21, p:0.01) and hematocrit (r:0.18, p:0.03) values showed weak positive correlations with mean survival. It was observed that the mean survival decreased as the systemic immune-inflammation index (r:-0.17, p:0.04) and NLR (r:-0.19, p:0.02) values increased. On the other hand, mean survival and lymphocyte-monocyte ratio had a significant positive correlation (r:0.21, p:0.01). When the parameters that had statistically significant differences among the groups were taken as control variables and the statistical analysis was re-performed, it was found that hemoglobin and hematocrit values as well as neutrophil-lymphocyte ratio and lymphocyte-monocyte ratio ratios lost their significant correlations with survival. However, the Systemic immune-inflammation index ratio was still negatively correlated with survival (r:-0.16, p:0.04).

Table 1. Demographic data (n=158)

Average age	63.97±9.15
Male	91 (57.6)
Smoking	70 (44.3)
History of asbestos	123 (77.8)
Stage	
1,2,3	129 (81.6)
4	29 (18.4)
Histological type	
Epithelioid	133 (84.2)
Sarcomatosis	5 (3.2)
Biphasic	20 (12.7)
Chemotherapy	132 (83.5)
Radiotherapy	35 (22.2)
Surgical	39 (24.7)
Extrapleural pneumonectomy	5 (3.2)
Hgb	13.1±1.9
Hct	39.7±5.9
Lymphocyte	10.23±11.3
Monocyte	3.69±4.1
Neutrophıl	35.9±36.2
PLT	327.8±118.4
SII	1427.2±1207.3
NLR	4.29±3.2
PLR	123.7±134.6
LMR	3.20±1.71
Survey months	15.3±12.9

(%) Column percentages Mean±sd, Hgb: Hemoglobın, Hct: hematocrit, PLT: platelet, SII: systemic immune-inflammation index, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, LMR: lymphocyte-monocyte ratio.

Tablo 2. Comparison of average life expectancy with demographic data

n=158		**p**
Gender		0.24
Male	91±15.1	
Female	67±15.6	
Smoking		0.30
Yes	14.1±9.2	
No	16.3±15.2	
History of asbestos		0.10
Yes	14.4±12.6	
No	18.5±13.4	
Stage		0.001*
1,2,3	17.3±13.2	
4	6.5±6.5	
Histological type		0.17
Epithelioid	16.1±13.1	
Sarcomatosis	12.0±19.7	
Biphasic	10.6±7.9	
Chemotherapy		0.34
Yes	15.8±11.8	
No	12.4±17.4	
Radiotherapy		0.08
Yes	18.3±11.2	
No	14.4±13.3	
Surgical		0.01*
Yes	20.4 ±14.4	
No	13.6±11.9	
Extrapleural pneumonectomy n=39		0.12
Yes	32.8±20.1	
No	18.7±12.9	

*p < 0.05

Table 3. Relationship between hematological values and mean survival

	Spearman correlation analysis		**Partial correlation analysis**	
	Correlation coefficient	**p**	**Correlation coefficient**	**p**
Age	-0.09	0.22		
Hgb	0.21	0.01*	0.15	0.05
Hct	0.18	0.03*	0.13	0.08
Lymphocyte	0.06	0.43		
Monocyte	-0.07	0.36		
Neutrophıl	-0.08	0.31		
PLT	-0.07	0.42		
SII	-0.17	0.04*	-0.16	0.04*
NLR	-0.19	0.02*	-0.15	0.05
PLR	-0.06	0.43		
LMR	0.21	0.01*	0.15	0.05

*p < 0.05, Control variables:Stage and surgical

DISCUSSION

There are few studies on mesothelioma since it is less frequent than lung cancers. Numerous cancer types have been researched to determine the connection between inflammation and cancer. We investigated the systemic immune-inflammation index (SII) in this study's individuals who had been diagnosed with mesothelioma.

MM most frequently involves the pleura (73-85%), followed by the peritoneum (7-18%). MM is more frequent in men (male: female ratio: 5:1) (10-11). Treatment options for MPM are systemic chemotherapy, radiotherapy, and surgery. Systemic chemotherapy is the preferred treatment modality in cases of an un-resectable tumor, in patients with tumor recurrence, and in those who do not prefer surgery. Preoperative or postoperative radiotherapy aims to relieve local symptoms (12).

If MPM is a tumor at an operable stage, tri-modal management including surgery, chemotherapy, and radiotherapy is preferred (13). Surgical treatment has been independently correlated with a favorable prognosis in operable cases (stages I, II, and III). The prognosis is often miserable, as most patients diagnosed with mesothelioma have inoperable tumors at the time of diagnosis. The surgical options are pleurodesis, pleurectomy/decortication, and extrapleural pneumonectomy (EPP) in the treatment of mesothelioma if the tumors are suitable for surgery (14). Patients who have surgery have been reported to have improved OS, which is consistent with our findings (15).

It has been known that inflammation may increase the tumor risk, triggering the genetic mutation mechanisms, and promoting tumor formation, metastasis, and progression (16). Studies have shown that hemoglobin levels are directly related to survival and tumor development in cancer patients (17). In our study, the Hgb and Hct values showed weak positive correlations with mean survival.

An essential component of the tumor microenvironment is inflammation, which has been linked to a poor prognosis in several tumor forms. It is possible to forecast the prognosis of malignancies using variables like neutrophil, lymphocyte, monocyte, and platelet counts, which may indicate the immunological condition of the host. A high inflammatory response generally indicates a worse prognosis (18-19). The onset and development of cancer are significantly influenced by systemic inflammation. Hematological parameters including serum lymphocyte, monocyte, neutrophil, and platelet counts, and NLR, LMR, and PLR calculated using these cell counts are prognostic parameters for malignancies (2,20,21). Recent studies have shown that certain blood markers, such as the ratio of neutrophils to lymphocytes (NLR), the ratio of platelets to lymphocytes (PLR), and the ratio of lymphocytes to monocytes (LMR), represent inflammatory changes in the tumor microenvironment (22).

It has been shown that lymphocytes, and particularly T cells, are associated with prognosis (23). Depending on their subgroup, monocytes can perform a variety of functions, including promoting blood vessel formation and secreting tumoricidal mediators. In conclusion, LMR calculated using two parameters may be a better prognostic parameter in non-small cell lung cancer. High NLR and PLR as well as a slow LMR predict shorter survival (24-26). In our investigation, it was found that the mean survival decreased as the NLR values increased; however, there was a statistically significant positive association between the mean survival and the LMR value.

The development of tumors is significantly influenced by inflammation.SII is a systematic indicator of inflammatory response that can be calculated by the following formula: neutrophil (N) count× platelet (P) count/lymphocyte (L) count. Pre-treatment SII may better reflect the inflammatory and immune status of the body. In many cancer types, previous studies have shown that pre-treatment SII is a significant prognostic parameter. These cancers include lung, stomach, bladder, cervix, breast, and hepatocellular carcinoma (27-31). Our research demonstrated a link between a high pre-treatment SII and a poor prognosis for MPM. SII is a noninvasive and inexpensive prognostic parameter for MPM. These findings are extremely valuable for the clinics that follow up on patients with MPM. These values may help clinicians establish treatment plans and follow-up with the patients.

Studies on the prognostic role of the pretreatment SII on MPM are limited. In our study, a negative correlation was found between the pre-treatment SII ratio and the mean survival, irrespective of tumor stage and surgical treatment.

Our study does have certain limitations. It might not be suitable to apply these findings to the general population because the first study had a single-center single-center design and a small sample size. The study is also retrospective.

CONCLUSION

This study was performed on patients with histo-pathologically proven MPM in our hospital. Hematological parameters may be easily obtained before treatment. These biomarkers may be easily incorporated into routine clinical practice. SII is a noninvasive and easily calculable biomarker in MPM. High SII is an independent negative prognostic factor in MPM. Regardless of the stage of the tumor and the performance of surgery, the SII ratio is negatively correlated with mean survival.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Atatürk Sanatoryum Training and Research Hospital Clinical Researches Ethics Committee (Date: 25.01.2023, Decision No: 2012-KAEK-15/2624).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article

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The effect of social media use on emotional eating in women aged 19-45

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ABSTRACT

Aim: This study aims to examine the relationship between social media use and emotional eating in women.

Material and Method: The study was cross-sectional and was conducted with 401 women aged 19-45 years living in Kadıköy, İstanbul. The introductory information form consisting of 4 stages, the Dutch Eating Behavior Questionnaire (DEBQ), Eating Attitude Test (EAT-40), and Social Media Usage Scale (SMUS) were applied to the participants of the study. Statistical analyzes were evaluated using the SPSS 23 package program.

Results: It was seen that 22.9% (n=92) of the participants were between the ages of 19-29, 57.1% (n=229) were between the ages of 30-39, and 20.0% (n=80) were between the ages of 40-45. According to the results of the analysis, there was no significant relationship between SMUS sub-dimensions, total SMUS scores and EAT-40 scores ($p>0.05$). In the continuance sub-dimension of the SMUS, a low-level significant positive correlation was found between emotional eating ($r=0.203$; $p<0.001$), external eating ($r=0.233$; $p<0.001$), and total DEBQ scores ($r=0.183$; $p<0.001$).

Conclusion: It has been observed that there is a very low positive relationship between social media use and emotional eating.

Keywords: Emotional eating, social media, disordered eating behavior, restrictive eating

INTRODUCTION

When they reach adulthood, individuals begin to have difficulty creating changes in their eating behaviors as they get older. The shaping of eating behavior, the foundation of which is laid in childhood, continues in adulthood. When it comes to eating behavior, people can act not only with their physiological needs but also with their emotional states. For example; Factors such as the frequency and amount of meals, and food selection may vary with the emotional state (1,2).

Emotional eating is the act of eating to cope with negative emotions and to regulate mood (3). Emotional eating; It can occur as a result of emotions such as boredom, stress, anxiety, and anger. Considering the effect of positive and negative emotions on eating, significant differences were observed; It was observed that food intake decreased with emotions such as fear, tension, and pain, while it increased with emotions such as depression, fatigue, and boredom (1,4). Emotional eating; It is stated that it is seen in women with eating disorders, and in obese individuals who continue to diet despite having a normal body weight (5). The fact that individuals do not feel hungry and tend to eat to feel good beyond the saturation point may cause an increase in calorie intake, resulting in weight gain. Studies are reporting a positive relationship between body mass index and emotional eating (6,7).

Although the mechanism underlying emotional eating is not fully known, there are theories about it. The theory that is the source of much of the emotional eating debate is the Psychosomatic Theory of Obesity (8). According to this theory, food is used as an emotional defense against the negative effects that lead to overconsumption and thus obesity. Although it is not known how eating reduces these feelings, it is emphasized that carbohydrate and protein consumption affect the synthesis of serotonin neurotransmitters in the brain (1,9). Another theory, according to the theory of Schachter et al. (10), while the desire to eat is suppressed in cases of fear and anxiety in people with normal weight, this situation is not observed in obese individuals. Obese people tend to eat with external stimuli such as smell and image, not depending on hunger-satiety signals (1,9).

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Restrictive eating is defined as the restriction of food intake to achieve weight control (11). Individuals with restrictive eating behavior tend to increase their consumption of low-calorie foods and reduce their consumption of high-calorie foods to reduce their energy intake. On the other hand, individuals with restrictive eating also have binge eating attacks in some cases (12, 13).

Social media is the general name given to websites where users can make friends, communicate with friends, share personal information about themselves, and share pictures or videos. Among the most widely used social media platforms today; There are Facebook, Youtube, Instagram, and Twitter (14, 15). Studies show that media is a risk factor for body dissatisfaction, eating behavior, and negative affect (16, 17). It has been reported that the ideal thin body perception shown by the media may cause eating behavior problems in women (18). It is thought that the increase in the number of individuals receiving treatment for eating disorders is related to the increase in social media platforms (19). It has been reported that being more visible through social media can cause this by strengthening the ideal thin body perception and increasing the desire to be thin (19).

Social media, which is frequently used by young people, is actively used by all age groups today. It is seen that the use of social media has a different place in people's lives depending on factors such as gender and age group. This study aims to examine the relationship between social media use and emotional eating in women aged 19-45.

MATERIAL AND METHOD

Type of Study and Sample Selection

The research type is cross-sectional and descriptive. The population of the research consists of women residing in the Kadıköy region of İstanbul and between the ages of 19-45. The sample of the study consisted of 401 women who met the inclusion criteria and voluntarily agreed to participate in the study. Statistically, it reflects the sample population. The 95% confidence interval was used in the creation of the research sample. The research was announced online through social media platforms and was conducted with individuals who agreed to participate in the study. Research data were collected between February and March 2022. As a result of the examination of the questionnaires, individuals who met the study criteria and filled out the form completely were included in the study. The study included people aged 19-45 who were female, residing in İstanbul, Kadıköy, filling out the questionnaires correctly and completely, knowing Turkish, and using social media.

Data Collection

The questionnaire used in the study consisted of 4 parts. In the first part, the Personal Information Form, in the second part, the Dutch Eating Behavior Questionnaire, in the third part, the Eating Attitude Test, and in the fourth part, the Social Media Usage Scale.

Personal Information Form: In the first part of the research questionnaire, questions were asked to determine demographic characteristics such as age, gender, marital status, and general health statuses such as weight, height, waist circumference, number of meals, and water consumption. Body Mass Index (BMI) was calculated according to the weight and height information of the participants.

Dutch Eating Behavior Questionnaire (DEBQ): The Dutch Eating Behavior Questionnaire was administered to the participants in the second part, and this questionnaire consists of three subscales examining emotional eating, external eating, and restricted eating behavior. The items in the questionnaire are evaluated with a 5-point Likert-type scale (1: never, 2: rarely, 3: sometimes, 4: often, 5: very often). The Cronbach alpha internal consistency coefficients obtained in the original study of DEBQ were for the emotional eating behavior subscale; 0.95 for the external eating behavior subscale; 0.81 and for the restricted eating behavior subscale; 0.95 was found (20). In present study, Cronbach alpha of Restrictive Eating, Emotional Eating and External Eating were found as .87,.92,.83.

Eating Attitude Test (EAT-40): In the third part of the questionnaire, it was aimed to examine the impaired eating behaviors of the participants with the Eating Attitude Test. The items in the questionnaire are evaluated with a 6-point Likert-type scale. It is thought that participants who score 30 and above on the test may have impaired eating behavior. The Cronbach alpha of the scale was reported as 0.70 (21). In our study, Cronbach's alpha internal consistency coefficient was determined as 0.72.

Social Media Usage Scale: In the last part, the Social Media Usage Scale was applied to the participants to examine their social media usage. The scale is evaluated with a 5-point Likert-type scale. (1: never, 2: rarely, 3: sometimes, 4: often, 5: very often). The total Cronbach alpha internal consistency coefficient of the social media usage scale was determined as 0.82 (15). In our study, Cronbach's alpha internal consistency coefficient was determined as 0.79.

Ethics Approval

This study was approved by the Ethics Committee of İstanbul Okan University (Date: 19.01.2022, Decision No: 148/17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent of the participants and their consent to participate in the research were obtained with the consent / reject options that they had to tick on Google Forms.

Statistical Analysis

Research data were evaluated using the IBM Statistical Package for Social Science (SPSS) 23 package program. While descriptive statistics are determined by numbers and percentages, continuous data are shown with mean and standard deviation values. Continuous data with skewness and kurtosis coefficients between -1,500 and +1,500 were considered to fit the normal distribution. While one-way ANOVA was used in the evaluation of more than two groups, the independent sample t-test was used to compare the means in the data with the distribution. Kruskal Wallis analysis of variance was used in the data comparing more than two groups that did not fit the normal distribution. Tukey's b test was applied in further analysis to find out which group caused the difference in multiple groups. While Pearson Correlation was applied for data that fit normal distribution in calculating the relationship between continuous data between groups, Spearman Correlation was used for data that did not fit a normal distribution. Results were evaluated at the 95% confidence interval and significance level of $p<0.05$.

RESULTS

The sociodemographic characteristics of the women participating in the study were examined in Table 1. 22.9% (n=92) of the participants were between the ages of 19-29, 57.1% (n=229) were between the ages of 30-39, and 20.0% (n=80) were between the ages of 40-45 are in the range. When the educational status of the participants was examined, 13.0% (n=52) had a high school or lower education level, 71.8% (n=288) had undergraduate education and 15.2% (n=61) had postgraduate education. stated level. When the employment status of the participants is examined, 12.5% (n=50) are not working, 16.5% (n=66) are housewives, 20.9% (n=84) are civil servants, 46.6% of them (n=187) stated that they worked as the private sector and 3.5% (n=14) of them said that they were in the private sector. When the marital status of the participants was examined, it was seen that 29.2% (n=117) were single and 70.8% (n=284) were married. When the participants were asked whether they had children, 61.1% (n=245) stated that they had children, while 38.9% (n=156) stated that they had no children. When the women participating in the study were asked about the number of children, 38.9% (n=156) stated that they had no children, 33.7% (n=135) had 1 child, and 27.4% (n=110) had 2 or more children. He said he had many children. The comparison of the life behavior characteristics of the individuals participating in the study with the Social Media Usage Scale is shown in Table 2. When the risk of eating behavior disorder and social media usage characteristics of the women who participated in the study were compared, it was observed that there was no relationship between the risk of eating behavior disorder and the continuity, competence, and total scores of the social media use scale.

The relationship between the social media usage levels of the individuals participating in the study and their eating attitude and eating behavior is shown in Table 3. According to the results of the analysis; No significant correlation was found between social media usage scale sub-dimensions and total scores and Eating Attitude Test scores ($p>0.05$). In the continuance sub-dimension of the Social Media Use Scale, there was a positive low level of emotional eating ($r=0.203$; $p<0.001$), external eating ($r=0.233$; $p<0.001$), and total Dutch Eating Behavior scores ($r=0.183$; $p<0.001$). A significant relationship was found. In the Social Media Use Scale competency sub-dimension, a very low level of positive relationship was observed only in the emotional eating sub-dimension ($r=0.112$; $p<.05$), while no relationship was observed between the other sub-dimensions and the total score. There is a very low correlation between emotional eating ($r=0.172$; $p<0.05$) and external eating ($r=0.172$; $p<0.05$) sub-dimensions of total SMQQ scores and total DEBQ ($r=0.153$; $p<0.05$) scores. It was found that there was a significant positive relationship at the level of the participants, but the relationship between restrictive eating sub-dimension scores was not significant ($p>0.05$).

Table 1. Distribution of participants' sociodemographic characteristics

Variables	n	%
Age (year) (mean±SD)		
19-29	92	22.9
30-39	229	57.1
40-45	80	20.0
Occupation		
Retired	50	12.5
Housewife	66	16.5
Officer	84	20.9
Employee	187	46.6
Self-Employment	14	3.5
Education		
≤ High School	52	13.0
Bachelor	288	71.8
Graduate	61	15.2
Marital status		
Single	117	29.2
Married	284	70.8
Status of having a child		
Yes	245	61.1
No	156	38.9
Number of children		
0	156	38.9
1	135	33.7
≥ 2	110	27.4
Total	401	100.0

Table 2. Comparison of the healthy living behavior characteristics of the participants according to the social media use scale

Variables	Social Media Usage Scale		
	Competence 12.42±4.06	**Perfection 12.32±4.24**	**Total 24.74±4.24**
Smoking status			
Smoker (n=106)	11.88±3.99	11.60±4.45	23.48±7.62
Non-smoker (n=295)	12.62±4.07	12.57±4.14	25.20±7.49
	t= -1.626	t= -2.025	t= -2.012
	p=0.105	p=0.044**	p=0.045**
Alcohol Consumption			
Drinker (n=134)	12.18±4.06	12.76±4.04	24.94±7.47
Non-drinker (n=267)	12.55±4.06	12.09±4.33	24.64±7.60
	t= -0.863	t=1.488	t=0.370
	p=0.388	p=0.137	p=0.712
Disease status			
Yes (n=98)	12.66±4.24	12.61±4.61	25.28±8.26
No (n=303)	12.35±4.00	12.22±4.12	24.75±7.32
	t=0.663	t=0.793	t=0.802
	p=0.507	p=0.428	p=0.423
Meals/day			
1-2 (n=199)	12.22±3.77	12.19±4.05	24.41±6.80
≥ 3 (n=202)	12.63±4.33	12.44±4.43	25.06±8.23
	t= -1.005	t= -0.589	t= -0.870
	p=0.316	p=0.557	p=0.385
Water consumption (lit.)			
<1 (n=98) a	13.23±3.94	12.70±4.24	25.94±7.61
1-1,49 (n=132)	12.47±4.05	12.49±3.88	24.84±7.19
1,50-1,99 (n=94)	12.33±4.23	12.37±4.35	24.82±7.85
≥2 (n=77) b	11.60±3.94	11.69±4.62	23.29±7.65
	F=2.653	F=1.004	F=2.006
	p=0.048**	p=0.391	p=0.113
Physical activity			
Regular (n=80)	11.61±4.28	11.99±4.17	23.60±7.77
No (n=321)	12.63±3.99	12.40±4.26	25.03±7.49
	t= -2.010	t= -0.775	t= -1.515
	p=0.045**	p=0.439	p=0.131
Sleep duration (hour)			
<7 (n=205)	12.54±4.14	12.37±4.50	24.91±7.92
≥7 (n=196)	12.30±3.99	12.27±3.96	24.57±7.17
	t=0.579	t=0.238	t=0.444
	p=0.563	p=0.812	p=0.657
Eating Disorder			
No risk (n=338)	12.33±4.06	12.21±4.22	24.54±7.57
At risk (n=63)	12.94±4.08	12.89±4.34	25.83±7.44
	t= -1.086	t= -1.166	t= -1.239
	p=0.278	p=0.244	p=0.216

F: One-way ANOVA; t: Independent sample t-test; **p<0,05; a>b

The Eating Attitude Test scores and the restrictive eating sub-dimension are low (r=0.296; p<0.001), the emotional eating sub-dimension is very low (r=0.113; p<0.05), and the total DEBQ score is very low. (r=0.205; p<0.001), while a significant positive correlation was observed, no statistically significant relationship was found for the external eating sub-dimension (p>0.05).

DISCUSSION

It is seen in the studies that the use of social media can cause a weakening in body image (22, 23). It is thought that the images shared on social media platforms with the theme of photo sharing may cause the development of weak body image in women (22). It is known that poor body image may be a risk factor for the development of eating disorders (24). In a study examining the relationship between internet use and an eating disorder, a positive relationship was found between university students' problematic internet use and eating attitudes (25). In a study by Santarossa and Woodruff (26), social media use, body image, self-confidence, and eating disorder symptoms of 147 young adults were examined. According to the results of the study, it was seen that problematic social media use was associated with low body image, low self-confidence, and increased eating disorder symptoms (26). Considering that social media can affect body image and accordingly cause the development of eating disorders, it was expected that participants who use social media more effectively might have higher eating disorder scores. However, when the results of this study were examined, no significant relationship was found between social media use and eating disorder. The reason for this is thought to be due to the difference between the age groups of the studies and this study group. While the studies generally included adolescents and university students, this study was carried out between the ages of 19-45.

It is thought that the focus of social media on the appearance of people with edited and unrealistic visuals may play a role in body dissatisfaction and impaired eating behavior (27). Social comparison

Table 3. The relationship between the participant's level of social media use and their eating attitudes and eating behaviors

Variables	EAT-40	The Dutch Eating Behavior Questionnaire			
		Restrictive	**Emotional**	**External**	**Total**
Social media usage scale					
Competence	r1=0.068 p=0.177	r2= -0.085 p=0.090	r2=0.203 p=0.000*	r2=0.233 p=0.000*	r2=0.183 p=0.000*
Perfection	r1=0.049 p=0.325	r2= -0.029 p=0.565	r2=0.112 p=0.026**	r2=0.093 p=0.063	r2=0.097 p=0.052
Total	r1=0.061 p=0.222	r2= -0.062 p=0.217	r2=0.172 p=0.001**	r2=0.172 p=0.001**	r2=0.153 p=0.002**
EAT-40	1	r1=0.296 p=0.000*	r1=0.113 p=0.024**	r1=0.020 p=0.684	r1=0.205 p=0.000*

r1 Spearman Correlation; r2 Pearson Correlation; *p<0,001; **p<0,05

theory states that individuals compare themselves to others to evaluate themselves, and this comparison is strengthened if individuals think that the person they are comparing is similar to them. In this context, social media platforms also provide a suitable basis for facilitating interaction and comparing appearance. As a result, this appearance comparison increases dieting and body dissatisfaction by comparing the appearance of young adults with their peers (28). It is also known that these two conditions are risk factors for the development of eating disorders. In a meta-analysis by Holland and Tiggeman (29), social media, body dissatisfaction, and impaired eating behaviors were examined. Measures such as social media use and time spent on social media, frequency of social media use, and the number of Facebook friends show that anxiety about body image and impaired eating behaviors are related (28). Walker et al. (19) associated the frequency of Facebook use with the comparison of increased physical appearance, and said that this was associated with more impaired eating behavior. However, despite the high frequency of Facebook use, people who do not compare their physical appearance are less likely to report impaired eating behavior. The reason for this is stated that Facebook provides more emotional and social support when individuals do not compare themselves physically with others, causing less sense of loneliness. It is known that loneliness and impaired eating behavior are positively related, whereas bonds with family and friends are associated with less impaired eating behavior (19).

In a recent study, Durmaz et al. (30) found that female students who spent more than 2 hours a day on social media had higher emotional eating scores. A study conducted with young adults and adolescents stated that social media use could cause unhealthy eating behaviors by affecting the physiopathological (stress, anxiety, depression, etc.) condition of individuals (31). In our study, when the risk of eating behavior disorder and social media use characteristics of the women who participated in the study were compared, it was observed that there was a relationship between the risk of eating behavior disorder and the perfection, competence, and total scores of the social media use scale ($p<0.05$). Previous studies have generally been done with adolescents and students. The majority (70.1%) of the women participating in our study were over the age of 30. Spending more time on social media increases the level of exposure to social media and can affect eating behavior. We determined that emotional eating ($r2=0.203$, $p=0.000$) and extrinsic eating ($r2=0.233$, $p=0.000$) were higher in women who scored high on the continuance sub-dimension of the SMUS scale.

When the relationship between emotional eating, external eating, and restrictive eating scores, which are the sub-dimensions of the DEBQ Scale, is examined, a weak positive relationship between emotional eating and restrictive eating shows that emotional eating behavior increases as restrictive eating behavior increases and emotional eating behavior decreases as restrictive eating behavior decrease. This correlation between the sub-dimensions of the DEBQ Scale is also consistent with the results of the reliability and validity studies of the original scale and the Turkish sample (20). In the study, one of the two highest correlation coefficients was found between the EAT-40 and restrictive and emotional eating. Emotional eating behavior is used to regulate emotions without the need for any hunger or physical energy, with mindful eating, which is expressed as the individual's realization of eating behavior by focusing on food without judgment and self-blame. There is a moderately negative relationship between eating and eating. Thus, as the eating awareness scores, which indicate a healthy eating style, increase, the emotional eating scores decrease, and as the emotional eating scores increase, the eating awareness scores decrease. The effectiveness of eating awareness training in the treatment of individuals with emotional eating problems was found to be consistent with the results of this study (32). In addition, this relationship between eating awareness and emotional eating is consistent with other results found in the literature (33).

Our study had some limitations. One of the limitations of the study was that the study was collected in a single center and the data were collected online. In addition, since the study was conducted with a single age group and gender, it cannot be generalized to the population. According to this study, no significant relationship was found between social media use and the risk of eating disorders. It is possible that this result was obtained due to the age group in which the study was conducted, the low number of samples and the fact that the study was conducted in an online environment.

CONCLUSION

This study was conducted only on women since the rate of eating disorders is higher in women. Gender differences can be compared by including male individuals of the same age group in future studies. In particular, individuals in adolescence, when body image gains importance, were not included in this study, but studies are mostly conducted with individuals in adolescence. It is thought that future studies to include age group comparisons will be useful in revealing the differences. From the past to the present, the effect of media tools on body perception and eating behavior

has been investigated. This study, it is aimed to examine the relationship with social media, the use of which has recently increased rapidly. Social media platforms differ within themselves and show differences visually and verbally. For this reason, the results may differ between social media platforms. Different effects may be observed when future studies are conducted with more specific frameworks. To show the effect of social media on eating behavior, it can be suggested to conduct intervention studies that can raise awareness of individuals at the same time. Measures such as body image, anxiety, depression, and stress can be included in studies that aim to investigate eating behavior with social media use. In particular, measuring how much time individuals spend on social media will help to make the results more comprehensive. More studies are needed to reveal the relationship between social media and impaired eating behavior and an eating disorder.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Okan University, Faculty of Health Sciences Ethics Committee (Date: 19.01.2022, Decision No: 148/17).

Informed Consent: All patients signed the free and informed consent form.

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Original Article

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Investigation of the effect of age-related hearing loss on visual memory

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ABSTRACT

Aim: To investigate the effect of age-related hearing loss on visual memory.

Material and Method: 20 participants with normal hearing loss and 38 participants with hearing loss were included in the study. All of the patients were older than 65 years. Pure tone audiometry, speech audiometry and Benton visual retention test were applied to all participants.

Results: Mean Benton test score of the hearing-normal and the hearing loss group were 13.10±1.48 and 8.81±3.27 respectively. Patients were divided into three groups as hearing-normal, hearing loss with WRS greater than 80% and hearing loss with WRS lower than 80%. In terms of Benton scores there was statistically significant difference between groups ($p<0.001$). Post-hoc tests revealed that Benton scores of the group hearing loss with WRS lower than 80% were significantly low ($p<0.001$). Benton scores of hearing-normal and hearing loss with WRS greater than 80% groups were statistically similar ($p=0.075$).

Conclusion: Impairment of cognitive functions is related to dysfunction of higher order cognitive processes rather than sensory impairment.

Keywords: Word recognition score, dementia, Benton visual retention test

INTRODUCTION

Dementia is an important health problem that is very common worldwide. In recent years, there have been studies showing a link between age-related sensorineural hearing loss (ARHL) and dementia. (1-4) In a prospective cohort study, it was shown that age-related hearing loss is an independent risk factor for dementia and carries a higher risk than other possible risk factors (depression, social isolation, smoking, hypertension, and diabetes) (5). ARHL occurs degeneration in the cochlea and the auditory pathway (6,7). The relationship between cognition and sensory impairments has been studied for decades. These studies investigated whether the decline in cognition is due to hearing loss, whether the cognitive decline is due to hearing loss, or whether the two are associated with a common cause (8, 9). The aim of this study is to investigate the effect of age-related hearing loss on visual memory.

MATERIAL AND METHOD

The study was carried out with the permission of Yıldırım Beyazıt University Yenimahalle Training and Research Hospital Clinical Researches Ethics Committee (Date: 18.01.2023, Decision No: E 2022-65) All study processes were conducted under the principles of the Declaration of Helsinki and ethical rules. All participants provided written informed consent.

Study Design

Fifty-eight people over 65 years of age were included in the study. Of these participants, thirty-eight participants had sensorineural hearing loss, twenty participants had normal hearing loss (pure tone average better than 20 dB HL). All participants had normal or corrected-to-normal vision and no any otologic or neurologic diseases. Mini-Mental State Examination was applied to all participants and all participants scored over 24 points.

Audiometric Examination

A pure tone audiometry was administered to all participants using a pure tone manual diagnostic audiometer (Model GSI 61, Grason-Stadler, Inc.). The subjects were tested in a sound-isolated chamber, and pure tone audiometries were conducted at 0.125, 0.5, 1, 2, 3, 4 and 8 kHz using both air and bone conduction. The

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subjects were asked to discriminate between low sound levels of different frequency pure tones, and responded by pressing a button. The lowest tone heard at each frequency was considered as the hearing threshold level. Pure tone average (PTA) was calculated by averaging the hearing thresholds of 0.5, 1, 2, and 4 kHz. Speech audiometry was conducted after pure ton audiometry. Speech measures consisted of speech recognition thresholds (SRT), in dB hearing level (HL), and word recognition scores (WRS), in percent correct. The words presented via monitored live voice, were used for SRT and WRS.

Benton Visual Retention Test

Benton visual retention test procedure involves the presentation of a complex geometric figure that the participant must remember and later recall or reproduce. The version that was used in this experiment was similar to the multiple-choice administration of the BVRT in that for the recall portion of the test, the participants were presented a grid of four rotated and altered designs and were asked to select the correct design that had not been altered (10, 11).

Statistical Analysis

Data was analyzed using the SPSS version 21.0 software program (Statistical Package for Social Sciences v.21, IBM, Chicago, IL). The student t-test was used to compare continuous numerical variables between two groups. One way ANOVA test was used to compare continuous numerical variables between tree groups. Chi-Square test was used to investigate the association between categorical sex variables. A p-value < 0.05 was considered statistically significant.

RESULTS

Twenty subjects with normal hearing and thirty eight subjects with hearing loss were included in the study. The mean age of the hearing-normal group was 67.9±1.07 and the mean age of the hearing loss group was 68.52±2.12. There was no statistically significant difference in terms of ages between the two groups (0.279). Pure tone average (PTA) of hearing-normal group was 14.05±3.59 for right ear and 14.60 ±3.43 for left ear. Pure tone average (PTA) of hearing loss group was 50.57±11.02 for right ear and 49.39 ±10.71 for left ear. Mean word recognition score (WRS) of the hearing-normal group was 92.10±4.02 for right ear and 91.50 ±5.18 for left ear. Mean word recognition score (WRS) of the hearing loss group was 56.42±22.21 for right ear and 57.05±19.77 for left ear. There was statistically significant difference in terms of WRS between the two groups (<0.001 both ears) (**Table 1**). Mean Benton test score of the hearing-normal and the hearing loss group were 13.10±1.48 and 8.81±3.27 respectively (p<0.001). There was statistically significant difference in terms of Benton test scores between the two groups. Patients were divided into three groups as hearing-normal, hearing loss with WRS greater than 80% and hearing loss with WRS lower than 80%. In terms of Benton scores there was statistically significant difference between groups (p<0.001). Post-hoc tests revealed that Benton scores of the group hearing loss with WRS lower than 80% were significantly low (p<0.001). Benton scores of hearing-normal and hearing loss with WRS greater than 80% groups were statistically similar (p=0.075). (**Table 2**)

Table 1. The characteristics of hearing-normal group and hearing loss group.

	Hearing-normal group	Hearing loss group	p
Age (mean±SD)	67.9±1.07	68.52±2.12	0.279
Gender (F/M)	11/9	21/17	0.985
PTA, Right	14.05±3.59	50.57±11.02	<0.001
PTA, Left	14.60 ±3.43	49.39 ±10.71	<0.001
WRS, Right	92.10±4.02	56.42±22.21	<0.001
WRS, Left	91.50 ±5.18	57.05±19.77	<0.001

F: female; M: male; SD: standard deviation, PTA: Pure tone average; WRS: word recognition score

Table 2. The comparison of Benton test scores in groups

	Hearing-normal group, n=20	Hearing loss with WRS≥ 80%, n=16	Hearing loss with WRS <80%, n=22	p
Benton test score	13.10±1.48	11.75±2.21	8.47±3.22	<0.001

DISCUSSION

In this study, the relationship between age-related hearing loss and cognitive functions was examined by using the Benton visual retention test. The relationship between cognition and sensory impairment has been investigated by various previous studies and there are different theories about this issue. These studies investigated whether the decline in cognition is due to hearing loss, whether the cognitive decline is due to hearing loss, or whether the two are associated with a common cause.

The "sensory deprivation" hypothesis suggests that there may be cognitive Impairment at the neuronal level due to decreased adequate sensory input over an extended period of time (8). But cognitive impairment does not always occur after hearing loss. It has been known that there are also cognitive impairments with normal hearing. According to resource allocation hypothesis, or "information degradation" hypothesis, cognitive processes are restricted because of increased sensory impairments (14). Hearing loss increases the cognitive load and diverts cognitive resources to auditory processing at the expense of other cognitive processes such as working memory (15-16). In other words, people try to compensate their sensory deficits with cognitive resources such as working memory and attention. For

example, too many cognitive resources are used to understand speech and resources are reduced for higher order cognitive processes. Two hypotheses mentioned above suggest that cognitive decline may result from reduced sensory function.

Cognitive load on perception" hypothesis suggests that cognitive decline leads to sensory decline (8, 17). According to this theory, cognitive impairment can cause hearing loss. A fourth theory, known as the "common cause" hypothesis, suggests that common factor causes sensory and cognitive impairment (18,19). Cognitive and sensory impairment may be the result of a common causal mechanism such as age- related degeneration of the central nervous system.

Other alternative theory suggests that, performance on tests of cognition may be negatively affected as a direct result of sensory impairment (i.e. visual- and/or hearing-impairment) (20). It was reported that hearing impairment was associated with lower scores on a screening questionnaire for cognitive dysfunction (20).

In the current study, we aimed to evaluate the effect of ARHL on visual memory by using WRS and Benton visual retention test. Benton visual retention test measures visual perception and visual memory. Benton visual retention test is used a measurement of short-term visual memory storage and recall (10). Benton test requires "complex perceptual analytic ability and short-term memory retention. Cognition is typically measured through auditory means (i.e. verbal questions/ instructions that rely on hearing ability to be correctly interpreted). If hearing ability is not considered at the time of neurocognitive assessments, cognitive abilities may be underestimated because of limitations to perform on the test due to sensory impairment rather than cognitive deficits (11). Therefore, the Benton visual retention test was used in this study to evaluate cognitive functions.

In this study, word recognition scores were used in addition to hearing threshold for evaluating the central auditory functions instead of peripheral auditory system. Most research to date has focused on hearing sensitivity measured only on a peripheral level (i.e. audiometric thresholds only). It was contended that using tests of higher order listening function and collecting detailed information about the nature of the hearing loss may result in a greater understanding of whether there is a causal relationship between hearing and cognition.

In the current study, it was found that Benton scores of hearing-normal and hearing loss with WRS greater than 80% groups were statistically similar. This finding suggests that ARHL does not affect the cognitive function if WRS is greater than 80%. It can be said that, impairment of cognitive functions is related to dysfunction of higher order cognitive processes rather than sensory impairment.

CONCLUSION

In the light of findings of this study it can be said that Benton scores are affected by word recognition scores as a representation of high order cognitive functions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Yıldırım Beyazıt University Yenimahalle Training and Research Hospital Clinical Research Ethics Committee (Date: 18.01.2023, Decision No: E 2022-65)

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Efficacy analysis between ultrasound and cytology criteria in the differentiation of malignant and benign thyroid nodules: TIRADS versus BETHESDA

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ABSTRACT

Aim: Thyroid nodules (TNs) are abnormal masses of different structures and sizes to be detected promptly. The present study aimed to investigate the relationship between Bethesda and TIRADS and their diagnostic efficiency in histopathologically diagnosed malign TNs.

Material and Method: 475 patients with TNs enrolled in this cross-sectional research. Laboratory parameters and clinical thyroid history were obtained from the automation system and analyzed retrospectively. They have been staged according to TIRADS, and the neck is evaluated in suspicious lymph nodes. FNAB results are then tracked for Bethesda staging.

Results: TIRADS showed a good sensitivity at the rate of 74.5% and average specificity at 68.1% for TNs. Bethesda had a higher sensitivity at 80.1% and 95.2% specificity rates. The positive predictive (98.1 vs. 88.2) and negative predictive (13 vs. 23.6) values were higher for Bethesda than TIRADS. The diagnostic accuracy for Bethesda was 79%. According to the ROC, Bethesda had a more expansive area under curve (0.81) than TIRADS (0.63). FNAC was a better diagnostic method than ultrasonography in evaluating thyroid nodules ($p<0.001$).

Conclusion: The risk of malignancy increased parallel to the increased Bethesda and TIRADS. While both scores helped predict malignancy, Bethesda is essential to physicians in assisting the discrimination of malign and benign TNs.

Keywords: Thyroid nodule, malignancy, TIRADS, Bethesda, ultrasound

INTRODUCTION

Thyroid nodules (TN) are abnormal masses of different structures and sizes that occur within the thyroid tissue, and most of them are harmless and benign (1). The steady worldwide increase in the incidence of thyroid cancers (TCs) would be insufficient to explain it with an increase in disease frequency, as this has contributed to the lack of diagnostic methods (2). When diagnosed early and well-differentiated pathologically, the prognosis of easily treated TCs is perfect (3). Especially the long-term survival rate of most stage-1 approaches is excellent at 100% (4).

Today, evaluation with ultrasonography (USG) is accepted as the first examination together with laboratory tests and is routinely used in preoperative planning and postoperative follow-up (3,5). USG has a very flexible diagnostic power and can distinguish between solid and cystic within the framework of the user's competence (6). In addition, it supports the distinction between benign and malignant nodules based on features such as the more solid structure of the nodule, its echogenicity, border irregularity, and the presence of microcalcifications (7,8).

Guidelines for classifying cytology results and identifying USG features suspected of malignancy of nodules provide more accurate management of follow-up and treatment of TNs (9). The thyroid imaging report and data system (TIRADS), published by the American Society of Radiology for managing patients with nodules by USG, determine the cancer risk based on USG findings and nodule size (10). This defines TNs management according to USG characteristics, scored between 1 and 5 levels, and aims to help decide whether fine needle aspiration (FNAB) is necessary and thus avoid unnecessary

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procedures (11). If FNAB is performed by experienced physicians, close to 95% successful sampling can be obtained in aspirations of solid nodules. Bethesda scoring includes reporting in one of 6 diagnostic categories as the standardized cytopathology classification system for interpreting FNABs (6). The limitations and diagnostic difficulties of FNAB may cause false-negative and false-positive results. Even if the initial cytological results are benign, it has been reported that the risk of malignancy is as high in TN with suspicious USG (12,13).

Exploring the relationship between TIRADS and Bethesda will provide beneficial results for endocrinologists to increase diagnostic power and reduce the rate of misdiagnosis. The present study aimed to investigate the relationship between the Bethesda and TIRADS scores and their diagnostic efficiency in TC cases diagnosed histopathologically.

MATERIAL AND METHOD

Study Design

The study was designed as a retrospective cross-sectional clinical analysis, including patient data between September - December 2022. A total of 1148 patients who applied to outpatient clinics were screened in the hospital automation system, and 475 patients were in the current study. Of the 475 patients included in the study, 475 TIRADS and 475 Bethesda. The histopathology reported 25 (5.2%) malignant patients in all participants.

Ethical Statement

The study was carried out with the permission of Karabük University Non-interventional Clinical Researches Ethics Committee (Date: 17.01.2023, Decision No: 2023/1216). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Laboratory parameters and patient histories were obtained from the automation system.

Participant Selection

Inclusion criteria included the followings: Adult patients over 18 years, thyroid nodules on USG, and scheduled for FNAB were included in this study. Cases with autoimmune disease, systemic disease, or infection were criteria of exclusion from the study. Demographic data for the analysis were collected using the retrospective report form of the patients and were obtained from the history, clinical examination, and research reports of all.

Bethesda System

Bethesda's system scores as (B1) Non-diagnostic, (B2) Benign, (B3) Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance, (B4) Suspicious/certain Follicular Neoplasm, (B5) Malignancy Suspect, and (B6) Malignant.

TIRADS System

The American College of Radiology determines the ultrasonographic character of thyroid nodules as TIRADS (Thyroid Imaging Reporting and Data System). Based on the sonographic results on the determination of nodules, this system needs to be analyzed for potential malignancy [3]. Internal composition, echogenicity, margins, echogenic foci, and nodule shape are essential for the scoring criteria. Scoring numbers are as follows: (TR1) normal thyroid gland, (TR2) benign lesions, (TR3) probably benign, (TR4) suspicious lesion, (TR5) probably malign.

Ultrasound Assessment

High-resolution USG using Hitachi Aloka F31 Dual Dynamic Display was performed on all patients. After the patient is supine, if there are thyroid nodules due to the USG examination, they have been staged according to TIRADS, and the neck is evaluated in terms of suspicious lymph nodes. FNAB results are then tracked for Bethesda staging. All thyroid ultrasounds were performed by the same staff (His experiences in thyroid ultrasound are as follows: Since the 2nd month of the endocrine fellowship, he received ultrasound training. He has been performing thyroid ultrasounds of between 60 and 70 patients a day).

Laboratory Analysis

Routine screening, including thyroid tests, was analyzed by a spectrophotometric method in the clinical biochemistry laboratory by AU5800 Beckman Coulter. Complete Blood Count parameters were analyzed with LH780 and Sedimentation with Alifax.

Statistical Analysis

Analyses were performed using SPSS v11. The conformity of the variables to normal distribution was examined visually (histogram and probability graphs) and analytically (Kolmogorov–Smirnov/ Shapiro–Wilk). Mann evaluated laboratory parameters–Whitney U test for non-normally distributed variables and by independent samples T-test for normally distributed variables. Descriptive analyses were presented with means and standard deviations for normally distributed variables. The relationship between the measured variables was examined with Spearman correlation. Two-to-two cells were compared with Pearson Chi-Square and Fisher's Exact Tests. $P<0.05$ were considered significant.

RESULTS

Demographics

Among the 475 participants, women were the majority, with 383 against 92 ($p<0.05$). While the age distribution of the participants was 53.8±12.8, the age range was 18-89 years. While the mean BMI (kg/m²) was 29.5±5.9, the distribution range was 16.8-57.7 kg/m². In **Table 1**, some

demographic characteristics, laboratory values, and thyroid nodule sizes of the patients participating in the study are given.

Table 1. Demographic details of participants

Variables	Mean±SD	Range
Age, year	53,8±12,8	18-89
BMI, k/m²	29,5±5,9	16,8-57,7
FT3, pg/ml	3,5±3,3	1,2-71,8
FT4, ng/dl	1,3±0,3	0,5-5,95
TSH, uIU/ml	2,7±6,3	0-97,2
Thyroglobulin, IU/mL	102±199	0-1964
Nodule Diameter, mm	18,8±9,9	0-65

Abbreviations. TSH, stimulating thyroid hormone; FT3, free triiodothyronine-free thyroxine; FT4, free triiodothyronine-free thyroxine; BMI, Body Mass Index.

Diagnostic Comparison of TIRADS and Bethesda

In **Tables 2** and **3**, information about TIRADS levels and Bethesda categories of the thyroid nodules are given. Preoperative TIRADS levels and Bethesda categories of 25 malign TNs detected histopathologically are as follows: TR2: (n:2), TR3 (n:10), TR4 (n:11), T5 (n:2) and B1 (n:3), B2 (n:1), B3 (n:6), B4 (n:3), B5 (n:8), B6 (n:4).

Table 3. Distribution of parameters according to nodule types

Variables	Non-operation	Histopathology: Benign	Histopathology: Malign
TIRADS			
2	57 (13,6%)	2 (6,4 %)	2 (8%)
3	182 (43,4%)	16 (51,6%)	10 (40%)
4	163 (38,9%)	11 (35,4%)	11 (44%)
5	17 (4%)	2 (6,4%)	2 (8%)
BETHESDA			
1	76 (18,1%)	1 (3,2%)	3 (14,3%)
2	213 (50,8%)	14 (45,2%)	1 (4%)
3	130 (31%)	11 (35,5%)	6 (24%)
4	0	2 (6,5%)	3 (12%)
5	0	3 (9,7%)	8 (32%)
6	0	0	4 (16%)
Gender			
M	77 (18,3%)	8 (25,8%)	7(28%)
F	342 (81,7%)	23 (74,2%)	18 (72%)
Family history of thyroid cancer			
Yes	9 (2,1%)	0	0
No	410(97,8%)	31 (100%)	25 (100%)
Radiotherapy history			
Yes	6 (1,4%)	0	1 (4%)
No	413 (98,5%)	31 (100%)	24 (96%)

Table 2. Distribution of BETHESDA & TIRADS categories

Variables	TR2 (n:61)	TR3 (n:208)	TR4 (n:185)	TR5 (n:21)
B1 (n:80)	12 (15%)	28 (35%)	37 (46,3%)	3 (3,8%)
B2 (n:228)	38 (16,6%)	126 (55,2%)	56 (24,8%)	8 (3,5%)
B3 (n:147)	11 (7,6%)	49 (33,1%)	81 (55,2%)	6 (4,1%)
B4 (n:5)	0	3 (60%)	2 (40%)	0
B5 (n:11)	0	2 (18,2%)	7 (63,6%)	2 (18,2%)
B6 (n:4)	0	0	2 (50%)	2 (50%)

Abbreviations. TR: Tirads, B: Bethesda

Preoperative TIRADS levels and Bethesda categories of 31 benign TNs detected histopathologically are also as follows, respectively: TR2 (n:2), TR3 (n:16), TR4 (n:11), T5 (n:2) and B1 (n:1), B2 (n:14), B3 (n:11), B4 (n:2), and B5 (n:3). Comparison of malign and benign TNs with similar TIRADS levels is as follows, respectively: TR3 (n:10) and TR4 (n:11) were malign TNs, TR3 (n:16) and TR4 (n:11) were benign TNs (p=0.01); there were two benign and two malign TNs in TR5 (p>0.05). Comparison of malign and benign TNs with similar Bethesda categories is as follows: At B3 and B4 categories, nine malign TNs and 13 benign TNs (p=0.014). While there were 12 malign TNs at the B5 (n:8) and B6 (n:4), there were three malign TNs B5 (n:3) and B6 (n:0) categories (p=0.004).

TIRADS showed a good sensitivity at the rate of 74.5% and average specificity at 68.1% for TNs. However, the Bethesda system of reporting FNAC had a higher sensitivity at 80.1% and 95.2% specificity rates. The positive predictive (98.1% vs. 88.2%) and negative predictive (13% vs. 23.6%) values were higher for cytology Bethesda-scoring compared to TIRADS-scoring. The diagnostic accuracy for Bethesda was 79%.

According to the ROC curve, as shown in **Figure 1**, Bethesda-scoring had a wider area under curve (0.81) than TIRADS-scoring (0.63). FNAC was a better diagnostic method than ultrasonography in evaluating thyroid nodules (p<0.001).

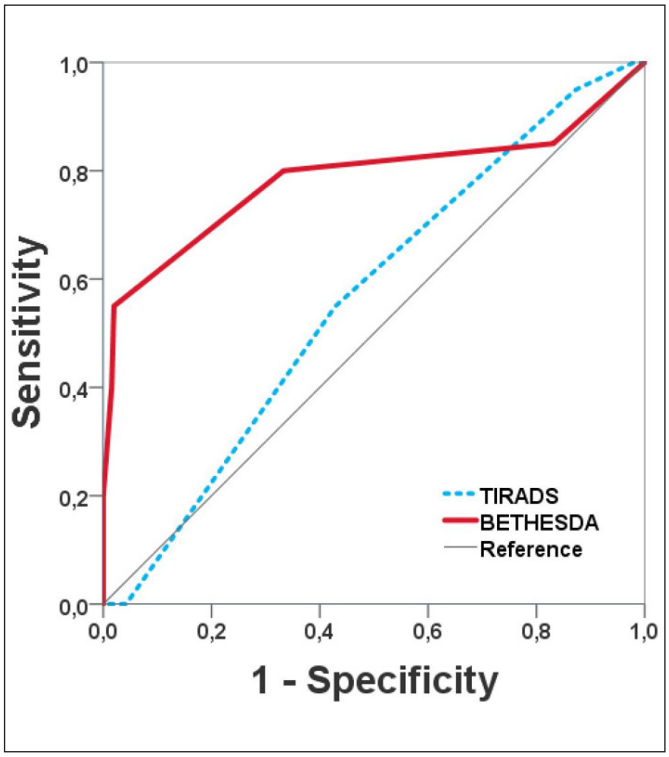

Figure 1. The ROC analysis for diagnostic accuracy of TIRADS and BETHESDA

DISCUSSION

The present analysis aimed to emphasize the importance of the correlation between Bethesda and TIRADS levels and remind that although cytopathology is superior in thyroid surgery/follow-up, TIRADS should also be considered. For scoring benign and malign TNs, the risk of malignancy increased as the Bethesda and TIRADS scores increased. With higher diagnostic accuracy, Bethesda was a better predictor of malignancy than TIRADS. While both scores helped predict malignancy, Bethesda is essential to physicians in assisting the discrimination of malign and benign TNs.

We know that the FNAB approach has a higher sensitivity and predictive value than other approaches in diagnosing TNs. It is a cost-effective, fast, and robust method in the classification of malignant TN, especially in need of reduction of unnecessary surgery or surgery. In Bethesda, numbered in 6 categories, the risk of malignancy increases for each type. While Mendes et al. (14) found TIRADS and FNAB to predict malignancy, the concordance rates with final histopathology were 75.4% and 95%, whereas Abdelkader et al. (15) showed 75.4% and 81.8%, respectively. Singaporewalla et al. (16) showed the sensitivity and specificity of TIRADS as 70.6% and 90.4%, respectively, while they were 72.3% and 66.7%, according to George et al. (17). Krzysztof et al. (18) reported that FNAB predicted thyroid carcinoma in patients with thyroid nodules as 95.8%. George et al. (17) noticed that the accuracy of FNAC in predicting malignancy with Bethesda was around 80% compared to TIRADS. According to Horvath et al. (19), thyroid malignancy was detected in 98.85% of TR5 nodules. According to Periakaruppan et al. (20), the risk of malignancy among TR5 thyroid nodules was 77.8%. In our research, TIRADS showed a good sensitivity at the rate of 74.5% and average specificity at 68.1%. However, Bethesda of reporting FNAB had a higher sensitivity at 80.1% and specificity at the rate of 95.2%. The positive and negative predictive values were higher for Bethesda-scoring compared to TIRADS-scoring. The diagnostic accuracy for Bethesda was 79%. Our results supported that FNAB was a better diagnostic method than ultrasonography in evaluating thyroid nodules.

In the analysis performed by Yılmaz and Bolukbasi (21), a similar design to our research, the nodule was reported as moderately suspicious (TR4) in 2 of 6 patients in category B1 and as highly questionable (TR5) in 1 patient. Although the risk of malignancy in the B1 category was relatively low, the TIRADS scoring was quite effective in the operation decision in 50% of the patients. According to the ultrasound findings, the nodule was reported as moderately suspicious (TR4) in 17 of 49 patients in the B3-4 category and as highly questionable (TR5) in 1 patient. While the risk of malignancy in B3 was 5-15%, it was 15-30% in B4. In 11 of 16 patients who were in the B5 category, the nodule was reported as moderately suspicious (TR4) and one highly questionable (TR5), according to ultrasound findings. While malignancy rates were 60-75% in B5, there was 75% malignancy in this patient group, according to TIRADS. 61 of 124 patients in category B6 were reported as moderately suspicious (TR4) and 13 as highly questionable (TR5), according to ultrasound findings. The malignancy rate in B6 was 90-97%. In our study, 21 malignant TNs were detected according to TR3 and TR4, while 27 were benign TNs. There were two benign and two malign TNs in TR5. According to B3 and B4, there were nine malignant TNs and 13 benign TNs. According to B5 and B6, there were 12 malignant TNs and three benign TNs.

The most substantial aspect of the present study was having a large number of participants in well-designed patient data. The main limitation of our study was its retrospective design and USG reports which were retrospectively reviewed and recategorized according to TIRADS. Finally, a lack of interpretation of the results in this study requires recognizing that more than a quarter of the subjects were female. This is probably because thyroid disease is significantly more common in women than men, and patients with autoimmune thyroid disease go to the doctor more often. This condition increases the likelihood of detecting nodules by palpation or ultrasound, defined as medical surveillance bias.

CONCLUSION

The primary purpose of using the reporting system is to determine the malignant potential of TNs and to help determine the treatment strategy in cases with benign biopsy results. Our study showed concordance between the thyroid ultrasound reported by TIRADS, FNAC reported by Bethesda, and the final histopathology report after thyroid surgery. Although the Bethesda evaluation showed superiority over TIRADS, more extensive, multicenter, randomized controlled trials are needed to confirm the role of TIRADS in the treatment of indeterminate thyroid nodules. Clinicians performing thyroid USG should associate ultrasound reports with TIRADS and follow the results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karabük University Non-interventional Clinical Researches Ethics Committee (Date: 17.01.2023, Decision No: 2023/1216).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Comparative assessment of patients' admission to urology departments during and before the COVID-19 pandemic: a retrospective cohort study

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ABSTRACT

Aim: To determine the diseases that presented to the urology department during the COVID-19 pandemic and for hospital-based comparison with the diseases that presented in the same period of the previous year.

Material and Method: In this retrospective follow-up study, patients who were admitted to the tertiary university hospital and secondary state hospital urology departments between April-July 2019 and April-July 2020 were included in the study. We searched the health administrative data using the International Classification of Diseases-10 codes. The number and variety of patients who were admitted to the urology departments in the same months of 2019 and 2020 were compared.

Results: In both hospitals, the total number of admissions decreased during the pandemic in 2020 compared to the pre-pandemic year. Also, elective admissions decreased in 2020 compared to the pre-pandemic year ($p < 0.001$). In a significant part of the urological disease group, the decrease in the number of admissions was found to be higher for the second-level center than for the tertiary center hospital.

Conclusion: We documented that uro-oncology outpatient admissions could continue during the COVID-19 pandemic in a university hospital- not primarily served as a pandemic hospital- by taking preventive measures and prioritizing healthcare personnel and patient safety.

Keywords: COVID-19, urologic diseases, pandemics

INTRODUCTION

Coronavirus disease (COVID-19) was first described by the World Health Organization (WHO) in the last months of 2019 (1). The first patients in Turkey were seen on March 11, 2020, when the World Health Organization declared the disease a pandemic.

The rapidly spreading epidemic creates an unprecedented burden on the effectiveness and sustainability of the health system. Especially because of this disease, emergency applications, and hospitalization rates are increasing. The rapid spread of COVID-19 has affected patient management in all countries, and non-emergency operations have begun to be reduced. At the same time, COVID-19 has caused significant changes in the form of outpatient care, which has an important place in health care. Providers postpone elective and preventive visits such as annual physical examinations to reduce the risk of transmitting the virus to patients or healthcare workers during their practice. Whenever possible, they also turn face-to-face visits into telemedicine visits. Many patients also avoid visits because they do not want to leave their homes and be exposed to risk.

Various guidelines have been presented about which groups should be given priority in the diagnosis and treatment of urological patients during the pandemic process (2,3). In our country, elective surgeries were postponed in line with the recommendations of these guidelines in urology clinics, and only emergency surgeries and oncological diagnoses were given to cases requiring surgical intervention.

In this study, we aimed to present the effects of COVID-19 on urology practice by comparing the number of patient examinations, and ICD codes before and during the pandemic in secondary and tertiary-level hospitals.

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MATERIAL AND METHOD

The study was carried out with the permission of Fırat University Non-interventional Researches Ethics Committee (Date: 26.05.2022, Decision No: 2022/07-41). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this retrospective cohort study, the data of Esenyurt State hospital and Firat University Hospital were used as secondary and tertiary care centers respectively.

We compared the number and variety of urological diseases coded during 2019 and 2020 in government hospitals and university hospital care facilities. The data was extracted from the hospital's electronic records. Age, gender, presentation date, and ICD-10 (International Classification of Diseases-10) diagnosis codes were obtained from the hospital data network. The presentation of the same patient within 10 days of the first presentation was regarded as a control visit. Patients with repetitive presentations for control or follow-up and their diseases were identified.

Since ICD-10 disease classification codes can't be assigned to some of the diseases experienced in the urology practice and the unique style of each urologist, standardization of the data was required. For this reason, the ICD-10 diagnosis codes of the patients recorded in the system were reconsidered. The diagnoses had been made based on the diagnostic classification of diseases indicated in the 12th edition of Campbell- Walsh Wein Urology (2020) to achieve standardization.

A single diagnostic code was used for separate diagnoses that attempted to designate the diseases. Acute cystitis and pyelonephritis merged under the name of infectious diseases of the urinary system. Renal stone, bladder stone, and ureteral stone merged under the name of urinary system stone diseases; epididymitis, orchitis, and anogenital (venereal) warts merged under the name of inflammatory disorders of the scrotum (overactive bladder, urinary incontinence, and neurogenic bladder = urine storage, and emptying disorders, etc.). Both institutions are primarily pandemic hospitals but also serve as public hospitals, with only a delimited section being reserved for patients suspected of having a COVID-19 infection.

Statistical analysis

Statistical Package for the Social Science (IBM SPSS version 20) was used to analyze the data in the study. Pearson's chi-square test was used in the analysis of categorical variables, and the Kruskal-Wallis H test or Mann-Whitney U test was used when independent samples were available for normally-distributed continuous variables. $p<0.05$ was considered statistically significant. Post-hoc analysis was used for correction after Kruskal-Wallis H and chi-square tests.

RESULTS

27,286 patients who applied to the urology outpatient clinic were included in the study. 18,072 patients were from the pre-pandemic period and 9214 patients were from the post-covid period. The demographic characteristics of the patients included in the study are summarized in **Table 1**. Compared to the pre-pandemic period, the mean age of female and male patients applied to the urology outpatient clinics decreased significantly in the tertiary and secondary hospitals after the declaration of the pandemic ($p = 0.028$ and $p = 0.032$, respectively).

Since the declaration of the pandemic, the number of applications to hospitals and urology outpatient clinics has decreased significantly. Also, emergency outpatient consultations decreased in both hospitals during the pandemic compared to the pre-pandemic period ($p<0.001$). The change in the number of applications to urology outpatient clinics before and after the declaration of the pandemic is shown in **Table 1**.

Table 1. Comparison of the secondary and tertiary level hospitals according to patient characteristics, the total number of outpatient clinics, and emergency admission.

Variables	2019			2020			Pc
	Secondary level hospital	Tertiary level hospital	Pa	Secondary level hospital	Tertiary level hospital	Pb	
Urology outpatients applications †	5035	13037	**0.024**	1180	8034	**<0.001**	**<0.001**
Uro-oncological applications †	182	1179	**<0.001**	65	685	**<0.001**	**<0.001**
Emergency outpatient consultations	682	3080	**0.011**	117	1997	**0.008**	**<0.001**
Age (year)							
Male	59 ± 17.3	58 ± 16.7	0.908	48.50 ± 7.7	48.1 ± 23.14	0.923	**0.028**
Female	57.8 ±19.1	54 ± 14.7	0.876	43.6 ± 19.1	41 ± 17.3	0.854	**0.032**
Gender (n)							
Male	3556 (70.6)	8677 (66.55)	**<0.001**	782 (66.27)	6432 (80.05)	**<0.001**	**<0.001**
Female	1479 (29.4)	4360 (33.44)	**<0.001**	398 (33.72)	1602 (19.95)	**<0.001**	**<0.001**

Data are expressed as the number of applications to the outpatient clinic (percentage). †: Repeated applications within 10 days after the first application were excluded. P value- a: The adjusted p-value for the secondary level hospital difference between the "before COVID-19" and "after COVID-19". P value- b: The adjusted p-value for the tertiary level hospital difference between the "before COVID-19" and "after COVID-19. P value- c: The adjusted p-value for the comparison of secondary level and tertiary level hospitals between the "before COVID-19" and "after COVID-19". COVID-19: Coronavirus disease-2019

Table 2 shows the distribution of patients admitted to hospitals before and after the pandemic, according to their diagnosis. There was no significant difference between admissions to both hospitals in terms of other inflammatory disorders of the penis, stress incontinence in both sexes, and undescended testicular diseases.

While there was no statistical difference in the number of patients diagnosed with ureteral stones, inflammatory diseases of the scrotum, other inflammatory diseases of the penis, myalgia, orchitis and epididymitis, and undescended testicles before and after the pandemic in tertiary care hospitals, the same situation was observed in secondary care institutions for other inflammatory diseases of the penis, myalgia, epididymo-orchitis, and undescended testicular pathologies.

The drop in the total number of uro oncology was 1,74-fold more for the secondary level center than for the tertiary center hospital (**Table 3**).

Table 2. Comparison of the secondary and tertiary level hospitals according to diagnosis frequencies to the admission of urology outpatient clinics before and after the announcement of the pandemic.

Disease	Secondary-level hospital			Tertiary-level hospital			Pc
	Years		P value-a	Years		P value-b	
	2019 n (%)	2020 n (%)		2019 n (%)	2020 n (%)		
Neuromuscular dysfunction of the bladder, unspecified	754 (88.1)	102 (11.9)	<0.001	109 (65.2)	58 (34.8)	<0.001	<0.001
Benign prostatic hyperplasia	1157 (77.6)	334 (22.4)	<0.001	2.887 (60.9)	1.851 (39.1)	<0.001	<0.001
Male erectile disorder	144 (64.5)	79 (35.5)	<0.001	0 (0,0)	0 (0,0)	-	-
Premature ejaculation	67 (65.1)	36 (34.9)	<0.01	9 (64.3)	5 (35.7)	<0.001	<0.001
Calculus of kidney	377 (88.5)	49 (11.5)	<0.001	769 (53.6)	666 (46.4)	<0.01	<0.001
Calculus of ureter	386 (88.7)	49 (11.3)	<0.001	20 (66.7)	10 (33.3)	>0.05	<0.001
Urinary tract infection, site not specified	1044 (80)	261 (20)	<0.001	8.476 (63.1)	4.963 (36.9)	<0.001	<0.001
Cyst of kidney acquired	319 (93.5)	22 (6.5)	<0.001	148 (67)	73 (33)	<0.001	<0.001
Azoospermia	81 (83.5)	16 (16.5)	<0.001	47 (79.6)	12 (20.4)	<0.001	<0.01
Inflammatory disorders of the scrotum	190 (91)	19 (9)	<0.001	5 (83.4)	1 (16.6)	>0.05	<0.001
Other inflammatory disorders of penis	15 (45.5)	18 (54.5)	>0.05	16 (59.3)	11 (40.7)	>0.05	>0.05
Myalgia	133 (52.8)	119 (47.2)	>0.05	6 (33.4)	12 (66.6)	>0.05	<0.001
Anogenital (venereal) warts	60 (73.2)	22 (26.8)	<0.001	4 (21.1)	15 (78.9)	<0.05	<0.001
Orchitis and epididymitis	15 (60)	10 (40)	>0.05	1 (25)	3 (75)	>0.05	<0.001
Scrotal varices	57 (90.5)	6 (9.5)	<0.001	285 (62.1)	174 (37.9)	<0.001	<0.001
Urethral stricture, unspecified	76 (89.5)	9 (10.5)	<0.001	107 (58.2)	77 (41.8)	<0.05	<0.001
Enuresis not due to a substance or known physiological condition	106 (84.2)	20 (15.8)	<0.001	94 (58.4)	67 (41.6)	<0.05	<0.05
Stress incontinence (female) (male)	49 (94.2)	3 (5.8)	<0.001	45 (63.4)	26 (36.6)	<0.05	>0.05
Undescended testicle, bilateral	5 (45.5)	6 (54.5)	>0.05	9 (47.4)	10 (52.6)	>0.05	>0.05
Total	5035 (81)	1180 (19)	**<0.001**	13037 (61.9)	8034 (38.1)	21071 (100)	**<0.001**

Data are expressed as the number of applications to the outpatient clinic (percentage). Data are expressed as the number of applications to the outpatient clinic (percentage). †: Repeated applications within 10 days after the first application were excluded. P value- a: The adjusted p-value for the secondary level hospital difference between the "before COVID-19" and "after COVID-19". P value- b: The adjusted p-value for the tertiary level hospital difference between the "before COVID-19" and "after COVID-19. P value- c: The adjusted p-value for the comparison of secondary level and tertiary level hospitals between the "before COVID-19" and "after COVID-19". COVID-19: Coronavirus disease-2019

Table 3. Uro-oncological diseases showed changes in the diagnostic distribution in the urology outpatient clinic before and after COVID-19 in both secondary-level and tertiary-level hospitals.

Malignancy	Secondary-level hospital			Tertiary-level hospital			P value- Pc
	Years		P value-a	Years		P value-b	
	2019 n (%)	2020 n (%)		2019 n (%)	2020 n (%)		
Malignant bladder disease	89 (70.1)	38 (29.9)	**0.017**	454 (81.7)	102 (18.3)	**0.001**	**<0.001**
Prostate cancer	37 (72.6)	14 (27.4)	**<0.036**	307 (67)	151 (33)	**0.021**	**<0.001**
Testicular cancer	11 (55)	9 (45)	0.058	90 (80)	23 (20)	**0.016**	**<0.001**
Upper urothelial tract tumors	17 (89.5)	2 (10.5)	**0.018**	89 (83.1)	18 (16.9)	**0.003**	**<0.001**
Kidney cancer	18 (90)	2 (10)	**<0.001**	239 (83.3)	48 (16.7)	**0.007**	**<0.001**
TOTAL	**182**	**65**		**1179**	**685**		

Data are expressed as the number of applications to the outpatient clinic (percentage). †: Repeated applications within 10 days after the first application were excluded. P value- a: The adjusted p-value for the secondary level hospital difference between the "before COVID-19" and "after COVID-19". P value- b: The adjusted p-value for the tertiary level hospital difference between the "before COVID-19" and "after COVID-19. P value- c: The adjusted p-value for the comparison of secondary level and tertiary level hospitals between the "before COVID-19" and "after COVID-19".

DISCUSSION

The COVID-19 pandemic, which first emerged in China and affected the whole world, affected the majority of countries despite all quarantine measures (4). In line with the Covid-19 pandemic, healthcare centers needed planning that would properly manage all their capabilities, staff, and supplies, especially operating rooms, to provide optimum healthcare to their patients (5). The WHO and EAU guidelines have recommended that all non-emergency surgeries be canceled due to the risk of spreading the virüs (3,6). Similarly, in the EAU Stone Working Group (EULIS) and EAU guidelines, it is recommended to delay the surgical and ESWL procedures as much as possible in urinary system stone patients and to provide urinary drainage with a double-J catheter or percutaneous nephrostomy in case of obstruction and/or serious infection (7,8). If the patient is suspected of having COVID-19, careful endoscopic procedures and urethral catheterization are recommended, and surgeons are fully protected against infection (9). The literature on urinary stone disease is clinically severe and when the literature is examined, we see that it is not much affected by the pandemic in terms of hospital admissions (10). When our study was evaluated, the number of cases in both hospitals in terms of kidney and ureteral stones decreased compared to the pre-pandemic period, but the decrease in the admissions to the tertiary hospital of the patients diagnosed with ureteral stones was not statistically significant. We think that this is the main reason for this situation to work as a treatment center of the hospital as a treatment center and to accept a referral from other centers.

It is claimed that cancer patients are at twice the risk of COVID disease than the normal population (11). Postponement of all elective surgeries or adjuvant chemotherapy is recommended for patients with stable cancer, and comprehensive treatment is recommended for patients with high-risk or COVID-19 cancer (12). Diagnosis and timely treatment of cancer patients are important during the pandemic process. Inadequate treatment and advanced age pose significant risks for these patients (13). The EAU guideline stated that the diagnosis and treatment of kidney masses smaller than 4 cm detected during the pandemic period may be delayed for up to six months, while the treatment of masses between 4-10 cm should be done within 3 months. It is recommended that patients with locally invasive vena cava thrombus and a mass larger than 10 cm should be operated on within 6 weeks. Similarly, advanced transitional cell cancer, renal cell cancers >6 cm in size, or adrenal carcinoma should be treated as a priority without delay (3,14).

Many publications have emphasized that prostate cancer surgeries can be postponed during the pandemic period, except for high-risk or locally advanced patients who cannot tolerate radiotherapy (2,15).

EAU guidelines recommend immediate cystoscopy and TUR-TM in patients presenting with macroscopic hematuria or bladder blood clot formation, or in whom a mass is detected in the bladder by imaging methods. Similarly, re-TUR-TM is recommended in cases where the initial TUR-TM pathology does not involve muscle tissue (16).

In patients with T3-4 and/or lymph node involvement, cisplatin-based adjuvant chemotherapy can be applied if neoadjuvant chemotherapy (NAC) is not given. Radiotherapy for hemostasis should be considered for MIBC with active bleeding who cannot undergo radical cystectomy (17,18).

Radical orchiectomy for testicular masses should be performed as soon as possible without delay. Radiotherapy is recommended in low-volume patients with Stage IIa and IIb seminomas, while chemotherapy containing cisplatin and Etoposide is recommended in high-volume cases (19). Chemotherapy should be discontinued until an active COVID-19 infection has been treated or until the diagnosis has been discontinued. Bleomycin should not be routinely omitted in the presence of COVID-19, as data on lung toxicity are unclear (20).

Since the beginning of the pandemic, there has been a remarkable reduction of up to 50% in uro-oncological cases in Europe. In a multicenter study conducted in our country during the pandemic period, a decrease of up to 80% in oncology cases was reported compared to the pre-pandemic period, which was parallel to Europe and the World (21). In this study, by the literature, significant decreases were observed in urooncological cases in both secondary and tertiary hospitals compared to the pandemic period. The decrease in the total number of urooncologic cases was 1.74 times greater for the second-level center than for the tertiary center hospital. This is an expected situation for a tertiary hospital.

According to the guidelines, operations such as urinary incontinence, reconstructive surgeries (urethral strictures), infertility, erectile dysfunction, and genitourinary prolapse, and especially BPH surgeries, should be postponed until the end of the pandemic (2,22).

The fact that the number of patients admitted due to prostate diseases is less than in the pre-pandemic period can probably be explained by the fact that patients continue to buy and use their current medication from pharmacies. Another reason for this decrease is that

chronic diseases can often accompany elderly men with lower urinary tract symptoms due to prostate enlargement. Due to the curfews during the pandemic, patients could spend time at home and reach the toilet from a close distance, so there were fewer urinary incontinence complaints and hospital admissions.

Although individuals spend more time with their partners during the pandemic period, there has been an increase in sexual problems such as erectile dysfunction and premature ejaculation. However, we saw that this situation was not reflected in hospital admissions (23). We can attribute this situation to the conditions of the pandemic and the fact that sexuality is still seen as a social taboo.

In considering the literature concerning urological patients during the COVID-19 pandemic, we observed that research and guideline recommendations have focused on urological emergencies. This study was carried out to better understand on what grounds patients with urological diseases in Turkey applied to the outpatient clinic during the pandemic period and which center was preferred for which disease.

The limitation of our study is its retrospective design and did not include all outpatients and outpatient procedures performed in our hospital during the above-mentioned period. Our results should be confirmed with multidisciplinary hospitals, some of which have recently been published during the pandemic.

CONCLUSION

In our study, we documented that urology outpatient clinic distribution could continue during the COVID-19 pandemic in a tertiary and secondary level hospital—primarily serving as a pandemic hospital—by taking preventive measures and prioritizing healthcare personnel and patient safety. Further studies are needed for safe urologic practices during outbreaks, especially concerning branch hospitals.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Fırat University Non-interventional Researches Ethics Committee (Date: 26.05.2022, Decision No: 2022/07-41).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Carotid Doppler ultrasound measurements in allergic rhinitis patients

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ABSTRACT

Aim: We aimed to determine with carotid Doppler ultrasound (CDU) whether the increase in inflammatory cells and mediators plays a role in intima-media thickening in patients with allergic rhinitis (AR) and to correlate this with the severity of the disease.

Material and Method: In this retrospective study, CDU reports and images of allergic rhinitis patients were evaluated in Group 1 (n=16). Score for allergic rhinitis (SFAR) and blood parameters that Hemoglobin (Hb), White Blood Cells (WBC), C-Reactive Protein (CRP), sedimentation levels were noted. Control group without AR consisted of 17 patients. In both groups, the presence of plaque on common carotid artery (CCA), and internal carotid artery (ICA) and all intima-media thickness were noted by CDU.

Results: In our study, CCA intima-media thickness and ICA intima-media thickness values of the AR group were significantly higher than those in the control group bilaterally ($p<0.05$). In the AR group, there were positive correlations between CCA intima-media thickness and ICA intima-media thickness values ($p<0.05$). In the AR and control groups, there were no plaques in ICAs bilaterally. However, left CCA plaques were detected in 2 patients (12.5%) of the AR group. In the AR group, CCA and ICA intima-media thicknesses increased in older patients; and right ICA intima-media thickness values increased in males ($p<0.05$).

Conclusion: Allergic rhinitis is one of the most common inflammatory diseases. It is known that the increase in mediators and inflammatory cells in the body can cause atherosclerosis. It should be kept in mind that AR patients may develop early atherosclerosis and therefore an increased cardiovascular risk.

Keywords: Allergic rhinitis, CCA intima-media thickness, ICA intima-media thickness, plaque

INTRODUCTION

Allergic rhinitis (AR), one of the most common respiratory diseases in the world, is defined as an inflammatory process triggered by mediators and cytokines in the nasal mucosaca used by exposure to allergens (1). The prevalence of AR varies between 5% and 22% worldwide (2). Its prevalence is increasing, especially in societies where industrialization has increased. AR affects the quality of life and saves the way for many diseases, especially lower respiratory tract diseases (3). AR has symptoms such as sneezing, nasal itching, runny nose, and nasal congestion (4). The diagnosis of AR can be made by anamnesis, physical examination and allergy tests.

Inflammation triggered by inflammatory mediators and factors plays an important role in the etiology of atherosclerosis (5,6). Carotid Doppler Ultrasonography (CDU) is the most commonly used method to evaluate atherosclerosis of the carotid artery and intima media layer thickening (IMT), which is the precursor of atherosclerosis (7,8).

In line with these informations, we aimed to determine with CDU whether the increase in inflammatory cells and mediators plays a role in intima-media thickening in patients with AR and to correlate this with the severity of the disease.

MATERIAL AND METHOD

This retrospective study was conducted in Radiology and Otolaryngology Departments of Kırıkkale Faculty of Medicine according to the principles of Declaration of Helsinki. Carotid Doppler ultrasound records

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were obtained from the Kırıkkale University Faculty of Medicine Radiology Department database. Ethics committee approval was obtained from the Non-invasive Clinical Researches Ethics Committee of Kırıkkale University (Date: 29.06.2022, Decision No: 2022.06.25).

Allergic Rhinitis Group

In this retrospective study, among the allergic rhinitis patients who came to the otorhinolaryngology outpatient clinic with the symptoms of nasal congestion, sneezing, runny nose and itching, Carotid Doppler Ultrasound were performed in the same month for other reasons was detected from our hospital data system. Carotid Doppler Ultrasound reports and images of allergic rhinitis patients younger than 50 years, were screened from the PACS (Picture archiving and communication systems) and data system of our hospital from current time to January 2022. The allergic rhinitis group consisted of 16 adults. The mean age of patients in allergic group is 34.75±10.51 (range 20 to 50). Score for allergic rhinitis (SFAR) (9-11) and blood parameters that Hemoglobin (Hb), White Blood Cells (WBC), C-Reactive Protein (CRP), sedimentation levels were noted.

Control Group

The measurements of 17 patients who were not diagnosed with allergic rhinitis and had similar age andgender characteristics with the AR group, who underwent Carotid Doppler US for any reason in the radiology department, were taken. Patients who had neck surgery, and malignancy were not included. The mean age of patients in control group is 29.64±7.46 (range 21 to 44).

Exclusion Criterias

Older patient from 50 years were excluded from the study because of the possibility of risk of aging-related atheroma plaque development. Those who have had carotid surgery or neck dissection and malignant patients were not included in the study group as this may affect the measurement results.

Score for Allergic Rhinitis (SFAR)

The SFAR is a structured scoring system that includes eight questions about AR symptoms, personal and family history of allergy, and allergy testing. According to the SFAR scoring system, as stated in previous studies, patients with a total score of 7 and above are considered for the diagnosis of AR (9,10). Turkish validation was performed for SFAR (11).

Carotid Doppler Ultrasound Measurements

Carotid Doppler Ultrasound (US) was evaluated with a digital device (LOGIQ E9; GE Healthcare, Waukesha, WI) with a linear 6–9-MHz multifrequency transducer by a radiologist with 12 years of experience in Doppler ultrasonography. Carotid Doppler US examinations were performed in a supine position. All US examinations of the left and right CCAs and ICAs were performed, including gray scale and color and pulsed Doppler ultrasound studies with using angle correction. Flow directions and whether the flow rate was normal or not were evaluated. The presence of plaque on common carotid artery (CCA), and internal carotid artery (ICA) and all intima-media thickness were noted as centimeters (cm) (12).

Statistical Analysis

SPSS for 21.0 (SPSS; IBM Inc, Chicago, IL) was used for statistical analysis. Mann Whitney U test was used for comparison between two groups. The Sperman's correlation rho efficient test was used for the correlations in the study group. Chi-square test was used to compare nominally categorized data in groups. For comparison within the same group (right and left sides of the same patient's one measurement), the non-parametric Wilcoxon signed ranks test was used because the numbers in the groups were small, did not show a normal distribution, and the p value was less than 0.05 in the Kolmogorov Smirnov test. A p value of<0.05 was considered statistically significant.

RESULTS

In the allergic rhinitis group, there were 9 (56,3 %) males and 7 (43,8 %) females; and in the control group, there were 8 (47.1%) males and 9 (52.9%) females (p=0.598, χ^2=0.279). There were no significant differences between ages of the AR and control groups (p>0.01) (**Table 1**).

In the AR group, blood parameters were as following: Hb: 14.80±1.08 gr/dL, WBC: 8125±1.87, CRP: 2.85±2.84, sedimentation rate: 12.37±7.30.

In the AR group, SFAR scores were 7.25 ± 3.31 (ranging 1.00 to 12.00).

Measurement results in the AR and control groups are shown on **Table 1**.

CCA Intima-Media Thickness

CCA intima-media thickness values of the AR group were significantly higher than those in the control group bilaterally (p<0.05) (**Table 1**).

In each of the AR and control groups separately, there were no significant differences between CCA intima-media thicknesses on the right and left sides (p>0.05) (**Table 1**).

ICA Intima-Media Thickness

ICA intima-media thickness values of the AR group were significantly higher than those in the control group bilaterally (p<0.05) (**Table 1**).

In each of the AR and control groups separately, there were no significant differences between ICA intima-media thicknesses on the right and left sides (p>0.05) (**Table 1**).

CCA Plaque

In the AR group, there were no plaques in right CCA. However left CCA fibrofatty plaque that does not cause significant stenosis, were detected in 2 (12,5 %) patients. In the control group, there were no CCA plaques bilaterally (p=0.082, χ2: 3.033) (**Table 1**).

ICA Plaque

In the AR and control groups, there were no plaques in ICAs bilaterally.

Correlation test results in group 1 (AR) are shown on **Table 2**:

There were positive correlations between CCA intima-media thickness, ICA intima-media thickness, and the presence of Left CCA plaques (p<0.05) (**Table 2**).

There were no significant correlations between SFAR; and blood parameters (Hb, WBC, CRP and sedimentation rate) and CCA and ICA intima-media thicknesses and left CCA plaques (p>0.05) (**Table 2**).

In older patients with AR, CCA and ICA intima-media thicknesses increased (p<0.05) (**Table 2**).

In male patients with AR, right ICA thickness values increased compared to females (p<0.05) (**Table 2**).

Table 1: Measurement results in the AR and control groups

	Group 1 (AR) (n=16)			Group 2 (Control group) (n=17)			P*
	Mean	**Median**	**Std. Dev.**	**Mean**	**Median**	**Std. Dev.**	
Age	34.75	36.5	10.51	29.64	28.00	7.46	0.213
Measurement results							
CCA intima thickness (mm)							
R	0.06	0.06	0.01	0.04	0.04	0.01	0.000
L	0.06	0.06	0.02	0.04	0.04	0.01	0.000
P**		0.974			0.166		
ICA intima thickness (mm)							
R	0.05	0.05	0.01	0.02	0.03	0.00	0.000
L	0.05	0.05	0.02	0.03	0.03	0.00	0.000
P**		0.158			0.763		
	n		**%**	**n**		**%**	**P*** **
Left CCA Plaque							
Present	2		12.5	0		0.0	P=0.082
Absent	14		87.5	17		100.0	χ2: 3.033

*p value shows the results of Mann Whitney U test, ** p value shows the results of Wilcoxon signed ranks test, ***p value shows the results of chi-square test

Table 2: Correlation test results in group 1 (AR)

			CCA intima thickness		ICA intima thickness		Left CCA Plaque (Code 1: Present, Code 2: Absent)
			R	**L**	**R**	**L**	
CCA intima thickness	R	r		0.551	0.879	0.606	0.568
		P		0.027	0.000	0.013	0.022
	L	r	0.551		0.491	0.747	0.504
		P	0.027	.	0.054	0.001	0.047
ICA intima thickness	R	r	0.879	0.491		0.709	0.563
		P	0.000	0.054	.	0.002	0.023
	L	r	0.606	0.747	0.709		0.515
		P	0.013	0.001	0.002	.	0.041
Left CCA Plaque (Code 1: Present, Code 2: Absent)		r	0.568	0.504	0.563	0.515	
		P	0.022	0.047	0.023	0.041	.
SFAR		r	0.095	0.347	-0.164	0.128	-0.103
		P	0.726	0.188	0.544	0.636	0.703
Hemoglobin (gr/dL)		r	0.095	0.347	-0.164	0.128	-0.103
		P	0.726	0.188	0.544	0.636	0.703
WBC		r	0.089	-0.186	0.109	0.170	0.288
		P	0.742	0.491	0.687	0.528	0.280
Sedimentation rate		r	0.096	0.472	0.043	0.259	0.126
		P	0.725	0.065	0.875	0.332	0.643
CRP		r	0.373	0.446	0.433	0.362	0.328
		P	0.154	0.083	0.094	0.168	0.215
Age		r	0.705	0.510	0.626	0.617	0.452
		P	0.002	0.044	0.009	0.011	0.079
Gender (Code 1: Male, Code 2: Female)		r	-0.253	-0.238	-0.556	-0.486	-0.333
		P	0.345	0.375	0.025	0.056	0.207

* p value shows the results of Spearman's correlation rho efficient test

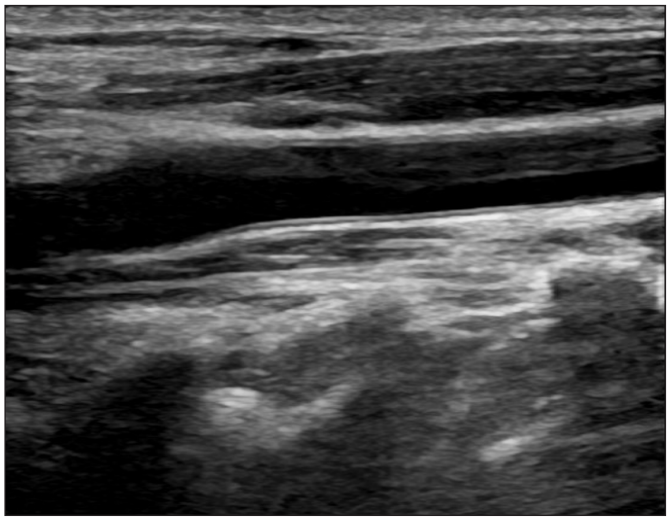

Figure 1: The figure shows the evaluation of the right common carotid artery with gray scale ultrasound.

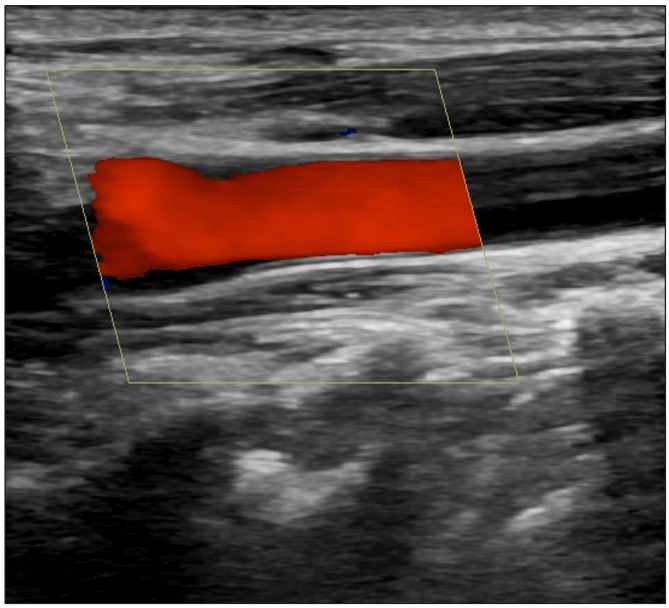

Figure 2: There is an evaluation of the flow direction in the right common carotid artery on the image.

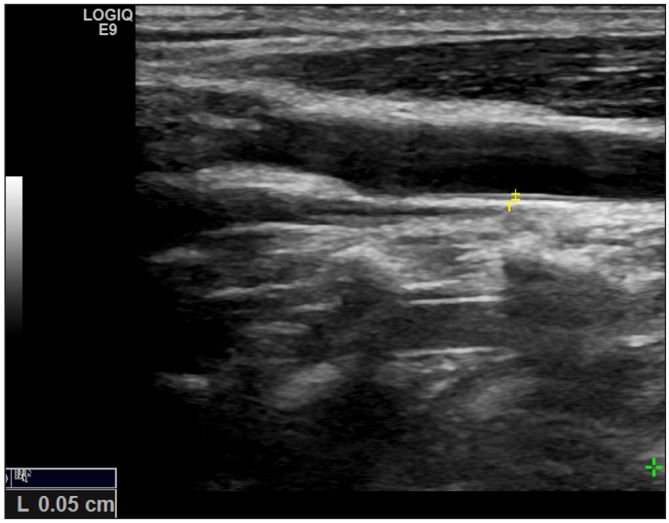

Figure 3: The measurement of intima-media thickness in the left internal carotid artery as centimeters is shown.

DISCUSSION

Allergic rhinitis is a health problem that is increasing in frequency according to recent publications and is caused by an inflammatory response to allergens (13,14). After the nasal mucosa is exposed to allergens, mast cells and basophil degranulation, immunoglobulin E production, and activation of eosinophils begin with the triggered immunomodulatory system. These are the mechanisms responsible for the clinical symptoms such as nasal congestion, sneezing, runny nose of AR (15,16).

SFAR, which was started to be used by Annesi-Maesano et al. (10) has been used for years in the diagnosis and follow-up of allergic rhinitis. AR patients were evaluated with SFAR, a score that has been validated andused in epidemiological studies (17). We aimed to obtain information about the severity of inflammation by adding SFAR results and blood values such as White Blood Cells (WBC), C-Reactive Protein (CRP), sedimentation to our study. There were nosignificant correlations between SFAR; and blood parameters (Hb, WBC, CRP and sedimentation rate) and CCA and ICA intima-media thicknesses and left CCA plaques. The reason why no significant results were obtained in this regard may be that the sample was a small group. More effective results can be obtained in larger case studies. An other reason may be that the SFAR scoring is subjective. More objective assessments are needed in this regard.

In our study, CCA intima-media thickness and ICA intima-media thickness values of the AR group were significantly higher than those in the control group bilaterally. In the AR group, there were positive correlations between CCA intima-media thickness and ICA intima-media thickness values. Moreover, in the AR group, CCA and ICA intima-media thicknesses increased in older patients; and right ICA intima-media thickness values increased in males. Looking at the literature, some studies mention that allergic diseases accelerate atherosclerosis (18,19). Although this issue has not yet been clarified, allergic disorders may be risk factors. Although allergic diseases are localized, they produce a systemic response by releasing vasoactive peptides and cytokines in to the circulation (20). Adhesion molecule expression increases not only in the nasal region, but also in distant endothelial cells. Leukocyte leakage from the endothelium increases and atherosclerosis occurs (21).

Carotid intima-media thickness is a noninvasive measurement for atherosclerosis (22). Many studies have evaluated that carotid intima-media thickness shows the risk of cardiovascular disease even in the absence of plaque (23,24). In our study, in the AR and control groups, there were no plaques in ICAs bilaterally. However, in

the AR group, there were left CCA plaque were detected in 2 (12.5%) patients. A significantly thicker IMT in the AR group may mean increased cardiovascular risk for these patients. In addition, these patients may have more plaques at advanced ages compared to the normal population. However, in the treatment of carotid plaque, questioning the presence of allergic diseases and their treatment should also take an important place.

There are also some limitations in this study. One of them is the small number of patients. Large case series are needed for better results. The presence or absence of inflammation in the body could not be excluded in the controlgroup. Further studies can contribute to the literature. Also follow-up studies are needed to demonstrate the development of atherosclerosis. Studies comparing age groups may also affect the results. Allergy tests were not performed on the patients. More meaningful results can be obtained with larger series diagnosed by allergy testing.

CONCLUSION

Allergic rhinitis is one of the most common inflammatory diseases. It is known that the increase in mediators and inflammatory cells in the body can cause atherosclerosis. It should be kept in mind that AR patients may develop early atherosclerosis and therefore an increased cardiovascular risk.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Non-invasive Researches Ethics Committee (Date: 29.06.2022, Decision No: 2022.06.25).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Risk factors for hypocalcemia and correlation between thyroid volume and incidental parathyroidectomy after total thyroidectomy: single center experience

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ABSTRACT

Aim: We aimed to investigate correlation between the effects of age, sex, disease, pathologic diagnosis, parathyroid autotransplantation, presence of parathyroid in the pathology specimen and clinicopathological variables and thyroid volume, postoperative hypocalcemia after bilateral total thyroidectomy.

Material and Method: A retrospective study planned in tertiary university hospital on patients undergone bilateral total thyroidectomy and neck dissection when necessary surgery for thyroid pathologies. Minimum calcium values in the postoperative period were recorded as transient or permanent hypocalcemia. The cases were statistically analyzed for the relationship between the volume of the thyroid gland removed and hypocalcemia. The effects of sex, pathological diagnosis, preoperative hyperthyroidism, anatomical retrosternal extension, number of parathyroid glands seen and preserved intraoperatively, parathyroid gland autoimplantation, parathyroid gland removal in the pathological specimen, nerve monitoring, bilateral total thyroidectomy and central and lateral neck dissection were analyzed for postoperative hypocalcemia.

Results: Totally 763 patients were included in the study. The mean age of the patients was 50.6 years (SD:12.8) and the sex of 575 (75.4%) patients was female. Hypocalcemia was more common in women than in men (31% vs 17%; p<0.001). Patients who underwent incidental parathyroidectomy (IPT) (yes, 43% vs no, 25%; p<0.001) and parathyroid autotransplantation (yes, 82% vs no, 27%; p=0.001) had statistically significantly higher rates of hypocalcemia. In the univariate analysis, it was determined from the available data that an increase in thyroid volume had a statistically significant effect on hypocalcemia, albeit at a low level [OR:1.002 (95%CI:1-1.004]. In the multivariate logistic regression model, the independent variables associated with postoperative hypocalcemia were female sex [OR: 2.33 (95%CI: 1.49-3.62)], thyroid volume [OR: 1.003 (95%CI:1-1.005)], IPT [OR:2.29 (95%CI:1.48-3.54)] and parathyroid autotransplantation [OR:1.999 (95%CI:2.1-47.5)]. While the effect of increased thyroid volume on hypocalcemia was very low, being female and incidental parathyroidectomy increased hypocalcemia 2.3 fold and parathyroid autotransplantation increased hypocalcemia 10-fold.

Conclusion: Incidental parathyroidectomy is a remarkable association, which determines the complication of postoperative hypocalcemia, and the presence of parathyroid tissue in the pathology specimen in cases with small thyroid volume.

Keywords: Hypocalcemia, thyroidectomy, thyroid volume, incidental parathyroidectomy

INTRODUCTION

Thyroid surgery is one of the most common surgical interventions performed today. Bilateral total thyroidectomy is the surgical procedure accepted by surgeons as the gold standard for thyroid cancer, suspected cancer, or bilateral benign conditions, and is now safely performed (1). Hypocalcemia is most commonly seen in surgery after bilateral thyroidectomy and requires temporary or permanent treatment (1,2). In different series, the incidence of transient hypocalcemia is reported to be 0.3-49%, and the incidence of permanent hypocalcemia is 0-13%. Hypocalcemia can be asymptomatic or cause a wide range of symptoms ranging from mild symptoms to life-threatening clinical findings. (2) In cases of hyperthyroidism and graves, post-surgical hypocalcemia is defined as hemodilution secondary to stress, increased urinary calcium excretion, hungry bone syndrome, osteodystrophy, and autoimmune fibrosis, while in severe hypocalcemia cases, hypoparathyroidism

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secondary to surgical trauma, devascularization, and iatrogenic parathyroidectomies are indicated. (3,4) Many studies have evaluated factors that may be risk for hypocalcemia after total thyroidectomy and various factors that may predict hypocalcemia in the preoperative period. (4) Predicting whether hypocalcemia will develop and starting treatment early is critical to reducing the length of hospital stay. In this study, the relationship between hypocalcemia, which is one of the complications encountered after thyroidectomy surgery, and the thyroid gland size of the patients was statistically analyzed to determine whether thyroid volume is an influential factor in the occurrence of hypocalcemia. Apart from this main objective, the effects of age, sex, disease, pathologic diagnosis, parathyroid autotransplantation, presence of parathyroid in the pathology specimen, and hormonal activity of the thyroid gland on thyroid volume were also analyzed.

MATERIAL AND METHOD

Tokat Gaziosmanpaşa University Clinical Researches Ethics Committee approval was received (Date:20.10.2022, Decision No:22-KAEK-215). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The data of the patients who underwent BTT and neck dissection when necessary, in the General Surgery Department of Tokat Gaziosmanpaşa University Faculty of Medicine between January 2010 and October 2022, and whose information was obtained, were evaluated retrospectively. Minimum calcium values in the postoperative period were recorded. Patients with abnormal preoperative serum PTH and calcium values, patients younger than 18 years of age, patients with hypocalcemia clinic as a result of the previous thyroidectomy, and patients with parathyroid adenoma were excluded from the study. A serum calcium level below 8 mg/dL was defined as hypocalcemia, recovery of hypocalcemia for less than 6 months was defined as transient hypocalcemia, and use of calcium and active vitamin D due to persistent hypocalcemia was defined as permanent hypocalcemia. The volume of the thyroid gland removed during the operation was calculated separately for each lobe using the standard ellipsoid formula (Miccoli formula: width x height x length x π / 6). The cases were statistically analyzed for the relationship between the volume of the thyroid gland removed and hypocalcemia. The effects of sex, pathological diagnosis, preoperative hyperthyroidism, anatomical retrosternal extension, number of parathyroid glands seen and preserved intraoperatively, parathyroid gland autoimplantation, parathyroid gland removal in the pathological specimen, nerve monitoring, BTT and central and lateral neck dissection on the development of hypocalcemia were evaluated. In statistical evaluation, Chi-square and Fisher's exact test were used for pairwise comparison of groups, and nominal regression analysis was used for multivariate evaluation. $p<0.05$ was considered significant.

Statistical Evaluation of Data

SPSS (Statistical Package for the Social Sciences) version 25.0 (IBM Corp., Armonk, NY, USA) program was used for statistical analysis. Whether the scores obtained from each continuous variable were normally distributed was analyzed by descriptive, graphical and statistical methods. The Kolmogorov-Smirnov test was used to test the normality of the scores obtained from a continuous variable by statistical method. While evaluating The relationship between two continuous variables was analyzed by Pearson correlation test. Univariate and multivariate logistic regression modeling was used to measure the effect of independent variables on the dependent variable. In addition, ROC analysis was used for the most appropriate thyroid volume discrimination to predict the presence of incidental parathyroidectomy. Results were evaluated at 95% confidence interval and significance was evaluated at $p<0.05$.

RESULTS

Patient Characteristics

Totally 763 patients were included in the study. The mean age of the patients was 50.6 years (SD:12.8) and the sex of 575 (75.4%) patients was female. BTT was performed in 737 patients (96.6%) and completion thyroidectomy in 26 patients (3.4%). Postoperative hypocalcemia was seen in 210 (27.5%) patients, 158 (20.7%) transient, and 52 (6.8%) permanent. Hypocalcemia was symptomatic in 106 (13.9%) and asymptomatic in 104 (13.6%) patients. Histopathologically, 231 (30.3%) patients were malignant and 532 (69.7%) were benign. Of the malignant patients, 214 (93%) were papillary carcinoma, 8 (4.4%) follicular carcinoma, 3 (1.3%) anaplastic carcinoma, 3 (1.3%) medullary carcinoma, and 3 (1.3%) mixed type carcinoma. Histopathologic examination revealed that 110 (14.4%) patients had IPT. There was one parathyroid gland in 90 (11.8%), two in 18 (2.4%), and three in 3 (0.3%) patients who underwent IPT. The mean postoperative Ca-Min. level was 8.29 mg/dl (SD: 0.68), median thyroid volume was 59 (Range: 3.5-627), and 106 (13.9%) patients received IV replacement therapy postoperatively. Patient demographic and clinicopathologic characteristics are detailed in **Table 1.**

Table 1. Patient characteristics

Variables (N=763)	n(%)
Age, mean (sd)	50.6 (12.8)
Male	188 (24.6)
Female	575 (75.4)
Malign	231 (30.3)
Benign	532 (69.7)
Thyroid volume, median (range)	59 (3.5-627)
Incidental parathyroidectomy	110 (14.4)
Total Thyroidectomy	737 (96.6)
Completion Thyroidectomy	26 (3.4)
Parathyroid autotransplantation	11 (1.4)
Lymph node dissection	23 (3.0)
Thyroiditis	208 (27.3)
Retrosternal goitre	102 (13.4)
Previous thyroid surgery	19 (2.5)
Preoperative hyperthyroid	242 (31.7)
Postoperative Ca-Min. (mg/dl), mean (sd)	8.29 (0.68)
Hypocalcemia	210 (27.5)
Symptomatic	106 (13.9)
Asymptomatic	104 (13.6)
Transient	158 (20.7)
Permanent	52 (6.8)
IV Ca supplementation	106 (13.9)
Calsitriol	52 (6.8)

sd:standard deviation

Factors Related to Postoperative Hypocalcemia

Univariate Analysis Results

Hypocalcemia was more common in women than in men (31% vs 17%; p<0.001). Patients who underwent IPT (yes, 43% vs no, 25%; p<0.001) and parathyroid autotransplantation (yes, 82% vs no, 27%; p=0.001) had statistically significantly higher rates of hypocalcemia. In the univariate analysis, it was determined from the available data that an increase in thyroid volume had a statistically significant effect on hypocalcemia, albeit at a low level [OR:1.002(95%CI:1-1.004]. Although not statistically significant, postoperative hypocalcemia was higher in patients with a preoperative diagnosis of hyperthyroidism (yes, 32% vs no, 26%; p=0.071). There was no statistically significant difference in the incidence of hypocalcemia according to age and other clinicopathologic features (p>0.05) (**Table 2**).

Multivariate Regression Analysis Results

Multivariate logistic regression analysis using the enter method was performed, including variables (sex, thyroid volume, IPT, parathyroid autotransplantation, and preoperative hyperthyroidism) that were statistically significantly (p<0.05) or nearly significantly (p<0.10) associated with hypocalcemia in univariate analyses. According to the results of the regression analysis, the coefficient of determination of the model was R2(Nagelkerke)=0.10. Accordingly, it was found that 10% of the variance in the dependent variable was explained by the independent variables. Since the p-value in the model (F=51.78, p<0.001) is smaller than the value, it is determined that the model is significant at 95% confidence level. The correct classification probability of the model was obtained as 74%. The model predicted hypocalcemia 74% correctly with the variables used. According to the multiple logistic regression model, the independent variables associated with postoperative

Table 2. Factors related to postoperative hypocalcemia (univariate and multivariate logistic regression analysis results)

Variables (N=763)	Category	n	n (%)	Hypocalcemia			
				Univariate		Multivariate	
				OR (95% CI)	p	OR (95% CI)	p
Age, mean(sd)	<50	333	97 (29.1)	1.15 (0.84-1.59)	0.382	NA	
	≥50	430	113 (26.3)	1		NA	
Sex	Female	575	179 (31.1)	2.29 (1.5-3.5)	<0.001*	2.33 (1.49-3.62)	<0.001*
	Male	188	31 (16.5)	1		1	
Thyroid pathology	Malign	231	63 (27.3)	0.98 (0.7-1.39)	0.919	NA	
	Benign	532	147 (27.6)	1		NA	
Thyroid volume	All	763	NA	1.002 (1-1.004)	0.036*	1.003 (1.001-1.005)	0.001*
Incidental parathyroidectomy		110	47 (42.7)	2.24 (1.48-3.4)	<0.001*	2.29 (1.48-3.54)	<0.001*
Thyroid surgery type	Total	737	205 (27.8)	1.62 (0.6-4.35)	0.340	NA	
	Completion	26	5 (19.2)	1		NA	
Parathyroid autotransplantation		11	9 (81.8)	12.34 (2.64-57.58)	0.001*	9.99 (2.1-47.5)	0.004*
Lymph node dissection		23	8 (34.8)	1.42 (0.59-3.4)	0.431	NA	
Thyroiditis		208	66 (31.7)	1.33 (0.94-1.88)	0.112	NA	
Retrosternal goitre		102	29 (28.4)	1.05 (0.66-1.67)	0.825	NA	
Previous thyroid surgery		19	4 (21.1)	0.7 (0.23-2.12)	0.525	NA	
Preoperative hyperthyroid		208	77 (31.8)	1.36 (0.97-1.9)	0.071	1.27 (0.88-1.83)	0.207

*:p<0.05, Multiple Logistic regression, Method=Enter, OR: Odd Ratio, CI: Confidence Interval, R2 (Nagelkerke)=0.10, Model $\chi 2$=51.78, p<0.001, Dependent variable: Hypocalcemia (1=yes, 0=no), Correct classification probability of the model:74%, 1: Reference value

hypocalcemia were female sex [OR: 2.33(95%CI: 1.49-3.62)], thyroid volume [OR: 1.003(95%CI:1-1.005)], IPT [OR:2.29(95%CI:1.48-3.54)] and parathyroid autotransplantation [OR:1.999(95%CI:2.1-47.5)]. While the effect of increased thyroid volume on hypocalcemia was very low, being female and IPT increased hypocalcemia 2.3-fold and parathyroid autotransplantation increased hypocalcemia 10-fold (**Table 2**).

Relationship Between Continuous Variables

There was a positive correlation between thyroid volume and age (r=0.170; p=<0.001) and a weak negative correlation between postoperative Ca minimum level (r=-0.088; p=0.015) and the number of parathyroid glands removed (r=-0.114; p=0.002) (**Table 3**).

Table 3. Relationship between continuous variables

Variables	Age	Thyroid volume
Thyroid volume	0.170*	
Postoperative CaMin	0.004	-0.088**
Incidental number of parathyroid glands	0.004	-0.114**

*:p<0.001, **:p<0.05, Pearson Correlation

ROC Analysis Result

The cut-off value for thyroid volume in determining the risk of IPT was 70 and the AUC value was 61%. For the thyroid volume cut-off value of 70, sensitivity 0.75 (95%CI: 0.66-0.84), specificity 0.45 (95%CI: 0.35-0.55), PPV 0.19 (95%CI: 0.11-0.27), NPV 0.92 (95%CI: 0.87-0.97) and accuracy 0.49 (95%CI: 0.39-0.59) were calculated (**Table 4**). Univariate analysis revealed that the only variable associated with IPT was thyroid volume. The IPT rate was higher in patients with a thyroid volume below 70 (19% vs 8%). When thyroid volume of 70 and above was accepted as reference, thyroid volume below 70 was 2.5 (95%CI: 1.59-3.99) times more associated with IPT (p<0.001).

Table 4. ROC curve analysis results

	Thyroid volume
Incidental parathyroidectomy	
Cut-off	70
AUC (95% CI)	0.614 (0.558-0.671)*
Sensitivity (95% CI)	0.75 (0.66-0.84)
Specificity (95% CI)	0.45 (0.35-0.55)
PPV (95% CI)	0.19 (0.11-0.27)
NPV (95% CI)	0.92 (0.87-0.97)
Accuracy (95% CI)	0.49 (0.39-0.59)

*:p<0.001, PPV:positive predictive value, NPV=negative predictive value, AUC: area under the curve

Table 5. Risk factors for incidental parathyroidectomy

Variables(N=763) Category	n	n(%)	Incidental parathyroidectomy Univariate	
			OR(95%CI)	p
Age				
<50	333	42 (12.6)	1	
≥50	430	68 (15.8)	1.3 (0.86-1.97)	0.213
Sex				
Male	188	22 (11.7)	1	
Female	575	88 (15.3)	1.36 (0.83-2.25)	0.224
Thyroid pathology				
Malign	231	36 (15.6)	1.14 (0.74-1.76)	0.545
Benign	532	74 (13.9)	1	
Thyroid surgery type				
Total	737	104 (14.1)	0.55 (0.22-1.4)	0.207
Completion	26	6 (23.1)	1	
Previous thyroid surgery				
Yes	19	2 (10.5)	1	
No	744	108 (14.5)	1.44 (0.33-6.34)	0.627
Preoperative hyperthyroid				
Yes	208	30 (14.4)	0.999 (0.64-1.57)	0.998
Thyroid volume (cm^3)				
<70	442	83 (18.8)	2.52 (1.59-3.99)	<0.001*
≥70	321	27 (8.4)	1	

*:p<0.05, OR: Odds ratio, CI: Confidence interval, 1: Reference value

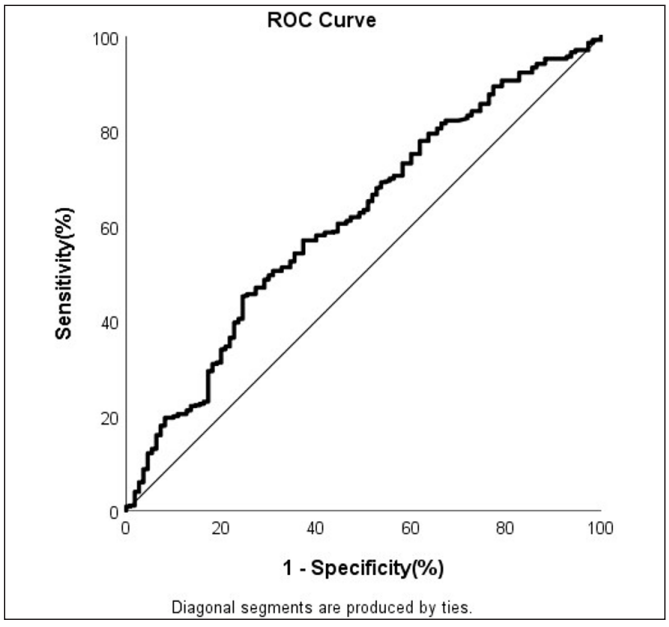

Figure 1. ROC curve of Incidental parathyroidectomy

DISCUSSION

Postoperative hypocalcemia was observed in 210 (27.5%) patients, 158 (20.7%) transient and 52 (6.8%) permanent. Hypocalcemia was symptomatic in 106 (13.9%) patients and asymptomatic in 104 (13.6%) patients. In the univariate analyzes of 12 variables evaluated on hypocalcemia in our study, it was seen that the variables that were statistically significant or close to significance were sex, thyroid volume, IPT, parathyroid

autotransplantation, and preoperative hyperthyroidism. According to the multivariate logistic regression model; the independent variables associated with postoperative hypocalcemia were found to be female sex, thyroid volume, IPT and parathyroid autotransplantation. While the effect of thyroid volume increase on hypocalcemia is very low; It was determined that being female and performing IPT increased hypocalcemia 2.3 times, and performing parathyroid autotransplantation increased hypocalcemia 10 times. However, age, recurrence, neck dissection, presence of thyroiditis, thyroid pathology and retrosternal extension, which were reported as risk factors for hypocalcemia in some studies, were not found to be significant risk factors in our study.

In a study, it was stated that hypocalcemia is related to young age (5). In another study, when age and hypocalcemia status were compared, the risk of hypocalcemia was determined to be high in those younger or older than the age range of 45-84 (6). In our study, however, no significant difference was found between age and the development of postoperative hypocalcemia and hypoparathyroidism. Female sex has been identified as a risk factor for postoperative hypocalcemia in studies with large series (7-10). Our study was performed on 575 (75.4%) female and 188 (24.6%) male cases. The female sex ratio was higher in patients with postoperative hypocalcemia compared to the other group. Postoperative hypocalcemia was observed in 210 (27.5%) patients, 158 (20.7%) transient and 52 (6.8%) permanent. 179 patients with hypocalcemia were female and 31 patients were male. In our study, it was seen that female sex was a significant independent risk factor in postoperative hypocalcemia.

There are studies on the risk of developing postoperative hypocalcemia in patients who underwent BTT due to hyperthyroidism. In another study involving 2108 patients who had undergone thyroid surgery, the relationship between early hypocalcemia and thyrotoxicosis was examined and no difference was found between those with and without Graves' disease in terms of the development of hypocalcemia. (11) In another study involving 380 patients who underwent BTT, 203 patients were operated for Graves' disease, 56 patients were operated for non-Gravesian hyperthyroidism, and 521 patients were operated for other benign reasons, and permanent hypoparathyroidism was found to be significantly higher in Graves patients compared to other patients. Although it was not statistically significant in patients with preoperative hyperthyroidism, postoperative hypocalcemia was higher.

While there are studies showing that malignancy has an effect on postoperative hypocalcemia in patients undergoing thyroidectomy (12-13), there are also studies claiming the contraversial (11). In our study, the pathology results of 231 (30.3%) patients were malignant, while the results of 532 (69.7%) patients were benign. There was no significant relationship between benign and malignant findings of the patients and postoperative hypocalcemia.

In a meta-analysis of 1132 patients including five studies, patients who had only BTT and those who had neck dissection combined with BTT were compared, and it was observed that transient hypocalcemia was statistically increased in patients with neck dissection added to thyroidectomy. In another study, which included 1030 patients who underwent BTT, temporary hypocalcemia developed in 28.2% of patients, permanent hypocalcemia developed in 2.6% of patients, and the development of hypocalcemia in patients who underwent central neck dissection and lateral neck dissection was found to be statistically significant (14). In a multicentric study examining retrosternal extension in 19,662 patients, it was reported that patients with retrosternal extension were more likely to develop temporary and permanent hypocalcemia than those without (15). In our study, when the operation, neck dissection and retrosternal extension were examined, it was seen that only BTT was performed in 737 patients, completion thyroidectomy was performed in 26 patients, and lateral neck dissection was added in 23 patients. Retrosternal extension was observed in 102 of the patients included in our study, and postoperative hypocalcemia was observed in 29 (28.4%) of them. When evaluated in terms of postoperative hypocalcemia; No statistical correlation was found between the type of operation, whether neck dissection was performed, and the presence of retrosternal extension.

In the literature, the leading surgical risk factors for transient hypocalcemia are the presence of the parathyroid gland in the surgery related to the parathyroid gland, parathyroid gland autotransplantation and IPT. In a meta-analysis evaluating 4 studies, it was determined that the incidence of transient hypocalcemia was significantly higher in patients who had one or more parathyroid gland autotransplantation. In a study of 271 patients who underwent thyroidectomy, permanent hypocalcemia was observed only in patients who did not undergo autotransplantation. Permanent hypoparathyroidism was not observed in any patient with postoperative hypocalcemia after autotransplantation (10). In a study involving 194 patients who underwent thyroid surgery, it was argued that routine autotransplantation almost completely eliminated postoperative permanent hypoparathyroidism (16). In a retrospective study, while autotransplantation was associated with transient hypocalcemia in 1482 patients who underwent thyroidectomy, permanent hypocalcemia was not.

They also stated that the existence of a relationship between parathyroid autotransplantation and transient hypocalcemia was independent of thyroidectomy width and neck dissection. It was found that the increase in the number of autotransplanted glands also significantly increased the incidence of transient hypocalcemia (17,18). In our study, symptomatic transient hypocalcemia developed in 9 of 11 patients who underwent parathyroid autoimplantation, while it did not develop in 2 patients. The risk of developing hypocalcemia in autotransplanted patients was determined as 81.8%. It is noteworthy that there is a statistically significant increase in the incidence of hypocalcemia with parathyroid autotransplantation. In terms of postoperative hypocalcemia, it was observed that parathyroid autotransplantation increased the risk of hypocalcemia 10 times.

In our study, one of the independent factors effective for postoperative hypocalcemia was IPT. Although there are studies reporting that IPT has no effect on postoperative hypocalcemia, the rate of transient hypocalcemia was found to be higher in patients who underwent one or more IPT (19-22). In a meta-analysis of 1482 patients from four studies, the incidence of transient hypocalcemia was found to be higher in patients who underwent IPT. In the presence of IPT, the incidence of hypocalcemia increases from 25% to 42.7%. IPT rates in the literature vary between 5-29% (18-22). In our study, the number of patients who had IPT was 110, and the rate was 14.4%. Permanent hypocalcemia was observed in 47 of our 110 patients who had IPT. In terms of postoperative hypocalcemia, it was observed that IPT increased the risk 2.3 times. When the risk factors for IPT were evaluated, univariate analysis revealed no relationship with age, sex, histopathology, type of operation, and history of previous thyroid surgery. It was found that the only variable associated with IPT was thyroid volume. Thyroid volume was found to be less than 70 cm^3 in 83 of 110 patients with IPT. The rate of IPT was higher in patients with a thyroid volume less than 70 cm^3 (18.8% vs 8.4%). When the thyroid volume of 70 cm^3 and above is accepted as a reference; Thyroid volume less than 70 cm^3 was associated 2.5 times more with IPT. Thyroid dissection may be easier in large thyroid volume. Low thyroid volume, especially if there is a thyroiditis background, makes thyroid surgery and identification of parathyroid glands difficult due to adhesion to the surrounding tissues. In addition, anatomically the parathyroid location may be intrathyroidal. Depending on this situation, incidental parathyroidectomy can be performed during thyroidectomy. For this reason, we believe that low thyroid volume increases the risk of incidental parathyroidectomy and therefore postoperative hypocalcemia.

In the postoperative pathological examination, parathyroid tissue was not observed in pathology in 653 patients, while parathyroid tissue was observed in pathology in 110 patients. The presence of postoperative hypocalcemia was found to be high in patients with parathyroid tissue in pathology. In terms of postoperative hypocalcemia, it has been observed that the presence of incidental parathyroid tissue in pathology is negatively correlated with thyroid volume, and the incidence of parathyroid tissue in pathology increases as the volume size decreases.

In a study, it was found that the risk of postoperative hypocalcemia increases as the thyroid gland volume decreases (23). In another study, it was reported that the risk of hypocalcemia increased in those with a small thyroid volume and the risk of bleeding in those with a large thyroid volume (24). In our study, it was determined that the increase in thyroid volume had a statistically significant effect on hypocalcemia, albeit at a low level. There was a weak positive correlation between thyroid volume and age, postoperative minimum calcium level, and the number of incidentally removed parathyroid glands. As a result of the univariate analysis performed in our study, it was determined that the only variable associated with IPT was thyroid volume. In our study, where the cut-off value for thyroid volume was found to be 70 cm^3 in determining the risk of IPT, the rate of IPT was 2.5 times higher in patients with thyroid volume below 70 cm^3.

One of the limitations of our study is that it is retrospective. Due to its retrospective nature, we realized that prophylactic calcium and vitamin d replacement in some patients led to limitations in clearly demonstrating hypocalcemia.

CONCLUSION

In our study, we found a remarkable association of IPT, which determines the complication of postoperative hypocalcemia, and the presence of parathyroid tissue in the pathology specimen in cases with small thyroid volume. For this reason, we recommend that the parathyroid tissues and their blood supply be not affected as much as possible intraoperatively for postoperative hypocalcemia, especially in cases with small thyroid volume in the preoperative period..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Tokat Gaziosmanpaşa University, Noninvasive Clinical Researches Ethics Committee (Date: 20.10.2022, Decision No: 22-KAEK-215)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Comparative analysis of second- and third-trimester complete uterine rupture cases followed up in a tertiary hospital: a retrospective cohort study

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ABSTRACT

Aim: There are not many studies that compared the uterine rupture cases pertaining to different trimesters of pregnancy in terms of the changes in relevant risk factors and fetomaternal outcomes. In this context, this study was carried out to comparatively analyze the cases who were diagnosed with complete uterine rupture and gave birth in the hospital where this study was conducted in terms of the relevant risk factors and fetomaternal outcomes.

Material and Method: The population of this retrospective study consisted of patients who were diagnosed with complete uterine rupture and gave birth in our hospital between January 2015 and June 2022. Patients' demographic characteristics, cesarean section, labor induction histories, and fetal and maternal outcomes were recorded. The patients included in this study were divided into two groups based on the trimester when the complete uterine rupture occurred as second- and third-trimester complete uterine rupture groups. The groups were compared in terms of fetal, maternal, and obstetric outcomes.

Results: Out of the 56718 deliveries performed during the study period, a total of 27 complete uterine rupture cases, of whom 10 had second-, and 17 had third-trimester uterine rupture, were included in the study sample. Accordingly, the incidence of rupture was calculated as 0.047%. Of these 27 cases, 9 had re-pregnancy. Bilateral hypogastric artery ligation was performed in seven patients and six of these patients were in the third trimester rupture group. Of the 27 cases with complete uterine rupture, 19 had a cesarean section history. All 8 cases that did not have a cesarean section history had a complete uterine rupture in the third trimester.

Conclusion: Complete uterine rupture is associated with adverse maternal and fetal outcomes. Fertility-sparing surgery (primary repair) is the first-line therapy. The prognosis of second-trimester uterine ruptures is more unfavorable compared to third-trimester uterine ruptures from the fetal point of view yet more favorable from the maternal point of view.

Keywords: Hysterectomy, perinatal mortality, cesarean section, uterine rupture

INTRODUCTION

Uterine rupture is the rupture of the uterine wall during pregnancy or childbirth. Uterine ruptures are associated with maternal and neonatal morbidities and mortalities (1). The overall incidence of uterine rupture reported in the literature ranges between 1 in 1096 and 1 in 2900 (2,3).

The severity of fetal and maternal morbidity depends on the extent of uterine rupture. In some cases, the rupture may be beyond repair, and thus a hysterectomy may be required. Fertility is often not adversely affected if tubal ligation is not performed within the scope of uterine rupture repair. There are a limited number of studies on the fertility of complete uterine rupture cases who underwent uterine-sparing surgery (4–6).

Infection, trauma, or malignancy may also cause the uterus to rupture (7). However, uterus rupture is predominantly observed in pregnant women (7). The importance of uterine rupture has increased in recent years due to the increased incidence of vaginal birth after cesarean section (VBAC). VBAC implies having vaginal delivery in any pregnancy after giving birth via cesarean section in a former pregnancy. The risk of uterine rupture is one of the main issues to be considered when counseling patients about VBAC (8).

The most critical risk factor for uterine rupture is previous cesarean delivery, followed by malpresentation, dystocia, labor induction, delivery after 42 weeks of gestation, and preterm delivery (2,3,9).

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Misoprostol, a synthetic prostaglandin analog administered during pregnancy, is the most commonly used medication in second-trimester pregnancy terminations (10). Uterine rupture due to misoprostol use has been reported more frequently in multiparous women and women with uterine scarring and term pregnancy than in the second trimester (11). The increase in the rate of cesarean deliveries also causes an increase in the rate of cases terminated due to pregnancy scarring (10,11). The International Federation of Obstetrics and Gynecology (FIGO) has prepared a chart detailing the recommended use of misoprostol for various gynecological and obstetric indications in light of new evidence (12).

In view of the foregoing, the objective of this study is to review the fetal and maternal outcomes of the cases that were diagnosed with complete uterine rupture and gave birth in the hospital where this study was conducted and pregnancy outcomes in those who have had a repeat pregnancy.

MATERIAL AND METHOD

The study was carried out with the permission of Zeynep Kamil Women and Children's Diseases Training and Research Hospital, Clinical Researches Ethics Committee (Date: 07/12/2022, Decision No: 138). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The population of this retrospective study consisted of patients who were diagnosed with complete uterine rupture and gave birth in our hospital between January 2015 and June 2022. Written informed consent could not be obtained from the patients due to the study's retrospective design.

Uterine rupture diagnosis was made based on the criteria outlined in the 2012 International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) with the diagnosis code 665.11 entitled "uterine rupture". Only the patients with complete uterine rupture, defined as the complete rupture of all layers forming the uterine wall, were included in the study sample. Patients with incomplete ruptures, who gave birth at the clinic where this study was conducted upon being referred from an external clinic with the prediagnosis of rupture, and patients who had a rupture due to placental invasion were excluded from the study.

Patients' maternal age, gravida & parity number, birth weight, gestational week, cause and site of rupture, duration of operation, length of stay in the intensive care unit, transfusion amount, and maternal and perinatal mortality data were recorded. Additionally, the onset of labor, the use of oxytocin and prostaglandin, the mode of delivery, the changes detected in cardiotocography, and the procedures performed during the operation were noted.

Among the obstetric risk factors, cesarean delivery history, presence of hypertensive disorder, amniotic fluid volumes, and premature membrane rupture history, if any, were recorded.

The patients included in the study sample were divided into two groups based on the trimester when the complete uterine rupture occurred as second- and third-trimester complete uterine rupture groups. The groups were then compared in terms of fetal, maternal, and obstetric outcomes.

The misoprostol dosages recommended in the updated FIGO guidelines were used in second-trimester pregnancy terminations (12). Patients who exceeded the dosages recommended by FIGO and required additional intervention were excluded from the study.

Subsequent pregnancies of all patients included in the study and the birth complications that occurred during these pregnancies were evaluated. Information on patients' fertility after rupture was obtained from the hospital records and through phone interviews conducted with the patients.

Statistical Analysis

The statistical analyses of the collected data were conducted using SPSS 22.0 (Statistical Product and Service Solutions for Windows, Version 22.0, IBM Corp., Armonk, NY, U.S., 2013) software package. The descriptive statistics obtained from the collected data were expressed as mean±standard deviation, percentage, and minimum-maximum values. Odds ratios (OR) and the respective 95% confidence intervals (CI) were calculated from the model. The probability (p) statistics of ≤ 0.05 were deemed to indicate statistical significance.

RESULTS

Out of the 56718 deliveries performed during the study period, a total of 27 complete uterine rupture cases, of whom 10 had second-, and 17 had third-trimester uterine rupture, were included in the study sample. Accordingly, the incidence of rupture was calculated as 0.047%. Demographic and obstetric characteristics of the cases are shown in **Table**.

There was no significant difference between the study groups in terms of age, gravida&parity numbers, height, weight, and the number of previous cesarean sections.

On the other hand, the rate of patients who developed disseminated intravascular coagulation (DIC), the rate of patients who required a hysterectomy, the estimated amount of bleeding, and the length of stay in the

intensive care unit were significantly more in the third-trimester rupture group than in the second-trimester rupture group, whereas widespread abdominal pain and monitoring of fetus in the abdomen were significantly more common in the second-trimester rupture group than in the third-trimester rupture group.

Table. Distribution of patients' demographic and obstetric characteristics by the trimester when the rupture has occurred

	Second-trimester rupture group (n=10)	Third-trimester rupture group (n=17)	p value
Gravida	3.30±0.94	4.29±2.36	0.130
Parity	2.10±0.73	2.76±2.27	0.280
Abortus	0.30±0.67	0.53±0.71	0.420
Survived	2.00±0.81	2.65±2.14	0.270
Age (years)	35.5±4.80	34.00±6.30	0.520
Height (cm)	158.4±4.80	161.4±3.90	0.085
Weight (kilograms)	88.2±15.40	78.94±9.69	0.110
The time between cesarean sections (years)	4.40±1.32	4.44±3.30	0.969
Number of cesarean sections	2.10±0.73	1.29±1.50	0.078
Rate of patients who had a hysterectomy	0%, (n=0)	23.5%, (n=4)	**0.041**
Rate of patients who had great artery ligation	20%, (n=2)	41%, (n=7)	0.256
Rate of patients who had disseminated intravascular coagulation	0%, (n=0)	23.5%, (n=4)	**0.041**
Rate of patients in whom fetus was monitored in the abdomen	60%, (n=6)	5.8%, (n=1)	**0.009**
Rate of patients with abdominal pain	100%, (n=10)	23.5%, (n=13)	**0.041**
Rate of patients with vaginal bleeding	60%, (n=4)	35.2%, (n=6)	0.819
Length of stay in the intensive care unit (days)	0.90±0.73	1.82±1.13	**0.030**

Of the 27 cases with complete uterine rupture, 19 had a cesarean section history. All 8 cases that did not have a cesarean section history had a complete uterine rupture in the third trimester. Two of these cases had a history of hysteroscopic septum resection, one had a history of myomectomy, and five had parity numbers greater than 5. Of the five patients with parity numbers greater than 5, two had fetal malposition, and three were administered a prostaglandin E2 analog for labor induction.

Live birth could not be achieved in any of the ten patients in the second-trimester rupture group. Pregnancy was terminated in six of these cases due to various trisomies and, in one case, due to structural anomalies. These seven cases were treated with misoprostol for termination. Misoprostol doses were administered according to FIGO guidelines. In the other three cases, spontaneous uterine rupture had already occurred at the time of admission to the hospital. All cases were taken to emergency laparotomy as soon as evidence of rupture was observed on ultrasound. Live birth occurred in 15 (88%) of the 17 patients in the third-trimester rupture group. When we examined these cases within themselves, fetal mortality was not observed in any of the VBAC and unscarred pregnant women who were followed up during labor. On the other hand, fetal loss already existed in the two cases with fetal loss during the first ultrasonographic examination of the patients performed at the time of their admission to the hospital. The mean (minimum-maximum) 1st-and 5th-minute APGAR scores of the cases in the third-trimester rupture group were 6.05 (min. 0, max. 8) and 7.94(min. 0, max. 10), respectively.

Analysis of the surgical interventions performed during the rupture revealed that bilateral hypogastric artery ligation was performed in seven patients and that six of these patients were in the third-trimester rupture group. In addition, hysterectomies were performed on four patients, three of which were in the third-trimester rupture group.

Transfusion was not needed in 8 cases, 6 of whom were in the second-trimester rupture group. The mean (minimum-maximum) erythrocyte suspension amounts in the second- and third-trimester rupture groups were 0.5 (min. 0, max. 2) units and 2.76 (min. 0, max. 8) units, respectively. Additionally, the mean (minimum-maximum) fresh frozen plasma transfusion amounts in the second- and third-trimester rupture groups were 0.5 (min. 0, max. 2) units and 0.88 (min. 0, max. 6) units, respectively.

Hysterectomy was required in four cases, and bilateral Pomeroy tubal ligation was performed in 6 cases. Of the remaining 17 cases, six stated that they were protected by various contraceptive methods, whereas a 32-year-old case could not get pregnant despite not using any contraceptive method for the last three years.

In terms of the presence of additional systemic disease, of the 27 cases, three had gestational diabetes mellitus, and two had chronic hypertension.

Analysis of the subsequent pregnancies revealed that nine cases had re-pregnancy (**Figure**). In six of these cases, on average, elective cesarean section was performed between the 36th and 37th weeks of gestation. It was learned that none of these six patients experienced any problems during pregnancy. A review of the surgical reports of these cases revealed that one case had intraoperative uterine dehiscence, one case had her pregnancy terminated twice by abortion between the 7th and 8th of gestation following rupture, one case had her amniotic membrane prolapsed from the uterine scar line to the abdomen at 27th week of gestation, and another case was in her 32nd week of gestation without any problems.

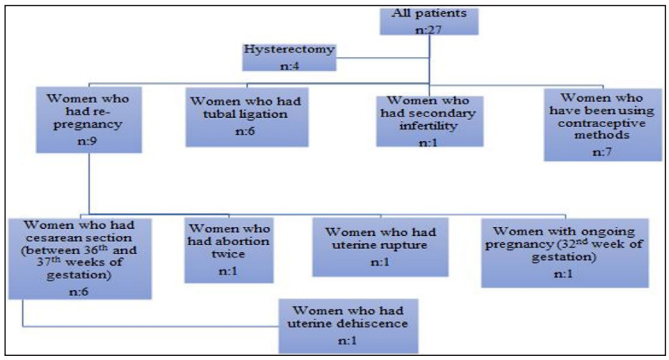

Figure. Patients' post-rupture fertility status

DISCUSSION

The incidence of uterine rupture was reported as 5.9 per 10,000 in the population-based systemic review of the World Health Organization (WHO) and 31 per 10,000 in facility-based studies (5). A study conducted in the Netherlands, including 371021 women, reported a comparable uterine rupture incidence to WHO (9). Similarly, the incidence of uterine rupture in this study was calculated as 4.2 per 10000.

A history of cesarean section is one of the primary risk factors for uterine rupture. The cesarean section rate and, ensuingly, the risk of obstetric complications have been on the rise globally (2,3,9). As a matter of fact, of the 27 complete uterine rupture cases included in this study, 19 had a history of cesarean section, two had hysteroscopic septum resection one year before the rupture, one had myomectomy one year before the rupture, and only four did not have any history of cesarean section. Of the five patients without any history of uterine surgery, two had presentation anomalies, and laparotomy was decided in the remaining three, given that vaginal bleeding did not stop despite postpartum medical treatment. The rupture sites were detected in the said three cases incidentally during the operation. They were administered prostaglandin for induction to prepare them for prenatal delivery, and tachysystole developed in all three. Numerous studies concluded that labor induction, grand multiparity, and malposition are risk factors for uterine rupture. In parallel, a significantly higher number of grand multiparous cases had a uterine rupture in this study (2,9,13,14).

In the literature, rupture of the scarless uterus has been associated with greater blood loss, higher incidence of hysterectomy, and higher composite maternal morbidity (death, hysterectomy, blood transfusion, or urological injury) than rupture of a scarred uterus (1). Similarly, in this study, cases with the rupture of the scarless uterus had significantly more blood loss and a significantly higher need for transfusion than those with the rupture of the scarred uterus. On the other hand, there was no significant difference between the two groups in terms of hysterectomy.

Although fetal complications such as the absence of a fetus in the abdomen and the absence of fetal heartbeat were significantly more common in the second-trimester rupture group, hysterectomy requirement, DIC development, and length of stay in the intensive care unit were significantly more common in the third-trimester rupture group.

It was reported in the literature that prolongation of the time between rupture and surgery increased maternal blood loss, the risk of coagulopathy, and fetal exposure to hypoxia (15). The neonatal mortality rates following uterine rupture reported in the literature ranged between 6% and 25% (5,16,17). In comparison, the material of this research did not include the data on the time that elapsed between uterine rupture and surgical intervention. However, the fact that live birth occurred in 15 of the 17 cases who developed uterine rupture in the third trimester and that the babies were given to their families after cesarean section suggests that the time between rupture and surgical intervention was not too long in these cases. On the other hand, the development of DIC without fetal heartbeat indicates more blood loss and a longer time between surgery and uterine rupture in the remaining two cases.

In a study by Gibbins et al. (1), the fetal mortality rate was reported as 10% and 2% in cases with a scarless uterus and scarred uterus, respectively. Another study reported the fetal mortality rate as 7.4% (18). Some studies reported that 1st- and 5th-minute APGAR scores decreased in cases with uterine rupture (2,3). In contrast, fetal loss was not observed in any of the patients who developed uterine rupture in the third trimester and were followed up during labor, and the mean 1st- and 5th-minute APGAR scores of these patients were better than expected. This study's low fetal loss rate might be attributed to the fact that the patients were followed up closely by a team with experience in all kinds of birth and that the time elapsed between rupture and surgery was short.

Recurrent rupture rates reported in the literature ranged between 4.9% and 33.3% in studies on pregnancies after uterine rupture repair (5,19). In comparison, the rate of patients who developed a uterine rupture in subsequent pregnancies in this study was 11.1%.

The primary strength of this study is that it is the first study to date that compared second-and third-trimester complete uterine ruptures. On the other hand, the primary limitation of this study was its retrospective design and limited sample size. Thus, large-scale case series are needed to corroborate the findings of this study.

CONCLUSION

The findings of this study revealed that uterine rupture was associated with adverse maternal and fetal outcomes and that the most critical risk factor for uterine rupture was previous cesarean delivery. Close prenatal follow-up and planned elective cesarean section will likely reduce the number of uterine rupture cases. Although second-trimester uterine ruptures have been associated with more negative fetal outcomes, such as the finding that the fetus has moved to the abdomen and that free fluid exists in the abdomen in ultrasound, and the absence of fetal heartbeat, the maternal prognosis associated with second-trimester ruptures was found to be better than that of the third-trimester ruptures. Families should be informed that the rupture may recur in subsequent pregnancies, and the ones with completed fertility should be encouraged to use contraceptive methods..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Zeynep Kamil Women and Children's Diseases Training and Research Hospital, Clinical Researches Ethics Committee (Date: 07/12/2022, Decision No: 138).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Evaluation of cases with early repolarization on electrocardiogram and normal population in terms of laboratory and clinical results

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ABSTRACT

Aim: Early repolarization (ER) is a frequent indication, and it is important to correctly evaluate the effects of its benign and malignant forms in terms of prognosis. It was aimed to compare ER cases with the normal population in terms of multi-vessel disease, bypass and mortality.

Material and Method: This study comprised 776 patients aged 18 and older who admitted the emergency department between January 2015 and December 2020. 377 of these patients had ER in the electrocardiogram (ECG), 409 patients had normal ECGs and were added to the study as the control group. Age, gender, multi-vessel disease, by-pass and mortality relations of the patients were evaluated with angiographic findings.

Results: The mean age of 786 patients was 50.49±6.82 years, 372 (47.3%) were female, and the age range was 23-66 years ($p<0.001$). Of the cases, 110 (14%) were in the horizontal ER, 267 (34%) were in the ascending ER, and 409 (52%) were in the normal group. Multi-vessel disease was observed in 58 (7.4%) of all cases ($p<0.001$), while 19 (2.4%) had a by-pass attempt because angiography could not be cured ($p=0.001$). Of the cases with early repolarization, 176 (22.4%) were inferior, 112 (14.2%) were inferolateral, 77 (9.8%) were anterior, and a small number of them were 12 (1.5%) common ER types ($p<0.001$). Angiography was normal in 575 (73.2%) cases, left anterior descending artery was occluded in 65 (8.3%), circumflex artery was occluded in 73 (9.3%) and right coronary artery was occluded in 73 (9.3%) cases ($p<0.001$). Eighteen (2.3%) patients resulted in mortality in the 60-month follow-up of all cases. Of these, 9 (8.2%) were horizontal, 2 (0.7%) were asending, and 7 (1.7%) were in the normal population ($p<0.001$).

Conclusion: Electrocardiography can be a helpful method to evaluate interventional angiography, prognosis and mortality in both early repolarization cases and normal cases.

Keywords: Emergency department, early repolarization, angiography, multiple vessel disease, mortality

INTRODUCTION

In electrocardiography (ECG), early repolarization (ER) is characterized by a positive J wave that begins with a notch at the end of the R wave and is followed by an ST-segment elevation of at least 0.1 mV in at least two consecutive derivations. Early repolarization is common, with a prevalence between 1% and 24%. Although it is more prevalent in young, healthy, athletic individuals as they mature, its prevalence decreases with age (1,2). Early repolarization is a common ECG finding in the inferior, inferolateral, and precordial leads. While ER has been regarded a harmless ECG finding for many years, recent research indicates that it may have arrhythmogenic effects (3,4).

The massive amount of early repolarization patients are asymptomatic and, they have a lower risk of arrhythmia. Few patients are at high risk for arrhythmia; therefore, identifying these patients is a significant challenge. In reality, the majority of research have investigated ER model variants that enhance the risk of sudden death. ER pattern, which is regarded benign, and the presence of ST segment elevation and J waves on the electrocardiogram are considered clinically inconsequential (5,6). In both the general population and patients with idiopathic ventricular fibrillation, the horizontal/descending ST segment of early repolarization poses a greater risk. This horizontal/descending group is believed to be aggressive. Therefore, it is crucial to differentiate between the common benign ER and the rare malignant type (7,8).

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Although the current criteria for early repolarization are inadequate for assessing the likelihood of ventricular arrhythmias and sudden cardiac death in younger individuals, they may be effective in the elderly. In these patients, the genetic susceptibility to idiopathic sudden cardiac death is essential for considering ER. It was revealed that cases with ER in the lateral and inferior leads were more genetically predisposed. Differentiate early repolarization from asthenic structure, acute pericarditis, brugada syndrome, ST-elevation myocardial infarction, idiopathic ventricular fibrillation, and congenital short QT syndrome. Moreover, sudden cardiac death and syncope are induced by catecholaminergic polymorphic ventricular tachycardia and long QT syndrome, both of which should be evaluated in the differential diagnosis (9-11).

In electrocardiography, it is also important to compare early repolarization with the normal population, apart from the benign and malignant distinction. Thus, it is possible to determine which of the normal population and early repolarization cases has a higher rate of multi-vessel disease, morbidity, and mortality. In the study, we aimed to determine the demographic characteristics of the cases, electrocardiographic findings, laboratory values, coronary angiography results, multi-vessel disease, by-pass, morbidity and mortality relationships by considering these groups.

MATERIAL AND METHOD

The study was carried out with the permission of Sivas Cumhuriyet University Non-Invasive Clinical Research Ethics Committee (Date: 11.12.2019, Decision No: 2019-12/06). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Population

This observational retrospective analysis comprised 776 individuals older than 18 who attended to the emergency department from January 2015 to December 2020. While 377 of these individuals revealed early repolarization on the ECG, 409 patients with normal ECGs participated as the study's control group. Data, age, gender, hemogram and biochemistry laboratory values were created from ECG findings taken in the emergency department. Patients diagnosed with ER in the emergency department were included in the follow-up program. Concurrently, a patient with a normal ECG close to the age of the patient diagnosed with ER was added. When selecting patients from the normal population group, patients with no cardiac history, or those with stable angina and low risk in stable clinic for the first admission were included. These patients were followed up until angiography during their follow-up. The average follow-up period for all patients was 52 months. The absence of these and ER findings was valid at the first admission of the cases. However, the patients who underwent angiography for any reason (chest pain, shortness of breath, ECG finding suggestive of non-ER ischemic pathology or elective because of high risk) were selected as the normal group during this entire follow-up period. Absence of no cardiac history is valid for the first admission, absence of ER is valid for all applications. The selection criteria for these were the absence of ER and the absence of cardiac pathology in the application, which was considered as the first admission. The study was conducted in a hospital with a tertiary education and research program's emergency department.

Inclusion criteria: The cases were split into two groups. Newly diagnosed patients or individuals previously diagnosed with ER were included in the ER group. Included in the study were individuals having a normal ECG at the time of admission who comprised the typical population for the control group. During the follow-up of the patients, the cases who admitted to the emergency or cardiology outpatient clinic for causes such as chest pain and arrhythmia, were hospitalized in the service and subsequently had angiography were included in the study. Two certified doctors who were blind to the research assessed the early repolarization diagnosis findings. After resolving inconsistencies by consensus, these patients were added to the research.

Exlusion criteria: Patients who did not satisfy the diagnostic criteria for the ER, patients under the age of 18, patients whose laboratory results were not evaluated in the emergency department, patients who did not undergo angiography within the first 60 months of the follow-up period, and cases with a history of heart valve disease, rhythm disorder, or bypass procedure were excluded. Patients with cerebrovascular illness and subarachnoidal hemorrhage, chronic liver disease, chronic kidney failure, myocardial infarction, cancer, and concurrent aneurysm appearance, and electrolyte disorder were also excluded. High-risk individuals with a history of cardiac pathology and those who were clinically unstable were excluded from the trial for the normal population group.

Early repolarization classification: Four classes were created; 1- anterior (V1-V6), 2- inferior (DII,DIII,aVF), 3- inferolateral (DII,DIII,aVF,V3-6), and 4- common (DII,DIII,aVF,aVL,V1-6) (12). In addition, ER cases were divided into two groups as horizontal and ascending.

Tikkanen's study was taken as reference in the sample of patients with horizontal or ascending ER (1). When the ST segment rises by more than 0.1 mV within 100 ms following the J point, or when the ST segment remains raised by more than 0.1 mV throughout the ST segment, we call this a concave/rapidly ascending ST segment. Within 100 ms of the J point, a ST segment elevation of 0.1 mV was considered to be of the horizontal/descending type.

Coronary angiography: It is the gold standard imaging approach for diagnosing coronary artery stenosis. Cardiologists performed coronary angiography in the research for chronic chest pain and arrhythmias, to exclude or confirm a diagnosis of coronary artery disease, to assess prognosis, and to choose the best medication or interventional therapy. According to the angiography data of the cases, four groups were formed as normal, Circumflex Artery (Cx), Right Coronary Artery (RCA), and Left Anterior Descending (LAD). According to the results of coronary angiography, multi-vessel disease was defined as >50% stenosis in more than one coronary artery and >75% stenosis in the LAD or >50% stenosis of the right coronary, circumflex, and left main coronary arteries (13). In addition, the gensini score was used to show the extent of coronary artery involvement (14). A gensini score between 1 to 20 indicated mild coronary atherosclerosis, whereas a score more than 20 indicated severe. By-pass indications in our study were defined as failure to relieve angina with medical or invasive treatment, obstruction of the left main coronary artery (>50%) and unresponsiveness to invasive treatment.

Electrocardiography: Using the Cardiofax ECG-9132K at the patient's bedside, a 12-lead ECG was recorded (Nihon Kohden, Tokyo, Japan).

Our hospital's registry system contains diagnoses, admission times, contact details, as well as demographic, clinical, and laboratory data. In our study, the follow-up of the patients was done through the hospital registry system and the call system for those who did not have access to the hospital afterwards. The patients were followed up for 60 months after the first diagnosis of ER and the results were recorded.

Statistical Analysis

The data were analyzed using the SPSS 20 (SPSS Inc., Chicago, IL, USA) software package. When studying the normal distributions of the variables, the Kolmogorov-Smirnov test was used. Descriptive statistics for continuous variables were supplied as meanstandard deviation or median (minimum-maximum), whereas descriptive statistics for nominal variables were reported as the number of cases and percentage (%). The Kruskal-Wallis H test was performed to compare the groups because the data did not have a normal distribution. Chi-square analysis was used to look at the relationships between groups of nominal variables. To associate early repolarization morphology and type with factors, Spearman's rho analysis was used. When analyzing the data, values less than 0.05 were considered statistically significant.

RESULTS

The mean age of the 786 cases was 50.49±6.62 years, with 372 (47.3%) being female and a range of 23-66 years (p<0.001). When the patients were evaluated based on ER morphology and the normal population, the total cholesterol value was 145.73±36.16 mg/dL (p<0.001), high density lipoprotein (HDL) 33.44±6.98 mg/dL (p=0.007), mean corpuscular volume (MCV) 87.60±4.98 fL (p<0.001), mean platelate volume (MPV) 8.36±0.89 fL (p<0.001), gensini score was 18. The patients' mean follow-up length till angiography was 52.06±5.36 months (p=0.007). The horizontal group had 110 cases (14%), the ascending group had 267 cases (34%), and the normal group had 409 cases (52%) (**Table 1**).

Table 1. Comparison of the early repolarization group and the normal population in terms of age and laboratory data

	Early Repolarization Morphology		Normal Population	All Patients	p-value
	Horizontal	Ascending			
	n (%) 110 (14) mean±SD	n (%) 267 (34) mean±SD	n (%) 409 (52) mean±SD	n (%) 786 (100) mean±SD	
Age (year)	51.78±10.13	48.31±6.24	51.58±5.66	50.49±6.82	**<0.001**
CHO (mg/dl)	149.63±36.89	139.03±35.98	149.05±35.54	145.73±36.16	**<0.001**
TG (mg/dl)	116.15±36.41	109.98±31.24	120.17±48.50	116.14±41.94	0.183
HDL (mg/dl)	32.33±3.96	34.35±5.38	33.14±8.35	33.44±6.98	**0.007**
LDL (mg/dl)	97.20±28.64	93.49±25.95	95.03±30.14	94.81±28.56	0.443
VLDL(mg/dl)	25.31±9.23	24.86±8.12	26.25±12.85	25.65±10.97	0.976
MCV (fL)	86.75±5.32	86.94±4.77	88.27±4.94	87.60±4.98	**<0.001**
MCHC(g/dL)	33.01±0.99	33.09±1.09	32.87±0.77	32.97±0.93	0.266
RDW (%)	14.72±1.58	14.43±1.32	14.24±0.83	14.37±1.15	0.069
MPV(fL)	8.46±0.90	8.56±0.88	8.20±0.86	8.36±0.89	**<0.001**
GS	40.16±36.13	13.45±20.85	15.36±24.85	18.18±27.00	**<0.001**
GLU (mg/dl)	134.37±46.50	117.59±28.11	150.10±63.88	136.86±53.92	**<0.001**
TTA (minute)	51.05±5.61	52.81±5.32	51.84±5.27	52.06±5.36	**0.007**

SD; Stanndard Deviation, CHO: Cholesterol, TG: Triglyceride, HDL: High Density Lipoprotein, LDL: Low High Density Lipoprotein, VLDL: Very Low Density Lipoprotein, MCV; Mean Corpuscular Volume, MCHC: Mean Corpuscular Hemoglobin Concentration, RDW: Red cell distrubition width, MPV:Mean Platelate Volum, GS: Gensini Score, GLU: Glucose, TTA: Time to Angiography , p<0.05 significance level

While the total cholesterol value was 156.17±37.13 mg/dL in the common group, it was lower in the anterior (p=0.027). The mean MCV value was 87.60±4.98 fL (p=0.001). Red cell distribution width (RDW) was highest in the common group with a value of 15.30±1.32 %, similar results were observed with the other groups (p=0.033). MPV was found to be higher in the common group with 8.77±0.94 fL (p<0.001). Gensini score of 40.68±35.15% was highest in the inferolateral and lowest in the inferior group (p<0.001). Blood glucose was found to be high in the normal population with a value of 150.10±63.88 mg/dL (p<0.001). The follow-up time of both groups until angiography was not statistically significant (**Table 2**).

Of the 786 patients, 372 (47.3%) were female and 414 (52.7%) were male. Of these, 40 (36.4%) were horizontal, 113 (42.3%) ascending, and 219 (53.5%) were females in the normal population (p=0.001). Multi-vessel disease was present in 58 (7.4%) of all cases (p<0.001), and bypass was performed in 19 (2.4%) cases, since there was no response to invasive treatment at the end of angiography (p=0.001). Of the cases with early repolarization, 176 (22.4%) were inferior, 112 (14.2%) were inferolateral, 77 (9.8%) were anterior, and 12 (1.5%) were common types (p<0.001). Angiography findings were normal in 575 (73.2%) cases, left anterior descending artery was occluded in 65 (8.3%), circumflex artery in 73 (9.3%) and right coronary artery in 73 (9.3%) cases (p<0.001). Mortality was observed in 18 (2.3%) patients in the 60-month follow-up of all cases. Of these, 9 (8.2%) were horizontal, 2 (0.7%) ascending, and 7 (1.7%) were in the normal population (p<0.001, **Table 3**).

Table 2. Comparison of occlusion localization with age and laboratory data

	Occlusion Localization					p value
	Inferior n (%) 176 (22.4) mean±SD	Inferolateral n (%) 112 (14.2) mean±SD	Anterior n (%) 77 (9.8) mean±SD	Common n (%) 12 (1.5) mean±SD	Normal n (%) 409 (52) mean±SD	
Age (year)	48.44±7.62	51.42±7.89	48.75±7.11	46.50±8.71	51.58±5.66	**<0.001**
CHO (mg/dl)	141.64±34.92	142.78±39.05	140.09±36.44	156.17±37.13	149.05±35.54	**0.027**
TG (mg/dl)	108.78±32.82	116.03±33.66	110.39±30.99	125.08±35.54	120.17±48.50	0.187
HDL (mg/dl)	34.23±4.82	32.87±5.39	34.34±4.91	31.50±5.90	33.14±8.35	0.054
LDL (mg/dl)	94.24±28.13	94.94±25.48	96.05±25.62	86.67±27.45	95.03±30.14	0.896
VLDL(mg/dl)	24.92±8.95	25.31±8.68	24.22±6.75	28.17±8.66	26.25±12.85	0.770
MCV (fL)	86.87±4.81	87.13±5.16	86.71±4.77	85.92±5.98	88.27±4.94	**0.001**
MCHC(g/dL)	33.06±1.08	33.07±1.06	32.99±1.01	33.72±1.24	32.87±0.77	0.114
RDW (%)	14.43±1.36	14.57±1.51	14.52±1.35	15.30±1.32	14.24±0.83	**0.033**
MPV(fL)	8.45±0.92	8.63±0.84	8.53±0.86	8.77±0.94	8.20±0.86	**<0.001**
GS	12.20±19.12	40.68±35.15	13.96±21.84	19.25±37.40	15.36±24.85	**<0.001**
GLU (mg/dl)	116.28±25.64	132.23±40.23	121.86±42.88	126.58±37.98	150.10±63.88	**<0.001**
TTA (minute)	52.16±5.50	52.39±5.61	52.69±5.12	51.00±5.95	51.84±5.27	0.562

SD; Stanndard Deviation, CHO: Cholesterol, TG: Triglyceride, HDL: High Density Lipoprotein, LDL: Low High Density Lipoprotein, VLDL:Very Low Density Lipoprotein, MCV; Mean Corpuscular Volume, MCHC: Mean Corpuscular Hemoglobin Concentration, RDW: Red cell distrubition width, MPV:Mean Platelate Volum, GS: Gensini Score, GLU: Glucose, TTA: Time to Angiography, p<0.05 significance level

Table 3. Evaluation of variables in normal population and early repolarization groups

Variables	Early Repolarization Morphology		Normal Population	All Patients	p value
	Horizontal n (%) 110 (14)	Ascending n (%) 267 (34)	n (%) 409 (52)	n (%) 786 (100)	
Gender					**0.001**
Female	40 (36.4)	113 (42.3)	219 (53.5)	372 (47.3)	
Male	70 (63.6)	154 (57.7)	190 (46.5)	414 (52.7)	
MVD					**<0.001**
No	84 (76.4)	258 (96.6)	386 (94.4)	728 (92.6)	
Yes	26 (23.6)	9 (3.4)	23 (5.6)	58 (7.4)	
Bypass					**0.001**
No	102 (92.7)	265 (99.3)	400 (97.8)	767 (97.6)	
Yes	8 (7.3)	2 (0.7)	9 (2.2)	19 (2.4)	
Localization					**<0.001**
Inferior	47 (42.7)	129 (48.3)	0 (0)	176 (22.4)	
Inferolateral	46 (41.8)	66 (24.7)	0 (0)	112 (14.2)	
Anterior	13 (11.8)	64 (24)	0 (0)	77 (9.8)	
Common	4 (3.6)	8 (3)	0 (0)	12 (1.5)	
Normal	0 (0)	0 (0)	409 (100)	409 (52)	
Angiography					**<0.001**
Normal	51 (46.4)	223 (83.5)	301 (73.6)	575 (73.2)	
LAD	13 (11.8)	19 (7.1)	33 (8.1)	65 (8.3)	
Cx	23 (20.9)	13 (4.9)	37 (9.0)	73 (9.3)	
RCA	23 (20.9)	12 (4.5)	38 (9.3)	73 (9.3)	
Mortality					**<0.001**
No	101 (91.8)	265 (99.3)	402 (98.3)	768 (97.7)	
Yes	9 (8.2)	2 (0.7)	7 (1.7)	18 (2.3)	

MVD: Multi-vessel disease LAD: Left anterior descending Cx: Circumflex RCA: Right coronary artery, p<0.05 significance level

In the analysis of early repolarization cases according to localization; multi-vessel disease was observed in 26 (23.2%) patients in the inferolateral cases and 23 (5.6%) in the normal population (p<0.001). Again, 7 (6.3%) of the patients who underwent by-pass were in the inferolateral group and 9 (2.2%) were in the normal population (p=0.018). Ascending type was the highest in all groups (p<0.001). The most common right coronary artery was in 25 (14.2%) patients in the inferior group, and the circumflex artery was most common in 19 (17%) patients in the inferolateral group. In the anterior and common groups, the most common left anterior descending was in 16 (20.8%) and 5 (41.7%) cases, respectively (p<0.001). Of the total 18 mortality patients, 8 (7.1%) were in the inferolateral, and 7 (1.7%) were in the normal population group (p=0.002, **Table 4**).

When the relationship between multi-vessel disease, by-pass and mortality was examined, 58 (7.4%) of all cases had multi-vessel disease (p=0.274). 19 (32.8%) of these cases required by-pass procedure (p<0.001). Multi-vessel disease was present in 26 (44.8%) cases in the horizontal group, 9 cases (15.5%) in the ascending group, and 23 (39.7%) cases in the normal population group (p<0.001). In addition, this vascular disease was seen most frequently in the inferolateral, least in the inferior and common groups (p<0.001). Mortality was highest in multi-vessel disease with 14 (24.1%) cases (p<0.001). Multi-vessel disease was most commonly seen in occlusion of the circumflex artery. No relationship with gender was found in 19 patients who underwent by-pass procedure. Mortality was detected in 11 (57.9%) of the bypass patients (p<0.001, **Table 5**).

Correlation results of early repolarization with morphologies and localizations with variables was performed. Total cholesterol, MCV, RDW, MPV, gensini score, multi-vessel disease, age, gender, mortality, blood glucose, and angiography results were weakly correlated, either negative or positive, according to the variables (**Table 6**).

Table 6. Correlation of early repolarization morphology and localization with variables

Variables	Correlation			
	Morphology		Localization	
	r	p	r	p
Morphology	-	-	**0.903**	**<0.001**
Localization	**0.903**	**<0.001**	-	-
CHO	**0.075**	**0.035**	**0.103**	**0.004**
TG	0.038	0.285	0.065	0.068
HDL	-0.025	0.480	-0.065	0.070
LDL	-0.020	0.569	-0.005	0.894
VLDL	-0.008	0.828	-0.001	0.974
MCV	**0.145**	**<0.001**	**0.139**	**0.001**
MCHC	-0.051	0.153	-0.047	0.186
RDW	**-0.076**	**0.033**	-0.043	0.227
MPV	**-0.176**	**0.001**	**-0.164**	**<0.001**
GS	**-0.105**	**0.003**	0.006	0.876
MVD	**-0.138**	**<0.001**	-0.020	0.584
Bypass	-0.053	0.139	-0.002	0.945
Age	**0.079**	**0.028**	**0.146**	**<0.001**
Gender	**0.135**	**<0.001**	**-0.121**	**0.001**
Anjiography	**-0.088**	**0.014**	0.009	0.810
Mortality	**-0.084**	**0.019**	-0.025	0.493
GLU	**0.159**	**<0.001**	**0.212**	**<0.001**
TTA	-0.018	0.622	-0.042	0.239

CHO: Cholesterol, TG: Triglyceride, HDL: High Density Lipoprotein, LDL: Low High Density Lipoprotein, VLDL:Very Low Density Lipoprotein, MCV; Mean Corpuscular Volume, MCHC: Mean Corpuscular Hemoglobin Concentration, RDW: Red cell distrubition width, MPV:Mean Platelate Volum, GS: Gensini Score, GLU: Glucose, TTA: Time to Angiography, MVD: Multi-vessel disease, p<0.05 significance level

Table 4. Evaluation of the relationship of variables between occlusion localization groups

Variables	Localization					p value
	Inferior n (%) 176 (22.4)	Inferolateral n (%) 112 (14.2)	Anterior n (%) 77 (9.8)	Common n (%) 12 (1.5)	Normal n (%) 409 (52)	
Gender						**0.010**
Female	72 (40.9)	45 (40.2)	31 (40.3)	5 (41.7)	219 (53.5)	
Male	104 (59.1)	67 (59.8)	46 (59.7)	7 (58.3)	190 (46.5)	
MVD						**<0.001**
No	174 (98.9)	86 (76.8)	72 (93.5)	10 (83.3)	386 (94.4)	
Yes	2 (1.1)	26 (23.2)	5 (6.5)	2 (16.7)	23 (5.6)	
Bypass						**0.018**
No	174 (98.9)	105 (93.8)	77 (100)	11 (91.7)	400 (97.8)	
Yes	2 (1.1)	7 (6.3)	0 (0)	1 (8.3)	9 (2.2)	
Morphology						**<0.001**
Horizontal	47 (26.7)	46 (41.1)	13 (16.9)	4 (33.3)	0 (0)	
Ascending	129 (73.3)	66 (58.9)	64 (83.1)	8 (66.7)	0 (0)	
Normal	0 (0)	0 (0)	0 (0)	0 (0)	409 (100)	
Angiography						**<0.001**
Normal	138 (78.4)	78 (69.6)	51 (66.2)	7 (58.3)	301 (73.6)	
LAD	6 (3.4)	5 (4.5)	16 (20.8)	5 (41.7)	65 (8.3)	
Cx	7 (4)	19 (17)	10 (13)	0 (0)	73 (9.3)	
RCA	25 (14.2)	10 (8.9)	0 (0)	0 (0)	73 (9.3)	
Mortality						**0.002**
No	174 (98.9)	104 (92.9)	77 (100)	11 (91.7)	402 (98.3)	
Yes	2 (1.1)	8 (7.1)	0 (0)	1 (8.3)	7 (1.7)	

MVD: Multi-vessel disease LAD: Left anterior descending Cx: Circumflex RCA: Right coronary artery, p<0.05 significance level

Table 5. Evaluation of three vessel disease, bypass and mortality with variables

Variables	MVD		p value	Bypass		p value	Mortality		p value
	No n (%) 728 (92.6)	Yes n (%) 58 (7.4)		No n (%) 767 (97.6)	Yes n (%) 19 (2.4)		No n (%) 768 (97.7)	Yes n (%) 18 (2.3)	
Gender			0.274			0.589			0.168
Female	349 (47.9)	23 (39.7)		363 (47.3)	9 (47.4)		366 (47.7)	6 (33.3)	
Male	379 (52.1)	35 (60.3)		404 (52.7)	10 (52.6)		402 (52.3)	12 (66.7)	
Bypass			**<0.001**			-			**<0.001**
No	728 (100)	39 (67.2)		-	-		760 (99)	7 (38.9)	
Yes	0 (0)	19 (32.8)		-	-		8 (1)	11 (61.1)	
MVD			-			**<0.001**			**<0.001**
No	-	-		728 (94.9)	0 (0)		724 (94.3)	4 (22.2)	
Yes	-	-		39 (5.1)	19 (100)		44 (5.7)	14 (77.8)	
Morphology			**<0.001**			**0.001**			**<0.001**
Horizontal	84 (11.5)	26 (44.8)		102 (13.3)	8 (42.1)		101 (13.2)	9 (50)	
Ascending	258 (35.4)	9 (15.5)		265 (34.6)	2 (10.5)		265 (34.5)	2 (11.1)	
Normal	386 (53)	23 (39.7)		400 (52.2)	9 (47.4		402 (52.3)	7 (38.9)	
Angiography			0.092			0.412			0.114
Normal	539 (74)	36 (62.1)		564 (73.5)	11 (57.9)		565 (73.6)	10 (55.6)	
LAD	58 (8)	7 (12.1)		62 (8.1)	3 (15.8)		62 (8.1)	3 (16.7)	
Cx	63 (8.7)	10 (17.2)		70 (9.1)	3 (15.8)		69 (9)	4 (22.2)	
RCA	68 (9.3)	5 (8.6)		71 (9.3)	2 (10.5)		72 (9.4)	1 (5.6)	
Localization			**<0.001**			**0.018**			**0.002**
Inferior	174 (23.9)	2 (3.4)		174 (22.7)	2 (10.5)		174 (22.7)	2 (11.1)	
Inferolateral	86 (11.8)	26 (44.8)		105 (13.7)	7 (36.8)		104 (13.5)	8 (44.4)	
Anterior	72 (9.9)	5 (8.6)		77 (10)	0 (0)		77 (10)	0 (0)	
Common	10 (1.4)	2 (3.4)		11 (1.4)	1 (5.3)		11 (1.4)	1 (5.6)	
Normal	386 (53)	23 (39.7)		400 (52.2)	9 (47.4)		402 (52.3)	7 (38.9)	
Mortality			**<0.001**			**<0.001**			-
No	724 (99.5)	44 (75.9)		760 (99.1)	8 (42.1)		-	-	
Yes	4 (0.5)	14 (24.1)		7 (0.9)	11 (57.9)		-	-	
Total	728 (100)	58 (100)		767 (100)	19 (100)		768 (100)	18 (100)	

MVD: Multi-vessel disease LAD: Left anterior descending Cx: Circumflex RCA: Right coronary artery, p<0.05 significance level

DISCUSSION

Even though there are a lot of studies on early repolarization and few studies on angiography results, we could not find a study that distinguishes horizontal and ascending, multi-vessel disease, by-pass, morbidity and mortality relationship with angiography findings compared to the normal population. In our research, we demonstrated that proper identification and interpretation of ER morphologies can predict the prognosis of patients independently. Recent reports indicate that early repolarization may have a malignant nature and be connected with abrupt cardiac mortality, despite the fact that it was previously seen as a positive sign (15). Since the pathophysiology of early repolarization has not been completely elucidated, its link with malignant arrhythmias remains obscure. As demonstrated by a number of experimental experiments, ventricular repolarization rises due to an increase in transmural heterogeneity, which contributes to an elevation at the J point (16). Additionally, it is hypothesized that the autonomous system can trigger ER-related ventricular arrhythmias. Due to reports that it occurs more commonly during elevated vagal tone or after overeating (17,18). Moreover, conditions involving adrenergic stimulation can inhibit ER and associated arrhythmias (19).

In early repolarization, the shape of the ST segment in electrocardiography provides crucial diagnostic and prognostic information (1,20,21). In terms of determining prognosis and death, it may be crucial to distinguish between the common benign ER type and the rare malignant ER form (22). According to James et al. (23) 's study, ER is more prevalent in young persons and men, and this disparity may be caused by gonadal hormones. Antzelevitch et al. (24) established a categorization based on arrhythmia risk and ECG leads. Bening lateral precordial leads (V5, V6), which are commonly observed in athletic males and athletes, are considered as type 1, but moderate-risk inferior (II, III, aVF) or inferolateral leads are accepted as type 2. In type 3, it was acknowledged that the inferior, lateral, and right side leads posed a high relative danger. In their investigation of 504 male patients, Hünük et al. (25) discovered 34 ECGs with ER abnormalities, 19 of which were in the lateral lead.

The majority of patients in our study were male. Early repolarization occurred more commonly in the inferior lead, but the inferolateral leads displayed multi-vessel disease, bypass, and mortality. Multiple-vessel disease was identified at a rate of 4.1%, bypass surgery at a rate of 2.9%, and mortality at a rate of 4.7%.

The ascending pattern is distinguished by a benign form of early repolarization morphology, a 0.1 mV increase in the ST segment 100 ms after the J point, and increasing convergence of the ST segment with the T wave. In the malignant variant, ST segment elevation of 0.1 mV occurs within 100 ms of the J point and remains horizontal until the T wave begins (7,8). Wasserburger et al. (26) postulated that ER is a normal variety by defining it as an elevation of the ST segment accompanied by a downward concavity of the ST segment at the junction of the QRS complex. Tikkanen et al. (1) discovered that in the general population, an ER with a horizontal/descending ST segment is associated with a higher risk of sudden cardiac death than an ER with an ascending ST segment. According to Uberoi et al. (27)'s research, the ascending ST segment was not linked with ER mortality. In their research, Rosso et al. (8) discovered that ER with a horizontal ST segment is related with sudden cardiac death. In our study, bypass surgery, multi-vessel disease, and death in the horizontal pattern were shown to be significantly higher in the asending and normal populations. Furthermore, for all multi-vessels, the gensini score and occlusion were higher in the horizontal pattern. This demonstrates that the horizontal pattern is associated with a higher prevalence of coronary artery disease.

In their investigation, Moritz et al. (28) demonstrated a correlation between ER and cardiac mortality, which is more prevalent in the inferior leads. In the same study, ER was found to be strongly linked with death due to both cardiac and noncardiac causes. Similarly, our study revealed that the ER group had a greater mortality rate than the general population. Moreover, despite the fact that diverse variables were utilized in numerous research, we did not uncover a correlation between the variables and the angiography data of the patients. In more 50% of the horizontal ER formations with a malignant pattern, blockage was observed by angiography. However, the majority of the ascending form's angiographic findings were normal. In the normal population, the incidence of coronary artery blockage was comparable to that of ascending form. We believe this is because the horizontal form has a worse and more malignant prognosis than other kinds. There were no normal angiography results found in any of the study's subjects who died. This may indicate a relation between angiographic findings and mortality. As a result of angiography, circumflex artery stenosis was also more prevalent in patients. This could be attributed to the high rate of death in the inferior and inferolateral regions. The relation between angiographic results and early repolarization in cardiac leads may be attributable to the vascular feeding areas of the heart.

Obviously, there were limitations. The fact that it is a retrospective, single-center study stands out the most among these limitations. Also, due to the wide time interval, the difficulties in accessing the data, the drugs used by the patients, the absence of such information other than the registered additional diseases were other important limitations.

CONCLUSION

The fact that there was no significant difference between the ascending form of early repolarization and the normal population, and the high rate of obstruction and mortality on angiography in horizontal morphology may be a admonitory for the clinician. In addition, the morphology and location of early repolarization in the ECG serve as an indicator of the patients' prognosis, mortality, and angiographic abnormalities. We believe that more prospective investigations on the interaction between early repolarization, multi-vessel disease, and bypass are required..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Sivas Cumhuriyet University Non-Invasive Clinical Researches Ethics Committee (Date: 11.12.2019, Decision No: 2019-12/06).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article

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The effect of the pretreatment systemic immune-inflammatory index and C-reactive protein-to-albumin ratio on prognosis in pediatric patients with IgA vasculitis

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ABSTRACT

Aim: Indices related to blood parameters that indicate inflammation have recently started to be used in determining prognosis for many diseases. Visceral involvement is the most important factor affecting prognosis in immunoglobulin A vasculitis (IgAV). In this study, we sought to explore the value of the systemic immune-inflammation index (SII) and the C-reactive protein-to-albumin ratio (CAR) in predicting visceral involvement in IgAV.

Material and Method: Patients diagnosed with IgAV who had gastrointestinal, renal, testicular, or central nervous system involvement were considered patients with visceral involvement. All patients with IgAV were divided into two groups, those with and without visceral involvement. The effect of SII and CAR in predicting visceral involvement was evaluated by logistic regression analysis.

Results: We found that in the summertime, the percentage of patients with visceral involvement was significantly higher than those without visceral involvement (p=0.010). The rates of the recurrence of the disease, arthralgia, arthritis, and fever were significantly greater in those with visceral involvement (p=0.032, p<0.001, p=0.027, and p=0.019, respectively). SII, CAR, and neutrophil-to-lymphocyte ratio (NLR) values were significantly higher in the patients with visceral involvement (p=0.017, p=0.046, and p=0.008, respectively). The results of the univariate analysis showed that the SII and NLR were significant predictors of visceral involvement (OR: 1.001, 95% CI: 1.000-1.001, p=0.036; OR: 1.344, 95% CI: 1.053-1.715, p=0.018, respectively). We found that NLR was of greater value than SII in terms of predicting visceral involvement.

Conclusion: SII can be a valuable indicator for predicting visceral involvement in IgAV. However, CAR was not found significant in predicting visceral involvement.

Keywords: IgA vasculitis, inflammation, prognosis

INTRODUCTION

Immunoglobulin A vasculitis (IgAV) is the most common form of systemic vasculitis in children. It mainly affects small vessels with a deposition of polyclonal Ig A complexes in vessel walls. Its clinical manifestations involve skin rash, arthralgias and/or arthritis, gastrointestinal (GI) tract symptoms, and renal symptoms. Neurological and other organ involvement can also be seen throughout the course of IgAV (1). Although the main trigger that causes the disease is unknown, factors such as infection, vaccination, and medications are implicated in individuals with genetic predisposition (2,3). The prognosis of IgAV is usually good and self-limiting while the two main types of involvement, GI (51–56%) and renal (30–54%) involvement, can seriously threaten the lives of patients (4,5). The involvement of the central nervous system (CNS), lungs, and male genital tract are also rare visceral involvements that can lead to serious complications. The most common GI symptom in IgAV is abdominal pain, which is caused by the submucosal hemorrhage and edema of the intestinal wall. The most serious GI complication is intussusception, affecting 3-4% of patients. Renal involvement may be in the form of asymptomatic microscopic hematuria, macroscopic hematuria, mild proteinuria, and nephrotic or nephritic syndrome. End-stage renal failure is seen in 2-5% of children (6). While skin and joint involvement in IgAV usually does not require immunosuppressant treatment,

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GI, renal, testicular, CNS, and other rare visceral involvement cases require treatment with corticosteroids and other immunosuppressant drugs (7,8).

Since visceral involvement is the main form of involvement determining treatment and prognosis, studies aiming to predict visceral involvement in IgAV are needed. Inexpensive and easily accessible laboratory parameters that can be used to assess the severity of systemic inflammation have been used in recent years to predict prognosis in many diseases. Neutrophils and lymphocytes, the two main cellular components of the immune system, reflect both ongoing inflammation and the activation of the immunomodulatory pathway. Like neutrophils, platelets produce important cytokines that play a role in inflammatory diseases. The neutrophil-to-lymphocyte ratio (NLR) is the most frequently reported parameter in the literature (9-11). In recent years, a new systemic immune-inflammation index (SII) (neutrophils x platelets/lymphocytes) based on lymphocyte, neutrophil, and platelet counts has been developed, and SII has been shown to be a potential prognostic indicator, especially in patients with malignancies (12). There are a limited number of studies related SII in rheumatic diseases (13-15). C-reactive protein (CRP) is a widely used acute phase protein that is regulated by proinflammatory cytokines. On the other hand, serum albumin is the most important serum protein in the human body, and inflammation causes hypoalbuminemia due to the reduced synthesis and increased catabolism of albumin (16,17). In comparison to CRP or albumin alone, the CRP-to-Albumin ratio (CAR), a newly introduced inflammation-based risk index, has been demonstrated to better reflect inflammatory status, and thus, the prognosis in patients with acute medical illness and malignancies (18,19). These indices have also been reported to predict prognosis in Behcet's disease and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (20,21).

Previous studies have used NLR to predict visceral involvement, which determines prognosis in patients with IgAV, but SII and CAR have not been evaluated. The aim of this study was to evaluate the role of these newly developed indices in predicting visceral involvement in IgAV.

MATERIAL AND METHOD

Study Design and Patient Selection

The demographic, clinical, and laboratory data of all patients diagnosed with pediatric IgAV in the Pediatric Rheumatology outpatient clinic between January 2017 and January 2020 were retrospectively obtained from patient files and the computer information system. The patients were diagnosed with IgAV according to the Ankara 2008 criteria, which were verified by the European League against Rheumatism, the Pediatric Rheumatology International Trials Organization, and the Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) (22,23). The diagnosis of IgAV is based on the presence of purpura (palpable) or petechiae (without thrombocytopenia) with lower extremity predominance (mandatory criterion) plus at least one of the following four features: (1) abdominal pain, (2) arthritis or arthralgia, (3) leukocytoclastic vasculitis or proliferative glomerulonephritis with predominant deposition of IgA in histology, and (4) renal involvement (hematuria, red blood cell casts, or proteinuria). Recurrence was defined as the presence of a fresh episode after a period of at least 3 months without symptoms (22).

Patients with additional chronic diseases (e.g., congenital heart disease, diabetes, autoimmune disease, hematological disease), BMI>30, acute infection, medication use, and those who did not attend follow-ups regularly were excluded from the study.

The patients were divided into two subgroups according to the presence of visceral involvement. Medical records were reviewed for demographic data, clinical symptoms, time of admission, and laboratory findings.

The study was carried out with the permission of Selçuk University Ethics Committee (Date: 02.09.2020, Decision No: 2020/333). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Definitions and Data Collection

GI involvement was defined as severe abdominal pain with or without GI bleeding indicators such as positive occult blood in stool, melena, or hematochezia. Renal involvement was defined as the presence of hematuria (>5 red blood cells per high-power microscopic field in a centrifuged specimen) and/or non-nephrotic proteinuria (in spot urine, protein/creatinine ratio >0.2 or 4-40 mg/m2/per hour), or nephrotic syndrome (in spot urine, protein/creatinine ratio >2 or 40 mg/m2/per hour). IgAV involving the male genital organs was defined as the development of epididymitis, orchitis, or hematoma around the testicle and testicular torsion in ultrasound accompanied by edema and pain in the scrotum and testicle. Scrotal involvement was confirmed by ultrasound (USG) in all patients with complaints. IgAV-associated CNS involvement was defined as patients with typical rash and accompanying neurological symptoms and signs in the absence of other primary neurological diseases. Magnetic resonance imaging (MRI) and diffusion MRI were used in patients thought to have CNS involvement. GI involvement, renal involvement, and CNS involvement were considered visceral involvement (24).

The infectious trigger was defined as a viral or bacterial infection within the last 2 weeks and a drug trigger as medication used within the last 1 week.

Leukocyte count, neutrophil count, lymphocyte count, platelet count, CRP levels, albumin levels, erythrocyte sedimentation rate (ESR), urine analysis, and fecal occult blood tests at the time of admission were retrospectively recorded. NLR was calculated as the ratio of the neutrophil count to the lymphocyte count. SII was calculated using the formula: neutrophil (K/uL) count X platelet (K/uL) count / lymphocyte (K/uL) count, and CAR was calculated by the ratio of C-reactive protein (mg/L) to albumin (g/dL) (12,18,25). All blood parameters were measured in the same laboratory with a regularly calibrated device.

Statistical Analysis

The normality of the distribution of the continuous data was determined using the Kolmogorov-Smirnov test. The normally distributed continuous variables are expressed as mean±standard deviation (SD), and the non-normally distributed variables are expressed as median and interquartile range (Q1-Q3). Differences between independent variables were compared using Student's t-test or the Mann-Whitney U test. The categorical data were compared using the chi-squared ($\chi 2$) test. Logistic regression analysis was used to identify variables associated with visceral involvement in IgAV. Receiver operating characteristic (ROC) curve analysis was used to determine the sensitivity and specificity of SII to predict visceral involvement. All statistical analyses were performed using the Stata/MP 16 (Stata Corporation, College Station, Texas, USA) software. A p-value below 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics of 123 Patients with IgAV

Of the 181 screened patients, 123 satisfied the inclusion criteria and were enrolled. While visceral involvement was not detected in 70 (56.9%) patients with IgAV, visceral involvement was present in 53 (43.0%). The mean age of all patients was 8.5±3.3 years. Seventy-one patients (57.7%) were female, and 52 patients (42.3%) were male. Although summer was the most common season for the condition, with 36 (29.3%) patients, no statistically significant difference was found among the seasons (p=0.214). While 95.1% of the patients had rash only on the lower extremities, 6 patients (4.9%) had rash all over the body. Thirty-eight patients (30.9%) had arthritis. Ankle arthritis was the most common localization in 25 patients (20.3%). GI involvement was seen in 50 patients (40.7%), renal involvement was seen in 19 patients (15.4%), CNS involvement was seen in 2 patients (1.6%), and testicular involvement was seen in 1 patient (0.8%). One patient was operated on for intussusception. IgAV recurred in 2 patients (1.6%). Complete recovery was observed in all patients (with or without visceral involvement).

Comparison of Baseline Characteristics and Laboratory Indices

A comparison of the demographic, clinical and laboratory data of patients with and without visceral involvement is shown in **Table 1**. There was a significant difference between patients with visceral involvement and patients without visceral involvement in terms of the season of occurrence (p=0.018). According to the x^2 trend analysis performed to determine the origin of this difference, visceral involvement was more likely to be seen in the summer season. In the post hoc test, the number of patients with visceral involvement in the summer season was significantly higher than those without visceral involvement (Z=3, x^2 =9, p=0.010). Among the clinical findings, the rates of arthralgia, arthritis, fever, and disease recurrence were significantly higher in the group with visceral involvement compared to the group without visceral involvement (p<0.001, p=0.027, p=0.027, p=0.019, and p=0.032, respectively).

In the laboratory examinations, CRP values were significantly higher in the group with visceral involvement than in the group without (p=0.048). The mean NLR, SII, and CAR values were significantly higher in the group with visceral involvement compared to the group without visceral involvement (p=0.008, p=0.046, and p=0.017, respectively).

Hospitalization and systemic steroid use (oral and iv pulse steroid) rates were significantly higher in the group with visceral involvement, as expected (p<0.001 in 3 patients).

Prognostic value of NLR, CAR, and SII

Univariate and multivariate logistic regression analyses were performed to determine the value of the SII, CAR, and NLR parameters in predicting visceral involvement. According to the results of the univariate regression analysis, SII and NLR were effective in predicting visceral involvement (OR: 1.001, 95% CI: 1.000-1.001, p=0.036; OR: 1.344, 95% CI: 1.053-1.715, p=0.018, respectively). CAR was not significant in predicting visceral involvement. When the three indices were evaluated together in the multivariate logistic regression analysis, NLR was found to be more significant in predicting visceral involvement compared to the other indices (OR:2.286, 95% CI:1.159-4.506, p=0.017) (**Table 2**).

Table 1. Comparison of baseline characteristics and laboratory indices

Variables	All patients with IgAV n=123	IgAV without visceral involvement n=70	IgAV with visceral involvement n=53	Tp-value
Age, mean±SD	8.55±3.35	8.47±3.47	8.65±3.21	0.77
Sex				0.34
Male, (n, %)	52 (42.3%)	27 (38.6%)	25 (47.2%)	
Female, (n, %)	71 (57.7%)	43 (61.4%)	28 (52.8%)	
Seasons				0.018
Spring, (n, %)	34 (27.6%)	21 (30.0%)	13 (24.5%)	
Summer, (n, %)	36 (29.3%)	†14 (20.0%)	†22 (41.5%)	
Fall, (n, %)	32 (26.0%)	23 (32.9%)	9 (17.0%)	
Winter, (n, %)	21 (17.1%)	12 (17.1%)	9 (17.0%)	
Infectious trigger, (n, %)	72 (58.5%)	45 (64.3%)	27 (50.9%)	0.14
Drug trigger, (n, %)	21 (17.1%)	10 (14.3%)	11 (20.8%)	0.35
FMF cooccurrence, (n, %)	4 (3.3%)	1 (1.4%)	3 (5.7%)	0.19
Family history of rheumatic disease, (n, %)	1 (0.8%)	1 (1.4%)	0 (0.0%)	0.38
Family history of IgAV, (n, %)	3 (2.4%)	3 (4.3%)	0 (0.0%)	0.13
Clinical Manifestations				
Disease recurrence, (n, %)	4 (3.3%)	0 (0.0%)	4 (7.5%)	0.032
Rash				0.23
Lower extremity, (n, %)	117 (95.1%)	68 (97.1%)	49 (92.5%)	
Whole Body, (n, %)	6 (4.9%)	2 (2.9%)	4 (7.5%)	
Scrotal Rash, (n, %)	3 (2.4%)	2 (2.9%)	1 (1.9%)	0.73
Edema				0.10
Face, (n, %)	30 (24.4%)	13 (18.6%)	17 (32.1%)	
Hands-Feet, (n, %)	92 (74.8%)	57 (81.4%)	35 (66.0%)	
Arthralgia, (n, %)	75 (61.0%)	33 (47.1%)	42 (79.2%)	<0.001
Arthritis, (n, %)	38 (30.9%)	16 (22.9%)	22 (41.5%)	0.027
Myalgia, (n, %)	70 (56.9%)	38 (54.3%)	32 (60.4%)	0.50
Fever, (n, %)	4 (3.3%)	0 (0.0%)	4 (7.5%)	0.019
Hospitalization, (n, %)	33 (26.8%)	8 (11.4%)	25 (47.2%)	<0.001
Treatment				
Anti-Histaminic, (n, %)	113 (91.9%)	68 (97.1%)	45 (84.9%)	0.014
NSAID, (n, %)	85 (69.1%)	48 (68.6%)	37 (69.8%)	0.88
Pulse Steroid, (n, %)	13 (10.6%)	1 (1.4%)	12 (22.6%)	<0.001
Oral Steroid, (n, %)	17 (13.8%)	1 (1.4%)	16 (30.2%)	<0.001
Laboratory features				
CRP (mg/dl), Median (Q1-Q3)*	12 (2-11.9)	6.8 (2-11)	9.2 (2-15.7)	0.048
ESR (mm/h), Mean±SD	18.53±15.00	18.03±11.92	19.15±18.22	0.69
WBC (K/uL), Mean±SD	9.35±3.47	9.00±2.72	9.77±4.19	0.23
HB (g/dl), Mean±SD	12.85±1.22	12.95±1.17	12.74±1.29	0.36
RDW (%), Mean±SD	13.69±1.23	13.52±1.11	13.91±1.34	0.14
MPV (fL), Mean±SD	7.64±0.81	7.71±0.78	7.55±0.83	0.27
Cre (mg/dL), Mean±SD	0.41±0.13	0.41±0.12	0.41±0.14	0.86
AST (U/L), Mean±SD	29.25±26.32	26.55 ±8.38	31.54±35.46	0.65
ALT (U/L), Mean±SD	14.60±7.88	14.11±6.68	15.20±9.21	0.47
Indices				
NLR, Mean±SD	2.56±2.18	2.07±1.24	3.14±2.84	0.008
CAR, Mean±SD	4.35±8.84	2.63±3.78	6.22±11.94	0.046
SII, Mean±SD	958.51 ±970.74	749.22±621.95	1197.70±1220.24	0.017

SD: Standard deviation, NSAID: Nonsteroidal anti-inflammatory drug, FMF: Familial Mediterranean fever, WBC: White blood cell, HB: Hemoglobin, RDW: Red cell distribution width, MPV: Mean platelet volume, Cre: creatinine, AST: Aspartate amino transferase, ALT: Alanine amino transferase, ESR: Sedimentation, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, CAR: CRP to albumin ratio, SII: Systemic immune-inflammation index.
† There was a significant difference between the two groups in terms of seasonal characteristics (p=0.018). Chi-squared trend analysis revealed that this difference occurred in the summer season, and post hoc analysis showed that IgAV with visceral involvement was significantly higher in the summer season compared to patients without visceral involvement (Z=3, 2=9, p=0.010). *Mann-Whitney U test

Table 2. Independent predictors of visceral involvement in IgAV

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
Age	1.016	0.913-1.130	0.770			
Sex	1.421	0.690-2.929	0.340			
NLR	1.344	1.053-1.715	0.018	2.286	1.159- 4.506	0.017*
CAR	1.065	0.990-1.145	0.087	1.059	0.978-1.148	0.154
SII	1.001	1.000-1.001	0.036	0.998	0.998-1.000	0.119

*p<0.05, OR: Odds ratio, CI: Confidence interval

The area under the curve (AUC) value in predicting visceral involvement in IgAV was 0.703 (p=0.036, sensitivity: 80%, specificity: 46%) for SII (**Figure 1**). The cut-off value of SII was found to be 677.14. The AUC value in predicting visceral involvement in IgAV was 0.711 (p=0.027, sensitivity: 60%, specificity: 54%) for NLR (**Figure 2**). The cut-off value of NLR was found to be 1.89.

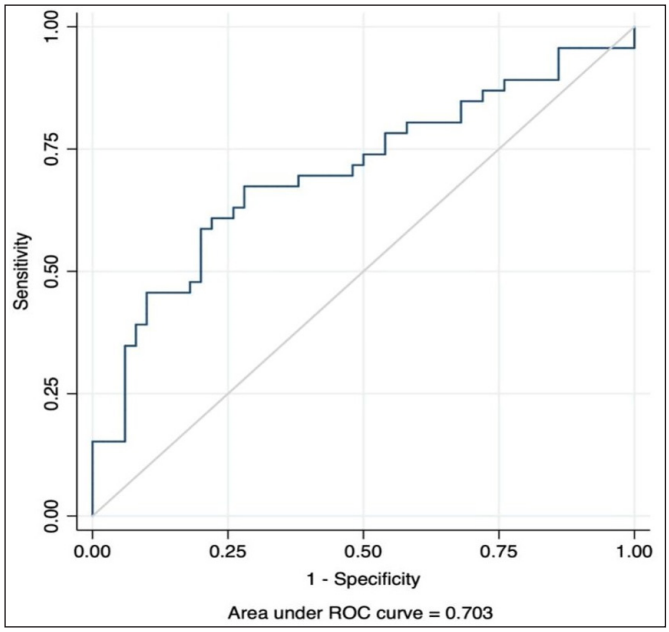

Figure 1. Receiver-operating characteristic curves of SII in predicting visceral involvement in IgAV

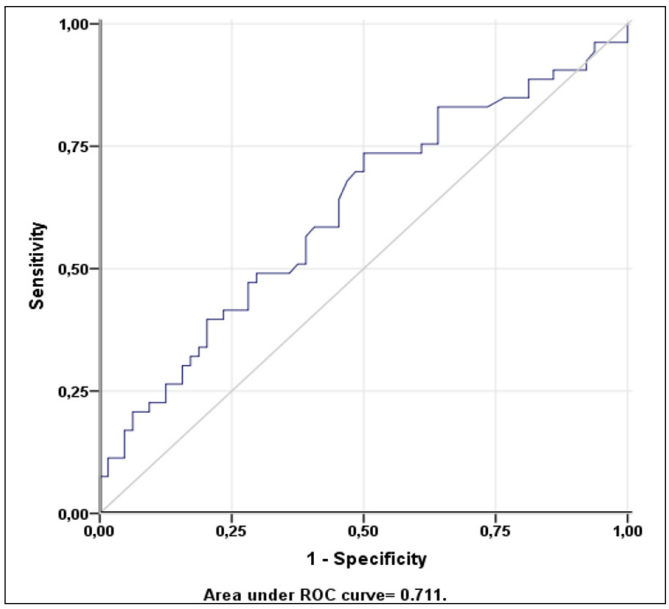

Figure 2. Receiver-operating characteristic curves of NLR in predicting visceral involvement in IgAV

DISCUSSION

IgAV is a benign form of vasculitis that is seen particularly in childhood. Although a complete cure is possible, GI system, renal system, CNS, and testicular involvement during the course of this disease can lead to the involvement of visceral organs and potential morbidity if untreated (26). It is because of this that many studies have been carried out for predicting visceral organ involvement, particularly in the GI and renal systems, using various indices and laboratory parameters. However, as far as we know, in recent studies, no assessment has been made regarding the place of SII and CAR in determining prognosis in illnesses such as cancer, MI, Behcet's Disease, and ANCA-associated vasculitis (15,19,20,27-29). We found in our study that CAR was not significantly effective in determining prognosis for visceral involvement in patients with IgAV, but SII was a significant predictor of visceral involvement. Predictability in this case, however, was weaker than the degree of predictability obtained with the more frequently used NLR parameter. At the same time, we found that visceral involvement was more prevalent in patients in the summer months. The clinical findings of fever, arthralgia, arthritis, and recurrent disease were found to be associated with visceral involvement.

It has been reported in previous studies that the prognosis of IgAV worsens with increasing age (30). In the present study, we found no significant difference in age between the patients with visceral involvement and those who had no visceral involvement. Male dominance in IgAV has been reported in many studies, although there are those that have reported the opposite (31-34). In our study, too, the female sex was predominant. However, we could not find any correlation between sex and visceral involvement in our sample.

While the pathogenesis of IgAV has not yet been discovered, it is considered that genetic predisposition and various environmental factors are instrumental in the development of the disease (35). A history of infection prior to the disease was found at a rate of 37-49% (3). In our study, this rate was much higher. Although it has been reported in some studies that the disease is more prevalent in the fall and winter seasons, our study revealed no significant difference in terms of seasonal occurrence (3,36,37).

In recent years, in fact, numerous studies have been conducted for the purpose of predicting GI and renal involvement, as these types of involvement are the main causes of morbidity in IgAV. Advanced age, persistent purpura, severe GI involvement, reduced levels of Factor XIII, and relapses have been associated with nephritis (38,39,40). A study carried out in Turkey indicated that severe GI involvement could be associated with arthralgia/arthritis, subcutaneous edema, and nephritis (3). In our study, we classified patients with renal and GI involvement and other rare visceral involvements under a single category and divided them into those with and without visceral involvement. To our knowledge, there is no other

study in the literature that has used this perspective to assess patients. Accordingly, we discovered that from a clinical point of view, fever, arthralgia/arthritis, and recurrent illness could be associated with visceral involvement.

It is believed that systemic inflammation plays a role in the pathogenesis of many diseases (12,41). Since IgAV is a disease that runs its course with IgA-related inflammation along the walls of the blood vessels, there are various studies that have worked with inflammatory markers and indices for the purpose of predicting prognosis. In previous studies, researchers have mostly focused on neutrophils and lymphocytes as it is thought that these primary inflammatory cells play an important role in the pathogenesis of IgAV (42). Neutrophils and lymphocytes are two main cellular components of the immune system and signal both ongoing inflammation and the activation of immunomodulatory pathways (43). Since neutrophils play a role in lymphocyte regulation in inflammation, NLR has been used in studying various autoimmune and inflammatory diseases (44). Moreover, when platelets are activated, they are considered to be important components of the inflammatory response that results from the secretion of many inflammatory factors such as chemokines, cytokines, and coagulation factors (45). Previous studies have shown that the NLR value is higher in patients with renal and systemic involvement in IgAV than in patients without renal and systemic involvement (3,22,44,46). In recent years, SII, which uses neutrophils, platelets, and lymphocytes together, and the CAR index, which evaluates CRP and albumin together, have attracted the attention of researchers and been used to evaluate disease pathogenesis and severity of inflammation in many diseases (15,19,21,27-29,47-50). Since CAR provides the opportunity to evaluate increased CRP and decreased serum albumin together in chronic inflammation, it has provided researchers with a two-way perspective.

SII has been found to be effective in predicting severe illness in AAV and Behcet's Disease, mortality in COVID-19, and advanced stages of colorectal cancer (21,29,48,51). Researchers have reported that CAR is helpful in predicting prognosis in myocardial infarction, sepsis, AAV, and hepatocellular cancer (19,20,29,50). On the other hand, we did not come across any study in the literature that reported the use of these indices in determining prognosis in IgAV. Since the most important factor affecting the prognosis of the disease in the short term is visceral organ involvement, this is how we approached the illness. While we found that CAR did not have a statistically significant value in predicting visceral involvement, we saw that SII was a tool that could be used to predict this condition. Because CAR indicates more likely severe and chronic inflammation, it may not be an effective predictor in IgAV, a disease that presents with visceral involvement in the acute stage. To be able to make the right decisions, there is a need for more studies to be conducted in this yet untouched area. The results of our study showed that NLR was superior to SII in predicting visceral involvement, and we found NLR to be the strongest indicator. Although SII, which is an indicator of three parameters of inflammation, did not yield the results we expected, and since ours is the first study on this subject as far as we know, it is reasonable to consider that more studies in the field will in time reveal the actual value of SII.

The present study had a few limitations. Most importantly, it was a retrospective, single-center study. Therefore, a large-scale prospective validation study is required to validate the results of this study.

CONCLUSION

Indices that are calculated through the use of simple inflammation markers are increasingly being used to determine prognosis in many illnesses. SII is a tool that has only newly begun to be employed, and therefore, its prognostic value has not been exactly understood yet. In IgAV, the most important factor affecting prognosis is visceral involvement. SII may be a valuable predictor of visceral involvement. Since there is no previous study on this subject, more comprehensive studies need to be conducted to unveil the value of this index.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University Ethics Committee (Date: 02.09.2020, Decision No: 2020/333).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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R-Spondin1 and tumor necrosis factor-alpha in infertile women with polycystic ovary syndrome: relationships with insulin resistance and other parameters

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ABSTRACT

Aim: To evaluate the relationship between R-spondin1 (RSPO1) and Tumor Necrosis Factor-Alpha (TNF-α) levels with insulin resistance (IR) and other parameters in infertile women with polycystic ovary syndrome (PCOS).

Material and Method: This case-control prospective observational study was carried out on 84 patients admitted to the University of Health Sciences Etlik Zübeyde Hanım Training and Research Hospital Gynecology and IVF Clinic and Medistate Hospital Gynecology and IVF Clinic between September 2020 and June 2021. Women aged 18-36 years diagnosed with infertility and PCOS constituted the PCOS group. Women who were diagnosed with infertility but not PCOS formed the control group. Cases were divided according to their body mass index (BMI) values into obese (BMI≥25) and non-obese (BMI<25) groups.

Results: The mean age of the study group was 26.9±5.37 years. RSPO1 and TNF-α levels were higher in PCOS patients ($p<0.001$). Hip circumference (HC) was found to be higher in those with a diagnosis of PCOS ($p<0.001$). The group with the highest waist-to-hip ratio (WHR) was the obese-PCOS group ($p<0.001$). Glucose, insulin, and homeostatic model assessment for IR (HOMA-IR) levels were the highest in the obese-PCOS group ($p<0.001$). A positive correlation was found between RSPO1 and TNF-α ($r=0.944$, $p<0.001$). There was a positive correlation between the hip circumference and RSPO1 ($r=0.255$, $p=0.0019$) and TNF-α ($r=0.\ 0.278$, $p=0.011$). There were positive correlations between blood glucose and RSPO1 ($r=0.343$, $p=0.001$) and TNF-α levels ($r=0.312$, $p=0.004$) and between insulin and RSPO1 (r value=0.577, $p<0.001$) and TNF-α levels ($r=0.569$, $p<0.001$). HOMA-IR values were also found to correlate with RSPO-1 and TNF-α levels ($r=0.619$ and 0.608, $p<0.001$).

Conclusion: It can be concluded that RSPO1 and TNF-α levels may guide the assessment and management of IR and diabetes risk in infertile women with PCOS.

Keywords: Polycystic ovary syndrome, R-Spondin1, tumor necrosis factor-alpha, obesity, insulin resistance

INTRODUCTION

Infertility refers to failure to conceive after 12 months of regular unprotected sex, and almost 8-12% of couples worldwide suffer from infertility (1). Polycystic Ovary Syndrome (PCOS) is the most prevalent endocrine dysfunction in childbearing-age women, which is also the most common cause of anovulatory infertility (~%90) (2,3). PCOS is a multifaceted disease characterized by polycystic ovaries, clinical or biochemical hyperandrogenism, and chronic oligo/anovulation (3). When women with PCOS become pregnant, they have a higher risk of pregnancy-related diabetes mellitus (DM) and pregnancy complications than pregnant women without PCOS; the former creates a significant burden on healthcare (3).

Obesity is one of the common complications in patients with PCOS (4). It has been reported that obesity is associated with the exacerbation of metabolic and ovulatory dysfunction associated with PCOS, and weight loss restores ovulation and reduces hyperandrogenism (5). Increased waist-to-hip circumference (WHC) ratio and abdominal obesity decrease the menstrual frequency and fertility in relation to insulin resistance (IR) (3). One

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of the characteristics of PCOS is IR with compensatory hyperinsulinemia (6). Hyperinsulinemia causes an increase in ovarian androgen biosynthesis in vitro and in vivo, in addition to a decrease in sex hormone binding globulin (SHBG) protein synthesis in the liver, which causes an increase in the free androgens bioavailability (6). This production increase of local ovarian androgen, which is increased by hyperinsulinemia, leads to early follicular atresia and anovulation, which impairs the ability to conceive (3).

In some previous in-vivo studies, it has been reported that R-spondin1 (RSPO1) regulates food intake and increases insulin secretion (7-9). RSPO consists of four proteins (RSPO1–4), secreted as potent enhancers of Wnt/β-catenin signaling. The signaling system of wnt/β-catenin is essential in maintaining adult stem cells, self-renewal, and embryonic development. (9). It has been shown that increasing serum RSPO1 level is significantly related to infertility, obesity and IR, although the exact mechanisms are unknown (10,11). The potential link between PCOS and the increase in pro-inflammatory cytokine Tumor Necrosis Factor-Alpha (TNF-α) levels is particularly important because TNF-α has a multifaceted effect on the functions of ovarian, such as corpus luteum regression, ovulation, and follicular growth and ovaries contain TNF-α receptors and produce TNF-α (12). Therefore, TNF-α levels are variable in PCOS, contributing to the disease's short-term ovarian dysfunction and hyperandrogenic state, and may be associated with long-term effects on the ovaries and other organs.

This study evaluates the relationship between RSPO1 and TNF-α levels with IR and other parameters in infertile women with PCOS.

MATERIAL AND METHOD

This case-control prospective observational study was carried out on 84 patients admitted to the University of Health Sciences Etlik Zübeyde Hanım Training and Research Hospital Gynecology and IVF Clinic and Medistate Hospital Gynecology and IVF Clinic between September 2020 and June 2021.

The procedures were conducted according to the Clinical Research and Ethics Committee regulations and the Helsinki Declaration. The study was carried out with the permission of the Research Ethics Committee of University of Health Sciences Etlik Zübeyde Hanım Training and Research Hospital (Date: 09.09.2020, Decision No: 2020/128). All the patients were given signed informed consent.

The PCOS group consisted of women aged 18-36 with a diagnosis of infertility and PCOS who applied to the clinic within the study period. Women admitted to the infertility clinic who were not diagnosed with PCOS formed the control group. Women in the PCOS and control groups were divided into obese (BMI≥25) and non-obese (BMI<25) groups according to body mass index (BMI) values. The BMIs of the obese and non-obese groups in the study and control groups were not significantly different. Patients who participated in the study, had a diagnosis of PCOS, and had not been able to conceive for at least one year between the ages of 18-36, were included in the PCOS group. Patients excluded from the study had diabetes mellitus, thyroid dysfunction, hypertension, impaired glucose tolerance, hypercortisolism, hyperprolactinemia or any endocrinopathy, used oral contraceptives or any drugs altering hormone, insulin, or lipid metabolism three months before the study. Patients with vitamin B6 or B12 deficiency or those who used vitamin supplements within the last six months to treat previously diagnosed deficiency (because it may have affected homocysteine metabolism) and smokers were not included in the study group.

Patients were diagnosed with PCOS based on meeting at least two of the 2003 Rotterdam Consensus criteria (13).

A routine clinical procedure (history, physical examination, ultrasonography (US), blood analysis, etc.) was performed. Venous blood samples were collected from all subjects in the morning after overnight fasting. Serum samples were obtained by centrifuging the venous blood samples for 10 minutes at 4000 rpm after the 30-minute coagulation period. Serum samples collected for biochemical and hormonal evaluation were examined in the biochemistry and hormone laboratory of Medistate Hospital.

BMI values were calculated by dividing the weight (kg) by the square of the height (m). Waist circumference, hip circumference, and waist-hip ratio (WHR) were determined. Patients' systolic and diastolic blood pressure values were measured and recorded with standardized devices.

SBP (mm-Hg) was measured by using the tail-cuff technique. DBP (mm-Hg) , AMH (ng/mL), LH (IU/L), FSH (mIU/mL), Estradiol (pg/mL), Free T4(ng/dL), Prolactin (µg/L), TSH (uIU/mL), LDL (mg/dL), HDL (mg/dL), Triglyceride (mmol/L), and Insulin (IU/mL) were measured by commercial enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN, USA). Total cholesterol (mg/dl) was measured by the cholesterol-oxidase method and Glucose (mmol/L) was measured by a glucometer.

The HOMA index is also used to evaluate insulin resistance. This index was calculated from the following formula using fasting serum glucose and insulin levels:

HOMA-IR = [Fasting Glucose (mg/dl) x Fasting Insulin (uU/ml)/22.5]

RSPO-1 and TNF-α measurements were performed with Human R-spondin-1 Enzyme-Linked Immunosorbent (ELISA) and TNF-α ELISA Kits (Reader Biotek ELx800). The ELISA quantitatively immunoassays human RSPO1 levels. The intra-assay coefficient of variation (CV) of the ELISA kit was 5.7% and the inter-assay CV of the ELISA Kit was 9.5% in our laboratory. Normal values for TNF-α were considered 75 +/- 15 pg/ml.

Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test determined the normal distribution. According to the normality of distribution, data are given as mean ± standard deviation or median. One-way variances (ANOVA) were used for normally distributed variables. Pairwise comparisons of these variables were performed with the Tukey or Tamhane test, depending on the homogeneity of variances. Kruskal Wallis test was used for non-normally distributed variables. The Bonferroni correction method was used for pairwise comparisons of these variables. Spearman correlation coefficients were calculated to evaluate relationships between variables. $p<0.05$ values accepted as statistically significant results.

RESULTS

The ages of the women in the study group ranged between 18-36, with a mean of 26.99±5.37 years. Waist circumference ($p<0.001$), BMI ($p<0.001$), and weight ($p<0.001$) were found to be higher in obese groups. Hip circumference was higher in those who were obese and those with a diagnosis of PCOS ($p<0.001$). The groups with the highest WHC ratio were obese women with PCOS and women in the obese control group, respectively ($p<0.001$). Systolic blood pressure was the lowest in the obese PCOS group ($p=0.013$).

As shown in **Figures 1-2** and **Table 1**, RSPO1 ($p<0.001$), TNF-α ($p<0.001$), and AMH ($p=0.006$) levels were significantly higher in the PCOS groups. LH level was significantly higher in obese women with PCOS than in other groups ($p<0.001$). LDL level was the lowest in the non-obese PCOS group ($p=0.022$). Glucose ($p<0.001$), insulin ($p<0.001$), and HOMA-IR ($p<0.001$) levels were highest in the obese PCOS group. The groups were similar in age, height, diastolic blood pressure, FSH, Estradiol, Free T4, TSH, Prolactin, total cholesterol, HDL, and triglyceride.

Table 1. Summary of the individuals characteristics and laboratory measurements with regard to groups

	Controls (BMI<25)	Controls (BMI≥25)	PCOS (BMI<25)	PCOS (BMI≥25)	P
N	21	21	21	21	N/A
Age (year)	25 (23-28)	27 (23-35)	26 (21-29)	27 (24-32)	0.55
Height (cm)	163 (158-165)	165 (160-168)	163 (159-167)	163 (158-170)	0.76
Weight (kg)	53 (52-58)[a]	75 (70-78)[b]	56 (53-61)[a]	81 (69-92)[b]	0.001
BMI (kg/m2)	20.31 (19.5-22)[a]	27.5 (25.8-30.1)[b]	20.96 (20.0-22.5)[a]	29.5 (27.8-31.3)[b]	0.001
WC (cm)	74.19±9.35[a]	88.19±13.06[b]	74.76±5.25[a]	97.43±13.43[b]	0.001
HC(cm)	94 (92-100)[a]	104 (98-112)[bc]	99 (93-102)[ab]	111 (107-119)[c]	0.001
WHR	0.78±0.07[ab]	0.83±0.07[bc]	0.76±0.05[a]	0.87±0.10[c]	0.001
SBP (mm-Hg)	110 (100-110)[ab]	120 (110-120)[b]	110 (110-120)[ab]	100 (100-110)[a]	0.013
DBP (mm-Hg)	60 (60-80)	65 (60-80)	60 (60-80)	60 (60-60)	0.131
RSPO1 (μg)	434.0 (386.8-550.4)[a]	691.7 (418.9-1079.1)[a]	2814.1 (1702.7-3762.0)[b]	2694 (2051-3371)[b]	0.001
TNF-α(ng/ml)	61.59 (54.3-71.91)[a]	87.71 (57.15-139.67)[a]	352.51 (227.44-487.7)[b]	287 (236.4-391.7)[b]	0.001
AMH (ng/mL)	1.96 (1.78-2.31)[ab]	1.69 (1.45-2.11)[a]	2.54 (1.94-2.85)[b]	2.19 (1.67-3.2)[b]	0.006
FSH (mIU/mL)	6.11±1.84	5.58±1.63	6.36±1.66	5.91±1.18	0.451
LH (IU/L)	4.56 (3.26-5.62)[a]	4.9 (4.1-5.25)[a]	4.5 (4.19-6.2)[a]	9.64 (6.93-12.2)[b]	0.001
Estradiol (pg/mL)	44 (28-51)	41 (32-52)	32.5 (29-55.8)	37 (33-48.4)	0.947
Free T4(ng/dL)	1.03 (0.98-1.11)	1.07 (0.96-1.37)	1.08 (1.05-1.13)	1.07 (0.96-1.13)	0.610
TSH (uIU/mL)	1.99 (1.46-2.39)	1.61 (1.28-2.13)	1.75 (1.26-2.36)	1.72 (1.26-2.36)	0.755
Prolactin (μg/L)	15.83±5.69	17.10±4.97	14.75±6.74	15.31±5.26	0.582
Total cholesterol (mg/dl)	201.29±29.41	222.57±67.01	192.43±51.80	189.19±41.08	0.263
LDL (mg/dL)	124 (92-142)[b]	102 (72-135)[ab]	89 (69-123)[a]	115 (105-151)[b]	0.022
HDL (mg/dL)	69.46±11.78	61.43±14.78	59.90±15.20	59.18±13.38	0.069
Triglyceride (mmol/L)	106 (98-125)	96 (68-132)	92 (84-108)	102 (68-126)	0.617
Glucose (mmol/L)	88 (85-92)[ab]	86 (82-92)[a]	95 (90-104)[bc]	96 (91-101)[c]	0.001
Insulin (IU/mL)	6.14 (5.4-8)[a]	8.1 (6.6-11.2)[ab]	10.3 (7.8-12.1)[bc]	12.1 (10.9-16.3)[c]	0.001
HOMA-IR	1.35 (1.22-1.63)[a]	1.65 (1.42-2.54)[ab]	2.35 (1.61-2.68)[bc]	3.15 (2.59-3.9)[c]	0.001

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) according to the normality of distribution
The same letters and format denote the lack of statistically significant difference between groups
BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; AMH, anti mullerian hormone; FSH, folicle stimulating hormone; LH, luteinizing hormone; TSH, thyroid stimulating hormone; LDL; low dansity lipoprotein; HDL, high dansity lipoprotein

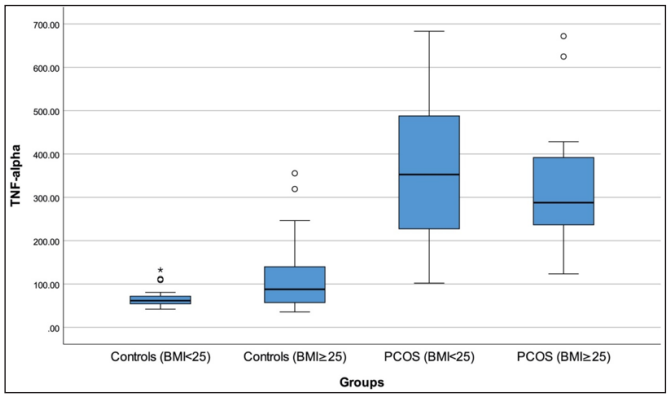

Figure 1: TNF-α levels in groups

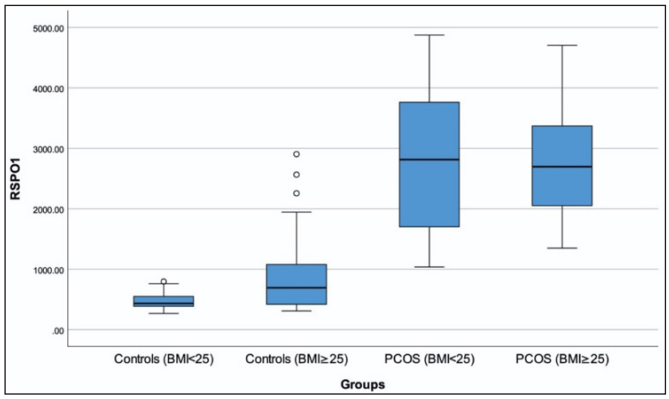

Figure 2. RSPO1 levels in groups

Table 2 shows a high positive correlation between RSPO1 and TNF-α levels (r=0.944, p<0.001). Positive correlations were found between the hip circumference and the concentrations of RSPO1 (r=0.255, p=0.019) and TNF-α (r=0.278, p=0.011). There were weak positive correlations between LH levels and the concentrations of RSPO1 (r=0.221, p=0.043) and TNF-α (r=0.242, p=0.026). There was a weak negative correlation between prolactin and TNF-α levels (r=-0.269, p=0.013). Weak positive correlations were found between blood glucose levels and the concentrations of RSPO1 (r=0.343, p=0.001) and TNF-α (r=0.312, p=0.004). Moderate positive correlations were found between insulin levels and the concentrations of RSPO1 (r=0.577, p<0.001) and TNF-α (r=0.569, p<0.001). Again, moderate positive correlations were found between HOMA-IR values and the concentrations of RSPO-1 (r=0.619, p<0.001) and TNF-α (r=0.608, p<0.001). No statistically significant correlation was found between other parameters and the levels of RSPO1 and TNF-α.

DISCUSSION

PCOS is one of the most common endocrine disorders in women of reproductive age. In addition to disorders related to the reproductive system, PCOS patients are relatively likely to have several systemic problems, such as functional disorders in adipose tissue, metabolic syndrome, Type 2 DM, and an increased risk of cardiovascular disease (14). This study investigated the association between RSPO1 and TNF-α level, IR, and other parameters in infertile women with PCOS.

Table 2. Correlations between RSPO1, TNF- alpha and other variables of participants

		RSPO1	TNF- α			RSPO1	TNF- α
RSOP1	r	-	0.944*	Estradiol	r	0.038	0.067
	p	-	<0.001		p	0.731	0.545
Age	r	0.004	-0.049	Free T4	r	-0.007	-0.007
	p	0.973	0.660		p	0.951	0.952
Height	r	0.046	0.101	TSH	r	0.029	-0.069
	p	0.676	0.362		p	0.795	0.530
Weight	r	0.151	0.161	Prolactin	r	-0.196	-0.269*
	p	0.171	0.142		p	0.074	0.013
Body mass index	r	0.152	0.147	Total cholesterol	r	-0.177	-0.188
	p	0.166	0.182		p	0.107	0.086
Waist circumference	r	0.131	0.144	LDL	r	-0.026	0.040
	p	0.236	0.192		p	0.816	0.720
Hip circumference	r	0.255*	0.278*	HDL	r	-0.169	-0.142
	p	0.019	0.011		p	0.124	0.196
Waist / Hip ratio	r	-0.046	-0.039	Triglyceride	r	-0.163	-0.098
	p	0.680	0.722		p	0.139	0.374
Systolic blood pressure	r	-0.002	0.016	Glucose	r	0.343*	0.312*
	p	0.989	0.883		p	0.001	0.004
DBP	r	-0.072	-0.073	Insulin	r	0.577*	0.569*
	p	0.515	0.508		p	<0.001	<0.001
AMH	r	0.147	0.163	HOMA-IR	r	0.619*	0.608*
	p	0.182	0.139		p	<0.001	<0.001
FSH	r	0.081	0.111				
	p	0.462	0.314				
LH	r	0.221*	0.242*				
	p	0.043	0.026				

r: Spearman correlation coefficient, * Correlation is significant at the 0.05 level (2-tailed).

Depending on the demographic characteristics of the studied populations and the definition of PCOS, 30 to 75% of women with PCOS have obesity, and 50-70% of those with normal BMIs have abdominal obesity (increased central fat) (15). The result we found in the present research supports this information. We found that hip circumference was higher in women diagnosed with PCOS, and the WHC ratio was higher in obese women with PCOS. Since obesity is more common in women with PCOS, these women are at greater risk of increased insulin resistance, Type 2 DM, metabolic syndrome, and impaired glucose tolerance (15,16). It has been reported that IR can be an integral part of the syndrome in 65-80% of PCOS patients and may have a role in its etiology (6). The current study found that glucose, insulin, and IR levels were highest in the obese-PCOS group. We believe it is necessary to repeat that PCOS patients must be monitored more closely regarding the risk of developing obesity and insulin resistance.

The Wnt signaling pathway significantly regulates cells' survival, proliferation, polarity, and fate during embryonic development and tissue homeostasis. Abnormal regulation of Wnt signaling often results in pathological conditions in humans, including congenital disabilities, cancer, and other diseases (17). RSPO1 contributes to ovarian differentiation by activating the standard Wnt signaling pathway (18). It is stated that RSPO1 has a critical role in inhibiting testis formation during early ovarian development since it stimulates the downstream catenin pathway (19). This has been evidenced by testis formation and the development of androgen-related features in female mice in an experimental study where RSPO1 deletion was performed (20). However, it has been reported that RSPO1 level is increased in 8% of ovarian cancers (18). Liu et al. (21) reported that RSPO1 promotes growth, survival, and migration in ovarian cancer cells and protects cancer cells against chemotherapy. No study evaluating the relationship between PCOS and RSPO1 could be found in the literature. It is noteworthy that the RSPO1 level is significantly higher in women with PCOS in our study group. Although we could not evaluate the mechanism and cause of this elevation, our finding is valuable in that it raises important questions about the role of RSPO1 in PCOS.

The RSPO family can bind to the LGR4–6 receptors and leucine-rich repeating domains containing G protein, thereby amplifying Wnt signaling (9). Wang et al. (22) reported that the ablation of LGR4 (which encodes the specific receptor for RSPO1) in mice caused a transition from white to brown adipose tissue with increased energy consumption and reduced fat. It has also been reported that LGR4 expression is significantly increased in obese patients' subcutaneous and intraabdominal fat tissue compared to normal individuals. Kang et al. (10) reported that RSPO1 levels were higher in obese patients than in non-obese patients, and RSPO1 serum levels showed a significant correlation with BMI. Our study found no significant difference between the RSPO1 levels of obese and non-obese patients. While there was no correlation between BMI and RSPO1 level, a positive correlation was found between the hip circumference and RSPO1 level.

Previous publications report that RSPO1 can be detected in murine islets and that RSPO1 could stimulate insulin secretion (regardless of glucose level) (23). In addition, it was reported that serum RSPO1 levels were higher in IR subjects compared to insulin-sensitive subjects, and the levels were correlated with fasting C-peptide level and the degree of IR (10). Furthermore, in some previous in-vivo studies, it has been reported that RSPO1 increases insulin secretion (7-9). Similarly, in the current study, a positive correlation was found between glucose, insulin, IR, and the concentration of RSPO1. The increase in RSPO1 level in infertile women with PCOS could be important in monitoring the risk of developing DM.

Low-grade chronic inflammation of PCOS patients plays a role in the disease pathogenesis, and PCOS is widely accepted as a pro-inflammatory condition (24). TNF-α is an inflammation marker that plays a role in many immunological functions as well as acute bacterial infection, viral replication, septic shock, and fever (15). In our study group, TNF-α level was significantly higher in women diagnosed with PCOS. Sayın et al. (25) reported similar results. Some studies reported no difference in serum TNF-α levels between obese women with and without PCOS (26). In the metanalysis performed by Toulis et al. (27), TNF-α levels were reported to be higher in women with PCOS compared to controls. Despite such supporting evidence, another meta-analysis study found no difference between PCOS and control groups in TNF-α levels (28), indicating a need for future studies with better design and patient selection to determine the TNF-α role in PCOS. The current study reports remarkably elevated TNF-α levels in the presence of PCOS, providing support to the former group of studies. However, it must be noted that the possible existence of many clinical situations related to TNF-α level may have caused the differences; however, this is true for all studies focusing on this topic and further highlights the necessity of collaborative attempts and prospective studies to elucidate TNF-α and its role in PCOS.

TNF-α is mainly expressed in monocytes, macrophages, and adipose tissue, and levels of TNF-α are elevated in obesity and Type 2 DM (29). Studies show that increased serum TNF-α levels in women with PCOS correlate positively with BMI (30). The present study found a

positive correlation between hip circumference and TNF-α level. Also, no significant correlation was found between BMI and TNF-α. No difference was found in TNF-α between obese and non-obese women in the PCOS and control groups. Sayın et al. (25) reported similar results. In the meta-analysis performed by Gao et al. (32), there was no relationship between TNF-α and BMI in women with PCOS. However, since TNF-α expression is implicated in the development of IR (29), it is evident that the lack of difference concerning obesity presence/absence deserves a more detailed analysis. Araya et al. (30) reported that increased serum TNF-α levels in women with PCOS were inversely correlated with insulin sensitivity. Some studies also report no relationship between TNF-α and glucose, insulin, and IR (25,26). As a result of a previously reported meta-analysis, the increase in TNF-α level is directly related to the increase in IR in PCOS (31). This study found a positive correlation between TNF-α and glucose, insulin, and IR, even though a difference was not observed concerning obesity status in either group of patients. The results may suggest that such elevations in TNF-α levels warrant investigation for the level of IR in PCOS patients. These findings also imply that, rather than the presence of obesity, the metabolic outcome of obesity or the progression towards clinically-relevant disease states are the triggering factors for the elevation of TNF-α.

Although the information on RSPO1 and TNF-α has increased, relatively little is known regarding the association between RSPO1 and TNF-α in women with PCOS. In the study conducted by Krönke et al. (32) on TNF-α -transgenic mice, they reported that RSPO1 was highly effective in protecting joint structural integrity in arthritis by preventing inflammation-related injury to the bone and cartilage. As a result, it was concluded that RSPO1 had therapeutic potential as an anabolic agent in arthritis. Another study reported significantly lower serum RSPO1 concentrations in rheumatoid arthritis patients compared to matched controls, and anti-TNF-α therapy significantly increased serum RSPO1 levels (33). The current study found a positive correlation between RSPO1 levels and TNF-α levels. The correlation between the two values is not surprising, as we found that both TNF-α and RSPO1 levels were significantly higher in the presence of PCOS. However, the dearth of evidence about RSPO1 and its effects on PCOS indicates a need for in-vivo and in-vitro studies evaluating the relationship between these two parameters in the presence of PCOS.

Apart from those mentioned previously, one of the study's limitations is that the research group consisted of a relatively small number of patients for a disease as prevalent and variable as PCOS. More robust evidence could be obtained with population-based and larger-scale studies to confirm the role of RSPO1 and TNF-α among PCOS patients (and possibly those with infertility due to PCOS). Another limitation is that the primary source of RSPO1 and TNF-α evaluated in the study cannot be determined since measurements were performed from serum samples. Finally, data were obtained from a single point in time, and since variations are possible –especially concerning period characteristics, there may be a need to assess patients longitudinally and possibly, concerning their management and treatment processes. On the other hand, we believe that this study, which compared infertile women with and without PCOS, is valuable for evaluating the relationship between obesity, insulin resistance, RSPO1, and TNF-α.

CONCLUSION

As a result of the analyses carried out in this study, it was found that RSPO1 and TNF-α levels were higher in women with PCOS than in controls. A very strong positive correlation was found between RSPO1 and TNF-α levels. IR was highest in the obese-PCOS group. While there was no correlation between BMI and the concentrations of RSPO1 and TNF-α, a notable positive correlation was between the levels of RSPO1 and TNF-α and the following parameters: hip circumference, insulin level, HOMA-IR, and glucose. Considering the lack of data on RSPO1 levels in PCOS or obesity and the conflicts in the literature concerning the role of TNF-α in these conditions, drawing direct conclusions about the results is difficult. Also, it may be feasible to suggest that RSPO1 and TNF-α levels may guide the assessment and management of IR and diabetes risk in infertile women with PCOS. More comprehensive studies are required to investigate the relationship of RSPO1 and TNF-α with IR and other parameters in PCOS patients in the presence/absence of obesity and infertility.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Etlik Zübeyde Hanım Training and Research Hospital Clinical Researches Ethics Committee (Date: 09.09.2020, Decision No: 2020/128).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Do we know the normal anterior-posterior diameters of the spinal cord and canal in newborns?

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ABSTRACT

Aim: We aim to reveal the normal anterior-posterior diameter of the spinal cord and canal at cervical, thoracic and lumbar levels in newborn with sonographic measurements and to create a reference value. Also, we aim to reveal whether the anterior-posterior diameter at these levels will vary with the newborn's head circumference, gender, height and weight. Thus, we aim to be one of the pioneering studies in the literature

Material and Method: Statistical analysis was performed to determine normal anterior-posterior diameter for the spinal canal and spinal cord at each vertebral level, and their correlations with birth weight, length and head circumference.

Results: 188 newborns were included. The mean anteroposterior spinal canal diameter in male newborns was significantly higher compared to females (9.27±0.83 vs 9.00±0.79, p=.020). There was a positive correlation between spinal cord anterior-posterior diameter and head circumference at thoracic level, which was statistically significant. There was a positive correlation between spinal canal diameter and height at thoracic level. There was a positive correlation between spinal canal diameter and weight at lumbar level.

Conclusion: The establishment of the normal values for anterior-posterior diameters of the spinal cord in healthy newborns may contribute the current literature data.

Keywords: Diameter, infants, neonates, spinal canal, spine ultrasound

INTRODUCTION

Neonatal spinal ultrasonography (US) is a valuable, noninvasive, does not contain ionizing radiation, first-line imaging modality that is frequently used in newborns, to investigate the spinal cord (1). US provides an excellent acoustic window that allows visualization of the spinal cord and canal since the posterior elements of the vertebrae are not fully ossified in newborns However, a complete and adequate neonatal spinal US examination requires plenty of experience, to precisely detect the pathologies of the spinal cord, it is necessary to accurately know the anatomy and the conditions that can be considered as normal (2). Except for a recently published study, there is no study including a large series of patients revealing normal values of the spinal cord and canal in newborns. Normal anterior-posterior (AP) diameter values of the spinal cord and canal are evaluated visually by radiologists so far (3). Determining objective normal values for AP diameters of the spinal cord and spinal canal on US may faciliate detecting pathologies such as mass formations in the spinal cord that do not create a recognizable echo difference, spinal cord injury and edema, and isoechoic hematoma that does not lead any significant echo difference.

In this prospective study, we aim to reveal the normal AP diameter values of the spinal cord and canal at cervical, thoracic and lumbar levels in newborn babies with sonographic measurements and to create a reference value range. Also, we aim to reveal whether the AP diameter values at these levels will vary with the newborn's head circumference, gender, height and weight. Thus, we aim to be one of the pioneering studies in the literature.

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MATHERIAL AND METHOD

The study was carried out with the permission of Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 30.06.2021, Decision No: 2021.06.133). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Oral and written consents were obtained from parents of all patients who participated in our study.

In this prospective study; 191 newborns were included between 2020-2021 years. Newborn babies who were reported as completely normal in obstetric US follow-ups and who were evaluated as normal in the postnatal physical examination were included in our study. It was excluded from our study because of the detection of lipoma at the level of the cauda equina fibers in 1 newborn, the detection of patency in the posterior vertebral elements (occult type spinal dysraphism) in 1 newborn, and the detection of diastometomyelia in 1 newborn. A total of 188 healthy newborns (89 male, 99 female) were included in our study. Newborns with any known abnormality in the antenatal obstetric US, those who had undergone any surgery in the neck or waist region, those with a known postnatal disease, and those with a known disease history such as diabetes in their mother were excluded from the study. Again, patients with sacral dimples, hair growth and lumbar lump in the postnatal physical examination were not included in the study.

All sonographic evaluations were performed by a radiologist who is specialized in the field of pediatric radiology (Ö.Ö.) with 6 years of experience. In all patients, US were performed in the prone position within 48-72 h of birth using Hitachi ARIETTA 850 SE (Hitachi, Tokyo, Japan). During the examinations, a pillow was placed under the infant's abdomen and the newborn was in the prone position. Prone position allow us to see a better acoustic window since the position leads lumbar cistern distention. All examinations are performed with a high-resolution (7–14 MHz) linear transducer through longitudinal and axial plane from the cervical region to the end of the coccyx.

The examination was started in the longitudinal plane, spinal cord morphology from the craniocervical junction level to the thoracic and lumbosacral regions, the level of termination of the conus medullaris, motion of the spinal cord and nerve roots and the morphology of the filum terminale was evaluated. The first vertebra that showed a deviation from the adjacent vertebrae at the level of the lumbosacral junction was determined as the sacral vertebra. Vertebrae were counted from the lumbosacral junction to the cranial vertebrae. In addition, when it comes to the thoracic region, the vertebra (T12) where the rib articulates was determined and the vertebral levels were also counted down from this level. Unossified or round shaped coccyx was determined. After counting the vertebral levels, the ten axial planes, vertebrae from the craniocervical level to the vertebral column, spinal canal and cord were examined. It was investigated whether there is any fusion defect in the posterior elements, echo of the spinal cord, whether there is any space-occupying lesion within the spinal cord, central echo complex and subarachnoid space, cases with pathology were excluded from the study. AP diameters of the spinal cord and spinal canal were measured. At the cervical level, spinal cord and canal AP diameters were measured at C4-6 levels. Three consecutive measurements were made at T5-8 vertebral levels and the lumbar enlargement (from above and below) level. By calculating the average of the 3 measurements, spinal cord and spinal canal ap diameters were noted for each level. Then, height weight head circumference for each newborn was noted from the medical records recorded in the local database of our hospital.

Statistical Analysis

All statistical analysis was performed using R 3.6.0 (https://www.r-project.org). Shapiro-Wilk's normality test and Q-Q plots were used to normality of the data, and also Levene's test was used to check the homogeneity of the groups. Continuous variables were expressed as mean±standard deviation. Independent samples t-test and Welch's t-test was used to compare the difference of the male and female cohorts at the cervical thoracic and lumbar levels according to spinal cord AP and spinal canal diameter. In addition to, the relationship between the AP diameter of spinal cord and spinal canal at each vertebral level and head circumference, weight, and height was examined using Pearson correlation analysis. A value of p less than .05 was considered as statistically significant.

RESULTS

188 newborns (89 male, 99 female) were included in this study. The mean weight of male patients was 3305.73±539.72 gr, and female patients were 3299.68±461.50 gr. The mean height of male patients was 51.55±2.41 mm, and female patients were 51.31±2.30 mm.

The comparisons of the male and female cohorts at the cervical, thoracic and lumbar levels according to AP diameter of spinal cord and canal was given in **Table 1**. The mean AP diameter of spinal cord for all

newborns at the cervical, thoracic and lumbar levels were 4.81±0.41, 3.85±0.36 mm and 5.00±0.31 mm (mean±standard deviation in milimeters), respectively. The mean AP diameter of spinal canal for all newborns at the cervical, thoracic and lumbar levels were (mm) 7.80±0.86, 7.43±0.75, 9.13±0.82 (mean±standard deviation in milimeters) respectively. The mean AP diameter of spinal canal in male newborns was significantly higher compared in female newborns (mm) (9.27±0.83 vs 9.00±0.79, p=.020). However, there was no statistically significantly difference between male and female newborns in terms of the mean AP diameter of spinal cord at any vertebral level, and also spinal canal diameter at cervical and thoracic level. There was statistically significantly difference between male and female newborns in terms of the mean AP diameter of spinal canal at lumbar level (p value= 0.02) (**Table 1**, **Graphic 1**, **Figure 1** and **2**).

Table 1. The mean AP diameter of spinal cord and canal for the male and female cohorts at the cervical, thoracic and lumbar levels

	All newborns (n=188)	Male (n=89)	Female (n=99)	p value (M. vs F.)
Spinal cord AP diameter				
Cervical	4.81±0.41	4.82±0.48	4.80±0.33	.803[a]
Thoracic	3.85±0.36	3.87±0.40	3.84±0.34	.550[b]
Lumbar	5.00±0.31	5.00±0.32	5.01±0.31	.806[a]
Spinal canal diameter				
Cervical	7.80±0.86	7.80±0.94	7.80±0.79	.960[a]
Thoracic	7.43±0.75	7.44±0.77	7.43±0.74	.889[a]
Lumbar	9.13±0.82	9.27±0.83	9.00±0.79	.020[a]

Values were presented as mean±standard deviation in milimeters. Bold values denote that statistically significant difference. [a]Independent samples t-test, [b]Welch's t-test

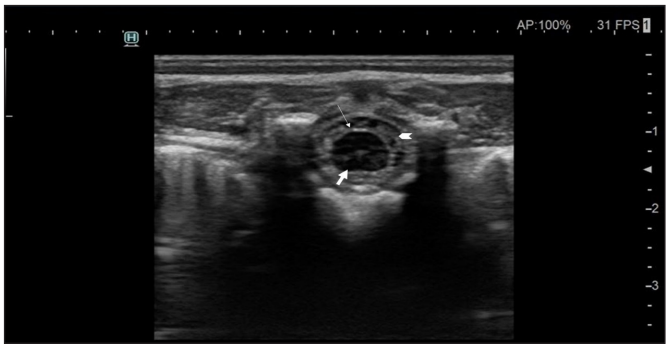
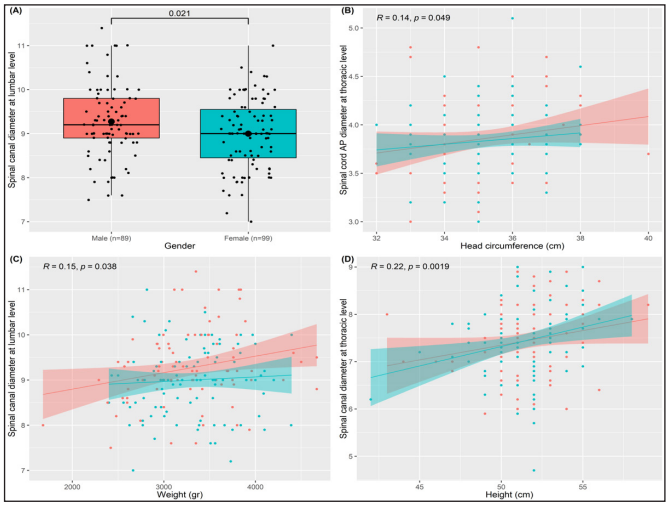


Figure 1. An axial images of spinal cord at the lumbal vertebral level has shown the spinal cord (thick arrow), the dura mater (thin arrow) and the nerve roots (arrowhead) in the subarachnoid space.



Graphic 1. (A) A box-plot, which shows the spinal canal diameter at lumbar level in male and female patients. Data are expressed as median with interquartile range, and dots shows mean value. (B) Scatter plot, which shows the relationship between spinal cord AP diameter at thoracic level and head circumference in each sex. Line shows regression lines, and light colors show confidence intervals in each sex. (C) (B) Scatter plot, which shows the relationship between spinal canal diameter at lumbar level and weight in each sex. Line shows regression lines, and light colors show confidence intervals in each sex. (D) (B) Scatter plot, which shows the relationship between spinal canal diameter at thoracic level and height in each sex. Line shows regression lines, and light colors show confidence intervals in each sex.

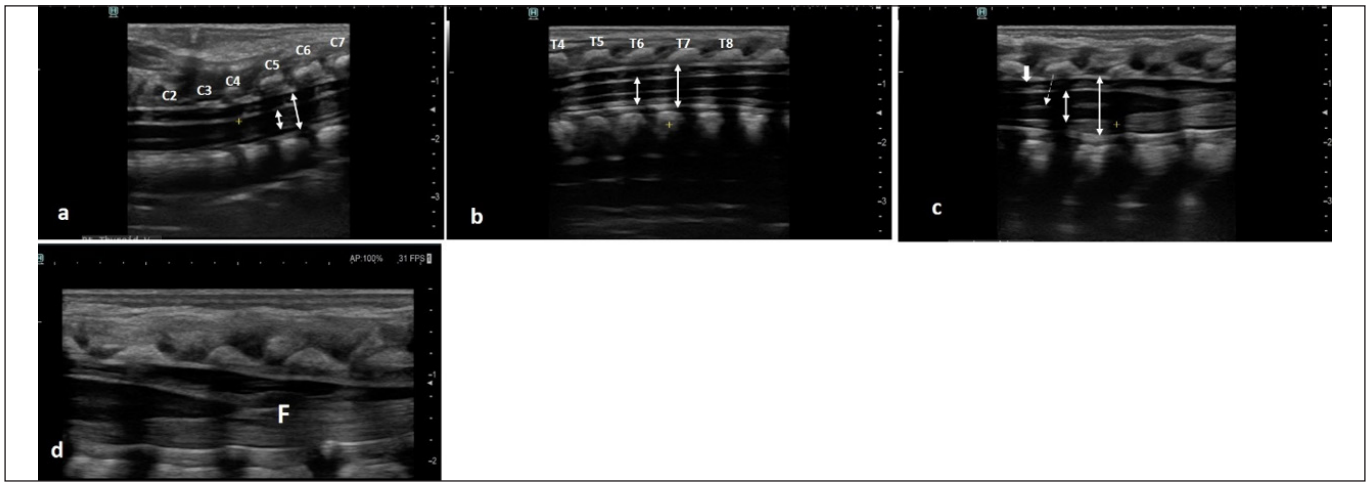


Figure 2. In a one-year-old newborn, median longitudinal scan of a.) the cervical region showing spinal cord (short line) and the spinal canal (long line). Cervical vertebrae are seen as echogenic foci. The cervical anterior-posterior diameter of the spinal cord and canal is measured at C5 and C6 levels. b.) On sagittal image of the thoracic spine, the spinal cord (short line) and spinal canal (long line) diameters measured at T6 and T7 levels. Spinous processes of the thoracal vertebrae are seen in as echogenic foci. c.) on lumbosacral level, central echogenic complex is seen (thin arrow), the lumbar enlargement (short line) and spinal canal (long line) whicch is below the the lumbar enlargement level is demonsrated. Subarachnoid space is also seen (thick arrow). d.) Median longitudinal scan of the lumbosacral region demonstrating the filum terminale (F) and the medullary cone

A Pearson product-moment correlation was run to determine the relationship between the AP diameter of spinal cord and canal at each vertebral level and head circumference, weight, and height, and results were given in **Table 2**. There was a positive correlation between spinal cord AP diameter and head circumference at thoracic level, which was statistically significant (r=0.144, p=0.049). There was a positive correlation between spinal canal diameter and height at thoracic level, which was statistically significant (r=0.225, p=0.002). There was a positive correlation between spinal canal diameter and weight at lumbar level, which was statistically significant (r=0.151, p=0.038). No statistically significant correlation was found between the other relationships (**Table 2**).

Table 2. Correlation of the AP diameter of spinal cord and canal for all cohorts at the cervical, thoracic and lumbar levels

	Head circumference (cm)	Weight (gr)	Height (cm)
All newborns (n=188)			
Spinal cord AP diameter			
Cervical	0.032 (.659)	–0.053 (.474)	–0.003 (.973)
Thoracic	0.144 (.049)	0.121 (.097)	0.042 (.565)
Lumbar	0.024 (.744)	0.043 (.556)	0.046 (.528)
Spinal canal diameter			
Cervical	–0.026 (.720)	0.064 (.380)	0.038 (.608)
Thoracic	0.092 (.207)	0.122 (.096)	0.225 (.002)
Lumbar	0.057 (.435)	0.151 (.038)	0.073 (.320)
Males (n=89)			
Spinal cord AP diameter			
Cervical	0.069 (.520)	–0.048 (.654)	–0.027 (.800)
Thoracic	0.163 (.126)	0.146 (.171)	–0.003 (.981)
Lumbar	0.120 (.264)	0.032 (.764)	0.007 (.945)
Spinal canal diameter			
Cervical	–0.024 (.824)	–0.005 (.960)	–0.035 (.747)
Thoracic	0.168 (.116)	0.174 (.104)	0.194 (.069)
Lumbar	0.165 (.121)	0.237 (.025)	0.058 (.590)
Females (n=99)			
Spinal cord AP diameter			
Cervical	–0.015 (.882)	–0.060 (.553)	0.029 (.773)
Thoracic	0.122 (.230)	0.090 (.374)	0.087 (.390)
Lumbar	–0.063 (.536)	0.056 (.585)	0.087 (.394)
Spinal canal diameter			
Cervical	–0.029 (.778)	0.151 (.135)	0.119 (.241)
Thoracic	0.023 (.823)	0.065 (.520)	0.254 (.011)
Lumbar	–0.056 (.582)	0.059 (.563)	0.072 (.477)

Values were presented as Pearson correlation coefficients (p-value). Bold values denote that statistically significant difference.

DISCUSSION

Spinal cord injury is mostly seen in small children in the pediatric population, however overall frequency is very rare in very young children. Young children are more prone to traumas in terms of the spinal injury because of less muscle development and increased head-body proportion in the head direction (4). Radiological evaluation of young children for spinal cord injury may be difficult due to undesirable radiation exposure and lack of experience. The incidence of pediatric spine injuries has been reported as 2% to 5% of all spine injuries (5). Although spinal cord injuries in the pediatric population are very rare, the situation leads to quite morbidity and mortality (6). Trauma, serious falls, sports injuries, or child abuse are among the known causes of spinal cord injury, and edema or hemorrhage that expands the ap diameter of cord can be seen in these patients. Launey et al. (7). reported in a metaanalyse that nearly 44% of the patients diagnosed with spinal cord injuries can not improve and continue to suffer from morbidity of injury. Cord injury, which is a rare but serious condition especially in young children, is often overlooked (8). Most studies in the literature on spinal injury in the pediatric population have not specifically examined newborns (6,9).

There is no widely accepted nomogram for the AP diameters of the spinal cord and canal in the newborn so far. No morphometric measurement is required to detect pathologies such as congenital malformations, such as myelomeningocele, lipoma, dermal sinus, tight filum terminale syndrome, diastematomyelia or syringomyelia. However, it may be difficult to accurately detect pathologies that cause swelling and do not cause significant echo difference in the cord, such as acquired intraspinal diseases, following birth trauma, or after lumbar puncture, without knowing the normal diameter values of the spinal cord (10). Also, for radiologists with little experience in spinal US, since they are not familiar with such rare conditions that may cause edema in the spinal cord, establishing normal and abnormal diameter values will facilitate the detection of this type of pathologies. In a recent study, Singh et al. (3) reported that the mean AP spinal cord diameter was 4.1±0.5 mm at the cervical level, 3.3±0.3 mm at the thoracic level and 4.4±0.6mm at the lumbar level. The mean AP spinal canal diameter was 7.7±0.7mm at the cervical level, 6.2±0.8mmat the thoracic level, and 8.4±0.7 mm at the lumbar level. In our study, we found that the mean spinal cord AP diameter for all newborns at the cervical, thoracic and lumbar levels were 4.81±0.41, 3.85±0.36 and 5.00±0.31 (mean±standard deviation in milimeters), respectively. The mean spinal canal AP diameter for all newborns at the cervical, thoracic and lumbar levels were 7.80±0.86, 7.43±0.75, 9.13±0.82 (mean±standard deviation in milimeters) respectively. The mean AP spinal cord diameters found in our study were similar to those of Singh et al (3). However we found the mean AP spinal canal diameters slightly larger. This may be secondary to our study has larger-scaled (188 newborns) compared to recent study (37 newborns), another reason may be difference of the nationality and race of this newborns.

The mean AP spinal cord diameters are ranged between 4,40-5,32 mm at different levels in normal and healthy newborns included in our study. And at the level of the lumbar enlargement which is the most prominent and largest level, the mean AP spinal cord diameters are 5.00±0.31 mm. Outside of these ranges may be considered abnormal. To elucidate this issue and determine normal range of the spinal cord and canal diameter; there is a need for larger-scaled, prospective studies examining abnormal values in infants with spinal cord injury and edema, especially in trauma centers. We also found a positive correlation between spinal cord AP diameter and head circumference at thoracic level.

Computed tomography enables excellent view of the bone structure but it cause ionizing radiation and can not reveal properly the soft tissue changes. MRI is the most preferred method in the evaluation of the spinal canal and cord, and US is less frequently preferred in outpatients clinics (11). MRI, on the other hand, is a expensive, is not available in every center and requires sedation for the newborn age group. Unfortunately, neonatal neurosonography is seen as just a basic first line imaging modality that shows only orienting information and does not reveal so much detailed information (12). The most important reason for this perception is poor quality US examinations, since there is a lack of specialized expertise in the field of neurosonography. US for the spinal cord and canal is a little-known issue that has not been emphasized much in radiology practice, and there are almost a few studies in the literature that reveal normal reference values (12). Horst et al. (13) reported that pediatric neurosongraphy results shown great variability and standardization of reporting may reduce such a huge interobserver variability. Due to the lack of a standard examination scheme, many studies on spinal cord injury in neonates have been done with MRI or CT (14,15).

We think that radiologists with limited knowledge and practice in neurosonography would not overlook rare pathologies such as post-traumatic cord edema or congenital stenosis if they knew normal references of spinal cord and canal. Thus, this paper will encourage the radiologist the more effective way while performing spinal US and highlight the value and potential of US.

Our study has several limitations. First we had relatively small sample size. And examinations were only performed by a radiologist, interobserver variability was not investigated. Only healthy newborns included the study which are normal on physical examination and has no symptoms. MRI of the newborns was not seen, which is superior to US in terms of detecting spinal pathologies. The race of the newborns were not investigated, there is a possibility the AP diameters may be change with the ethnicity.

CONLUSION

Paediatric and particularly neonatal neurosonography is still the cornerstone of the neonatal imaging. The normal reference ranges of the spinal canal and cord diameter at different levels in newborns are still remain unknown and there are only few studies on this subject. Revealing abnormal values will provide convenience in difficult-to-diagnose situations such as spinal cord edema that does not cause a pronounced echo and mass effect on the cord. We also think that determining the lower limit values for the cord will increase the role and contribution of US in the visualization of the spinal cord and canal stenosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 30.06.2021, Decision No: 2021.06.133).

Informed Consent: All patients signed the free and informed consent form.

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Original Article

HEALTH SCIENCES
MEDICINE

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Distribution of ABO blood groups and Rh factor in benign and malign thyroid nodules

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ABSTRACT

Aim: Many factors affect the diagnostic value of the fine-needle aspiration biopsy applied for these thyroid nodules. I aimed to investigate whether one of these factors would be ABO blood groups and Rh factor and examine the relationship of these factors with the Bethesda categorization. Additionally, I aimed to evaluate ABO blood groups and Rh factors in patients with thyroid cancer.

Material and Method: This study was planned in a cross-sectional retrospective design. The data of the patients were obtained from the hospital data bank. In the analysis of 801 patients following the acceptance criteria, 412 patient data were obtained. Patients were divided into 4 (O, A, B, and AB groups) according to their blood groups and analyzed for nodules (solitary/ multinodular). Nodules were divided into malignant and benign, according to histopathological diagnosis, and all were analyzed.

Results: There was no difference in analyzing the demographic data according to the blood groups. The rates of the FNAB history were 51 (32.3%), 39 (24.2%), 14 (26.4%), and 13 (32.5%) in the same order of blood groups (p=0.393). In the analysis of the nodule type, multinodular did not differ from solitary nodules among the blood groups [O: 141 (89.2%); A:140(87%), B: 46(86.8%), and AB: 35(87.5%)]. Thyroid function status (euthyroid, hypothyroid, or hyperthyroid) was similar for all the blood groups (p=0.815). The O-group had 1 (0.6%) patient with Bethesda score-6, and the A-group had 2 (1.2%) patients with Bethesda score-6. For Bethesda score-5, per blood group had 2 patients. The histopathological distribution of malign nodules (p=0.782) is as follows: O-groups: 6 (33.3%) (Rh+:27%; Rh-:5,5%), A groups: 7(63,6%) (Rh+:54,5%; Rh-:0,9%), B groups: 2(20%)(Rh+:20%; Rh-:0%) and AB groups: 1(33%) (Rh+:33%) Rh-:0%).

Conclusion: Malign nodule rate was highest in the A-group and lowest in the B groups, although it did not differ in the overall analysis. No relationship was found between the Bethesda categorization of nodules, their sizes, type of nodules, type of thyroid cancer, and ABO blood groups.

Keywords: Thyroid biopsy, Bethesda score, ABO blood group, Rh factor, malign nodule, benign nodule

INTRODUCTION

Thyroid nodules are growths that develop within the thyroid gland, and while they are often benign, they can also be cancerous (1). It is important to note that the presence of nodules does not necessarily imply that the person has any disorder or that the nodules are malignant; many thyroid nodules are benign and do not require any treatment (2). They can be associated with changes in specific blood parameters, including thyroid hormone and thyroid-stimulating hormone levels. It is essential to consult a doctor or endocrinologist for accurate diagnosis and management. The appearance of these nodules is closely related to the personal susceptibility of the patients and varies (3). One of these individual characteristics is blood group type.

The presence or absence of specific antigens on the surface of red blood cells determines blood type (4). Some research suggests that certain blood types may be associated with an increased risk for certain diseases. However, it is essential to note that blood type alone is not a significant risk factor for most conditions, and other factors such as lifestyle, diet, and genetics play a much more substantial role (5). Blood type A may have a slightly increased risk of developing certain digestive tract cancers, such as stomach cancer (6). AB may have an increased risk of developing pancreatic cancer (7). Blood type O may have a slightly reduced risk of developing blood clots and venous thromboembolism compared to other blood types. Blood type B may

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have a slightly increased risk of developing lupus, an autoimmune disease (8). It is important to note that these associations are inconclusive, and more research is needed to understand the relationship between blood type and disease risk fully. Blood type and thyroid nodule are not known to have a direct connection. However, some studies have shown an association between blood type and certain thyroid disorders (9, 10). Individuals with blood type A had a higher risk of developing autoimmune thyroid disease than those with other blood types (11), and blood type O had a higher risk of developing benign thyroid nodules than those with blood type A (12). Although the correlation between autoimmune thyroid diseases and blood type has been shown (13), there is no study on nodules, as we reviewed the existing literature. The present study investigated the distribution of ABO blood groups and thyroid nodules.

MATERIAL AND METHOD

The study was carried out with the permission of Karabük University Non-interventional Clinical Researches Ethics Committee (Date: 20.12.2022, Decision No: 2022/1195). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This study was planned in a cross-sectional retrospective design.

The data of the patients were obtained from the hospital data bank. In the analysis of 801 patients following the acceptance and rejection criteria, 412 patient data were obtained, whether they were eligible to participate in the study. Demographic and clinical data of the patients, as well as blood groups and thyroid nodule data, were analyzed together.

Patients' Groups

Two separate groupings were made for the patients. In the first grouping, patients were divided into 4 (O, A, B, and AB groups) according to their blood groups and analyzed for nodules (solitary/multinodular) and clinical effects. In the second classification, nodules were divided into two malignant and benign, according to histopathological diagnosis, and all were analyzed. They were evaluated as hypothyroid, euthyroid, and hyperthyroid according to thyroid functions. Blood groups were compared with this 6-point system in the Bethesda classification used diagnostically. Inclusion criteria for the study were that the patient was an adult (>18 years), all hospital data were complete with details, and blood group analysis was available. Our exclusion criteria included: those with unclear etiology, short follow-up, missing thyroid biopsy/Bethesda results, or those younger than 18.

Statistical Analysis

Statistical analysis was performed by the MS Windows 64x-based SPSS-v23 package program (IBM Inc., USA). After evaluating the conformity of the data with normal distribution with the Kolmogorov-Smirnov test, the normal distribution of numerical variables was shown as mean ± standard deviation and categorical variables as numbers and percentages. While Student's t-test was preferred to determine numerical variables that differed between two groups, the ANOVA test was used between 3 or more groups. We selected chi-square and Fisher exact chi-square tests to compare the categorical data. The $p<0.05$ was considered significant in the analysis.

RESULTS

In analyzing the demographic data according to the blood groups, there was no significant difference in the mean age (p=0.397) and BMI (p=0.153). The cross-table analyses of blood groups showed similarities in gender between the groups (p=0.282). These results showed that the participants' demographic data in terms of blood groups were compatible, and there was no difference, as seen in **Table 1**.

The rates of thyroid operation were 15 (9.5%), 10 (6.2%), 1 (1.9%), and 2 (5%) in order of O, A, B, and AB groups (p=0.194). The rates of the FNAB history were 51 (32.3%), 39 (24.2%), 14 (26.4%), and 13 (32.5%) in the same order of blood groups (p=0.393). In the analysis of the nodule type, multinodular did not differ from solitary nodules among the blood groups [O: 141 (89.2%); A:140 (87%), B: 46 (86.8%), and AB: 35 (87.5%)]. Thyroid function status (euthyroid, hypothyroid, or hyperthyroid) was similar for all the blood groups (p=0.815).

In malignancy analysis, the O group had 1 (0.6%) patient with Bethesda score-6, and the A group had 2 (1.2%) patients with Bethesda score-6. For Bethesda score-5, per blood group had two patients. However, the overall analysis did not differ for 4 group comparisons for Bethesda scoring (p=0.377). The histopathological distribution of malign nodules (p=0.782) is as follows: O-groups: 6 (33.3%) (Rh+:27%; Rh-:5.5%), A groups: 7 (63.6%) (Rh+:54.5%; Rh-:0.9%), B groups: 2 (20%) (Rh+:20% ; Rh-:0%) and AB groups: 1 (33%) (Rh+:33%) Rh-:0%).

DISCUSSION

In the present study, we analyzed the characteristics of thyroid nodules and the distribution of blood groups using clinical data. Malign nodule rate was highest in the A-group and lowest in the B groups, although it did not differ in the overall analysis. No relationship was found between the Bethesda categorization of nodules, their sizes, type of nodules, type of thyroid cancer, and ABO blood groups.

Table 1. Demographics and thyroid outputs of blood groups

Variables	0 Group		A Group		B Group		AB Group		P value
	Rh (+)	Rh (-)	Rh (+)	Rh (-)	Rh (+)	Rh (-)	Rh (+)	Rh (-)	
Gender									0,282
Male	33 (20.8%)	8 (5%)	30 (18.6%)	4 (2.4%)	11 (20.7%)	1 (1.8%)	3 (7.5%)	2 (5%)	
Female	86 (54.4%)	31 (19.6%)	119 (73.9%)	8 (4.9%)	32 (60%)	9 (16.9%)	30 (75%)	5 (12.5%)	
Age,year	53.2±11.7		52.6±13.2		51.6±12.2		55.9±14.2		0.397
BMI, kg/m²	29.1±5.7		29.1±5.5		28.1±5.8		30.8±6.2		0.153
Diameter, mm	18.3±9.9		19±9.6		20.3±13		17.7±10.5		0.562
Thyroid operation									0.194
No	109 (68%)	34 (21%)	139 (86%)	12 (7.4%)	42 (79%)	10 (18.8%)	31 (77.5%)	7 (17.5%)	
Yes	10 (6%)	5 (2.9%)	10 (6%)	0	1 (1.8%)	0	2 (5%)	0	
History of FNAB									0.393
No	79 (50%)	28 (17.7%)	113 (70%)	9 (5.5%)	32 (60.3%)	7 (13.2%)	23 (57.5)	4 (10%)	
Yes	40 (25%)	11 (6.9%)	36 (22%)	3 (1.8%)	11 (20.7%)	3 (5.6%)	10 (25%)	3 (7.5%)	
Nodule type									0.629
Solitary	12 (7.5%)	5 (3.1%)	21 (13%)	0	6 (11.3%)	1 (1.8%)	4 (16%)	1 (2.5%)	
Multinodular	107 (67.7%)	34 (21.5%)	128 (79%)	12 (7.4%)	37 (69.8%)	9 (16.9%)	29 (72.5%)	6 (15%)	
Thyroid function status									0.815
Euthyroid	72 (45.5%)	27 (17%)	87 (54%)	8 (4.9%)	26 (49%)	7 (13.2%)	20 (50%)	5 (12.5%)	
Hypothyroid	29 (18.3%)	5 (3%)	40 (24.8%)	2 (1.2%)	11 (20.7%)	3 (5.6%)	5 (12.5%)	2 (5%)	
Hyperthyroid	18 (11.3%)	7 (4.4%)	22 (13.6%)	2 (1.2%)	6 (11.3%)	0	8 (20%)	0	
Bethesda classification									0.377
1	22 (13.9%)	5 (3%)	19 (11.8%)	0	5 (9.4%)	2 (3.7%)	8 (20%)	3 (7.5%)	
2	57 (36%)	19 (12%)	74 (45%)	3 (1.2%)	20 (37.7%)	8 (15%)	17 (42.5%)	3 (7.5%)	
3	35 (22%)	15 (9.4%)	51 (31.6%)	9 (5.5%)	14 (26.4%)	1 (1.8%)	7 (17.5%)	1 (2.5%)	
4	2 (1.2%)	0	1 (0.6%)	0	1 (1.8%)	0	0	0	
5	2 (1.2%)	0	2 (1%)	0	2 (3.7%)	0	1 (2.5%)	0	
6	1 (0.6%)	0	2 (1%)	0	0	0	0	0	
Nodular nature									0.782
Non-malign	152 (96.2%)		154 (95.7%)		51 (96.2%)		39 (97.5%)		
Malign	6 (3.8%)		7 (4.3%)		2 (3.8%)		1 (2.5%)		

Table 2. Histopathology results and blood groups

Histopathology	0 Group		A Group		B Group		AB Group	
	Rh (+)	Rh (-)	Rh (+)	Rh (-)	Rh (+)	Rh (-)	Rh (+)	Rh (-)
Benign nodule	9 (50%)	3 (16.6%)	4 (36.3%)	0	5 (50%)	1 (10%)	1 (33%)	0
Malign nodule	5 (27%)	1 (5.5%)	6 (54.5%)	1 (0.9%)	2 (20%)	0	1 (33%)	0
Unknown	0	0	0	0	2 (20%)	0	1 (33%)	0

As a result of studies on the relationship between malignant diseases and blood groups have determined that some blood groups carry a higher risk of developing certain types of cancer (6). For example, people with A Rh-negative blood type have been found to have a higher risk of developing cancer in some types, such as colon cancer, which has a higher incidence (14). Likewise, people with B Rh-negative blood group have a higher risk of developing some types of cancer, such as kidney cancer (15), where it has a higher incidence. However, there is not enough evidence that these results have a definite cause-effect relationship (12). In particular, more detailed information about the relationship between malignant diseases and blood types can be obtained if more studies are carried out. This can help develop more effective strategies for the early detection and treatment of diseases.

Blood type and thyroid nodule are not known to have a direct relationship (16). Thyroid nodules are growths that develop within the thyroid gland, and while they are often benign, they can also be cancerous (2). On the other hand, blood type is determined by the presence or absence of specific antigens on the surface of red blood cells. However, some studies have shown an association between blood type and certain thyroid disorders (9, 12). There are few studies on differentiated malignancies of thyroid tissue (10). In the study of Vasan et al. (17), similar to ours, they could not detect any relationship between thyroid cancers and blood groups. Contrary to these results, another study determined that the risk of thyroid cancer showed lower incidence in patients with A compared to the O-group and reported that the non-B blood group compared to B-group showed similar results in their study (18).

Although the incidence of thyroid nodules in the population varies with each study, it is widespread, and 10% are malignant. In the study of Dagdeviren et al. (9), all nodules were benign, according to their biopsy results. According to them, there was no difference between the cases with and without benign thyroid nodules in ABO and Rh blood groups. In patients with benign thyroid disease, the blood distribution was O>A>B>AB, unlike A>O>B>AB, which is the distribution in the general Turkish population (19). Dagdeviren et al (9). attributed this difference to the fact that most of the study participants included in the study were patients with Hashimoto's thyroiditis and the high rate of O group. In our study, the participants' demographic data regarding blood groups were compatible, and the blood distribution was A>O>B>AB, similar to other studies in Turkey. The rates of thyroid operation were 15 (9.5%), 10 (6.2%), 1 (1.9%), and 2 (5%) in order of O, A, B, and AB groups. The rates of the FNAB history were 51 (32.3%), 39 (24.2%), 14 (26.4%), and 13 (32.5%) in the same order of blood groups. In the analysis of the nodule type, multinodular did not differ from solitary nodules among the blood groups. The histopathological distribution of malign nodules was as follows: O-groups: 6 (33.3%) (Rh+:27%; Rh-:5,5%), A groups: 7 (63,6%) (Rh+: 54,5%; Rh-:0,9%), B groups: 2 (20%) (Rh+:20%; Rh-:0%) and AB groups: 1 (33%) (Rh+:33%) Rh-:0%).

The most substantial aspect of the present study is that it is the first analysis to include the Bethesda classification and the clinical evaluation of the relationship between blood groups and thyroid malignancy. The most important limitation of the study was that we performed the study retrospectively and could not reach long-term follow-up data. Although there is a possibility that the data may not reflect the general population and may cause bias, with the absence of a control group and the inclusion of patients followed in a single center, it is almost impossible to provide this entirely in analyzes where distribution such as blood group is essential.

CONCLUSION

In conclusion, the malign nodule rate was highest in the A-group and lowest in the B groups, although it did not differ in the overall analysis. No relationship was found between the Bethesda categorization of nodules, their sizes, type of nodules, type of thyroid cancer, and ABO blood groups. While there may be a possible association between blood type and thyroid nodules, more research is needed to confirm and understand the underlying mechanisms.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karabük University Non-interventional Clinical Researches Ethics Committee (Date: 20.12.2022, Decision No: 2022/1195).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
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Which of the three different intramedullary nail designs is superior in the treatment of femoral shaft fractures?

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ABSTRACT

Aim: The aim of this study a retrospective comparison was the clinical and radiological results results of patients with femoral shaft fracture made oftreated with three different types of intramedullary nail (IMN).

Material and Method: The study included 54 patients operated on in our clinic because of femoral shaft fracture. The records were retrospectively examined of 18 patients applied with locked IMN (LIMN), 17 with blade expandable IMN (BEIMN), and 19 with talon distalfix IMN (TDIMN). The groups were compared statistically in respect of age, gender, BMI, affected side, operating time (mins), radiation exposure (number of shots), time to union (weeks), visual analog scale (VAS) score, soft tissue problems associated with implant irritation, amount of shortening (mm), coronal, sagittal and torsional angulation (degrees).

Results: The mean VAS score of the TDIMN group was determined to be statistically significantly higher than that of the LIMN and BEIMN groups (p=0.008, p=0.045). The operating times were similar in the BEIN and TDIMN groups (p=0.768) and significantly shorter than in the LIMN group (p<0.001). Radiation exposure was similar in the TDIMN and BEIMN groups (p=0.039), and the number of shots in the LIMN group was significantly higher than in the other two groups (p<0.001). The coronal angulation values were lower in the TDIMN group than in the BEIMN and LIMN groups (p=0.001, p=0.020). The sagittal angulation values were lower in the TDIMN group than in the BEIMN and LIMN groups (p=0.001, p<0.001). No significant difference was determined between the groups in respect of time to union, limb shortness, rotational deformity, and soft tissue problems related to implant irritation (p>0.05).

Conclusion: TDIMN is less resistant to axial loads due to its hook structure design. In fact, this is sometimes seen as a hook break. High VAS scores explain this. The sagittal and coronal angulation of the TDIMN is less, but the time to union, rotational angulation, and shortness development are similar in all three nails. This showed that all three nails did not have a significant advantage over each other in providing fracture stability.

Keywords: Femoral shaft fracture, intramedullary nail, distal hook, locking, blade expandable

INTRODUCTION

Intramedullary nails are most often selected because of the success in stabilisation of long bone fractures (1). Intramedullary nail (IMN) fixation is the standard treatment method for both femoral shaft fractures (FSF) and tibial shaft fractures. Bone union has been reported at the rate of 97% with IMNs applied in femoral fractures (2,3). IMNs are implants with the advantages of being minimally invasive, they can be applied rapidly, provide good fracture fixation, and allow early mobilisation (3). The factors of IMNs determining resistance to various forces are the nail design, whether or not it is grooved, the number, diameter, and placement of locking screws, the distance of the locking screws from the fracture region, and bone quality (1,4,5).

Different designs of IMNs are currently used in the treatment of femoral fractures. Some of these are screw and locking IMN (LIMN), blade-expandable intramedullar nail (BEIMN), and adjustable talon distalfix intramedullar nail (TDIMN) (6-8).

LIMN is currently often used for FSF. Rotational and axial stable fixation is thought to be provided due to the proximal and distal locking screws. However, important points that still have to be overcome are the risk of soft tissue damage, number of fluoroscopy images taken, prolonged operating time, and difficulties in the placement of distal locking screws (4,5). With the use of TDIMN, while fixation is provided in the proximal with

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classic locking screws, fixation in the distal is provided by the attachment of the adjustable hooks to the inner surface of the bone cortex (7). Although distal adjustable hooks seem to eliminate screw application problems in the distal, there can be considered to be a need for further research on the subject of stability. In BEIMN applications, there is no proximal or distal screw, but instead there is a blade and a grooved nail which passes within this blade. The blade expands the nail in the isthmus, proximal and distal diaphysiometaphyseal regions. Compression between the nail in the intramedullar canal and the endosteal region of the bone provides stability in the fracture line. In this design, no screw is applied in the proximal or distal (3,6,8)

To summarise the designs, in LIMN there is both proximal and distal screw locking, in TDIMN there is a locking screw only in the proximal, and in BEIMN there is no locking screw (3-8). These three nail designs show different biomechanical properties and are often used in FSF, so it is necessary to determine the advantages and disadvantages of each in respect of application and healing and to know the superiority of each over the others. The aim of this study was to determine the most stable IMN design, which would provide timely and healthy fracture healing, which can be applied easily, rapidly, and economically, with the least number of fluoroscopy images taken, for use in femoral fractures. The question we seek to answer in our hypothesis is: Can intramedullary nails with different designs used in the treatment of femoral shaft fractures show different healing patterns on fracture healing? Therefore, a retrospective comparison was made of the results of patients applied with LIMN, TDIMN, and BEIMN in our clinic in the treatment of FSF.

MATERIAL AND METHOD

Participant

The study was carried out with the permission of Hitit University Non interventional Clinical Researches Ethics Committee (Date: 28.02.2022, Decision No: 2022-04). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. In this study, patients who were operated by the same surgical team on between January 2014 and December 2020 using 3 different nails: Blade Expandable Nail System (Tianjin Walkman -China), Femoral İnterlocking Nail System (Double Engine-China) and Talon Distal Fix Femoral Nail System (USA). Fractures were classified according to the AO/OTA classification.

The patients included were those with AO 32A1, AO 32A2, and AO 32A3 type femoral shaft fractures who had been operated on with the correct technique and at least 2 years of regular follow up. The distribution by fracture subtype of AO 32A1, AO 32A2, and AO 32A3 consisted of 6, 7, 5 patients in the LIMN group, 5, 6, 6 patients in the BEIMN group, and 6, 7, 6 patients in the TDIMN group, respectively. Patients were excluded had an open fracture, pathological fracture, a fracture other than in the femur, a history of femur operation, multiple trauma of other systems, if they were smokers, had diabetes mellitus, any chronic systemic disease, or did not have complete radiological imaging or demographic data.

Experimental Approach

All of the 2-way femoral radiographs taken at 4-6 week intervals for union were evaluated chronologically. Presence of callus in at least 3 cortices was evaluated as radiological fracture healing (9, 10). Sagittal and coronal angulations were measured simultaneously by an experienced radiologist and orthopedist on leg length radiographs during patient follow-up. When fracture healing was detected, radiological measurements were assessed to decide if there is an angular deformity. For torsional evaluation, the whole femur was scanned with CT and axial scans of the femoral neck and femoral condyles were evaluated by drawing the first line along the posterior border of the femoral condyles and the second line through the femoral neck. Two vertical lines were drawn with respect to these lines respectively and the angle between them is referred as femoral torsion. The difference between the angle of the fractured leg and uninjured leg was compared to identify the angle of deformity in the fractured leg.

A record was made of operating time (mins), number of fluoroscopy images taken and time to fracture healing (weeks). The radiological images were examined of the patients with regular records at the end of follow up in respect of the mean amount of shortening in the fractured femur, the amount of angulation in the sagittal and coronal planes, and the development of rotational deformity (**Figure 1**). The visual analog scale (VAS) score at the end of one year postoperatively was taken as the criteria for functional results. The body mass index (BMI) data of the patients were evaluated. Differences between the groups were evaluated by comparing the available data.

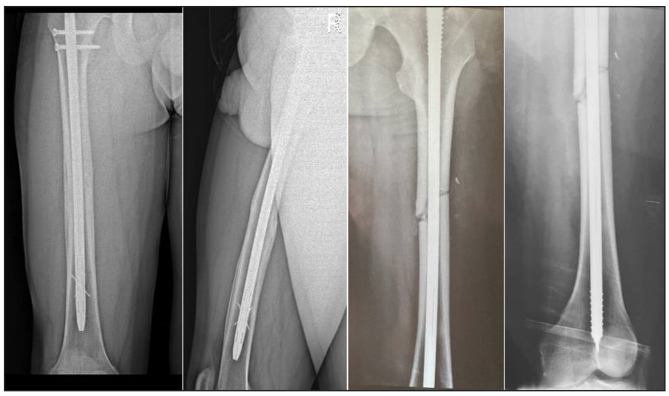

Figure 1. X-ray images of patients in the TDIMN and BEIMN groups

Procedures

Closed reduction of the fracture was obtained with a reduction device after entry to the intramedullar canal and femoral nail applications were made from the fossa priformis or the trochanteric region. A guidewire was advanced IMN within the reduction device. Sufficient reaming was obtained with reamers advanced over the guidewire in the intramedullar canal. When the fracture was reduced, final fixation was provided by the nail (2, 4).

In the first group, the LIMNs applied within the canal at 1mm smaller diameter than the diameter of the last reamer, were determined to be fixed with interlocking screws in the proximal (n:2) and distal (n:2). In the second group, the BEIMN diameter was determined to be selected as 1mm smaller than the diameter of the last reamer. The nail was adjusted to be facing the anterolateral of the femur that would provide compression of the blade groove. The length of the nails was selected to be of an appropriate length equivalent to the metaphysiodiaphyseal junction of the proximal and distal areas, which would provide expansion with the blade, and after the application, that the blade ends were in contact with the bone endosteum was determined with fluoroscopy. In the third group, the TDIMN diameter was determined to be 1mm smaller than the diameter of the last reamer. The adjustable distal hooks were attached to the bone inner cortex and by applying maximum torque, the hook opening was confirmed under fluoroscopy (**Figure 2**). To provide stronger fixation, the hooks were placed in the distal diaphyseal region without passing to the metaphyseal region. Fixation was provided with 2 locking screws in the proximal and 6 adjustable/retractable hooks of 38 mm diameter in the distal.

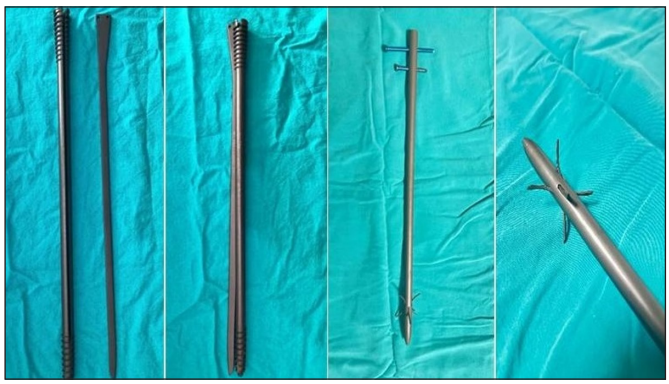

Figure 2. Images of the BEIMN and the adjustable TDIMN length and diameter measurements drawing

It was recorded that the nailing was performed in all the patients in the lateral decubitus position with the patient lying laterally and the affected side uppermost. Closed reduction was applied after traction of all the fractures. The applications were made with a lateral approach in the proximal femur. Under fluoroscopy guidance, the distal screws were applied free in LIMN applications, and in LIMN and TDIMN applications, the proximal screws were applied over the system guide.

Statistical Analysis

Statistical analysis of the data was conducted with the SPSS (SPSS Inc., Chicago, IL, USA) package program. The normal distribution of the data was tested with the Shapiro-Wilks test. Descriptive statistics for categorical variables were presented with frequency and percentage (%). Descriptive statistics of normally distributed continuous data were reported as mean±standard deviation (SD) and median (min-max) of non-normally distributed data. Comparison of continuous data between more than two independent research groups was performed with One-Way ANOVA for normally distributed data and Kruskal Wallis test for non-normally distributed data. Following the statistically significant ANOVA test, Tukey post-hoc pairwise comparison tests were used to determine between which groups the difference was. Following the statistically significant Kruskal Wallis test, Dunn-Bonferroni post-hoc pairwise comparison tests were used to determine between which groups the difference was. Comparisons of proportion between research groups were performed with either the Chi-square test or Fisher's exact test, depending on the sample size in the crosstab cells. The statistical significance level was evaluated as $p<0.05$.

RESULTS

The data of a total of 54 patients were analyzed. The groups were composed as 18 (33.3%) in the LIMN group, 17 (31.5%) in BEIMN, and 19 (35.2%) in TDIMN. The operated side was the left side in 27 (50%) patients, and the right side in 27 (50%) patients. The mean age of the patients was 35.29±10.47 years (range, 17-55 years) and the mean VAS score was 1.87±1.40 (range, 0-6). Soft tissue problems associated with implant irritation were seen in 5 (9.3%) patients.

The statistical findings of the comparisons between the groups in respect of age, gender, BMI, affected side, operating time, number of fluoroscopy images taken, time to fracture healing, VAS score, soft tissue problems associated with implant irritation, amount of shortening, coronal, sagittal, and torsional angulation, are shown in **Table 1**.

No statistically significant difference was determined between the groups in respect of age, gender, BMI, and affected side ($p=0.346$, $p=0.810$, $p=0.915$, $p=0.686$, respectively).

Table 1. Comparison of gender, side, age, VAS score, operation time, number of fluoroscopy images taken, time to fracture healing, shortening amount, coronal angulation, sagittal angulation, rotational angulation, and implant irritation variables among research groups

	LIMN (1) (n=18)	BEIMN (2) (n=17)	TDIMN (3) (n=19)	r (54)	p	Post-hoc p
Gender (F/M)	10/8	9/8	12/7	0.421	0.810[a]	-
Side (R/L)	10/8	9/8	8/11	0.755	0.686[a]	-
Implant irritation (Yes/No)	3/15	0/17	2/17	2.840	0.304[b]	-
	mean±SD (min-max)	**mean±SD (min-max)**	**mean±SD (min-max)**	**F (2,53)**		
Age	36.33±9.97 (19-54)	32.24± 8.04 (19-44)	37.05±12.59 (17-89)	5.755	0.346[c]	-
BMI	21.83±1.86 (18-25)	22.12±2.06 (18-25)	22.05±2.35 (19-27)	0.089	0.915[c]	-
Number of fluoroscopy images taken	93.11±7.17 (80-103)	51.59±7.77 (39-65)	45.21±7.79 (33-58)	213,105	**<0.001[c]**	**1-2:<0.001 1-3:<0.001 2-3:0.039**
Operation time (minutes)	77.89±9.44 (66-94)	46.06±4.99 (35-51)	43.05±8.03(33-65)	111.771	**<0.001[c]**	**1-2:<0.001 1-3:<0.001** 2-3:0.768
	median (min-max)	**median (min-max)**	**median (min-max)**	**Z(2)**		
Time to fracture healing (weeks)	20 (18-52)	22 (20-30)	20 (16-28)		0.061[d]	-
Shortening amount (mm)	2 (0-3)	3 (1-4)	2 (0-16)	2.830	0.243[d]	-
Visual Analog Scale Score	1 (0-2)	1 (0-2)	3 (0-6)	10.394	**0.006[d]**	1-2:1.000 **1-3:0.008 2-3:0.045**
Coronal angulation (degrees)	3 (2-4)	3 (2-4)	2 (0-6)	13.362	**0.001[d]**	1-2:1.000 **1-3:0.020 2-3:0.001**
Sagittal angulation (degrees)	4 (2-5)	3 (2-5)	1 (0-6)	20.090	**<0.001[d]**	1-2:1.000 **1-3:<0.001 2-3:0.001**
Rotational angulation (degrees)	3 (2-4)	3 (2-5)	3 (2-5)	5.295	0.071[d]	-

[a]Pearson Chi-Square test with frequencies, [b]Fisher exact test with frequencies, [c]One Way ANOVA test with mean±standard deviation, [d]Kruskal Wallis test with median (min-max), F: Female, M: Male, R: Right, L: Left, LIMN: Locked intramedullary nail, BEIMN: Blade expandable intramedullary nail, TDIN: Disafix talon intramedullary nail

The VAS scores showed a statistically significant difference between the groups (Z(2)=10.394; p=0.006). According to the post-hoc multiple comparisons, the VAS scores of the TDIMN group were statistically significantly higher than those of the LIMN and BEIMN groups (p=0.008, p=0.045). There was no significant difference between the VAS scores of the LIMN and BEIN groups.

Statistically significant differences were determined between the groups in respect of operating time (F(2,53)=111.77; p<0.001), number of fluoroscopy images taken (F(2,53)=213,105; p<0.001), angulation in the coronal plane (Z(2)=13.362; p=0.001), and sagittal angulation (Z(2) =20.090; p<0.001). According to the post-hoc multiple comparisons, the operating time of the LIMN group was statistically significantly longer than that of the TDIMN and BEIMN groups (p<0.001, p<0.001). There was no significant difference between the operating times of the TDIMN and BEIMN groups.

In respect of number of fluoroscopy images taken was significantly higher in the LIMN group than in the BEIMN and TDIMN groups (p<0.001, p<0.001). The number of fluoroscopy images taken in the BEIMN group was significantly higher than in the TDIMN group (p=0.039). The coronal angulation values of the TDIMN group were determined to be statistically significantly lower than those of the LIMN and BEIMN groups (p=0.020, p=0.001). The sagittal angulation values of the TDIMN group were determined to be statistically significantly lower than those of the LIMN and BEIMN groups (p<0.001, p=0.001).

No significant difference was determined between the groups in respect of time to fracture healing, limb shortness, rotational deformity, and soft tissue damage related to implant irritation (p=0.061, Z(2)=2.830; p=0.243, Z(2)=5.295; p=0.071, r(54)= 2.840; p=0.304, respectively). The operating times, number of fluoroscopy images taken, and time to bone union of the three groups are shown as a boxplot in **Figure 3**.

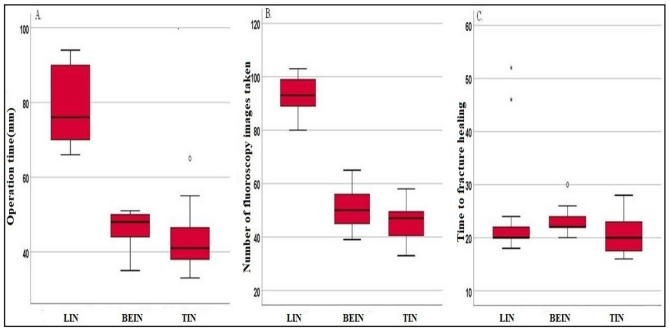

Figure 3. Boxplot of the distribution of operation time (minutes), number of fluoroscopy images taken and time to fracture healing among research groups

DISCUSSION

In this study, we compared the clinical and radiological results of our applications of three different designs of intramedullary nails, which are commonly used in femoral shaft fractures. The most important findings of our study are shorter operation times and less need for fluoroscopy in TDIMN and BEIMNs. TDIMN sagittal and coronal angulation was less common, but this had no effect on clinical improvement. The time to fracture healing, rotational angulation and shortening development were similar in all three nails. As a result, we determined that three different nails used in femur fractures did not have a significant clinical and radiological advantage over each other in ensuring fracture stability.

The primary aim of fracture treatment is to provide the optimum mechanical and biological environment for every stage of fracture healing (11, 12). It can be considered that the results of clinical studies of IMNs with different biomechanical properties will be of guidance to orthopaedic surgeons, as different nail designs may lead to different complications or may affect the fracture healing. Mechanical stimulation in the fracture region is necessary for bone repair. The stability of the fixation system and the movement formed as a result of functional loading are important for bone union (13,14).

The best means of stimulating callus development allows movements such as compression that support healing and prevents movements that could impair healing such as curving, rotational angulation, and tranlational shift (13,15,16). Axial and rotational stability in other nails is not as good as in IMNs. Delayed fracture healing and non-union associated with this property have been reported in many publications (3,7,17,18). Non-union rates have been reported as 10.5% in middle-aged patients with a closed femoral shaft fracture treated with closed reduction and LIMN (15). Shorter time to fracture healing have been reported in expandable nails compared to locking nails, but there are higher rates of non-union (22.6%) and revision surgery (16.1%) (3). Fracture stability is an important determinant of rapid union (12) and this is related to nail design. In studies that have compared the adjustable hook nail with conventional locking nails used in femoral and tibial fractures, these have been reported to delay bone union, but as expected the operating and fluoroscopy usage times were shorter (7,18).

In a study by Başaran et al. (6), the time to fracture healing in tibia shaft fractures was found to be longer with BEIN nail design compared to LIMN, but non-union did not develop in any patient. Full union was obtained in all the patients in the BEIMN group in the current study. In contrast to expectations, because of delayed union in 2 patients in the LIMN group, which is thought to be of more stable design, dynamisation was applied in the 16th week, and then full bone union was seen in the follow up. In the TDIMN group, there was a need for revision surgery because of non-union in 4 patients. In this TDIMN group, nonunion and revision surgery were performed with a rate of 21.05%. Delayed union was 11.1% in the LIMN group. Similar to the literature, the reflection of this in all cases consisting of 54 patients was found to be 3.7% for delyed union and 7.4% for nonunion. When the times to bone union were examined, the times were similar in the BEIMN, TDIMN, and LIMN groups. It was thought that in the TDIMN group, there could have been more rapid union because of the dynamic structure of the distal hook allowing axial loading and micromovement. In some patients of the current study TDIMN group, translational shift in the fracture line was determined and breaks associated with overloading in the hooks providing distal retention. This was evaluated as a sign that the hook design could not sufficiently withstand axial and translational loading. This condition originating from the structure of the hook providing distal retention could be responsible for the development of non-union related to stability failure in the TDIMN group. We think that the higher VAS scores in the TDIMN group are an indication that fracture healing is adversely affected. The delayed union seen in the LIMN group can be attributed to the reduced micro-movement in the fracture line associated with strong fixation, because problem-free union was obtained with nail dynamisation. It is striking that there were no union problems in the BEIMN group and the biomechanical compatibility between the bone and fixation material was seen to be more balanced.

It is known that just as the radiation-related risk of cancer is increased as a result of exposure to high doses, it may also develop with an accumulation over years of low doses such as in medical imaging (19). Radiation exposure associated with C-arm fluoroscopy used in operations increases the risk of lung and colon cancer in both males and females (20). Ionised radiation increases the risk of malignancy in the orthopaedic surgical team (21), and it has been reported that the cancer risk of orthopaedic surgeons is 5-fold higher than that of the general population (22). This risk is though to be related to the total ionised radiation from fluoroscopy used in all operations (20). It should therefore be a basic aim to minimise the lifetime cumulative radiation exposure of surgeons and the associated risks that can develop (23). Appropriate fluoroscopy safety precautions must be followed such as wearing suitable protective equipment, reducing the duration of fluoroscopy, and keeping the greatest distance from the radiation source (23, 24). Following the standard safety precautions will enable the surgical team to be exposed to the minimum level

of radiation and be within permissible limits (24, 25). To increase awareness of the dangers of radiation, it is important that surgeons, nurses, and technicians have information related to this (26). While this is the situation, there is a need for the development of surgical methods that will minimise the use and effects of radiation to be developed and become more widespread with accessible technologies. The minimising of radiation effects can be considered to be the second most important point after stability in the design of IMNs. By forming an electromagnetic field, nail designs with distal locking significantly reduce the duration of exposure to ionised radiation (27), suggesting that this could be a good alternative in the treatment of long bone diaphyseal fractures (28).

The operating time and fluoroscopy time have been found to be shorter in simple femoral shaft fractures treated with expandable nails compared to locking nails (3). In the treatment of long bone fractures applied with TDIMN, shorter operating and fluoroscopy times have been obtained (7, 18). Similarly, in both tibia and femur fractures applied with BEIMN, a shorter operating time and less use of fluoroscopy have been reported (8, 29). The number of scopy shots can be an indirect indicator of the radiation dose received. Because each scope chute emits radiation to the environment and we think that this is correlated with radiation exposure (30, 31).

When the numbers of fluoroscopy shots were examined in the current study, there was seen to be an increase in the order of TDIMN, BEIMN, and LIMN. The mean operating time was similar in the BEIMN and TDIMN groups, and this was shorter than in the LIMN group. The ease of application of the TDIMN and BEIMN nail designs reduced the operating time and the need for fluoroscopy. Distal locking screw fixation in the LIMN design was determined to have prolonged the operating time because of the freehand technique of application without an external guide and increased the duration of fluoroscopy to be able to confirm the appropriate distal screw placement.

Translational and rotational forces in the fracture line prevent fracture healing (1, 32, 33). Femoral malrotation has been reported in 20-30% of cases after IMN. While rotational angulation differences of <10° are accepted as normal variations, a difference of 10-14° shows a potential deformity, and ≥15° is accepted as a clinically and functionally significant real rotational deformity (34-36). A rasping procedure causing reduced rotational resistance of the bone prepares the ground for the development of rotational deformity (37), but that alone may not be effective as appropriate rasping and the placement of a nail of appropriate diameter will increase retention to the medullar canal.

Despite rasping applied to all three nail groups in the current study, that the rates of rotational deformity were similar in the groups supports this view. Rotational malalignment of the femur is stated as a difference in femoral anteversion between the healthy and injured legs. This can be determined clinically or with radiological measurements (38-40). Measurements were taken in this way in the current study and the results obtained were consistent with literature, with the highest rotational angulation of 5°. In previous biomechanical studies conducted with some expandable nail designs (41, 42), these were found to be insufficient in respect of rotational loading compared to locking nails. In contrast, there are also studies showing that resistance to rotational loading is similar to that of classic nails and resistance to compressive loading is weak (43). Bekmezci et al. (8) recommended that therefore, non-locking nails should not be used in multi-fragmented fractures and metaphyseal region fractures.

The relatively high rotational angulation in the TDIMN group of the current study and the translational shift determined on the radiographs may explain the rate of 21% non-union determined in this group.

Another problem in IMN is axial instability and this may result in shortness. Most authors advocate that static locking is appropriate for the prevention of rotation and shortening (44). By limiting micro-movement, static locking provides length of the fracture line and rotation is prevented (43). Static locking controls loading, shortening and rotation, but as stress is reduced in the fracture line, bone union is slowed down and osteolysis develops (44). In such a case, first dynamisation may be necessary if the nail design is suitable. There are many studies in literature about the timing of dynamisation. In different studies, the time of dynamisation applied to accelerate fracture union has been shown to vary between 9 and 24 weeks (45-47). With dynamisation, the loading on the bone over the implant stimulates callus formation and increases the hardness of existing callus (48-50). It was observed in the current study TDIMN group that the structure of the distal hook could not sufficiently withstand axial loading and broke, resulting in the development of shortness in the fracture line. As there was high stability against axial loading in the LIMN group, there was less development of shortness. The group where the least shortness developed assiciated with axial loading was the BEIMN group. However, the difference between the three groups was not statistically significant.

Angulation at the rate of 9% in sagittal and coronal planes has been reported in IMN applications in femoral fractures. This rate varies between 10% and 30% in fractures close to the proximal and distal regions in particular, and the rate for femoral shaft fractures is 2% (49).

It is thought that the angular deformities that develop could be due to malreduction, an unstable fracture pattern, or insufficient stability formed with IMN. Although these deformities are more frequent especially in young patients, it is possible to prevent them with correct bone fracture reduction and correct implant placement (52, 53)

No studies could be found in literature that showed a relationship between different nail designs and coronal and sagittal plane angulations following IMNs applied in femoral shaft fractures. Another subject of interest is what effects there could be of sagittal and coronal angulation on fracture healing. In the current study, while the coronal and sagittal angulations were similar in the BEIMN and LIMN groups, the values in the TDIMN group were lower than those of the other two groups. The low coronal and sagittal angulation values in the TDIMN group were thought to be due to the nail design. As the adjustable distal hooks provide more stable fixation, obtaining fixation from the cortical diaphyseal region with more compact bone provides resistance to bowing forces which can develop. In addition, reducing the distance between the fracture line and the distal fixation point of the fracture increases the fracture stability. It is recommended that to increase fracture stability there is a distance of at least 2cm between the fracture region and the screws distal of the nail (4, 31). These angular deformities that developed in all three groups did not have any effect on bone union.

Limitations

The limitations of our study, it can be said that it could not be studied in groups with larger sample sizes, since it was a retrospective study. Another limitation is the inability to perform biomechanical studies. However, time to fracture healing and the development of angular problems in IMNs indirectly give an idea about biomechanical stability. In our study, we assumed that the patients' initial alignment after surgery was anatomically normal. Comparing the clinical and radiological results of three different nail designs that have not been examined in the literature in FSF can be said to be the superior aspect of our study. Due to the small sample size, no comparison of fracture subtypes was made for all three intramedullary nails according to the AO classification. This is one of the limitations of our study.

CONCLUSION

In this study, we compared the results of three different IMN applications in FSFs. Since there is no need for screw locking in TDIMN and BEIMN designs, the need for fluoroscopy is less. Accordingly, the surgical time is shorter in these two groups. Although the sagittal and coronal angulation of the TDIMN is less, time to fracture healing, rotational angulation, and shortening development are similar in all three nails. This showed that all three nails did not have a significant advantage over each other in providing fracture stability. Revision surgery was required as a result of nonunion at a rate of 21.05% in the TDIMN group, and dynamization due to delayed union of 11.1% in the LIMN group. Nonunion or delayed union was not seen in BEIMN group.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Non-interventional Clinical Researches Ethics Committee (Date: 28.02.2022, Decision No: 2022-04).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Original Article

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Functional outcomes of periprosthetic and non-periprosthetic distal femur fractures: a comparative study

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ABSTRACT

Aim: The purpose of this study was to compare the outcomes of locked plating in closed distal femur periprosthetic, and non-periprosthetic fractures. We hypothesized that the outcomes would be superior in the non-periprosthetic distal femur fracture group.

Material and Method: Patients who underwent surgery for distal femur fractures between January 2019 and January 2022 were retrospectively reviewed. Patients aged under 18 years, who had multiple fractures, pathological fractures, follow-up less than 6 months, previous history of revision knee arthroplasty, interprosthetic fractures between hip and knee arthroplasties, fixation performed other than distal locking femoral plate and intra-operative periprosthetic fractures were excluded. Patients' age, gender, laterality, length of hospital stay, and follow-up duration were obtained from hospital registry notes. Fractures were classified using the AO classification system. At the last follow-up, visual analogue scale (VAS), Tegner activity score, Lysholm knee score, and short form 36 (SF-36) scores were noted.

Results: A total of 30 patients met the inclusion criteria and were included in the study. There were 14 patients in the non-periprosthetic fracture group and 16 patients in the periprosthetic fracture group. The periprosthetic group had significantly lower mean VAS score (p=0.047), Tegner activity score (p=0.015), and Lysholm knee score (p=0.034) than the non-periprosthetic group. The periprosthetic fracture group had significantly inferior quality of life scores compared to non-periprosthetic groups based on SF-36 sub-parameters.

Conclusion: Periprosthetic distal femoral fractures have inferior clinical outcomes and quality of life than non-periprosthetic fractures despite having similar fracture healing rate. Orthopaedic surgeons should be aware of the frailty of the patients caused by prior total knee arthroplasty surgery.

Keywords: Distal femur fracture, periprosthetic fracture, total knee arthroplasty, locking plate fixation, non-union

INTRODUCTION

Distal femur fractures account for less than 1% of all fractures. These fractures commonly occur secondary to high-energy trauma in young adults or low-energy trauma in the elderly. In addition, distal femur fractures in patients aged above 35 years of age are associated with generalized osteopenia or localized osteopenia around fracture (1,2). The number of periprosthetic distal femur fractures is increasing due to the high volume of primary knee arthroplasty performed. The reported incidence of these fractures ranges between 0.3% and 5.5% (3). The patient population of periprosthetic fractures and non-periprosthetic fractures after low-energy trauma generally have similar demographic characteristics (4,5).

Locking plates have become the primary treatment choice in both non-periprosthetic and periprosthetic distal femur fractures, with contemporary improvements in locking plate designs allowing minimally invasive fixation options. Locking plates designed in accordance with distal femur anatomy, brought the advantage of indirect reduction of the fracture during surgery, in addition to the improved bone-implant surface congruity. As these locking plates have anatomical design and are not suitable for bending, in the instances of femoral deformity, locking plates may not match the surface anatomy(6, 7).

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Although non-periprosthetic and low energy periprosthetic fractures have similar patient demographics, only a limited number of comparative analyses of functional healing and quality of life are available on either fracture type. In this study, we aimed to compare the clinical and radiographic outcomes of patients with non-periprosthetic, and periprosthetic distal femur fractures treated with locking plates.

MATERIAL AND METHOD

The study was carried out with the permission of Karabük University Clinical Researches Ethics Committee (Date: 13.12.2022, Decision No: 2022/1203). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants who participated in this study.

Patients who underwent surgery for distal femur fractures between January 2019 and January 2022 were retrospectively reviewed after local ethics committee approval. Patients aged under 18 years, who had multiple fractures, pathological fractures, follow-up less than 6 months, previous history of revision knee arthroplasty, interprosthetic fractures between hip and knee arthroplasties, fixation performed other than distal locking femoral plate and intra-operative periprosthetic fractures were excluded. Patents with a periprosthetic fracture and requiring revision knee arthroplasty due to implant loosening were also excluded. Patients with periprosthetic fractures after primary total knee arthroplasty and primary distal femur fractures were included in the study (**Figure 1**).

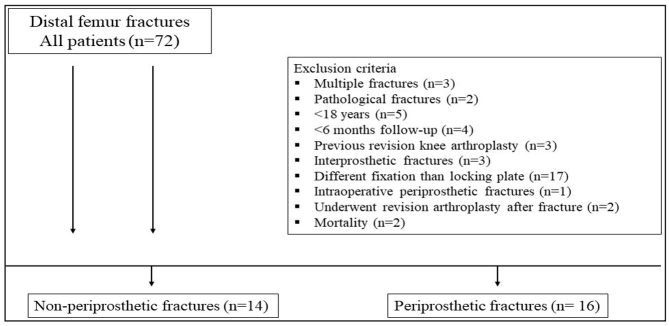

Figure 1. Flowchart of the included patients

Patients' age, gender, laterality, length of hospital stay, and follow-up duration were obtained from hospital registry notes. Fractures were classified using the AO classification system. At the latest follow-up, visual analogue scale (VAS), Tegner activity score, Lysholm knee score, and short form 36 (SF-36) scores were noted. Three bridging cortices in anteroposterior and lateral radiographs are considered as a bony union. Fractures that do not demonstrate three bony bridging cortices in AP and lateral radiograph at 6 months are considered as non-union. Complications were recorded. Patients were divided into two groups: the non-periprosthetic group (**Figure 2**) and the periprosthetic group (**Figure 3**). Groups were compared based on demographics, functional outcomes, quality of life parameters, and complication rates.

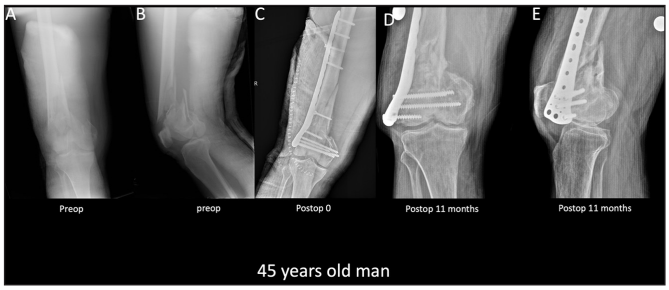

Figure 2. Anteroposterior (A) and lateral (B) radiographs of a 45-year-old male patient with a distal femur fracture treated with less invasive stabilization system plate (C). Anteroposterior (D) and lateral (E) radiographs demonstrating fracture healing.

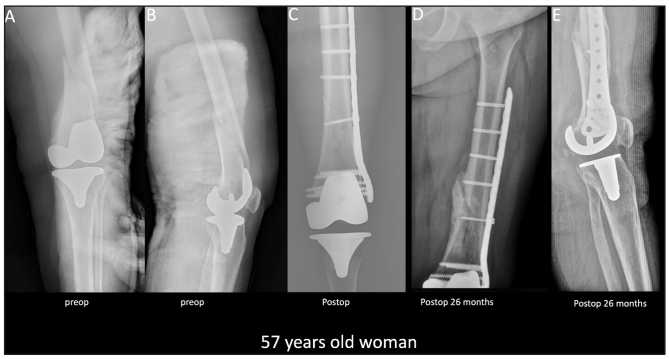

Figure 3. Anteroposterior (A) and lateral (B) radiographs of a 57-year-old female patient with a periprosthetic distal femur fracture treated with less invasive stabilization system plate (C). Anteroposterior (D) and lateral (E) radiographs demonstrating fracture healing.

Descriptive statistics were expressed as mean±standard deviation for continuous numerical variables, categorical variables were expressed as the number of patients and percentage. Distribution of variables was measured with the Kolmogorov-Smirnov test. Statistical analysis was performed for continuous variables with student t-test and Mann Whitney-U test when appropriate. Categorical variables were compared with Pearson Chi-square test. Analyses of the data were performed using the IBM SPSS Statistics 23.0 (IBM Corporation, Armonk, NY, USA) program. The results were considered statistically significant when the p-value was <0.05.

RESULTS

A total of 30 patients met the inclusion criteria and were included in the study. There were 14 patients in the non-periprosthetic group and 16 patients in the periprosthetic group. Other than periprosthetic group having more female patients (p=0.010), there were no statistically significant differences in demographic parameters between the groups (**Table 1**). Of the 14 non-periprosthetic fractures, 4 were AO 33A2, 2 were AO 33A3, 4 were AO 33B1, 1 was AO33B2, and 3 were AO 33C2 fractures. Of the 16 periprosthetic fractures, 13 were AO 33A2 and 3 were AO 33A3 fractures.

Table 1. Demographics of the patients.

	Non-periprosthetic group (n=14)	Periprosthetic group (n=16)	P value
Age	65.8±13.4	71.0±8.7	0.294
Gender (M/F)	8/6	2/14	0.010
Side (R/L)	7/7	6/10	0.491
Mean length of stay (days)	3.0±1.9	5.4±5.1	0.257
Mean time to union (months)	5.3±0.6	5.6±0.4	0.316
Mean follow-up (months)	21.0±8.6	21.3±13.3	0.984

(M: male, F: female, R: right, L: left)

The mean time to union and length of stay was similar between the groups (**Table 1**). The periprosthetic group had significantly lower mean VAS score (p=0.047), Tegner activity score (p=0.015), and Lysholm knee score (p=0.034) than the non-periprosthetic group. The periprosthetic group had significantly inferior quality of life scores compared to non-periprosthetic groups based on SF-36 sub-parameters (**Table 2**).

Table 2. Comparison of non-periprosthetic group and periprosthetic group on clinical parameters

	Non-periprosthetic group (n=14)	Periprosthetic group (n=16)	P value
Mean VAS score	1.4±1.3	3.3±2.6	0.047
Mean Tegner activity score	2.7±1.6	1.3±1.4	0.015
Mean Lysholm knee score	74.2±22.4	63.9±16.9	0.034
Mean SF-36 scores			
Physical functioning	58.5±35.5	15.6±24.4	0.001
Role limitation due to physical health	62.5±48.7	13.7±31.2	0.013
Role limitation due to emotional problems	61.9±48.6	13.7±32.2	0.022
Energy/fatigue	58.5±25.4	42.5±23.8	0.047
Emotional well-being	64.8±23.9	57.5±12.8	0.224
Social functioning	61.6±31.9	30.4±26.6	0.017
Pain	70.8±21.6	46.8±24.4	0.009
General health	63.5±22.3	34.0±15.8	<0.001

There was one non-union in the non-periprosthetic group. This patient was treated with retrograde intramedullary nailing and an augmentation plate. There was one non-union in the periprosthetic group who underwent surgery with dual plating and iliac crest grafting.

DISCUSSION

Distal femur fractures are challenging injuries due to high non-union rates and relatively unfavourable functional outcomes. There is paucity in the literature in regard to the quality-of-life changes after periprosthetic and non-periprosthetic distal femur fractures. In this study, we compared the clinical outcomes of patients underwent surgery due to both periprosthetic and non-periprosthetic distal femur fractures. We showed that the periprosthetic group had inferior functional outcomes and lower quality of life despite being treated with the same surgical approach utilizing locking plates.

Distal femur fractures are more common in female patients. In the present study, periprosthetic fractures were observed more in female patients, in line with the literature, however non-periprosthetic group had a more even gender distribution. We suspect this difference between the groups may have been caused by the low number of patients. In addition, the mean age of both groups were above 65, consistent with previous literature (8).

Poor bone quality at distal femoral region is one of the obstacles in the treatment of distal femur fractures. Although it is known that, locking plates are biomechanically advantageous to non-locking plates on osteoporotic bone, there are several studies pointing at the poor outcomes related to their use (9). These unfavorable outcomes can be attributed to wide facture gap and increased stiffness leading to delayed union or non-union (10). Furthermore, implant related complications has also been reported with use of locking plates (11). A meta-analysis done by Hendersen et al. (12) showed complication rates can reach up to 32% with locking plates including nonunion, delayed union, or implant failure. In a comparative study assessing the outcomes of locking versus non-locking plates in the treatment of periprosthetic fractures, non-locking plates showed inferior clinical outcomes, higher incidence of varus collapse, and earlier micromotion at the fracture (13-15). In current study, locking plates were used with minimally invasive percutaneous plate osteosynthesis (MIPPO) technique with locking and non-locking screws, given the theoretical advantages. Both periprosthetic and non-periprosthetic groups had comparable union rates (93.75% and 92.9%, respectively). There were no implant failure or reduction loss, and only one nonunion occurred in either groups. The high union, low complication rates could be attributed to the MIPPO technique preserving the soft tissues, maintaining the fracture gap below 1 mm, and establishment of dynamic osteosynthesis with locking plates.

There is controversy in the literature regarding the outcomes following the treatment of periprosthetic and non-periprosthetic fractures. Patients with periprosthetic fractures are believed to be frailer than with non-periprosthetic fractures. Therefore, periprosthetic fractures can be expected to have inferior outcomes than non-periprosthetic fractures. On the other hand, fixation of both periprosthetic and non-periprosthetic fractures are reported to have similar outcomes (4, 16). Our results show that, although

union rates and mean time to union were similar, periprosthetic group had significantly lower functional outcomes. It can be speculated that previous total knee arthroplasty is associated with frailty in patients, despite having similar fracture healing rates.

Arthroplasty is an option in the setting of a distal femur fracture. Relatively higher dissatisfaction and complication rate of fixation of these fractures influence the choice of arthroplasty. The advantages of the use of arthroplasty include immediate weight bearing and lack of non-union problem after surgery. However, the risk of infection and high cost are also disadvantages that should be considered (19, 20). Due to the possible lower functional outcomes after treatment with osteosynthesis of periprosthetic fractures, distal femoral arthroplasty may be a promising alternative option in these fractures (21).

Hintedra et al. (22) showed satisfactory functional outcomes in 24 elderly patients undergoing fixation with distal locking plates secondary to distal femur fractures, supported by our results for the non-periprosthetic group. However, there are several studies showing unfavorable outcomes with internal fixation in the treatment of elderly distal femur fractures (23,24). Hoffman et al. (25) stated that successful bone healing was achieved with locking plates in 36 patients with periprosthetic fractures but two thirds of the patients needed an ambulatory aid device in long term. In another study, results of distal femur fractures treated with locking plates by MIPPO technique was evaluated and age groups was compared. Patients younger than 35 years had excellent outcomes, while good results in between 35 and 50 year old group and only moderate and poor results in the patients aged above 50 group were reported (26). In contrast, study by Schütz et al. (27) evaluating the effect of fracture type, age, mechanism of injury, reduction technique and soft tissue injury on the outcomes of distal femur fractures failed to reveal any correlation. In the present study, periprosthetic group had lower functional outcomes parallel to the study done by Hoffman et al. (25) Older age, comorbidities, a secondary major surgery after total knee arthroplasty could be the factors compromising the mobility and functional capacity of the patients thereby decreasing the functional outcomes.

There are several limitations of this study. It has the disadvantage of its retrospective design and limited patient population. Moreover, it is a single centre study therefore the outcomes may not be generalized to the entire population. A study with a longer follow-up would be beneficial.

CONCLUSION

The results of this study suggest that periprosthetic distal femoral fractures have inferior clinical outcomes and quality of life than non-periprosthetic fractures despite having similar fracture healing rate. Orthopaedic surgeons should be aware of the frailty of the patients caused by prior total knee arthroplasty surgery.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karabük University Clinical Researches Ethics Committee (Date: 13.12.2022, Decision No: 2022/1203).

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Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Efficiency of low-intensity laser therapy in the treatment of lateral epicondylitis

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ABSTRACT

Aim: Lateral epicondylitis is the most common cause of lateral elbow pain and dysfunction, mainly caused by repetitive gripping or wrist extension during various activities. Although also known as tennis elbow, lateral epicondylitis often develops as a work-related condition and therefore poses an important public health concern. The aim of this study was to investigate the efficacy of laser in the treatment of patients diagnosed with lateral epicondylitis.

Material and Method: Patients who received low-intensity laser therapy (LILT) treatment and patients who received placebo LILT while waiting for extracorporeal shock wave therapy (ESWT) treatment with the same diagnosis were included in the study. A total of 60 patients in two groups of 30 were included in the study. The patients who received LILT treatment constituted the treatment group (n=30), and the patients receiving placebo LILT constituted the control group (n=30). VAS for resting and resisted wrist extension, HAQ, PRTEE-T pain, function, and total scales were used to measure patients' pain status and response to treatment. Results were compared by analyzing patient files and recorded data.

Results: A total of 48 (80%) subjects were female and 12 (20%) were male. The mean age of the control group was 47.8±7.4 years, and the mean age of the treatment group was 45.7±8.5 years. There was no significant difference between the two groups in terms of age, gender, and occupational distribution ($p>0.05$). In our study, the group treated with LILT showed statistically significant improvement in all parameters (VAS, HAQ, PRTEE) we investigated compared to the control group ($p<0.05$).

Conclusion: We concluded that LILT therapy has positive effects on symptoms and clinical findings in the conservative treatment of lateral epicondylitis. Further research is necessary to solidify the results and determine the optimal use of LILT for this condition.

Keywords: Lateral epicondylitis, ESWT, elbow pain

INTRODUCTION

Lateral epicondylitis (LE), commonly known as tennis elbow, is a musculoskeletal disorder affecting 1-3% of the population, particularly individuals aged 35-50 and women (1). The dominant elbow is more frequently affected by activities that cause repetitive and forceful wrist extension and supination. Symptoms usually associated with LE present with lateral elbow pain provoked by wrist extension and weak grip strength (2). Although "epicondylitis" literally means an inflammatory condition, studies have shown that no inflammatory cells are detected in or around the painful area (3). Instead, the cause of the condition is attributed to the rise in fibroblasts that results from tendon damage. This results in an alteration in the arrangement of collagen and an increase in vascular tissue at the extensor carpi radialis brevis origin. Therefore, lateral epicondylitis is characterized as a tendinosis caused by fibroblastic and vascular responses to angio-fibroblastic injuries, rather than an inflammatory condition (4).

To achieve a successful outcome in treating lateral epicondylitis, several factors including the patient's age, gender, duration of symptoms, triggering factors, and location of the lesion, are important to consider for recovery (5). A wide range of treatments have been studied for lateral epicondylitis, including protective ergonomic measures, kinesiotaping, acupuncture therapy, medical conservative and surgical treatments, and restriction of triggering activities in daily life. Physical therapy (PT) agents, such as laser, transcutaneous electrical nerve stimulation, and shock wave therapy (ESWT), are also commonly used (6-8).

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Laser therapy is a noninvasive, painless treatment that is often used in physical medicine and rehabilitation (PM&R) clinics. Recent studies have highlighted the efficacy of high-intensity laser therapy (HILT) in managing a range of athletic injuries, including tendon damage, bruises, and muscle cramps (9-12). However, the outcomes of utilizing low-intensity laser therapy (LILT) for the management of LE have been conflicting. The aim of this study is to examine the effectiveness of LILT in treating LE and contribute to the existing literature.

MATERIAL AND METHOD

The study was carried out with the permission of the İstanbul Training and Research Hospital Clinical Researches Ethics Committee (Date: 27.10.2011, Decision No: 05). All procedures were conducted in accordance with ethical guidelines and the principles of the Declaration of Helsinki.

This clinical trial included 60 patients (44 female and 16 male) who were followed up for 1 month at our PM&R outpatient clinic. The participants had unilateral elbow pain and an average age of 46.75±6.6 (ranging from 18 to 65). The same physician evaluated both the LILT treatment group and the placebo group before and one month post-treatment. Both groups were prohibited from taking pain relievers, except for paracetamol, and the control group was given only paracetamol and physical activity restriction. The physician evaluating the patients was blinded to group allocation. Individuals who didn't meet the following criteria were excluded from the study: a diagnosis of fibromyalgia, previous treatment for LE, on the same side, significant Rheumatoid Arthritis or inflammatory joint disease affecting the elbow or wrist, cervical radiculopathy, carpal or cubital tunnel syndrome, prior surgery on the elbow, prior radius or ulna fractures causing deformities in the affected limb, other elbow conditions, neurological issues in the affected arm, systemic metabolic diseases, disorders in the cervical or shoulder region, and bilateral elbow pain. The participants underwent a comprehensive patient history review and complete blood count and routine biochemistry tests. Clinical diagnoses were made using Mill's, Cozen's, resistant middle finger extension, and Thomsen's tests. The examination included assessment of pain in the elbow and forearm, pain on palpation of the lateral epicondyle, and pain during forced wrist extension. Participants who had a history of systemic inflammatory rheumatic disease, common infections, malignancy, heart failure, pregnancy, bursitis in the elbow, pacemaker, chronic respiratory disorders, epilepsy, neurological pathology in the upper extremity, recent arm or cervical surgery, local injections or physiotherapy to the elbow, or complaints in both elbows, cervical vertebrae, or other upper extremity problems were excluded from the study.

The study group received a total of 10 sessions of laser therapy applied to the affected elbow. A Class 1 type BF LED Gallium-Aluminum-Arsenide diode laser device with a wavelength of 808 nm and output of 1.6 W (made by Elettronica Pagani in Italy) was used at a dose of 3 Joule/cm^2 with a pulse rate of 3500 Hz and full contact technique at a right angle for six-minute treatment sessions, five days a week. For the control group, the same treatment process was followed as for the treatment group, but the laser device was not activated during the treatments. Symptoms and signs were assessed using the Visual Analog Scale (VAS) for wrist extension pain at rest and with resistance, the Health Assessment Questionnaire (HAQ) for general health status, and Patient Rated Tennis Elbow Evaluation (PRTEE-T) for lateral epicondylitis, including pain, special activities, and activities of daily living subgroups.

Statistical Analysis

The data analysis was conducted using SPSS version 25.0, developed by IBM Inc located in Chicago, USA. The descriptive statistics, including the frequency, proportion, mean, and standard deviation, were calculated. The Kolmogorov-Smirnov test was used to examine the distribution of the data. Comparison of independent samples were evaluated using independent sample T-test and Mann-Whitney U test. To assess repeated measurements, the paired sample T test and Wilcoxon test were employed. Chi-square test was used for proportional data analysis, while Fischer test was applied if Chi-square test was not suitable. The study has established a p-value of less than 0.05 as the threshold for statistical significance.

RESULTS

The study recruited a total of 60 participants, of whom 48 (80%) were female and 12 (20%) were male. The gender distribution of both groups showed no significant difference, with a p-value greater than 0.05. The ages of those in the control group averaged 47.8±7.4 years, while the mean age of the treatment group was 45.7 ± 8.5 years, with no significant difference in age distribution between groups. The initial patient demographics and clinical features are displayed in **Table 1**.

There was no statistically significant disparity in occupational distribution between the control group (with 2 civil servants, 14 housewives, 6 workers, and 8 retirees) and the treatment group (with 2 civil servants, 20 housewives, 7 workers, and 1 retiree), as determined by a p-value greater than 0.05.

The dominant hand distribution between the two groups did not yield any significant differences, with the majority being right-handed (27 in control group, 29 in treatment

group) and only a few being left-handed (3 in control group, 1 in treatment group) (p>0.05). The duration of complaints was 6.5 ± 5.6 months in the control group and 5.8±4.2 months in the treatment group. No statistically significant variations were seen regarding the two groups (p>0.05). Additionally, no statistically significant disparities were found in the frequency of reported traumas, repetitive movements, additional illnesses, or drug use between the two groups (p>0.05) as shown in **Table 1**.

Table 1. Socio-demographic and clinical characteristics of the participants

	Control group (mean±SD/n (%)	LILT group (mean±SD/n (%)	p value
Age (years)	47.8±7.4	45.7±8.5	0.319
Sex			1
Female	24 (80%)	24 (80%)	
Male	6 (20%)	6 (20%)	
Occupation housewife	14 (46.7%)	20 (66.7%)	>0,05
Retired	8 (26.7%)	1 (3.3%)	
Worker	6 (20.0%)	7 (23.3%)	
Official	2 (6.7%)	2 (6.7%)	
Duration of symptoms (months)	6.5±5.6	5.8±4.2	0.098
Dominant arm			0.612
Right	27 (90%)	29 (96.7%)	
Left	3 (10%)	1 (3.3%)	
Arm Affected			0.190
Right	20 (66.7%)	15 (50%)	
Left	10 (33.3%)	15 (50%)	
Trauma	0	0	-
Repetitive movement	5 (16.7%)	6 (20%)	0.573
Additional diseases	10 (26.7%)	8 (23.3%)	0.766

LILT: Low-intensity laser therapy, SD: Standard deviation (Chi-squared test)

The results revealed that VAS resting scores in the control group increased significantly compared to baseline (p<0.05), while VAS rest scores in the treatment group showed a significant decrease (p<0.05) after treatment compared to baseline. When the differences between the groups' initial and post-treatment VAS resting scores were compared, the difference was found to be statistically significant (p<0.05) (**Table 2**).

In the control group, the VAS-resistant wrist extension scores showed a rise after treatment compared to the baseline. However, the treatment group showed a significant reduction in VAS-resistant wrist extension scores (p<0.05) after treatment. The comparison of VAS-resistant wrist extension scores between the treatment and control groups showed a significant difference (p<0.05) post-treatment, with the treatment group exhibiting a decrease while the control group showed an increase (**Table 2**).

Our findings showed that the control group exhibited a rise in HAQ scores (p<0.05) post-treatment compared to pre-treatment, whereas the treatment group demonstrated a decrease in HAQ scores (p<0.05) post-treatment. The comparison of HAQ scores between the two groups showed a significant difference (p<0.05) in favor of the treatment group. The results also indicated that there was a significant difference (p<0.05) in HAQ scores after treatment in the treatment group compared to the control group, where there was an increase in the latter but a decrease in the former (**Table 2**).

In comparison, the PRTEE-T Questionnaire Pain Score showed a significant difference (p<0.05) between the two groups post-treatment, with a rise in the control group and a significant decrease in the treatment group. The difference was statistically significant (p<0.05) in the treatment group as seen in **Table 2**.

The findings demonstrated that the PRTEE-T Questionnaire Functional Score increased in the control group compared to pretreatment (p<0.05). Meanwhile, the treatment group showed a significant decrease (p<0.05) in the PRTEE-T Questionnaire Functional Score post-treatment. A notable discrepancy between the two groups was identified in **Table 2** and found to be statistically significant. significant (p<0.05) After treatment, the PRTEE-T Questionnaire Total Score in the control group increased significantly (p<0.05). In contrast, it significantly decreased (p<0.05) in the treatment group. **Table 2** highlights the significant difference (p<0.05) between the two groups in the PRTEE-T Questionnaire Total Score.

Table 2. Comparison of VAS, HAQ, and PRTEE scores of the groups before and after treatment

Outcome measure	Control Group			LILT group			p-value Between groups
	Baseline mean±SD	PT mean±SD	Difference	Baseline mean±SD	PT mean±SD	Difference	
VAS-R	5.0±1.9	6.3±1.9	+1.30±1.15	5.2±1.8	3.2±1.7	-2.20±1.69	p<0.00
VAS-RWE	6.0±2.4	7.4±2.2	+1.4±1.22	7.1±1.9	4.0±1.7	-3.13±1.5	p<0.00
HAQ	2.2±0.9	2.6±0.9	+0.47±0.42	3.0±1.1	1.6±0.8	-1.33±0.78	p<0.00
PRTEE-P	32.6±6.9	36.7±5.7	+4.03±4.9	35.2±5.6	22.8±7.1	-12.4±6.07	p<0.00
PRTEE-F	27.5±7.5	31.5±7.4	+4.03±4.4	35.3±7.1	21.8±6.7	-13.5±7.5	p<0.00
PRTEE-T	60.1±13.3	68.2±12.1	+8.07±9.01	70.6±11.6	44.6±13.5	-25.9±12.5	p<0.00

LILT: Low-intensity laser therapy, VAS-R: Visual Analog Scale resting pain, VAS-RWE: Visual Analog Scale resistant wrist extension pain, PRTEE Patient-Rated Tennis Elbow Evaluation Questionnaire, PRTEE-P: PRTEE pain score, PRTEE-F: PRTEE function score, PRTEE-T: PRTEE total score, SD: Standard deviation

DISCUSSION

Tennis elbow, or lateral epicondylitis, is a medical condition characterized by discomfort and pain in the elbow and arm, which originates from the lateral epicondyle of the forearm. It is aggravated by activities that require grasping, elbow extension during supination and pronation. Despite its name, tennis elbow affects individuals who are not involved in sports. Several treatments have been proposed for this condition, including local inections (steroids, PRP, dextrose prolotherapy) nonsteroidal anti-inflammatory drugs, splints, education, exercises, and ESWT, but a standart treatment with a clear consensus has not yet been established (13,14). In recent years, low-intensity laser therapy, a physiotherapy method, has been widely used for the treatment of LE, however, its efficacy continues to be disputed in the literature. The objective of this research is to assess the efficacy of LILT in treating LE, and to add to the existing knowledge base on the topic.

In our study, we examined the demographic characteristics of the groups, factors in the etiology of the disease, duration of symptoms, general health status, and treatment results in terms of pain and functional status. The incidence of lateral epicondylitis increases in females and between the ages of 30 and 60 (15,16) The mean age of participants in the control group in the study was 47.8±7.4 years, while it was 45.7±8.5 years in the treatment group. No significant age difference was observed between the two groups ($p>0.05$). These results match up with the findings from previous research in the field (17,18).

Stasinopoulos et al. (19) found that the disease was more prolonged and severe in women in their studies. Considering the gender distribution of our cases, 48 were female and 12 were male. In both groups, the gender distribution was 24 females and 6 males. Our study findings support the literature that the female gender ratio is high in LE cases.

The dominant arm is mostly affected in LE and may rarely be bilateral (20-22). In our research, we discovered that the majority of individuals with LE had their dominant side affected. The right side was dominant in 56 patients (93.33%) in the study, and the dominant side involvement was present in 39 patients (65%). The non-dominant extremity was involved in 21 patients (35%). This suggests that the dominant side is more at risk in daily life activities, but it can also be protected by keeping it on the non-dominant side to a large extent.

As reported in the literature, LE is commonly associated with excessive use of wrist extensors (23,24). Our study showed that the majority (80%) of individuals with this disorder were housewives. The conclusion aligns with previous studies, given that these occupational groups are known to frequently use wrist extensors.

In our study, all individuals with LE tested positive for the resistant wrist extension test (Cozen's Test). Additionally, the patients' pain levels during this test were evaluated using the VAS. The study found that those in the LILT treatment group had a significant improvement in various evaluation parameters, compared to the control group, including VAS rest and VAS resistant wrist extension, pain, functional, and total scores of the PRTEE-T questionnaire, and HAQ scores.

The utilization of LILT was first introduced in the 1960s, primarily for retinal detachment in 1962. Since LILT uses low energy levels, the tissue temperature remains below 1 degree, ruling out thermal effects as an explanation for its observed effects. Instead, nonthermal mechanisms are emphasized (25). There are several explanations for the pain-relieving effects of LILT, including alterations in neurotransmitter release, enhancement of intracellular messengers like ATP and calcium, and facilitation of tendon cell growth and collagen production (21,22). The potential mechanisms of LILT can be explained by preventing oxidative stress, reducing fibrosis in tendons, accelerating healing, and decreasing inflammation and pain in tendons (26,27).

Stergioulas et al. (28) randomly divided 50 patients into two groups to examine the effectiveness of LILT for LE. The laser group received GaAs laser treatment (Wavelength: 904 nm, Dose: 2.4) while the placebo group received fake laser treatment. The treatment protocol for both groups involved receiving 12 sessions over eight weeks, with two sessions per week in the first four weeks, and one session per week in the remaining four weeks. Patients' progress was evaluated before treatment, after eight weeks of treatment, and eight weeks post-treatment. The LILT group showed significant improvement in elbow range of motion, hand grip strength, pain during wrist extension, and rest pain (28). Our study demonstrated the effectiveness of LILT on hand grip strength, pain during wrist extension, and rest pain, which were similar to the findings in this study. However, since the elbow range of motion was not among our evaluation parameters, we could not compare it. Additionally, plyometric exercises were administered in both the control group and LILT groups in the aforementioned study, resulting in better control group scores than baseline levels, unlike in our study.

Lundeberg et al.'s (29) randomly assigned 57 patients to three groups to examine the effectiveness of LILT for LE. The study participants were divided into three groups, with 19 receiving GaAs laser treatment, 19 receiving HeNe laser treatment, and 19 receiving a placebo laser treatment. GaAs laser at 904 nm wavelength, 0.004 Joules/point energy dose, and HeNe laser treatment at 632.8 nm wavelength, 0.1 Joules/point energy dose were administered. A total of 10 treatment sessions were administered over 5-6 weeks, twice a week. Patients were evaluated for resting pain, resistant wrist extension pain, strength test, and hand grip strength. The study found that low-dose laser therapy did not produce a difference between the groups and therefore was not effective(29). However, our study showed that LILT is effective in treating LE, which contradicts the findings of Lundeberg et al. We think this difference may be because Lundeberg et al.'s treatment method did not irradiate the tendon but only targeted acupuncture points.

In a research study on the treatment of LE, the results showed that HILT (1,064 nm) was more effective than LILT (904 nm) in terms of SF-36 score, hand-grip strength, and QDASH scores, with a statistical significance of $p<0.05$. The trial involved 60 patients, with half receiving HILT and half receiving LILT, administered three times a week over a period of three weeks (17). Although HILT treatment was found to be more effective than LILT in that study, both were reported to be effective in the treatment of LE. Since we did not administer HILT treatment to our patients in our study, we could not compare it with LILT. However, the results found in our study were similar to the results regarding the efficacy of LILT in that study.

The short follow-up period and the low number of participants are the limitations of our study. In the literature, the long-term results of the improvement in disease parameters after the end of treatment are controversial.

Our findings align with previous research indicating LILT to be a viable treatment option for LE.

CONCLUSION

Our study found that the group receiving LILT for the conservative treatment of LE experienced a statistically significant improvement in all variables related to pain, functional activities, and activities of daily living. The results demonstrate that LILT is an effective treatment method for the short-term management of LE. Further research with larger participant numbers, extended observation periods, and various dosages and wavelengths is required to bolster these results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the İstanbul Training and Research Hospital Clinical Researches Ethics Committee (Date: 27.10.2011, Decision No: 05).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Correlations of renal parenchymal attenuations and CT severity scores on three consecutive CTs in COVID-19 patients

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ABSTRACT

Aim: We aimed to investigate the correlation between the temporal changes of computed tomography severity score (CT-SS) and mean renal parenchymal attenuation (MRPA) values in consecutive chest computed topographies (CT).

Material and Method: This retrospective, single-center study included 65 (≥18 years) COVID-19 patients with positive RT-PCR tests. A radiologist calculated three consecutive chest CT-SSs and measured the MPRAs on CTs from the upper half of each kidney included in the cross-section. Paired samples test and Wilcoxon signed-rank test were used to evaluate the temporal changes of mean renal parenchymal attenuation (RPA) and median CT-SS values, in three consecutive CTs. Spearman's test was used to evaluate the correlation of each RPA and CT-SS value on three consecutive CTs.

Results: The study population included 65 patients with a mean age of 61.49±13.91 years. A total of 36/65 (55.4%) were male. We found a significant increase between the first and second CT-SS ($p<0.001$) values, and a significant decrease between the first and second RPA ($p<0.001$) values. There were statistically significant moderate negative linear correlations between MRPA values and consecutive CT-SSs in COVID-19 patients (correlation coefficient [r]1=-0.320, p=0.009; r2=-0.381, p=0.002; r3=-0.393, p=0.001).

Conclusion: The decrease in renal parenchymal attenuation in non-enhanced computed tomography is related to the severity of pneumonia in COVID-19 patients and may be an attention factor for acute kidney injury.

Keywords: COVID-19, Coronavirus, CT severity score, renal parenchymal attenuation

INTRODUCTION

Coronavirus disease 2019 (COVID-19) affects the pulmonary system or extrapulmonary systems in severe cases. The responsible microorganism is "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2) (1). Many studies have reported that angiotensin-converting enzyme 2 (ACE2) is a functional receptor for SARS-CoV-2. Due to the dense presence of ACE2 receptors in the lungs, the lung is one of the most affected organs and can be seen in a wide clinical range from mild to severe (2). It is the intracellular entry receptor for SARS-CoV-2 of ACE2, which is also found in many organs such as the kidney, liver, and gallbladder outside the lung (3–5). The two most common kidney complications after COVID-19 are electrolyte imbalance with an incidence of 12.5%, and acute kidney injury (AKI) with an incidence of 11.0%, respectively. (6). In addition, the physiopathology in patients with elevated serum creatinine (SCr) levels after COVID-19 is unclear and the occurrence of AKI has been reported to be associated with poor prognosis (7–9). However, in a few studies, it has been reported that kidney damage may be due to cytokine storm, direct damage to the virus, hyperinflammatory immune response, and hypercoagulation (10–12).

On non-enhanced computed tomography (NECT) imaging of patients with AKI, there are thickening of the perirenal fascia, linear density increases due to inflammatory changes in the perinephric adipose tissue, and increases in fluid-related density (13,14). In NECT, due to fluid-related density changes, Hounsfield Units (HU) values are increased in low-density areas such as adipose tissue, while HU values are decreased in high-density areas such as parenchymal organs. In chest CT, the upper half of the renal parenchyma is included in the image, from which density measurements can be made.

CT severity scores (CT-SS) were developed to determine the pneumonia severity of patients on CT (15). CT-SS shows the severity of COVID-19 pneumonia, so it is a very

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important CT finding for the prognosis of patients. Total CT-SS was significantly higher in deceased COVID-19 patients than in convalescent patients, and in critical and severe patients compared to mild stages (16,17). A previous study suggests that renal parenchymal attenuation (RPA) measurement could be used as a quantitative method for COVID-19-associated kidney failure (13). In the literature, there are limited studies that measured CT density values in the renal parenchyma and compared these values with the severity of pneumonia (13,18). In these studies, CTs that were performed at the time of admission were used, and temporal changes of CT-SS and RPA values were not compared in follow-up CTs.

In this study, we investigated the correlation between severity scores (CT-SS) values and attenuation changes in the renal parenchyma in consecutive chest CTs.

MATERIAL AND METHOD

Our study is a retrospective, single-center study of 582 patients who applied to our hospital (February 2021 and February 2022). The study was carried out with the permission of Amasya University Faculty of Medicine Clinical Researches Ethics Committee (Date: 06.10.2022, Decision No: 96). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Study Population

Inclusion criteria: Patients older than 18 years of age and positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test were included in the study.

Exclusion criteria: Pediatric patients, pregnant women, patients with negative RT-PCR tests, those with image artifacts that prevent evaluation on NECT, patients with contrast enhancement CT, incomplete clinical data and chest CT images, outpatients, with urolithiasis, and/or hydronephrosis, unilateral or bilateral atrophic kidney, chronic kidney disease (CKD) and acute pyelonephritis were excluded from the study.

We excluded a total of 517 patients according to our exclusion criteria. So finally, a total of 65 COVID-19 patients were included in the study (**Figure 1**).

Clinical and Laboratory Data

All patients' demographic information, comorbidities, the laboratory findings obtained within 1 day from the initial chest CT data were reviewed from the electronic medical records of our hospital.

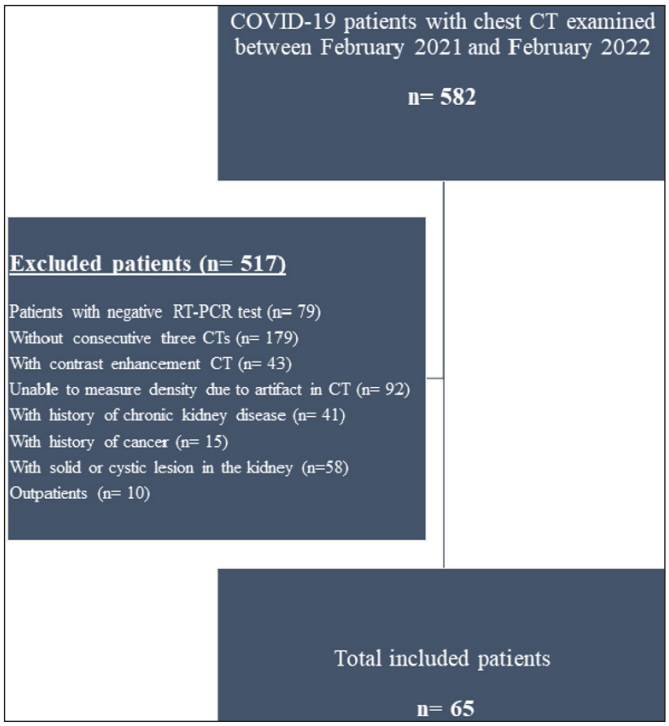

Figure 1. Flowchart for patient inclusion

Chest CT Image Acquisition

In all non-contrast chest CT scans, patients were instructed to hold their breath in the supine position. Axial images included areas from the beginning of the thorax to the middle part of the kidneys. Chest imaging was performed with a 128-slice CT scanner [(GE Healthcare Revolution EVO CT Milwaukee, WI)] using the routine protocols in our hospital.

Image Analysis

Chest CT images of the patients were retrospectively reviewed by a radiologist with 9 years of experience (XX), unaware of the patient's clinical data. CT severity scores (CT-SS) for COVID-19 pneumonia were calculated using a visual scoring system in CT images previously used in the literature (15). It was calculated as, 0 if there is no lung involvement; 1 if < 5% involvement; 2 if 5–25% involvement; 3 if 26–49%; 4 if 50-75% involvement; 5 if there is > 75% involvement. Total CT-SS is obtained by summing 5 lung lobe scores (score range: 0-25) (15) (**Figure 2a-c**).

The radiologist (XX) measured the renal parenchyma density on CT from the upper half of each kidney included in the cross-section. Renal parenchymal attenuation (RPA) values were measured by placing regions of interest (ROIs), each of approximately 0.5 cm^2, in three different areas of the parenchyma of each kidney. The average of 3 RPA values of each kidney was accepted as the RPA value of that kidney. The mean value of both kidneys [(Right RPA+Left RPA)/2] of each patient was used as the mean RPA (MRPA) value. This analysis was calculated on a total of three CTs of each patient, initially at admission and two at follow-up CTs (**Figure 2d-f**).

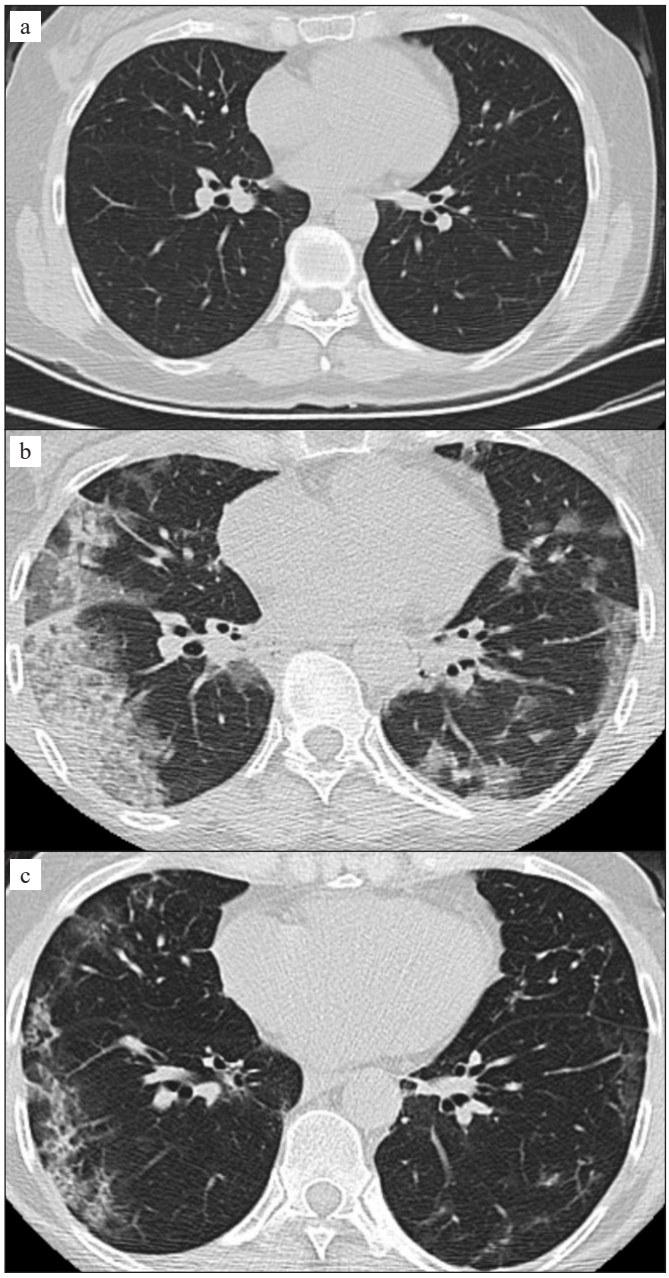

Figure 2 a-c. In three consecutive axial plane non-contrast CT images, **(a)** the first CT was normal, **(b)** the second CT showed peripherally located ground glass opacity, consolidation, and crazy paving pattern areas in both lungs. **(c)** On the third CT, the lesions appear to regress and linear band formations are observed [**(a)** CT-SS1=0; **(b)** CT-SS2=19; **(c)** CT-SS3=13].

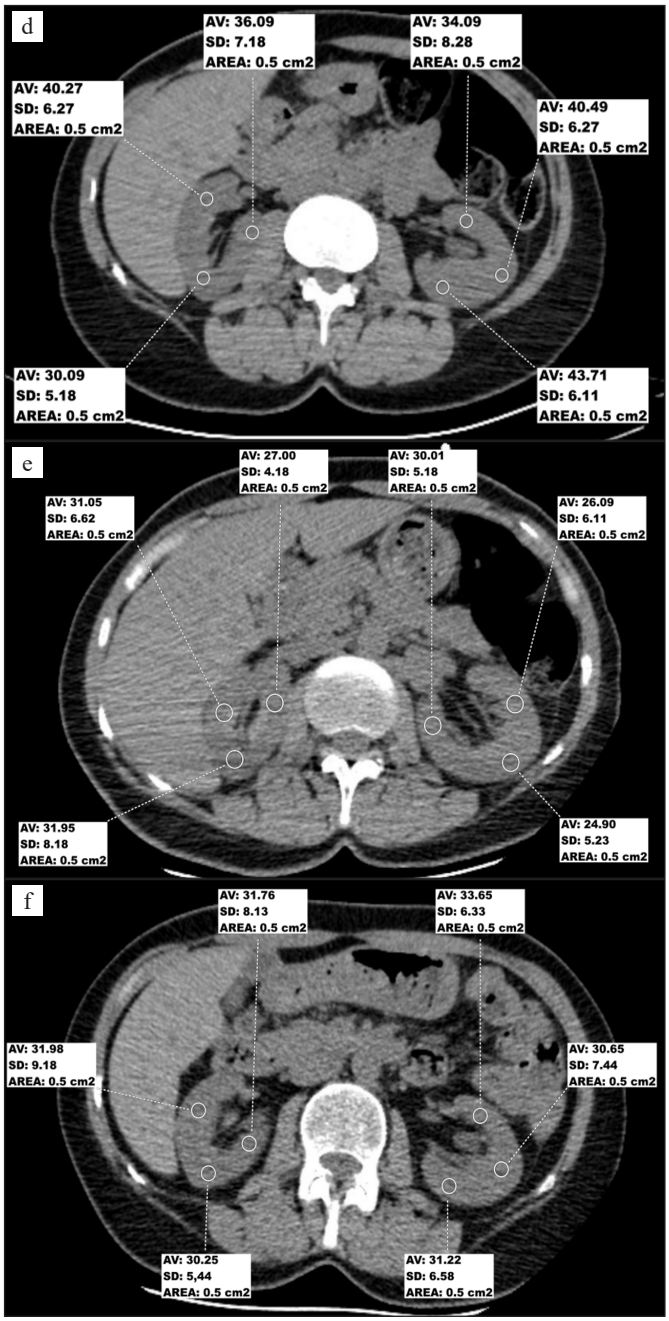

Fig 2 d-f. Renal parenchymal attenuation measurements are seen from slices passing through the kidney level on three consecutive axial plane non-contrast CT images [(a) mean RPA1=36.66 HU; (b) mean RPA 2=28.50 HU; (c) mean RPA 3=31.59 HU].

Statistical Analysis

We used SPSS Statistics for Windows, Version 22.0 (IBM Corp. Released 2017. Armonk, NY) for statistical analysis. The Kolmogorov-Smirnov test was used to examine the conformity of the variables to the normal distribution. CT-SS was considered the ordinal variable. In descriptive analyses, frequency and percentage were used for categorical variables; mean and standard deviation were used for continuous variables. Paired samples test and Wilcoxon signed-rank test (*) were used to evaluate the temporal changes of mean RPA and median CT-SS (*) values, in three consecutive CTs. Spearman's test was used to evaluate the correlation of each MRPA and CT-SS value on three consecutive CTs. A $p<0.05$ value was considered a statistically significant result.

RESULTS

Demographic Features

The study population included 65 patients with a mean age of 61.49 ±13.91 years. A total of 36/65 (55.4%) were male. Of all patients, 11/65 (16.9%) patients were treated in the ICU and 6/65 (9.2%) died. The most common comorbidities of the study population were cardiovascular disease (40/65; 61.5%), and diabetes mellitus (DM) (21/65; 32.3%) (**Table 1**). The mean CT-

SS on CT at admission was 7.72 ± 7.42 (0-25) and the mean MRPA was 39.69±5.54 (27.34-59.21). Among the laboratory findings, the mean serum blood urea nitrogen (BUN) value was 35.23±18.41 (11.00-103.00) and the mean serum creatinine (Scr) value was 0.94±0.35 (0.48-2.52) (**Table 2**).

Table 1

		Frequency	Percent (%)
Gender	Female	29	44.6
	Male	36	55.4
Death or alive	Alive	59	90.8
	Death	6	9.2
ICU?	Non ICU	54	83.1
	ICU	11	16.9
Chronic pulmonary diseases	Absent	49	75.4
	Present	16	24.6
Cardiovascular disease	Absent	25	38.5
	Present	40	61.5
Diabetes mellitus	Absent	44	67.7
	Present	21	32.3
Neurological Diseases	Absent	61	93.8
	Present	4	6.2

Table 2

	Mean	Std. Deviation	Min	Max
Age	61.49	13.91	32	89
First CT-SS	7.72	7.42	0	25
Second CT-SS	14.97	7.48	0	25
Third CT-SS	14.38	8.10	0	25
First MRPA	39.69	5.54	27.34	59.21
Second MRPA	35.12	4.30	26.00	45.00
Third MRPA	35.20	5.54	23.00	51.95
First RRPA	39.88	5.95	27.82	61.92
Second RRPA	35.10	4.54	21.67	46.27
Third RRPA	35.00	6.07	23.00	51.56
First LRPA	39.50	5.88	25.51	56.49
Second LRPA	35.15	4.85	23.00	47.67
Third LRPA	35.40	6.08	23.00	56.61
WBC (3.39–8.86; 10^9/l)	7.87	7.92	3.19	63.34
Neutrophil count (1.65-4.97; 10^9/l)	5.93	8.55	1.76	69.00
Lymphocyte count (1.17-3.17; 10^9/l)	1.41	0.78	0.32	4.64
CRP (0-5; mg/L)	41.55	47.20	1.17	174.00
Ferritin (22-322; ug/L)	320.18	818.03	6.30	6300.60
ESR. (0-30; mm/H) 1. hour	48.58	26.28	7.00	112.00
Blood urea nitrogen (16.6-48.5; mg/dl)	35.23	18.41	11.00	103.00
Serum creatinine (SCr) (0.7-1.2; mg/dl)	0.94	0.35	0.48	2.52
Creatinine kinase. (0-190; U/l)	112.80	99.28	17.00	676.00
Sodium (136-145; mmol/l)	137.63	2.84	129.00	143.00
Potassium (3.5-5.1; mmol/l)	4.37	0.40	3.72	5.57

CT-SS: CT Severity Score; RRPA: Right renal parenchymal attenuation (HU); LRPA: Left renal parenchymal attenuation (HU); MRPA: Mean renal parenchymal attenuation [(RRPA+LRPA)/2]

Temporal Changes of Consecutive CT-SSs and RPAs

We compared the temporal changes of the values of CT-SSs and MRPAs in three consecutive CTs, respectively. While there was a significant increase between the first and second CT-SS (p<0.001) values, there was a statistically significant decrease between the first and second RPA (p<0.001) values (**Figure 3**) (**Table 3**).

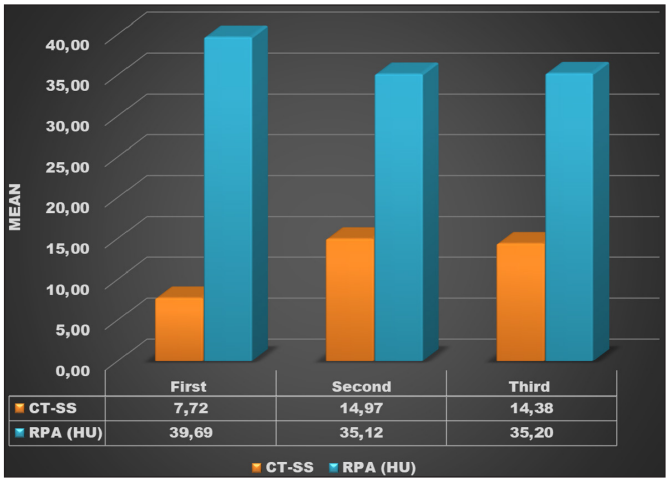

Figure 3. Bar chart showing the temporal changes of the mean CT-SS and RPA values in consecutive CTs.

Table 3

	Mean/Median	p value
CT-SS*		
Pair 1		<0.001
First CT	6.00	
Second CT	16.00	
Pair 2		0.566
Second CT	16.00	
Third CT	14.00	
RPA		
Pair 1		<0.001
First CT	39.69	
Second CT	35.12	
Pair 2		0.920
Second CT	35.12	
Third CT	35.20	

Pairwise comparisons were made using the Paired Samples t-test and Wilcoxon test (*). * Median values were used

Correlation Between RPA and CT-SS

We compared the correlations of CT-SS and MRPA values in three consecutive CTs, respectively. There were statistically significant moderate negative linear correlations between MRPA values and consecutive CT-SSs in COVID-19 patients (correlation coefficient [r]1=-0.320, p=0.009; r2=-0.381, p=0.002; r3=-0.393, p=0.001) (**Figure 4**).

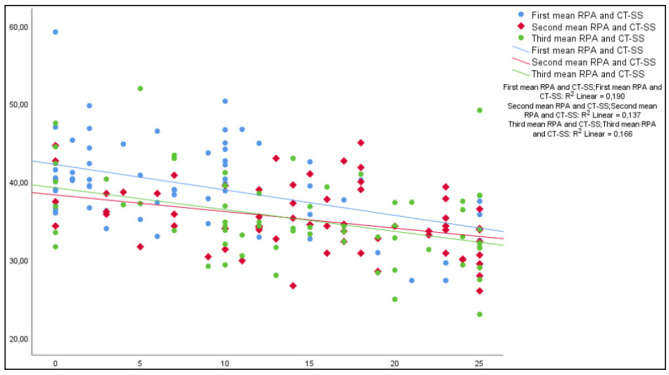

Figure 4. Scatterplot showing the correlation of the mean CT-SS and RPA values in consecutive CTs.

DISCUSSION

In our retrospective analysis, we investigated the temporal variation and correlation, between mean renal parenchymal attenuation (MRPA) and CT severity score (CT-SS). Our results showed that there was a significant negative correlation between MRPA and CT-SS in three consecutive CTs. While there was a significant increase between the first and second CT-SS, there was no significant increase between the second and third CT-SS. In addition, there was a significant decrease between the first and second MRPA, there was no significant decrease between the second and third CT-SS.

The most common kidney-related laboratory disorders after COVID-19 are hyperkalemia in blood analysis, proteinuria and hematuria due to AKI in urine analysis (6). ACE2 receptors, which are the entry gate of SARS-CoV-2 into the cell, are found in many organs in the body, but mostly in the ileum and kidneys (19,20). Since there are many ACE2 receptors in functional units of the kidney, the mechanism of damage by SARS-CoV-2 in this organ is not clear, but it has been suggested that many factors are effective (21). Many causes have been reported such as direct damage of the virus due to the intense content of ACE2 receptors in kidney cells, especially tubular and endothelial cells (22), disruption of the renin-angiotensin-aldosterone system (RAAS) (19), kidney damage due to treatment in severe patients, rhabdomyolysis associated with hyperventilation, renal hypoperfusion due to hypovolemia, abnormal coagulation and "cytokine storm" due to excessive inflammatory response (10,19,23). Prerenal factors cause AKI more frequently than renal factors in COVID-19 (24). Depending on these factors, RPA may decrease as a result of acute pyelonephritis, acute tubule damage, and swelling of endothelial cells due to an increase in the amount of intracellular fluid (10). The increased amount of fluid in the intracellular and extracellular areas of the renal parenchyma spreads to the extrarenal fatty tissue, resulting in hyperdense perinephric fat stranding on CT (10). Kunutsor et al. (6) reported the incidence of chronic kidney disease (CKD) before COVID-19 was 5.2% (2.8–8.1), while the incidence of AKI after COVID-19 was 11.0% (7.4–15.1) in their review. It has also been reported that pre-existing chronic kidney disease (CKD) is associated with poor prognosis in COVID-19, and the incidence of AKI increases after the disease (6,25,26). In our study, we eliminated patients with CKD that could contribute to changes in density because our main aim was to demonstrate the change in kidney parenchyma due to COVID-19 on CT. In addition, a decrease in RPA may occur in urinary obstruction, after the spontaneous passage of a stone, renal infection, inflammation, renal vascular disease, and renal trauma (27). Therefore, we excluded patients with urinary stones or hydronephrosis and underlying renal failure and pyelonephritis in our study.

Consistent with our study, Huang et al. (13) reported a statistically significant decrease in MRPA values compared to the control group after COVID-19. Huang et al. (13) compared the MRPA values of each COVID-19 patient with the control group in their study. Unlike this study, we investigated the mean values of RPA changes in consecutive CTs. We also included only inpatients to avoid heterogeneity of the patient population in our study. In our results, while there was a significant increase in CT-SS in the first and second CT, there was a statistically significant decrease in MRPAs. CT-SS and MRPA values in the first and second CTs of the patients showed a statistically significant negative correlation. As the severity of pneumonia increased and the patient's clinical worsened, kidneys were also affected and MRPA values decreased. There was no significant change in the second and third CT-SS values after appropriate treatment in the following period. As a result, no significant difference was found in the second and third MRPA measurements due to pneumonia and clinical stabilization of the patient. There was no significant change in the second and third CTs for both CT-SS and MRPA. In addition, MRPA values of consecutive CTs in COVID-19 showed a statistically significant negative linear correlation between CT-SS values (r1=-0.320, p=0.009; r2=-0.381, p=0.002; r3=-0.393, p=0.001). These findings suggest that RPA measurement and temporal variation may be a potential indicator for AKI associated with COVID-19 severity.

Differently, we found a negative correlation between MRPA and CT-SS values in three consecutive CTs. To our knowledge, this is the first study to evaluate temporal changes in CT-SSs and MRPAs in consecutive CTs in COVID-19 patients. We found that increasing CT-SS values caused a decrease in MRPAs.

The current study has several limitations. First, our study was a single-center retrospective analysis. Therefore, a multicenter prospective study is needed for more validation. Second, as the patients' non-contrast chest CTs were evaluated, the upper pole and middle parts of the kidneys were included in the images. It was more appropriate for the entire kidney to be included in the evaluation area. But in our study, chest CTs of COVID-19 patients were scanned retrospectively.

CONCLUSION

The decrease in renal parenchymal attenuation (RPA) in NECT is related to the severity of pneumonia in COVID-19 patients and may be an attention factor for acute kidney injury. Therefore, when evaluating chest CT scans of COVID-19 patients, examination of the renal parenchyma and adjacent fatty tissue for RPA may provide useful information about COVID-19-related kidney damage.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Amasya University Faculty of Medicine Clinical Researches Ethics Committee (Date: 06.10.2022, Decision No: 96).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Does recipient weight and surgical approach really matter in pediatric renal transplantation?

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ABSTRACT

Aim: To compare the outcomes between low-weight (<15 kg) and normal-weight (≥15 kg) children who underwent renal transplantation (RT) and investigate the impact of the surgical approach (intraperitoneal or extraperitoneal RT).

Material and Method: This study was designed as an observational single-centre study and was conducted in Istinye University Hospital, Istanbul, Turkey, between January 2018 and June 2021. Data including age, gender, weight, surgical approach (intraperitoneal/extraperitoneal), complications, length of hospital stay, graft and patient survival were collected. Low-weight (LW) and normal-weight (NW) patients were compared. A p value less than 0.05 was considered statistically significant.

Results: Overall, 107 (33 LW and 74 NW) patients aged between 1 and 17 were included. The LW group had a significantly lower age and a significantly longer duration of intensive care unit (ICU), and inpatient floor stays than the NW group ($p<0.001$). Intraperitoneal RT (IRT) was significantly more common in the LW group (57.6% vs 42.4%), while ERT was more frequent in the NW group (87.8% vs 12.2%) ($p<0.001$). Both early complication and mortality rates were significantly higher in the LW group than in the NW group ($p<0.001$ and $p<0.031$). A comparison between the LW and NW patients who underwent ERT revealed that the mean patient age was significantly lower, while the duration of ICU stay was higher in the former than in the latter group ($p<0.001$ and $p<0.004$). However, the length of inpatient floor stay, early-term complication, and mortality rates were similar ($p>0.05$).

Conclusion: The extraperitoneal approach should be encouraged in children weighing less than 15 kg.

Keywords: Renal transplantation, pediatric, low-weight, extraperitoneal, intraperitoneal

INTRODUCTION

Renal transplantation (RT) is the ideal treatment method for pediatric patients with end-stage renal disease (ESRD) (1). Nevertheless, RT can be challenging in children due to size mismatch between donors and recipients (2). Therefore, there is a relatively higher risk of surgical complications, graft loss, and recipient mortality in children than in the adult patient population (3). These risks are amplified particularly in low-weight (LW) children (i.e., children weighing 15 kg or less).

In these children, the traditional surgical approach is intraperitoneal RT (IRT) performed by a midline laparotomy incision (4). Surgeons performing IRT defend that the intraperitoneal space will provide a relatively larger compartment for the insertion of the renal graft, especially for kidneys donated by adult donors (5). On the other hand, some surgeons prefer performing extraperitoneal RT (ERT) in both adults and children irrespective of recipient weight. These surgeons believe that IRT can increase the risk of bowel complications and therefore lengthen the duration of hospital stay (4).

In our pediatric RT program, both IRT and ERT are performed in both LW and normal-weight (NW) (i.e., 15 kg or more) pediatric patient populations. Therefore, our study aimed to compare the outcomes between LW and NW children who underwent RT and investigate the impact of the surgical approach (IRT or ERT) in the results of this comparative analysis.

MATERIAL AND METHOD

Children (age<18) who underwent RT at our center between January 2018 and June 2021 constituted the target population of this study. The study was carried out with the permisson of İstinye University Human Researches Ethics Committee (Date: 10.02.2022, Decision No: 21-90). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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The transplant program's patient database was reviewed. Patients with incomplete data, those who underwent multi-organ transplantation, or deceased donor en bloc RT were omitted. Demographic parameters such as age, gender, and clinical data, including primary disease, history of RT, pre-RT dialysis status (preemptive/hemodialysis/peritoneal dialysis), recipient weight, recipient body mass index (BMI), donor type (live or deceased donor), donor kidney side (left or right kidney), donor data including age, gender, BMI, glomerular filtration rate (GFR) and renovascular variations, type of surgical approach (IRT/ERT), need for concurrent surgery during RT, intraoperative and early-term complications, length of inpatient floor and intensive care unit (ICU) stay, functional status of the renal graft (functioning/failed) and patient survival one year after transplant were collected from the database. In addition, immunological data such as panel reactive antibody (PRA), and human leukocyte antigen (HLA) mismatch, were retrieved from the database and analyzed. A comparative analysis was performed between LW and NW patients regarding these data parameters. We made a similar comparison within the group of patients who underwent ERT.

Perioperative Care

Hemodynamic states of the children were continuously monitored during RT surgeries. A central venous catheter was inserted in all cases to measure the central venous pressure (CVP) constantly. The CVP was maintained at levels higher than 15 cmH2O immediately before reperfusion. All children were referred to the pediatric ICU and followed in the ICU for at least 24 hours. Urine output was monitored hourly, and intravenous fluid replacement was performed according to the patients' urine output and hemodynamic status. Renal function tests, including urea, creatinine, and electrolytes, were performed twice daily during the ICU stay. Perfusion of the renal graft was checked by a bedside Doppler ultrasound during the postoperative first day regardless of the patient's urine output. It was repeated during the inpatient stay as needed. The decision regarding referral to the inpatient floor was given by the ICU and transplant surgery teams. Renal function tests were performed daily during the inpatient floor stay.

Standard immunosuppression (IS), including intravenous basiliximab on days 0 and 4 and intravenous methylprednisolone or oral prednisone, tacrolimus, and mycophenolate mofetil (MMF) was given in all cases. Oral prednisone doses were reduced daily, and MMF was replaced with mycophenolate sodium in patients complaining about gastrointestinal symptoms. We preferred anti-thymocyte globulin (ATG) for IS induction in hypersensitized or deceased donor kidney recipients.

The RT surgeries were performed as IRT or ERT according to the surgeon's preference. In IRT, a transperitoneal midline incision was made, and the kidney was transplanted to the retroperitoneal space after colon mobilization. However, in ERT, a Gibson incision was made, and the kidney was transplanted to the iliac fossa after pushing the peritoneum aside for exposure to the iliac vessels. The renal artery was anastomosed to the common iliac artery or aorta by continuous sutures. The common iliac vein or inferior vena cava was preferred for venous anastomosis. The extravesical Lich-Gregoir method with a 5F double J stent insertion was used for all ureteral reimplantation procedures. A Jackson-Pratt surgical drain was routinely used. The primary surgeon gave the decision regarding drain removal based on drain output. The double J stent was removed after the completion of the third postoperative week.

Early surgical complications were defined as complications occurring between the transplant surgery and the patient's discharge.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 25.0 software (IBM Corporation, Armonk, NY, US). In order to investigate whether the normal distribution and, variance homogeneity assumptions were met were analyzed by Shapiro-Wilk and, Levene tests; respectively. Categorical data were expressed as numbers (n) and percentage (%) while quantitative data were given as mean ± SD and median (25th - 75th) percentiles. While the mean differences between groups were compared Student's t test, otherwise, Mann Whitney U test was applied for the comparisons of not normally distributed variables. Pearson's $\chi 2$test was used in the analysis of categorical data unless otherwise stated. On the other hand, in all 2 x 2 contingency tables to compare categorical variables; the Continuity corrected $\chi 2$test was used when one or more of the cells had an expected frequency of 5-25, otherwise, the Fisher's exact test was used when one or more of the cells had an expected frequency of 5 or less. In all R x C contingency tables to compare categorical variables; Fisher Freeman Halton test was used when ¼ or more of the cells had an expected frequency of 5 or less. A p value less than 0.05 was considered statistically significant.

RESULTS

After applying the inclusion and exclusion criteria, 107 patients aged between 1 and 17 were included in this study. Among all, 60 (56%) were male, while 47 (44%) were female. All but 3 patients underwent the first RT. In total, 99 (92.5%) recipients underwent living donor kidney transplantation (LDKT), while 8 (7.5%) received kidneys from deceased adult donors. The results of the comparative analysis between LW and NW children are displayed in **Table 1** and **Table 2**.

Table 1. Demographic and clinical characteristics of cases compared regarding body weights

	<15 kg (n=33)	≥15 kg (n=74)	p-value
Age (years)	3 (2-4)	13 (10-16)	<0.001†
Gender			0.675‡
Boys	20 (60.6%)	40 (54.1%)	
Girls	13 (39.4%)	34 (45.9%)	
Height (cm)	80.0 (73.5-87.0)	140.5 (124.5-155.0)	<0.001†
Weight (kg)	11.0 (10.0-13.0)	37.5 (25.0-45.5)	N/A
Body mass index (kg/m²)	17.2 (14.4-19.0)	17.6 (16.0-20.8)	0.254†
Second transplantation	0 (0.0%)	3 (4.1%)	0.551¶
Diagnosis			0.215¥
Nephrotic syndrome	13 (39.4%)	16 (21.6%)	
Lower urinary system pathology	5 (15.1%)	16 (21.6%)	
Polycystic kidney disease	3 (9.1%)	5 (6.8%)	
Focal segmental glomerulosclerosis	0 (0.0%)	9 (12.1%)	
Atrophic kidney	2 (6.1%)	4 (5.4%)	
Other	3 (9.1%)	5 (6.8%)	
Unknown	7 (21.2%)	19 (25.7%)	
Dialysis status			0.005§
Preemptive1	16 (48.5%)a	18 (24.3%)a	
Hemodialysis2	9 (27.3%)b	45 (60.8%)b	
Peritoneal dialysis	8 (24.2%)	11 (14.9%)	
History of abdomen surgery	4 (12.1%)	9 (12.1%)	>0.999¶
Surgical approach			<0.001‡
Intraperitoneal	19 (57.6%)	9 (12.1%)	
Extraperitoneal	14 (42.4%)	65 (87.9%)	
Concurrent surgery	23 (69.7%)	14 (18.9%)	<0.001‡

† Mann Whitney U test, ‡ Continuity corrected χ2 test, ¶ Fisher's exact test, ¥ Fisher Freeman Halton, § Pearson's χ2 test. N/A: Not applicable.1 p=0.024 for the comparison in terms of preemptive, 2p=0.003 for the comparison in terms of hemodialysis.

Table 2. Demographic and clinical characteristics of cases compared regarding body weights – continued

	<15 kg (n=33)	≥15 kg (n=74)	p-value
Donor's age	36.0 (30.0-46.0)	39.0 (35.0-49.0)	0.109†
Donor's gender			0.889‡
Male	14 (42.4%)	34 (45.9%)	
Female	16 (48.5%)	35 (47.3%)	
Cadaver	3 (9.1%)	5 (6.8%)	
Donor's height (m)	1.65±0.089	1.66±0.078	0.726¶
Donor's weight (kg)	78.2±15.2	77.4±13.3	0.787¶
Donor's body mass index (kg/m2)	28.8±5.5	28.3±5.3	0.710¶
Kidney size	110.1±8.0	107.5±9.6	0.199¶
Localization			0.026¥
Right	2 (6.7%)	20 (29.4%)	
Left	28 (93.3%)	48 (70.6%)	
Donor's GFR	114.3±21.9	107.7±17.3	0.112¶
Short term complication	14 (42.4%)	9 (12.1%)	<0.001¥
Mortality	4 (12.1%)	1 (1.4%)	0.031§
Duration of mortality (months)	0.36 (0.21-18.1)	N/A	N/A
Failed graft	1 (3.0%)	1 (1.4%)	N/A
Mismatch			0.562#
0	2 (6.1%)	7 (9.5%)	
1	3 (9.1%)	9 (12.1%)	
2	1 (3.0%)	8 (10.8%)	
3	20 (60.6%)	32 (43.2%)	
4	4 (12.1%)	14 (18.9%)	
5	1 (3.0%)	2 (2.7%)	
6	2 (6.1%)	2 (2.7%)	
PRA 1 positivity	3 (9.1%)	12 (16.2%)	0.385§
PRA 2 positivity	9 (27.3%)	21 (28.4%)	>0.999¥
Vascular variation			0.269§
Single artery – single vein	32 (97.0%)	66 (89.2%)	
Double artery – single vein	1 (3.0%)	8 (10.8%)	
Length of ICU stay	1 (1-3)	1 (1-1)	<0.001†
Hospitalization	9 (7-14)	7 (6-9)	<0.001†

†Mann Whitney U test, ‡ Pearson's χ2 test, ¶ Student's t test, ¥ Continuity corrected χ2 test, § Fisher's exact test, # Fisher Freeman Halton test, GFR: Glomerular filtration rate, PRA: Panel reactive antibody, ICU: Intensive care unit, N/A: Not applicable.

There were 33 patients in the LW and 74 patients in the NW group. The LW group had a significantly lower age, height, and a significantly longer duration of ICU and inpatient floor stays than the NW group (p<0.001). In addition, the rate of preemptive RT was significantly higher in the LW group, while the rate of hemodialysis (HD) patients was higher in the NW group (p=0,024 and p=0.003). Two groups were similar regarding the rate of peritoneal dialysis (PD) (p=0,369).

The comparison regarding the surgical approach revealed that IRT was significantly more common in the LW group (57,6% vs. 42,4%) while ERT was more frequently performed in the NW group (87,8% vs. 12,2%) (p<0.001). In addition, the rate of concurrent surgeries was significantly higher in the LW group than in the NW patient group (p<0.001). The most common simultaneous procedure was unilateral or bilateral nephrectomy of native kidneys in the entire cohort (35 of 107 cases; 32,7%). While the left donor kidney was transplanted more frequently in the LW group, the right kidney was used significantly more often in the NW group (p=0.026).

The comparison of complication rates revealed that both early complication and mortality rates were significantly higher in the LW group than in the NW group (p<0.001 and p<0.031). The most common complications were ileus (n=5), followed by urosepsis (n=4), wound infections (n=3), and renal allograft compartment syndrome (RACS) (n=1). Four patients (2 due to urosepsis, 2 due to cardiac failure) in the LW and one (due to urosepsis) in the NW group died during early-term follow-up. There was no difference between the LW and NW groups regarding other analyzed data parameters (p>0.05) (Tables 1 and 2). One patient in the LW group had graft thrombosis due to RACS, while another patient in the NW group experienced graft failure due to rejection. Although a similar comparison was not possible in the IRT group due to low patient numbers, our study also included a comparative analysis of the demographic and clinical data of the LW and NW patients who underwent ERT (**Tables 3** and **4**).

Table 3. Demographic and clinical characteristics of cases with extraperitoneal approach compared regarding body weights

	<15 kg (n=14)	≥15 kg (n=65)	p value
Age (years)	3 (3-4)	13 (11-16)	<0.001†
Gender			>0.999‡
Boys	7 (50.0%)	34 (52.3%)	
Girls	7 (50.0%)	31 (47.7%)	
Height (cm)	80.0 (79.5-86.2)	142.0 (125.0-155.0)	<0.001†
Weight (kg)	11.0 (9.9-12.1)	38.0 (25.0-46.0)	N/A
Body mass index (kg/m2)	16.2 (13.9-19.0)	17.7 (16.0-20.4)	0.085†
Second transplantation	0 (0.0%)	3 (4.6%)	>0.999¶
Diagnosis			0.311¥
Nephrotic syndrome	7 (50.0%)	15 (23.1%)	
Lower urinary system pathology	1 (7.1%)	10 (15.4%)	
Polycystic kidney disease	2 (14.3%)	4 (6.1%)	
Focal segmental glomerulosclerosis	0 (0.0%)	9 (13.9%)	
Atrophic kidney	0 (0.0%)	4 (6.1%)	
Other	1 (7.1%)	5 (7.7%)	
Unknown	3 (21.4%)	18 (27.7%)	
Dialysis status			<0.001¥
Preemptive1	9 (64.3%)	14 (21.5%)	
Hemodialysis2	2 (14.3%)	43 (66.2%)	
Peritoneal dialysis	3 (21.4%)	8 (12.3%)	
History of abdomen surgery	1 (7.1%)	7 (10.8%)	>0.999¶
Concurrent surgery	11 (78.6%)	5 (7.7%)	<0.001¶

† Mann Whitney U test, ‡ Continuity corrected χ2 test, ¶ Fisher's exact test, ¥ Fisher Freeman Halton. N/A: Not applicable.1 p=0.003 for the comparison in terms of preemptive, 2 p<0.001 for the comparison in terms of hemodialysis.

Table 4. Demographic and clinical characteristics of cases with extraperitoneal approach compared regarding body weights – continued

	<15 kg (n=14)	≥15 kg (n=65)	p-value
Donor's age	35 (27.5-58.5)	40 (35-48.5)	0.509†
Donor's gender			>0.999‡
Male	6 (42.9%)	28 (43.1%)	
Female	7 (50.0%)	33 (50.8%)	
Cadaver	1 (7.1%)	4 (6.1%)	
Donor's height (m)	1.61±0.077	1.66±0.075	0.075¶
Donor's weight (kg)	76.8±18.8	77.3±13.8	0.924¶
Donor's body mass index (kg/m2)	29.5±7.2	28.2±5.2	0.539¶
Kidney size	109.9±5.9	107.7±9.7	0.433¶
Localization			0.017¥
Right	0 (0.0%)	19 (31.1%)	
Left	13 (100.0%)	42 (68.9%)	
Donor's GFR	112.3±19.9	107.7±16.4	0.382¶
Short term complication	4 (28.6%)	8 (12.3%)	0.210¥
Mortality	1 (7.1%)	1 (1.5%)	N/A
Failed graft	0 (0.0%)	1 (1.5%)	N/A
Mismatch			>0.999‡
0	1 (7.1%)	6 (9.2%)	
1	2 (14.3%)	8 (12.3%)	
2	1 (7.1%)	6 (9.2%)	
3	7 (50.0%)	27 (41.5%)	
4	3 (21.4%)	14 (21.5%)	
5	0 (0.0%)	2 (3.1%)	
6	0 (0.0%)	2 (3.1%)	
PRA 1 positivity	2 (14.3%)	11 (16.9%)	>0.999¥
PRA 2 positivity	4 (28.6%)	20 (30.8%)	>0.999¥
Vascular variation			0.338¥
Single artery–single vein	14 (100.0%)	57 (87.7%)	
Double artery–single vein	0 (0.0%)	8 (12.3%)	
Length of ICU stay	1 (1-2)	1 (1-1)	0.004†
Hospitalization	7 (6-12.5)	7 (6-8)	0.211†

†Mann Whitney U test, ‡ Fisher Freeman Halton test, ¶ Student's t test, ¥ Fisher's exact test, GFR: Glomerular filtration rate, PRA: Panel reactive antibody, ICU: Intensive care unit, N/A: Not applicable.

There were 79 patients in this group. This analysis revealed that the mean patient age and height were significantly lower, while the duration of ICU stay was higher in the LW group than in the NW group (p<0.001 and p<0.004). However, the length of inpatient floor stay was similar between the two groups (p=0,211). While the rate of preemptive RT was significantly higher in the LW group, the rate of the patients on HD at the time of RT was significantly higher in the NW group (p=0.003 and p<0.001). The two groups were not different regarding the rates of patients on PD at the time of RT (p=0.401). The rate of concurrent surgery was significantly higher in the LW group than in the NW group (p<0.001). While the left kidney was more often transplanted in the LW group, the right kidney was significantly more commonly used in the NW group (p=0.017). Although the rate of early-term complications was relatively higher in the LW group than in the NW group, the difference was statistically insignificant (p=0.210). The mortality rates were also similar between these two groups (p>0.05). There was no difference between the groups concerning other data parameters.

DISCUSSION

Renal transplantation is the preferred method in the treatment of ESRD in children (1). It was reported that RT at an early age positively affected patients' survival and increased the longevity of the renal allograft (2). Also, an early RT saves the child from a long period of dialysis therapy and its adverse effects (3). Therefore, RT is considered a valuable treatment option in LW pediatric patients, despite the small caliber of the major vessels and the potential size mismatch between the donor and the recipient. Traditionally, IRT is preferred for children weighing less than 15 kg (2). This approach has advantages such as consenting more space for the renal allograft and facilitating the closure of the abdominal wall (5).

On the other hand, IRT is believed to have disadvantages, including increased risks of ileus and twisting of the renal allograft due to its hypermobility in the abdominal cavity (6,7). Thus, ERT became popular in some transplantation centers (8-15). These centers believe ERT provides advantages such as the reduced

risk of gastrointestinal complications, ease of access to the graft for percutaneous biopsy, and the ability to use the peritoneal cavity when dialysis is needed after RT. In our pediatric RT center, RT is performed in both NW and LW children by intraperitoneal or extraperitoneal approach according to the surgeon`s preference. Therefore, we compared the clinical data and short-term outcomes of the LW and NW children who underwent IRT or ERT in our center.

Ghidini et al. (16) retrospectively reviewed the data of 108 children who underwent ERT. They compared the LW (i.e., weighing less than 15 kg) and NW (i.e., weighing 15 kg or more) children regarding early outcomes. These authors reported that the two patient groups had similar overall early complication rates except for venous thrombosis, which was more common in the LW patient group. However, they ascribed this finding to the patient characteristics in the LW group rather than patients` weight per se. In our cohort, 79 patients underwent ERT. The comparison of the LW and NW patients in this group regarding early complication rates did not reveal a significant difference. Of note, one of our LW patients developed graft thrombosis due to RACS. We had to do a graft nephrectomy in this case.

Chiodini et al. (17) reviewed the outcomes of pediatric RT in 72 children weighing 15 kg or less. They reported an early complication rate of 35%; however, these authors did not give any technical details regarding their surgical approach. The 1-year graft survival was 94% in this cohort. In our study, we calculated a similar 1-year graft survival rate (i.e., 97%).

In 2017, Gander and coworkers reported the results of their comparative analysis regarding RT in patients weighing 15 kg or less and those weighing more than 15 kg (18). Overall, their cohort included 164 patients. In the LW group, all but two patients underwent ERT. They noted that the two patient groups were similar regarding complication and graft survival rates. Their 1-year graft survival rate was 81%. However, it should be considered that all renal allografts were received from deceased donors in this study. They concluded that RT was challenging in LW pediatric recipients but was not associated with increased complication and graft failure rates. This finding is in line with ours.

ElSheemy et al. (19) retrospectively analyzed the outcomes of pediatric patients weighing less than 20 kg who underwent live-donor ERT. They had 26 patients with a mean weight of 16,4 kg. In this study, the early complication rate was 26,9%. These authors reported a 3-year graft survival rate of 96% and concluded that excellent graft and patient survival rates could be achieved by ERT in children weighing less than 20 kg. Similarly, Nahas et al. (20) worked on 46 children weighing less than 20 kg and underwent ERT at their center. The mean patient weight was 16,6 kg. While 5 cases had deceased donors, others underwent live donor ERT. These authors reported that 6 (13%) patients had complications during early-term follow-up, and one renal graft was lost due to a surgical complication.

Vitola et al. (21) analyzed the data of 62 children weighing less than 15 kg who underwent ERT. Among these patients, 32 underwent live-related RT, while deceased donor RT was performed in 30 cases. The mean patient weight was 12,3 kg. This study reported a 1-year graft survival rate of 85,2% and concluded that ERT was a valid approach in children weighing less than 15 kg.

Furness et al. (22) retrospectively investigated the clinical data of 29 LW (i.e., weighing less than 15 kg) children who underwent ERT. The mean patient weight was 11,2 in this study. These authors reported that two renal grafts were lost during early-term follow-up due to vascular complications. However, they concluded that ERT was technically feasible in children weighing less than 15 kg.

Our analysis revealed that the length of ICU and hospital stays were significantly longer in the patients with LW. In addition, early-term complication and mortality rates were significantly higher in the LW group than in the NW group. However, the comparative analysis performed within the group of patients who underwent ERT did not show a difference in length of hospital stay and the early-term complication and mortality rates. This finding is in favor of the extraperitoneal approach.

Our study has some limitations that must be considered while evaluating its results. First, it is a retrospective study that might have been affected by the inherent weaknesses of its design. Second, RT surgeries were performed by different transplant surgeons preferring ERT or IRT in LW children. Third, these decisions were not given based on predetermined specific institutional criteria. In addition, long-term outcomes were not included in the analysis.

CONCLUSION

Despite the weaknesses mentioned above, we conclude that RT is a challenging procedure in children weighing less than 15 kg. However, ERT should be encouraged in this patient population, considering that RT is the gold standard renal replacement treatment method, and these patients should not be deprived of the advantages of this approach.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permisson of İstinye University Human Researches Ethics Committee (Date: 10.02.2022, Decision No: 21-90).

Informed Consent: All patients signed the informed consent forms.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Changes in nasolabial angle may alter nasal valve morphology and airflow: a computational fluid dynamics study

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ABSTRACT

Aim: Nasal valve (NV) dysfunctions are a significant cause of nasal obstruction. Changes in the nasolabial angle (NLA) may also cause changes in NV morphology. The effect of changes in the 3D structure of the nasal valve region (NVR) on nasal airflow has yet to be studied sufficiently. The accuracy of computational fluid dynamics (CFD) simulation results of nasal airflow has been confirmed by in vitro tests. Therefore, this study aimed to evaluate the effect of changes in NV structure and volume on nasal airflow based on the CFD method.

Material and Method: We used CT images to create a 3D structural model of the NVR. First, CT images were transferred to MIMICS® software, and the nasal air passage was modeled. A solid reference model of the NVR was then created using SolidWorks software. Five different solid 3D nasal valve models were created with nasolabial angles of 85˚ in Model 1, 90˚ in Model 2, 95˚ in Model 3, 100˚ in Model 4, and 105˚ in Model 5. To simulate breathing during rest and exercise using the CFD method, the unilateral nasal airflow rates were set at 150 ml/s and 500 ml/s, respectively. The CFD method was then used to calculate each model's airflow properties. Finally, the volumes of the models, pressure at the NV outlet, and airflow velocity were evaluated and calculated to investigate each model's NV airflow characteristics.

Results: Our study found a significant correlation between the nasolabial angle (NLA) and NVR volume (r=-0.998, p=0.000), flow rate and velocity (r=0.984, p=0.000), velocity and maximum pressure (r=0.920, p=0.000), velocity and minimum pressure (r=-0.969, p=0.000), flow rate and maximum pressure (r=0.974, p=0.000), and flow rate and minimum pressure (r=-0.950, p=0.000). There was no correlation between NLA increase and nasal airflow velocity. We determined that the highest pressure and lowest airflow velocity values were in the upper angle region and that the lowest pressure and highest airflow velocity values were at the bottom of the NVR in all models.

Conclusion: Using the CFD method, we found a decrease in NVR volume and an increase in airflow velocity with an increase in NLA. In addition, we found that the pressure values in the NVR did not change significantly with the increase in NLA.

Keywords: Septorhinoplasty, nasal valve, computational fluid dynamics, nasal airflow, nasal breathing, nasolabial angle

INTRODUCTION

Nasal valve (NV) stenosis is a significant cause of nasal obstruction. NV dysfunctions have been reported to play a role in up to 13% of cases where adults suffer from nasal obstruction and 95% of cases where nasal obstruction is experienced after septoplasty (1). Even minor anatomical variations have been proven to have a significant impact on nasal airflow and related physiological functions, such as regulation of exhaled air and perception of odors (2). For this reason, patients' complaints should be listened to carefully, and the NV region (NVR) should be carefully evaluated during pre-surgical planning.

According to some authors, the NV is divided into the internal (INV) and external nasal valve (ENV). The INV is located approximately 1.3 cm behind the nostrils and is the narrowest part of the nasal airway, causing the most significant resistance to all airflow. It constitutes 50% of the total airway and approximately 70% of nasal resistance (3). Its anatomical borders are formed by the nasal septum medially, the caudal edge of the superior alar cartilage and anterior part of the inferior turbinate laterally, and the nasal floor inferiorly. The angle between the nasal septum and the

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upper alar cartilage is normally 10 to 15 degrees (4). However, as an anatomical structure, the NV is not a two-dimensional cross-sectional area but a three-dimensional (3D) volumetric structure formed by many anatomical structures and cross-sectional areas. The boundaries of this 3D structure are the nostril caudally, the INV posteriorly, the alar cartilage and fibrofatty tissue anterolaterally, and the septum and medial crura medially (5). Tripathi et al. (6) opposed the division between an INV and ENV as separate structures and referred to their combination as a nasal gateway (**Figure 1**A).

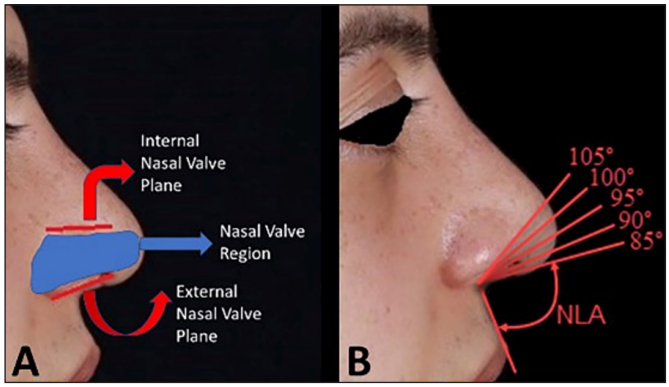

Figure 1. Nasal valve (A) and nasolabial angle (NLA) (B).

The nasolabial angle (NLA) is the angle between the base of the nose and the upper lip. This angle should be between 100–110 degrees for women and 90–105 degrees for men (**Figure 1**B) (7, 8). Changes in the NLA may cause changes in the angles and distances of the INV and ENV planes relative to each other and can change the morphology and volume of the NVR (9). However, the effect of changes in the 3D structure of the NVR on nasal airflow has not been studied sufficiently.

Computational fluid dynamics (CFD) is a discipline that combines fluid mechanics, mathematics, and computer science. CFD uses numerical simulations to analyze data on the interactions of liquids, particles, or gases whose motion is constrained by solid surfaces (10). In medicine, the results of CFD simulations are considered reliable in preoperative planning and predicting surgical outcomes, but they still require validation in real life (11, 12). In recent years, CFD has been used to predict nasal airflow and related events. The accuracy of the CFD simulation results of nasal airflow has been confirmed by in vitro experiments (13-15). CFD is low-cost, non-invasive, and makes it easier to obtain detailed results than other methods (16, 17).

This study aimed to evaluate the effect of changes in NVR structure and volume on nasal airflow based on the CFD method.

MATERIAL AND METHOD

Since our study was an experimental computer modeling, we did not receive ethics committee approval. All procedures were carried out in accordance with the ethical rules and the principles.

Model Creation

Our study used maxillofacial computed tomography (CT) images of a 33-year-old male patient with no nasal complaints to create an anatomically correct 3D structure of the NVR. CT sections were obtained using the GE Revolution CT 128-Slice (GE Healthcare, USA) with 0.625-mm thick sections in the axial plane. CT sections were analyzed using a picture archiving and communication system.

The CT images were transferred to Materialise's interactive medical image control system (MIMICS®; NV, Belgium), an interactive software program that uses CT images for visualization and segmentation operations. First, the nasal air passage was modeled in 3D using MIMICS. A threshold range of -1024 to -300 Hounsfield units (HU) was set in the air modeling, in line with previous models (18). The air passage from the nostrils to the INV was designated as the NVR. Since our aim was only to investigate the effect of the NVR on the airflow, this area was manually separated from the rest of the nasal passage, and a 3D model of the NVR was created (**Figure 2**).

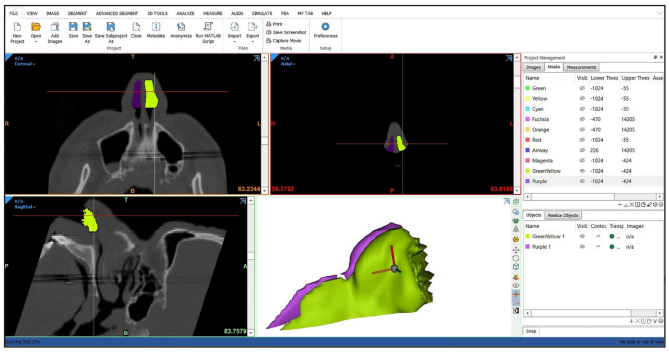

Figure 2. Creation of nasal air passage model from CT images.

The NLA was measured as 85˚ in the soft tissue measurements of the patient's CT images. The measurements obtained from MIMICS were transferred to SolidWorks (Dassault Systems), a computer-aided 3D solid modeling and design software. A solid reference model of the NVR was created with this software (**Figure 3**A). The INV and ENV cross-sections and cross-sectional areas were measured in the NVR modeled in 3D using the MIMICS program (**Figure 3**B).

As seen in **Figure 3**C, five different models were performed using the ideal NLA values in the literature by increasing the ENV plane by five degrees compared to the reference model to ensure the change in the NLA by keeping the INV plane constant on the simple reference model with an NLA of 85˚ (7). Thus, five different solid

3D NV models were created with NLAs of 85˚ in Model 1, 90˚ in Model 2, 95˚ in Model 3, 100˚ in Model 4, and 105˚ in Model 5. Using the CFD method, we then calculated the changes in airflow properties for each model.

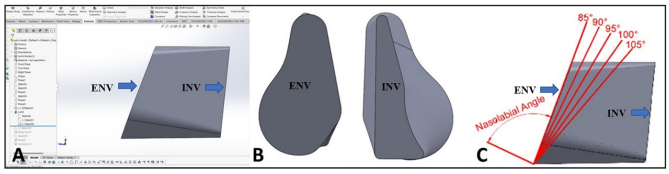

Figure 3. A. 3D creation of a simple solid model of the NVR in Solidworks. B. ENV and INV cross-sectional areas. C. Models created with NLA increments.

Numerical Method

The CFD method was used to examine the effects of changes in the NLA on airflow in the NVR, and calculations were made using ANSYS-Fluent 21.0 (ANSYS, Inc.) software (19). Since the Reynolds number calculated for the NVR input was less than 2,300, the flow was assumed to be laminar in the NVR, where all calculations were made (20, 21). Previous studies have also shown that nasal airflow is laminar in NVR (16, 22). Based on previous research, our study applied the airflow regime as a laminar flow for CFD simulations. The conservation and continuity equations used for laminar flow were as follows:

$$\rho\frac{\partial u}{\partial t}+\rho(u.\nabla)u=-\nabla p+\mu\nabla^2 u$$

$$\nabla.u=0$$

In the equations, "u" represents the air velocity vector, ρ=a 1,225-kg/m3 air density, μ=1.7894 × 10−5 kg/(m.s) dynamic viscosity of the air, p is pressure, and t is time. The SIMPLEC algorithm was used to analyze the pressure–velocity pair. The second-order method for pressure correction and the second-order UPWIND method for discretization conservation equations were used. In the time-dependent analysis, the first-order temporary closed formulation was used (23). The analyses were terminated when the residual values for the conservation of mass and momentum equations were less than 10−6. The network structure created for the calculation is shown in **Figure 4A**. The mesh structure was tetrahedral. The mesh structure was concentrated in areas close to the NV walls. A growth factor of 1.1 and bias factor of 5 were chosen near the NV walls. As seen in **Figure 4B**, when the number of grids increases above 300,000 B, the values for pressure and speed are negligible. Therefore, a grid number of 301,859 was chosen for our study.

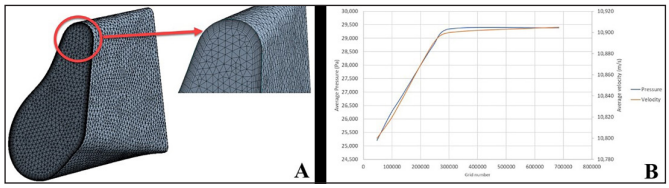

Figure 4. A. Mesh structure for NVR model. B. Grid independence test.

The velocity inlet boundary condition is given at the entrance of the calculation region, and the outflow boundary condition is given because the pressure value cannot be estimated at the outlet. In the NVR, the inner walls were considered rigid, and the no-slip velocity condition (u=0) was assigned. An inlet pressure boundary condition with zero-gauge pressure was applied in the nostril. To simulate breathing during rest and exercise in the CFD method, the airflow rates passing through the nostril section were set in previous studies as 150 ml/s in the resting state for the single nasal passage and 500 ml/s in the exercise state (13, 16, 18, 24). To provide these flow rates, the inlet pressure in the nostril was accepted as the atmospheric pressure, and the outlet pressure was adjusted. Parameters such as the pressure at the NV outlet and airflow rate were then calculated to determine the NVR's airflow characteristics.

Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) (IBM) version 25 software. The Pearson Correlation test was used to evaluate the correlation between the data obtained from the NVR models. Values with a "p" value below 0.05 were considered significant for correlation.

RESULTS

The data from the experimental NVR models and the pressure and velocity results obtained from the study are shown in **Table 1** and **Figure 5**.

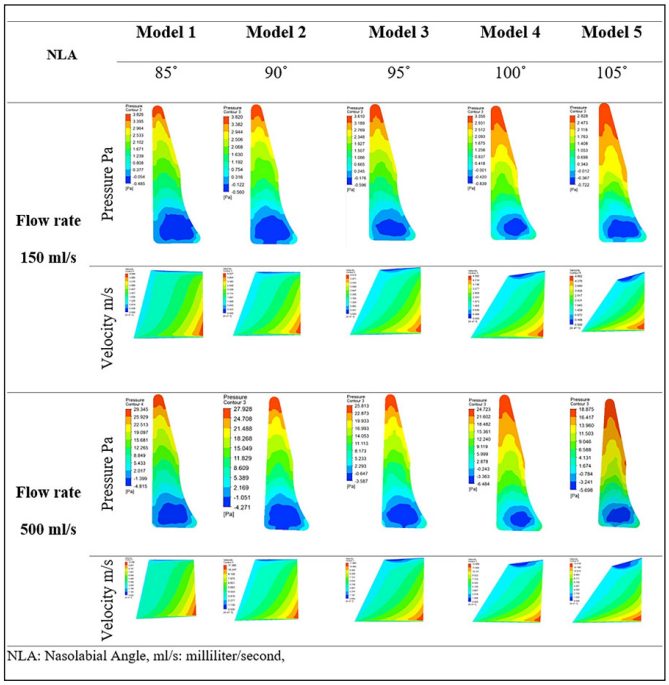

Figure 5: Cross-sectional velocity contours and pressure patterns of the nasal airflow at flow rates of 150 ml/s and 500 ml/s.

Table 1. Data obtained from models and pressure and velocity values.

NLA	Model 1	Model 2	Model 3	Model 4	Model 5
	85˚	90˚	95˚	100˚	105˚
150 ml/s					
Max.Pressure (Pa)	3.83	3.82	3.61	3.35	2.83
Min.Pressure (Pa)	-0.49	-0.56	-0.6	-0.84	-0.72
Velocity (m/s)	4.1	4.23	4.41	4.68	4.86
500 ml/s					
Max.Pressure (Pa)	29.35	27.93	25.81	24.72	18.88
Min.Pressure (Pa)	-4.82	-4.27	-3.59	-6.48	-5.7
Velocity (m/s)	11	11.39	11.87	12.89	13.52
Angle between INV–ENV planes	15˚	20˚	25˚	30˚	35˚
Volume (mm^3)	5,575	5,267	4,908	4,506	4,071
Mesh numbers	301,859	287,412	270,690	250,726	229,548

NLA: Nasolabial Angle, Max.:Maximum, Min.: Minimum, ml/s: milliliter/second, Pa: Pascal,

The NVR volume in the generated 3D NV models decreased as NLA increased. While the volume was 5574.9 mm^3 in Model 1, it was 4070.7 mm^3 in Model 5. The angle between the INV and ENV planes increased as the NLA increased. The Pearson correlation (r) and p values of the data are given in **Table 2**.

Table 2. Pearson correlation values (r) between variables.

	Max. Pressure	Min. Pressure	Velocity	Volume
Flow rate	0.974*	-0.950*	0.984*	0.000
NLA	-0.168	-0.119	0.154	-0.998*
Max. Pressure		-0.891*	0.920*	0.170
Min. Pressure			-0.969*	0.125
Velocity				-0.155

NLA: Nasolabial angle, Max.: Maximum, Min.: Minimum, *p < 0.001

DISCUSSION

Nasal breathing has multiple functions and is essential for maintaining a good quality of life. The geometry of the nose, which provides the physical boundary condition of healthy breathing, is highly complex. The NVR is generally defined anatomically as the region of the nasal cavity that offers the most significant resistance to airflow. Therefore, it is the most critical region for nasal airflow (25). Even the slightest change in the NVR can substantially affect airflow within the nasal cavity (11). Garcia et al. (26) confirmed that anterior septal deviation, including in the NVR, increases nasal resistance more than median and posterior deviations. Small changes in the NLA significantly affect patient satisfaction aesthetically (27, 28). However, there will inevitably be a change in the NVR, a 3D structure, when increasing or decreasing the nasal tip rotation with the methods applied during nasal-type surgery.

The primary purpose of nasal surgery is to provide the patient with a functional nose that breathes well. However, if adequate airflow cannot be achieved after the surgery, patients may complain of shortness of breath, and even an aesthetically pleasing nose will not necessarily satisfy the patient functionally (29).

The perception of nasal airflow is a subjective sensation; therefore, it is difficult to determine its amount and possible causes of obstruction. For objective measurements of nasal obstruction, tests such as rhinomanometry, acoustic rhinometry, peak nasal inspiratory flow, and laser doppler anemometry can be used in the clinic. However, the results of these tests are weakly associated with subjective nasal obstruction. Therefore, they have not entered into routine clinical use because their clinical value is controversial and the cost of testing is high (11, 12, 18, 30).

In recent years, CFD has been a generally accepted and clinically correlated method for evaluating nasal airflow (31). Zhu et al. (13), in their study using CFD, determined that a curved external nose created greater nasal resistance in the nasal passage than the normal situation. In contrast, nasal passage stenosis caused by turbinate hypertrophy increased resistance even more. The effects of septal deviation and atrophic rhinitis in the nasal cavity on nasal airflow have also been reported by CFD studies (26). Nasal functions, such as nasal airflow structures and heating capacity, were also numerically evaluated using CFD (13).

In our study, we examined the effect of changes in the 3D structure of the NVR on nasal airflow by designing a solid model using the CFD method. Borogeni et al. (18) reported that subjective nasal airflow scores were more compatible with unilateral CFD results than bilateral results. In addition, Andre et al. (12) found that nasal airflow perception was better associated with unilateral airflow. For these reasons, we used unilateral nasal modeling.

To evaluate the airflow characteristics in the NVR, the airflow velocity and the pressure at the NVR outlet are essential indicators (31). We evaluated these two parameters in our study.

According to Bernoulli's principle, the airflow velocity and pressure will increase when the nasal cavity narrows (31). The narrowing of the nasal passage causes an increase in airflow velocity (13). From this point of view, an increase in the volume of the NVR will slow down the airflow, while a decrease in the volume will increase the speed. In our study, as the NLA increased, the volume decreased in the NVR models, and the airflow velocity increased in line with the literature (18, 25). However, there was no correlation detected between the NLA

and nasal airflow velocity. This is probably because our study was performed on a single anatomical model, with few angle models and flow rates of only 150 ml/s and 500 ml/s. With more modeling, statistical data with more evidence could be obtained. There was a very high negative correlation between NLA and volume, which was statistically significant (p=0.000). We also found a very high positive correlation between nasal flow rate and airflow velocity, which was statistically significant (p=0.000). Similarly, we found a very high positive correlation between nasal airflow velocity and maximum pressure and a very high negative correlation between nasal airflow velocity and minimum pressure at the NV outlet, both of which were statistically significant (p=0.000), (p=0.000). Finally, there was a strong positive correlation between flow rate and maximum pressure and between flow rate and velocity, and a negative correlation between flow rate and minimum pressure. All these correlations were statistically significant (p=0.000), (p=0.000), (p=0.000).

The pressure values at the NV outlet are essential parameters for nasal airflow evaluation (32). Changes in nasal passage anatomy may also cause changes in pressure values. For example, in their CFD study, Zhao et al. (21) found that the INV was the narrowest cross-sectional area of the entire nasal airway, and 50%–73% of the entire nasal airway pressure drop was in the NVR. In the same study, pressure changes were detected at the highest value in the NVR and were compatible with clinical tests and scoring (21). Our study found that all models' maximum pressure values at the NV outlet decreased as the NLA increased. However, no correlation was detected. Moreover, no correlation was detected between NLA increase and minimum pressure. We found that as the NLA increased, the maximum pressure values increased at an airflow of 500 ml/s, but the minimum pressure values decreased to 95˚, then increased to 100˚ NLA, and decreased to 105˚ NLA again. In the evaluation made with a 500-ml/s flow rate, we think that the fluctuation of the minimum pressure values at the NV outlet, diverging from the values with a 150-ml/s flow rate, is most likely due to the possibility of the airflow passing from a laminar to turbulent flow in this region due to high velocity (11).

As a result of the evaluation of the NVR with CFD, we determined that the highest pressure values were in the upper angle region, which is the narrowest part of the NVR. The nasal airflow velocity values in this region were the lowest. On the contrary, we found the lowest pressure and highest airflow velocity values at the bottom of the NVR in all models. Similar to Li et al. (17), our study determined that the peak airflow velocity was located in the lower part of the NVR in all models.

Limitations

The limitation of our study was that it was an isolated experimental study in which only the NVR was examined out of the entire nasal passage, and only a few parameters were studied using a single anatomical model.

CONCLUSION

In our study, which used the CFD method, we found a decrease in NVR volume and an increase in airflow velocity with an increase in NLA. In addition, we found that the pressure values in the NVR did not change significantly with the increase in NLA.

Primary data may have been obtained in our study, and it shows the efficacy of the CFD method. However, in the future, more studies in which the entire nasal passage is modeled, and supported by relevant clinical data could be obtained with higher levels of evidence.

ETHICAL DECLARATIONS

Ethics Committee Approval: Since our study was an experimental computer modeling, we did not receive ethics committee approval.

Informed Consent: Since our study was an experimental computer modeling, no written informed consent form was obtained from patient.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
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Sloped marginal configuration design of implants as an alternative innovation to the grafting operations: a three-dimensional finite element analysis

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ABSTRACT

Aim: Dental implant operations often require bone grafting due to bone resorption in the buccal area, which make the treatment more complicated, increase the risk of complications, and results in extra costs and prolongation of treatment. This study aimed to evaluate the biomechanical behavior of the implants with a sloped marginal configuration design in the alveolar ridge with a level difference between the buccal and lingual bone levels using three-dimensional finite element analysis (FEA) method.

Material and Method: Two implant models with different marginal configuration designs were used in this study. Implants were placed in the posterior edentulous mandible models in which the buccal region had a 2 mm more resorption according to lingual region which were created by imitating natural bone resorption with FEA. Bone grafting was performed on the exposed buccal surface in the conventional flat marginal configuration implant model (Model 1). In contrast, the sloped marginal configuration implants were compatible with the difference in bone level and placed directly without any additional surgical procedures (Model 2). Than three unit fixed partial dentures were designed. The design of cortical and cancellous bones, prosthetic components, implants, abutment screws and abutments covering those in the edentulous mandible models were transferred to digital three-dimensional models that were created to mimicking the real structures. The models were fixed below and behind of the mandible with zero movement. Load transfer characteristics of both models under these essential limitations were evaluated under 200N foodstuff force.

Results: The highest von Mises stress value was observed as 69.300 MPa in Model 1 and 126.870 MPa in Model 2. The maximum principal stress values were 28.236 N/mm² and 63.449 N/mm²; the minimum principal stress values were 38.346 N/mm² and 43.643 N/mm² in Model 1 and Model 2, respectively. The highest von Mises stress value, maximum principal stress and minimum principal stress values were found higher in Model 2 which was created with sloped marginal configuration design of implants but all values were observed within acceptable physiological limits.

Conclusion: The sloped marginal configuration design of implants can be a non-invasive and more economical treatment alternative modality compared to conventional flat marginal configuration implants with advanced surgeries during implant placement.

Keywords: Dental implant design, grafting, sloped marginal configuration, innovation, biomechanics

INTRODUCTION

Dental implants have become widely used in the oral rehabilitation of complete or partial edentulous patients in recent years. Numerous studies conducted over the years have demonstrated the success of using implants in the dental treatments (1). A successful dental implant treatment requires osseointegration of the implant surface with the surrounding bone. In addition, dental implants should be placed in ideal position, and have hard tissue components and adequate soft tissue contact. Compatibility between the bone and the soft tissues is crucial for the successful, comfortable and cosmetic outcomes of the implant treatments (2). Selection of the dental implant type may be affected from alveolar crest anatomy of the placement site. Bony defects and insufficient bone dimensions can be compelled to apply various surgical procedures, such as resection or bone augmentation, in the surgical site due to prepare the bone morphology before placing the implant (3,4).

Different reasons cause to bony defects with variety of sizes, and it has been documented because of alveolar crest remodeling after tooth extraction. Clinical studies have shown that the horizontal dimensions of the alveolar

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crest generally decrease, and the width of the alveolar bone significantly decreases, especially in the first three months following the tooth extraction. Resorption of the buccal side of the alveolar crest has been demonstrated to be substantially significant than that of the lingual side (4-6).

The level differences between the buccal and lingual crests have been reported to provoke certain difficulties during implant surgeries. When the implant is placed by taking into consideration the lingual bone height as a reference, the buccal part of the implant is not completely submerged into the bone, so that this condition requires bone grafting subsequently. On the other hand, when the buccal bone level is taken as a reference, the implant is embedded into the bone at the lingual area and a resection osteotomy is needed to equalize the planes (7,8).

Advance surgery techniques including bone grafting in the implant marginal configuration areas may be necessary for immediate or delayed implant placements in order to eliminate the level differences. With the developing implant technology, implants with different marginal configuration designs mimicking the natural contour of the alveolar crest have been introduced into the market. A lot of studies reported high survival rates and stable soft tissues around the implant for this sloped configuration (7,9,10).

Dental implant performance and the distribution of forces in the implant and the surrounding bone has been investigated using finite element analysis (FEA) to predict potential failures. FEA has several advantages, such as reliable stress and strain distribution, simple model modification, and accurate representation of complex geometries. FEA can be used efficiently in dentistry to assess the biomechanical responses of dental implants, prostheses, and bone structures simulating chewing forces, and serve as a guide for clinical applications (11-13).

Biomechanical behavior can completely alter whilst changing the design of implant. Therefore, it is important to examine different and complex designs of implants and the surrounding bone using FEA. Different marginal configuration designs of the implant illustrated similar biomechanical behavior with conventional flat marginal configuration dental implant while presence of different buccal and lingual bone levels (14).

The purpose of this study is to evaluate the biomechanical behavior of implants, prosthetic structures and the adjacent bone by using grafted conventional flat neck implants and sloped implants with a design to tolerate the buccal bone resorption in posterior edentulous mandible models using three dimensional FEA.

MATERIAL AND METHOD

Materials and methods used in the study don't require ethical committee approval and/or legal specific permission because of the study design. All procedures were carried out in accordance with the ethical rules and the principles.

Model Design

The 3D geometry data of the edentulous mandibular model with a 2 mm cortical bone layer surrounding the cancellous bone and 2 mm mucosa covering this structure, was obtained from the Visible Human Project (US National Library of Medicine) using VRMesh Studio (VirtualGrid Inc, Bellevue City, WA, USA) software and Rhinoceros 4.0 (3670 Woodland Park Ave N, Seattle, WA 98103 USA) software programs.

A computer with Intel Xeon ® R CPU 3.30 GHz processor, 500gb Hard disk, 14 GB RAM and Windows7 UltimateVersion Service Pack1 operating system was used to arrange and homogenize the three-dimensional mesh structure. The components of implant and prosthesis were scanned three dimensionally using an optic scanner (Activity 880, SmartOptics Sensor Technick GmbH, Sinterstrasse 8, D-44795 Bochum, Germany). VRMesh Studio was used to constitute three dimensional images that were developed from the obtained images. The models created in the standard triangle language (.stl) format were imported into Rhinoceros 4.0 software. Compatibility between prosthetic components, implants, abutments and bone structures was achieved and load was applied using the Boolean method with Rhinoceros.

A mandibular model with a buccal bone level that is 2 mm lower than the lingual bone was created in the posterior region, starting from the first premolar #44, and including the first molar #46. Following the decomposition process, three-dimensional models were created using the 3D Complex Render method, resulting in the modeling of bone tissue. Cancellous bone was obtained from the bone tissue with the offset method.

The design of cortical and cancellous bones, prosthetic components, implants, abutment screws and multiunit abutments covering those in the edentulous mandible model were transferred to digital three-dimensional models that were created to mimicking their real structures. The process of modelling was completed upon the placement of the models produced in three dimensions with Rhioceros software in alignment with the correct coordinates. The meshed models in Rhinoceros were transferred to the FEA program (ALGOR.FEMPRO, .Algor, Beta Drive Pittsburg, PA, USA) for solid modeling while maintaining the three-dimensional coordinates. Occlusal load was applied as foodstuff design to create a more realistic simulation of the mastication.

In this study, two implant models with different marginal configuration designs were used, that are the Quattrocone implant made of Grade IV titanium with a standard conventional flat marginal configuration design (Medentika Straumann Group, Calw, Germany) and the Quattrocone30° implant made of Grade IV titanium with a sloped marginal configuration design (Medentika Straumann Group, Calw, Germany) (**Figure 1**).

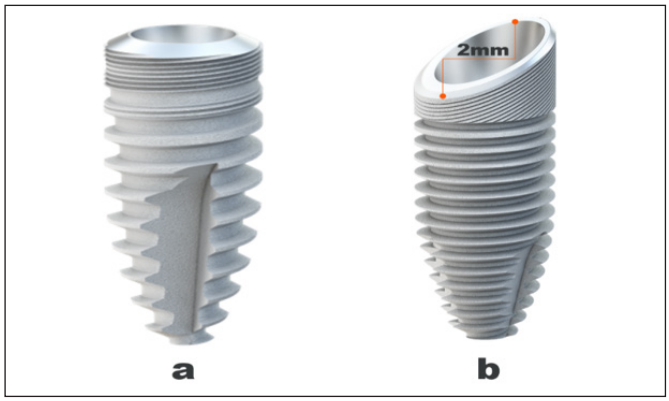

Figure 1. a) Conventional flat neck implant b) Implant with sloped marginal configuration

Model 1: Two standard conventional Grade IV titanium implants (4.3 mm in diameter – 11 mm in length, Quattrocone, Medentika Straumann Group, Calw, Germany) were placed axially in tooth areas #44 and #46 of the edentulous mandible. A bone design was created that fully encloses the implant on the lingual, mesial, and distal. Bone grafting was done to the exposed buccal implant surface due to the difference in buccal bone level. 5-mm titanium abutments and internal screws connecting the abutment to the implant were designed on these implants. Three dimensional finite element models of the implants, abutments, adjacent cortical and cancellous bone, and prosthetic structures were modelled and a screw-retained porcelain fused to cobalt-chromium metal fixed partial denture was designed in both models (**Figure 2**).

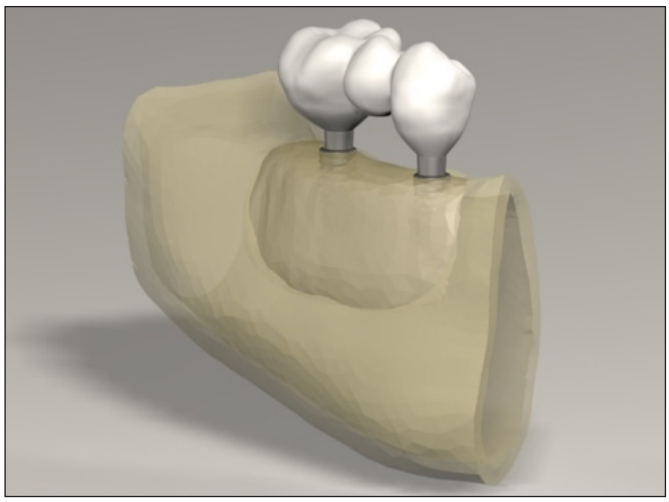

Figure 2. Model 1: Grafted buccal bone wall for implants with conventional marginal configuration design and the prosthetic components

Model 2: Two implants with a sloped marginal configuration (4.3 mm in diameter - 11mm in length on the lingual; 9 mm in length on the buccal, Quattrocone30°, Medentika Straumann Group, Calw, Germany) were placed axially on the areas of #44 and #46 in the edentulous mandible to be compatible with the difference in bone level. Bone design was created that fully encompasses the implant from the lingual, mesial, distal, and buccal sides. 5-mm titanium abutments and internal screws connecting the abutment to the implant were designed on these implants. Three dimensional finite element models of the implants, abutments, surrounding cortical and cancellous bone and prosthetic structures were modelled and a screw-retained porcelain fused to cobalt-chromium metal fixed partial denture was designed in both models (**Figure 3**).

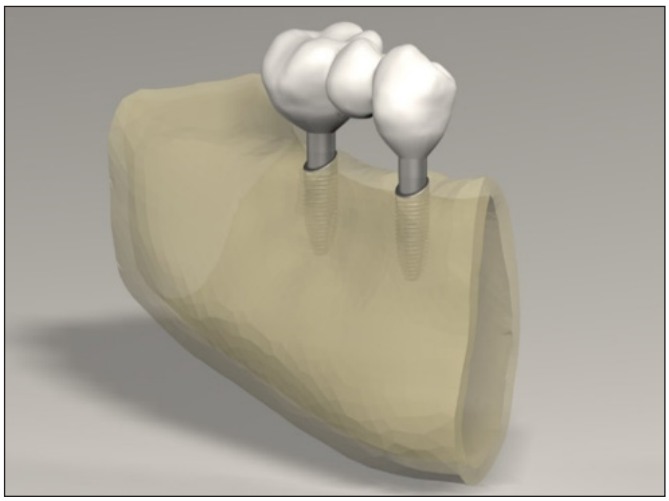

Figure 3. Model 2: Implants with sloped marginal configuration designed for bone resorption in the buccal side and prosthetic components

The number of nodes and elements used in mathematical models including scenarios were determined as 293358 nodes and 1510122 elements for Model 1, and 340720 nodes and 1843448 elements for Model 2.

Meshing Procedure

The models were created geometrically with the VRMesh software and then transferred in .stl format to the ALGORFEMPRO software for analysis and assessment. The structures were constructed and assigned material values in the models (the Poisson's ratio and the modulus of elasticity), which are used to define their physical qualities. The solid body characteristics were accepted as elastic, linear, isotropic, and homogenous by the program. The characteristics of the materials were developed by using the characteristics in the literature as an example (13-19) (**Table 1**).

Table 1. Mechanical characteristics of the materials used for the FEA

	Modulus of Elasticity (GPa)	The Poisson's Ratio
Cortical bone	14	0.30
Cancellous bone	1.4	0.30
Titanium (Grade IV implants and abutments)	110	0.35
Porcelain	96	0.29
Cobalt-chromium metal framework	218	0.33
Graft (medium stiff)	2	0.30
Food stuff	200	0.29

GPa: GigaPascal

Essential Limitations

The models were fixed below and behind the mandible with zero movement at each degree of freedom (DOF). A total of 200 N load was applied with foodstuff from mesial to distal of denture that was distributed with 50 N to the first premolar area, 50 N to the second premolar area, and 100 N to the first molar area, and then analyses were performed for each model (**Figure 4**).

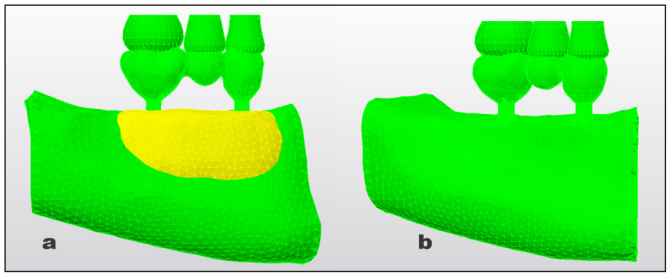

Figure 4. a) Foodstuff loading for Model 1 b) Foodstuff loading for Model 2

Von Mises analyses evaluate fragile materials such as implants, abutments, abutment screws, and prosthetic components. The maximum principal stress (Pmax) refers to the tensile stress, and the minimum principal stress (Pmin) states to the compression stress for flexural materials like cortical and cancellous bone (3,20). In this study, von Mises analyses were performed for implants, abutments, metal framework and prosthetic components while Pmax and Pmin were evaluated for cortical and cancellous bones. Then, a comparative analysis was performed between the models. The maximum equivalent von Mises value is observed on the image for each model. The results of the analyses were quantified and converted into color-coded visual materials. Red color is indicated the Pmax, and blue color is referred to the Pmin.

RESULTS

Both models had a similar stress distribution on the fixed partial dentures. The molar area showed that higher stresses rather than the premolars. A similar stress distribution was observed in the both groups and metal frameworks. The stresses were typically observed high around the implant-abutment connection site, and this trend continued thorough the abutments and surrounding crestal bone.

The highest stresses were observed in the molar implants for both groups. The von Mises values were observed high in the marginal configuration of the posterior implants. Stress values were similar for abutments in each model as well as the abutments showed more equitable stress distribution in Model 2. The implant marginal configuration in the first molar area showed the highest von Mises stress value with 126.869826 MPa during the total loading of the three-unit fixed partial denture in the same model (**Figures 5, 6**).

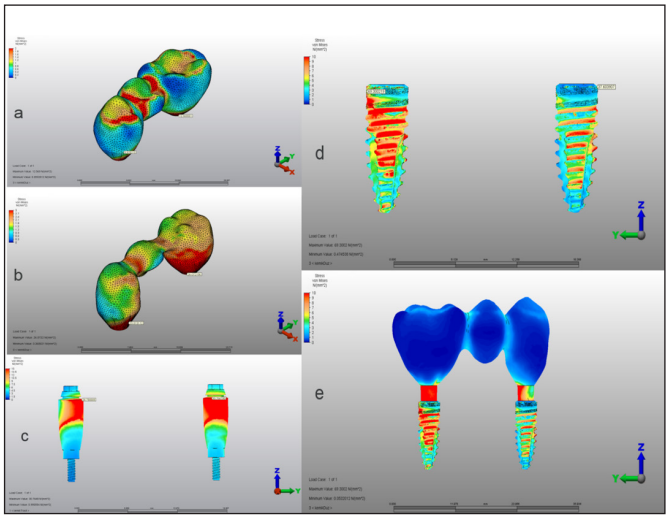

Figure 5. The von Mises stress values in Model 1 a) fixed partial denture b) metal framework c) abutments d) implants e) all components

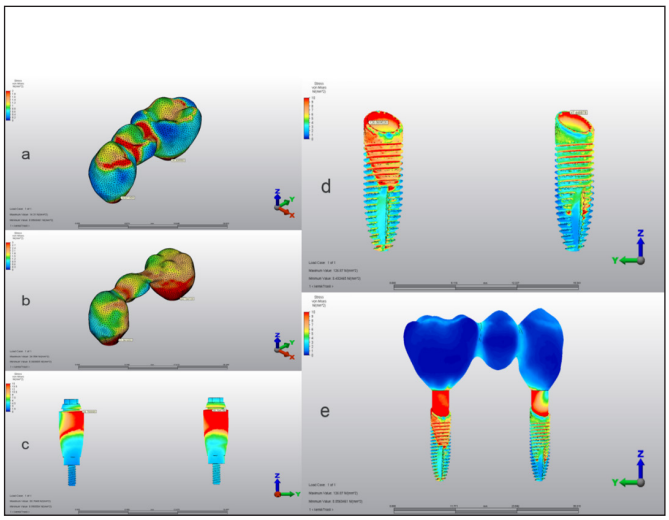

Figure 6. The von Mises MPa stress values in Model 2 a) fixed partial denture b) metal framework c) abutments d) implants e) all components

The von Mises stress values are presented for the implants, abutments, cobalt-chromium framework, and fixed partial denture components (**Table 2**).

Table 2. The von Mises stress values (MPa) in each implant area

	Model 1		Model 2	
	#44	#46	#44	#46
Porcelain fixed partial denture	9.970978213	12.569001	13.071959	14.309950
Cobalt-chromium framework	23.013112	25.551378	21.941692	24.134729
Abutment	21.910128	30.471224	26.750005	30.764798
Implant	37.603907	69.300219	47.448879	126.869826

MPa: MegaPascal

Pmax values were intensified around the lingual areas, and that was increased through the posterior regions in the both models. Connection area between the posterior implant marginal configuration and the lingual cortical bone has the greatest Pmax in Model 2 (63.4487 N/mm²).

Pmin values were intensified around the buccal areas. The grafted marginal configuration surface showed substantially less compressive stress in Model 1. Therefore, it was concluded that the Pmin values were higher in the cortical bone around the posterior implants' marginal configuration in the both models. Connection area between the posterior implant marginal configuration and the buccal cortical bone has the greatest Pmin in Model 2 (43.6434 N/mm²) (**Figures 7,8**).

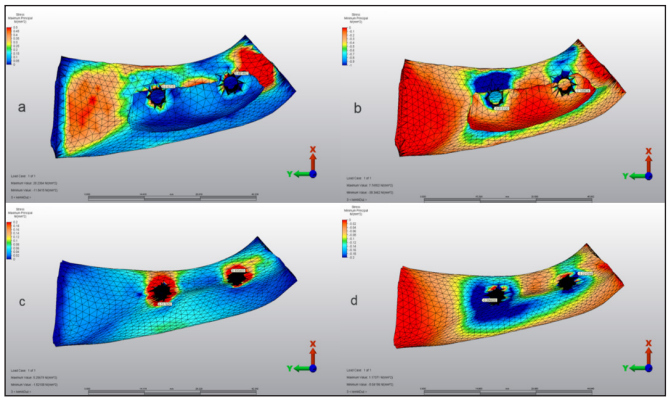

Figure 7. Model 1 a) cortical bone Pmax b) cortical bone Pmin c) cancellous bone Pmax d) cancellous bone Pmin

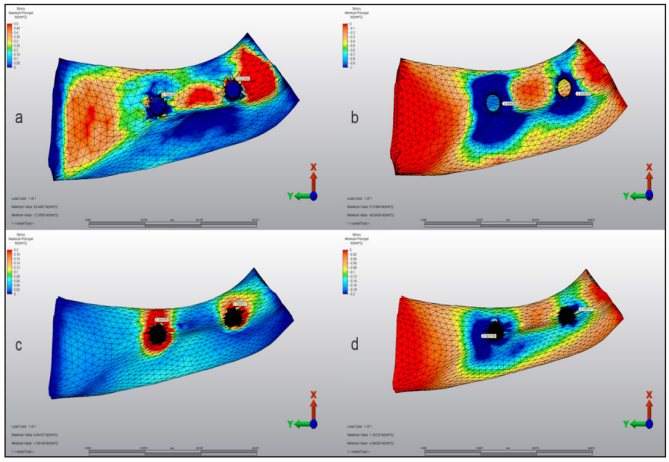

Figure 8. Model 2 a) cortical bone Pmax b) cortical bone Pmin c) cancellous bone Pmax d) cancellous bone Pmin

The Pmax and Pmin values of cortical and cancellous bones were presented for tested models (**Table 3**).

Table 3. The stress values created by the load on tested models (N/mm²)

		Pmax	Pmin
Model 1	Cortical bone	28.2364	38.3462
	Cancellous bone	5.25679	5.04196
Model 2	Cortical bone	63.4487	43.6434
	Cancellous bone	4.04167	4.94283

DISCUSSION

In this study, three dimensional FEA was used to investigate stress distribution characteristics of two different implant designs, that were conventional flat marginal configuration implants with bone grafting and sloped marginal configuration implants, in the light of literature which indicated that bone resorption patterns following tooth extraction (4,5,7,14,21).

Bone augmentation surgeries, including alveolar ridge split method, lateralization of the alveolar nerve, and maxillary sinus lift operations, can be performed in case of inadequate bone volumes, that would intercept appropriate placement of a conventional implant. However, such surgeries prolong the treatment time, increase the financial costs, and may also affect the general health status, especially in geriatric patients (13,19).

Irregularities in the alveolar bone can be encountered during the remodeling phase following tooth extraction. The buccal bone area is known to be resorbed more compared to the lingual. In dental implantology, the most of the stresses are stood out by cortical bone layer (22,23). The success in the implant marginal configuration area makes this data more important. The use of sloped marginal configuration implants is one potential treatment strategy to prevent bone resorption or grafting in the buccal area (22).

Numerous clinical studies have been carried out to evaluate the biomechanical aspects of dental implant design (1,10,14,21,22). The quality and strength of osseointegration, and the bone-implant connection are crucial to acquire the long-term success of implant treatment in edentulous jaws. However, there have not been defined for optimum implant design features to be considered as the best treatment outcome yet. Dental implant design can be improved to maximize strength, interface stability, and load transfer using appropriate materials, surface treatment, and groove shape (1,24).

The biomechanical characteristics of a dental implant, such as size, shape, geometry, and marginal configuration design, are significant for successful long-term outcomes.

Bone resorption in the marginal configuration of an implant is the most common manifestation of implant failure in the literature. Bone resorption may be induced by sex, surgical trauma, plaque accumulation, smoking, biological bone width, bone quality, implant design and biomechanical factors (11,13,25). Similar to other studies, it was determined that the stresses were mostly concentrated around the implants' marginal configuration and adjacent cortical bone to these regions in this study (8,10,11,13).

Abrahamsson et al. (9) conducted an experimental study on animals, and they placed different dental implant types into resorbed jaw with lower buccal bone height compared to the lingual bone level. The authors investigated bone loss characteristics of conventional implants and sloped marginal configuration implants that were fully compatible with the marginal bone area of implant marginal configuration after the osseointegration. The histological examination of the buccal bone defect showed that any marginal bone support was observed on the exposed surface of the implants with the conventional marginal configuration design, while the bone level was stable in the sloped implants. In the current study, the sloped marginal configuration implants exhibited acceptable biomechanical behaviors close to the conventional dental implants with bone grafting.

Moreover, two prospective, multicenter studies that evaluated applications and long-term results of sloped marginal configuration implants in humans. These studies showed that clinical results were promising, and these type of implants could be an alternative to conventional implants with complicated surgeries and additional treatment costs (7,21). Schiegnitz et al. (22) highlighted that the sloped marginal configuration implants might be challenging to maintain stable and resilient peri-implant keratinized mucosa compared to conventional implants.

The tensile strength threshold value is 680 MPa for dental implants which made from a grade IV cold-worked titanium (14,15). In the present study, the Von Mises stress values of grade IV titanium implants were found to be within acceptable limits under an occlusal load simulating a 200N mastication in tested groups. As the von Mises stress values are much lower than the maximum strength values (680-1110 MPa), that were obtained for dental implants made by the titanium alloys (14-16), in both models of this study. The risk of fracture in implants and abutments is almost non-existent.

The Pmax value has been reported to be around 100-121 MPa, and the Pmin value to be around 167-173 MPa to withstand without bone damage (16,26,27). Considering these values, the results of our study are well below the maximum acceptable values, and do not pose any problem for the bone. Thus, implants with a sloped marginal configuration can be used within the confidence limit instead of performing a complicated, costly, and advanced surgery such as bone grafting.

One of the limits of the study is that the osseointegration between the implant models used in the FEA and the bone was assumed as 100% bone-implant connection. It is known that this cannot be achieved in clinical conditions. In the literatures, maximum bone osseointegration was reported that between 75% and 90% histologically by researchers (15,17,28). Other limitations of the current study included that the equal consideration of the bone healing and transformation potential of the graft material. Moreover, bone resorption pattern presumed same level on the buccal area due to essential limitations. Based on the results of this FEA study, multicenter clinical studies should be conducted to evaluate positive findings about implant with sloped marginal configuration.

CONCLUSION

Grafting the marginal configuration areas of the conventional implants is an accurate approach in the posterior edentulous mandible with resorbed buccal area, but it is also possible to simplify the surgery, to reduce the clinical hours and the number of surgeries, and to avoid additional costs by using sloped marginal configuration implants. The.von Mises.stresses of.sloped marginal configuration implants were within the physiological limits, Pmax and Pmin values of the surrounding bone are acceptable. Sloped marginal configuration implants can be used as an innovative product that can facilitate the treatment process when a level difference exists in the bone. This specially designed implant can be a useful alternative treatment modality to conventional implants with advanced surgical operations.

ETHICAL DECLARATIONS

Ethics Committee Approval: The author of this article declare that the materials and methods used in the study don't require ethical committee approval and/or legal-specific permission because of the study design.

Informed Consent: Because of the study design, no written informed consent form was obtained from the patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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The relationship between uric acid variability and cardiovascular risk factors in patients with diabetes

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ABSTRACT

Aim: This study aimed to evaluate the relationship between uric acid variability and cardiovascular risk factors, primarily albuminuria and blood lipids, in patients with diabetes.

Material and Method: Data from 174 patients with diabetes whose biochemical parameters were examined at least once a year were collected over the course of five years of regular follow-up. The five-year averages and standard deviations of each parameter for each person were calculated. The adjusted standard deviation for each parameter was considered as a measure of individual variability. The patients were divided into two groups according to the median of the mean uric acid and the median of the adjusted standard deviation of uric acid.

Results: Between low and high uric acid variability groups, while there was no statistically significant difference for the mean values of following parameters, there was a difference in the variability of glucose (p=0.010), HbA1c (p=0.016), total cholesterol (p=0.008), and low-density lipoprotein-cholesterol (p=0.002). Moreover, there was difference in mean albuminuria (p= 0.019), albuminuria variability (p=0.040), mean triglyceride (p=0.011), triglyceride variability (p=0.018), and mean high-density lipoprotein-cholesterol cholesterol (p=0.008).

Conclusion: Clinicians should pay attention to uric acid variability in addition to basal uric acid levels since it is associated with albuminuria, an atherogenic lipid profile, renal functions, and the variability of these parameters, independent of HbA1c and glucose levels.

Keywords: Uric acid, diabetes mellitus, albuminuria, dyslipidemia, cardiovascular disease

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INTRODUCTION

Despite improvements in cardiovascular disease (CVD) mortality rates, the incidence of obesity, metabolic syndrome, and diabetes mellitus (DM) continues to rise. It is estimated that DM prevalence, worldwide, will be 643 million by 2030 and 783 million by 2045 (1). CVD is the primary cause of death in adults with DM, and traditional cardiovascular (CV) risk factors do not account for a major portion of the disease burden in patients with DM.

Elevated blood uric acid (UA) levels have been linked to several diseases that are recognized to be associated with CVD, including obesity, insulin resistance, metabolic syndrome, DM, hypertension, and renal disease (2-7). There is a close association between UA levels and CV risk factors (2-7) and reports state that UA is an independent risk factor for CVD (8,9). But the cause and effect relationship between UA and CVD has not been fully proven. Moreover, some studies have reported that there is a U-shaped association between UA and CVD, (10,11) while other studies have found no association (12,13) between them. While arguments over the association between UA levels and CVD continue, data on the relationship of UA variability with CVD, mortality, and CV risk factors, have begun to be published in the last decade (14-18). Thus, in addition to the variability of HbA1c, lipid parameters, and blood pressure, which have been taken into account in recent years, the metabolic effects of uric acid variability are now being investigated.

Epidemiologic researches suggest that elevated serum UA concentrations are risk factor for the development of renal disease, DM, and related complications. But, differences in the methodologies used in the studies

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and the fact that UA levels are easily affected by drugs, hemodynamic variability, and variable renal functions, make the conclusions of these researches unsatisfactory. There for, a study evaluating the relationship of long-term mean UA values and UA variability rather than basal/cross-sectional serum UA values with CV risk factors, can offer a different viewpoint. In this study, we aimed to reveal the association of UA variability with albuminuria and CV risk factors with single center outpatient clinic data. The association of UA variability with the variability of these CV risk factors were also evaluated.

MATERIAL AND METHOD

The study was carried out with the permission of Erzincan Binali Yıldırım University, School of Medicine, Non-invasive Clinical Researches Ethics Committee (Date: 28.01.2021, Decision No: 30/06). All procedures were carried out in accordance with ethical rules and the principles of the Declaration of Helsinki.

Patients

Patients with a diagnosis of Type 2 Diabetes, who were followed up in our outpatient clinic for 5 years and who admitted at least once a year were included in the study. Within the five-year period examined; patients older than 80 years of age, younger than 18 years of age, patients with end-stage renal disease, patients with pregnancy, patients undergoing major surgery, or hospitalized for any reason were excluded from the study.

Using the archive system of our hospital, 174 patients with DM admitted to the Endocrinology Outpatient Clinic regularly for five years, whose glucose, HbA1c, albuminuria, UA, lipid profile, urea, creatinine, glomerular filtration rate (GFR), and albumin levels were studied at least once a year, were enrolled in the study. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Assessment of Variability

The gender, age, height, and weight of the patients were recorded. Glucose, HbA1c, albuminuria, UA, lipid profile, urea, creatinine, albumin levels, and GFR of the patients for each admission were recorded. Five-year averages and standard deviations (SD) of each parameter were calculated for each person. The calculated standard deviation value of the parameters was used as an indicator of variability. Because the number of separate visits (n) might impact the SD, the SD values were divided by [n/(n-1)]0.5 to compute adjusted SD and minimize any effect of distinct measurements on the calculated results (19). The adjusted SD for each parameter was considered to be the measure of "variability" for each patient. Then, the calculated mean and adjusted SD of the parameters were evaluated for each person. The patients were separated into two groups based on the median of "mean UA values" and the median of the "adjusted SD of the UA values (UA variability)".

Statistical Analysis

Statistical Package for Social Sciences for Windows, v. 15.0 (SPSS, Chicago, IL, USA) was used to conduct the statistical analyses. For each variable (for every 5-year average value and 5 year adjusted SD of each parameter), descriptive statistics were established. The mean and SD were used to express the normally distributed data. For variables without a normal distribution, the median and minimum-maximum values were used. Student's t-test was used to compare data that had a normal distribution. The Mann-Whitney U test was used to compare continuous data with the asymmetric distribution. The Pearson correlation coefficient and Spearman's rho were used to investigate the relationships between the variables (for data that were not normally distributed).

RESULTS

Retrospective data of 174 patients with diabetes, 98 of whom were female (56.3%) and 76 of whom were male (43.7%), were included in the study. The mean age of the patients was 57.2±14.0 years. The five-year average of HbA1c was found to be 8.4±1.4%. Body mass index (BMI) was found to be 30.0±5.5 kg/m². **Table 1** shows the baseline characteristics and laboratory data of the patients based on the adjusted SD of UA levels. While there were no significant differences between the two groups according to sex distribution, age, mean glucose, mean HbA1c, mean total cholesterol (TC), mean low-density lipoprotein-cholesterol (LDL-C), adjusted SD of high-density lipoprotein-cholesterol (HDL-C), and adjusted SD of albumin, there were statistically significant differences between groups for the following variables: BMI, adjusted SD of glucose, adjusted SD of HbA1c, mean albuminuria, adjusted SD of albuminuria, mean UA, adjusted SD of TC, adjusted SD of LDL-C, mean triglyceride (TG), adjusted SD of TG, mean HDL-C, adjusted SD of urea, mean creatinine, adjusted SD of creatinine, mean estimated GFR (eGFR), adjusted SD of eGFR, and mean albumin.

The correlations between UA variability and several other parameters were tested using bivariate correlation analysis. As shown in **Table 2**, the adjusted SD of UA was significantly correlated with BMI, adjusted SD of glucose, mean HbA1c, adjusted SD of HbA1c, mean albuminuria, adjusted SD of albuminuria, adjusted SD of TC, adjusted SD of LDL-C, mean TG, adjusted SD of HDL-C, adjusted SD of urea, mean creatinine, adjusted SD of creatinine, mean eGFR, adjusted SD of eGFR, mean albumin, and adjusted SD of albumin.

Table 1. Demographic, clinic, and laboratory features of the study groups according to uric acid variability

Parameters	Group 1 Patients with low uric acid variability (Adj. SD of UA <0.584)≠ n= 87	Group 2 Patients with high uric acid variability (Adj. SD of UA ≥0.584)≠ n= 87	P value
Sex (f/m)	51/36	47/40	0.541*
Age (years)	58 (49.75-65.25)	60 (55-67)	0.077**
BMI (kg/m²)	28.4±5.1	31.5±5.5	0.006***
Mean Glucose (mg/dL)	180±52	185±55	0.536***
Adj. SD of Glucose	57.83±34.89	74.06±46.26	0.010***
Mean HbA1c (%)	7.97 (7.28-9.35)	8.47 (7.26-9.50)	0.429**
Adj. SD of HbA1c	0.92 (0.60-1.29)	1.23 (0.80-1.81)	0.016**
Mean Albuminuria (mg/g)	17.93 (9.18-35.93)	25.94 (8.93-145.98)	0.019**
Adj. SD of Albuminuria	11.90 (5.50-24.60	19.80 (5.40-139.70)	0.040**
Mean Uric Acid (mg/dL)	4.7±1.2	5.4±1.1	<0.001***
Adj. SD of Uric Acid	0.42 (0.32-0.48)	0.84 (0.70-1.08)	-
Mean Total Cholesterol (mg/dL)	205 (175-235)	200 (179-226)	0.866**
Adj. SD of Total Cholesterol	23.03 (15.08-28.29)	24.42 (18.87-35.95)	0.008**
Mean LDL-Cholesterol (mg/dL)	118 (99-146)	119 (101-135)	0.347**
Adj. SD of LDL-Cholesterol	19.35 (14.32-24.26)	23.80 (15.71-31.78)	0.002**
Mean TG (mg/dL)	144.67 (111.52-200.14)	179.79 (134.51-245.48)	0.011**
Adj. SD of TG	40.72 (26.64-59.75)	52.74 (33.71-76.28)	0.018**
Mean HDL-Cholesterol (mg/dL)	46.53 (40.50-55.04)	42.99 (39.67-48.18)	0.008**
Adj. SD of HDL-Cholesterol	4.67 (3.42-6.09)	4.89 (3.79-6.53)	0.289**
Mean Urea (mg/dL)	30.89 (25.43-36.52)	31.85 (27.92-42.42)	0.062**
Adj. SD of Urea	5.41 (3.91-6.99)	6.37 (4.77-12.36)	0.001**
Mean Creatinine (mg/dL)	0.85 (0.73-0.99)	0.90 (0.77-1.05)	0.036**
Adj. SD of Creatinine	0.09 (0.073-0.12)	0.12 (0.09-0.19)	0.001**
Mean eGFR mL/min/1.73 m²	85.69 (74.03-94.21)	80.61 (66.40-86.98)	0.014**
Adj. SD of eGFR	6.67 (5.39-8.46)	7.48 (6.01-10.26)	0.005**
Mean Albumin (g/dL)	4.25 (4.11-4.40)	4.15 (3.98-4.32)	0.007**
Adj. SD of Albumin	0.26 (0.18-0.34)	0.27 (0.21-0.37)	0.189**

≠ The variability was determined with the adjusted SD. Considering the median of the adjusted SD value of Uric Acid, the patients were divided into 2 groups as patients with low and high uric acid variability. Sex, age, and anthropometric indices were recorded at the initial evaluation. The parameters presented with the term "Adjusted SD" represent the 5-year variability of the parameters. The parameters presented with the term "Mean" represent the 5-year average of the parameters. * Chi-Square Test, ** Mann-Whitney U test [Continuous variables without anormal distribution presented as; median (IQR)] *** Student's t-test Test (Continuous variables without normal distribution presented as; mean ± standard deviation). BMI: Body Mass Index, HbA1c: Glycosylated Hemoglobin, LDL- Cholesterol: Low-Density Lipoprotein Cholesterol, HDL- Cholesterol: High-Density Lipoprotein Cholesterol, TG: Triglyceride, eGFR: Estimated Glomerular Filtration Rate, Adj. SD: Adjusted Standard Deviation/Variability.

Table 2. Bivariate correlation results between uric acid variability (Adjusted SD of Uric Acid) and other significant parameters in diabetic patients

Parameters	Correlation Coefficient (rs)	P value	Parameters	Correlation Coefficient (rs)	P value
BMI (kg/m²)	0.326	0.001	Adj. SD of HDL-Cholesterol	0.203	0.007
Adj. SD of Glucose	0.238	0.002	Adj. SD of Urea	0.374	<0.001
Mean HbA1c (%)	0.151	0.047	Mean Creatinine (mg/dL)	0.174	0.021
Adj. SD of HbA1c	0.249	0.001	Adj. SD of Creatinine	0.418	<0.001
Mean Albuminuria (mg/g)	0.250	0.001	Mean eGFR mL/min/1.73 m²	-0.215	0.004
Adj. SD of Albuminuria	0.259	0.001	Adj. SD of eGFR	0.212	0.005
Adj. SD of Total Cholesterol	0.209	0.006	Mean Albumin (g/dL)	-0.236	0.002
Adj. SD of LDL-Cholesterol	0.241	0.001	Adj. SD of Albumin	0.195	0.010
Mean TG (mg/dL)	0.149	0.049	-	-	-

The parameters presented with the term "Adjusted SD" represent the 5-year variability of the parameters. The parameters presented with the term "Mean" represent the 5-year average of the parameters. BMI: Body Mass Index, HbA1c: Glycosylated Hemoglobin, LDL- Cholesterol: Low-Density Lipoprotein Cholesterol, HDL- Cholesterol: High-Density Lipoprotein Cholesterol, TG: Triglyceride, eGFR: Estimated Glomerular Filtration Rate, Adj. SD: Adjusted Standard Deviation/Variability.

When patients were divided into two groups based on the median of mean UA levels (Group 1 – mean UA <6 mg/dL and Group 2 – mean UA levels ≥ 6 mg/dL), for the following variables, there were statistically significant differences between the groups: age, mean albuminuria, adjusted SD of albuminuria, adjusted SD of UA, adjusted SD of LDL-C, mean urea, adjusted SD of urea, mean creatinine, adjusted SD of creatinine, and mean GFR (**Table 3**).

Table 3. Demographic, clinic, and laboratory features of the study groups according to 5 year mean uric acid levels

Parameters	Group 1 Mean Uric Acid <6 mg/dL n= 87	Group 2 Mean Uric Acid ≥6 mg/dL n= 87	P-value
Sex (f/m)	75/56	23/20	0.666*
Age (years)	58 (51-65)	62 (54.5-70)	0.004**
BMI (kg/m²)	29.55±5.61	31.01±5.12	0.233***
Mean Glukoz (mg/dL)	186.86±55.11	172.50±48.15	0.106***
Adj. SD of Glukoz	67.40±41.24	61.53±43.09	0.436***
Mean HbA1c (%)	8.34 (7.38-9.53)	7.9 (7.17-9.02)	0.138**
Adj. SD of HbA1c	1.03 (0.64-1.44)	1.07 (0.70-1.57)	0.987**
Mean Albuminuria (mg/g)	18.10 (8.48-43.08)	61.21 (9.93-272.77)	0.004**
Adj. SD of Albuminuria	11.84 (5.31-29.33)	39.43 (6.21-214.53)	0.018**
Mean Uric Acid (mg/dL)	4.52±0.87	6.70±0.61	-
Adj. SD of Uric Acid	0.54 (0.42-0.81)	0.77 (0.55-1.08)	0.007**
Mean Total Cholesterol (mg/dL)	198.5 (178.47-226.41)	206.57 (177.50-233.25)	0.382**
Adj. SD of Total Cholesterol	23.26 (16.35-30.08)	24.53 (16.88-36.71)	0.090**
Mean LDL-Cholesterol (mg/dL)	118.75 (99.6-138.41)	119.75 (100.91-151.12)	0.587**
Adj. SD of LDL-Cholesterol	20.82 (14.93-25.83)	24.40 (15.27-32.36)	0.036**
Mean TG (mg/dL)	159.43 (115.78-239.57)	180.92 (130.58-229.14)	0.050**
Adj. SD of TG	43.74 (31.72-67.98)	52.35 (30.39-71.66)	0.239**
Mean HDL-Cholesterol (mg/dL)	44.62 (40.27-51.77)	42.22 (39.36-48.03)	0.100**
Adj. SD of HDL-Cholesterol	4.92 (3.57-6.34)	4.62 (3.81-5.60)	0.699**
Mean Urea (mg/dL)	30.72 (26.05-35.13)	42.15 (30.61-51.16)	<0.001**
Adj. SD of Urea	5.93 (4.44-7.36)	7.78 (4.61-15.81)	0.004**
Mean Creatinine (mg/dL)	0.85 (0.74-0.95)	1.04 (0.86-1.23)	<0.001**
Adj. SD of Creatinine	0.10 (0.08-0.13)	0.13 (0.08-0.19)	0.004**
Mean GFR mL/min/1.73 m²	85.29 (75.81-93.37)	71.15 (50.63-82.33)	<0.001**
Adj. SD of GFR	7.38 (5.74-9.58)	7.10 (5.72-7.97)	0.379**
Mean Albumin (g/dL)	4.2 (4.05-4.34)	4.15 (4.03-4.34)	0.664**
Adj. SD of Albumin	0.26 (0.20-0.36)	0.26 (0.22-0.34)	0.807**

Sex, age, and anthropometric indices were recorded at the initial evaluation. The parameters presented with the term "Adjusted SD" represent the 5-year variability of the parameters. The parameters presented with the term "Mean" represent the 5-year average of the parameters. * Chi-Square Test, ** Mann-Whitney U test [Continuous variables without anormal distribution presented as; median (IQR)], *** Student's t-test Test (Continuous variables without normal distribution presented as; mean ± standard deviation). BMI: Body Mass Index, HbA1c: Glycosylated Hemoglobin, LDL- Cholesterol: Low-Density Lipoprotein Cholesterol, HDL- Cholesterol: High-Density Lipoprotein Cholesterol, TG: Triglyceride, eGFR: Estimated Glomerular Filtration Rate, Adj. SD: Adjusted Standard Deviation/Variability.

DISCUSSION

Since the results of the Diabetic Control and Complications Trial were published in the early 1990s, the question of glucose fluctuation as a factor in diabetic complications has been debated (20). Following the definition of glucose variability as a target in DM, the term variability is frequently used negatively when referring to human pathologies. The importance of variations in diverse biological processes has attracted the interest of researchers in the field of metabolic disorders during the last decade. For some biological parameters, it seems imperative to always keep them within a very tight narrow range. For example, blood pressure variability has been reported to be associated with CV morbidity and mortality in different studies (21-23). Other studies have reported that glucose and blood pressure variability may be an independent risk factor for albuminuria progression and reduction in GFR in type 2 DM patients (18, 24, 25). Research has also revealed that body weight variability is associated with coronary events and CV deaths (26, 27). The variability of UA is another factor that researchers have recently begun to investigate.

According to the studies, high serum UA levels are strongly associated with obesity, insulin resistance, metabolic syndrome, DM, essential hypertension, and kidney disease (2-7). Additionally, some studies have argued that high serum UA level is an independent risk factor for CV mortality and all-cause mortality (8, 9). According to some reports, the correlation between hyperuricemia and CVD, for which a cause-effect relationship cannot be established, is found to be particularly strong, especially in individuals at high risk for CVD (28). Conversely other studies have reported that UA has no connection with all-cause and CV death after adjusting for other CV risk factors (12, 13).

While it is still unclear whether UA is an independent predictor of all-cause mortality or whether UA plays a significant role in the development of all-cause mortality, the studies mentioned above stated that UA levels consist of a basal single measurement that can be influenced by many factors, including drugs, diet, and renal functions in daily life, and that its variability should be assessed

to make long-term predictions. In this respect, it is important that the mean uric acid value of 5 years was used in our study and that the mean uric acid value was found to be associated with some of cardiovascular risk factors such as albuminuria.

In our study, uric acid variability was evaluated in addition to 5-year mean UA. Only a few research have investigated the effect of UA variability on clinical outcomes. In their community cohort analysis, Wang et al. (14) discovered that increased UA variability was related to increased all-cause mortality. Additionally they reported that UA variability was an independent risk factor for all-cause mortality. Grossman et al. (15) reported that UA variability was linked with all-cause mortality in men. Lim et al. (17) reported that UA variability was significantly linked with the increased incidence of major adverse cardiac events in patients receiving percutaneous coronary intervention. Ceriello et al. (18) proposed that HbA1c, blood pressure, lipid, and UA variability may have varying degrees of effect on the development of albuminuria and other components of diabetic kidney disease in DM patients. In the present study, UA variability was found to be associated with some of the metabolic syndrome parameters. After the HbA1c and glucose levels were equalized in both groups, the variability of UA was associated with the variability of glucose and HbA1c. Interestingly, while there was no difference in the LDL-C and TC levels in the low and high UA variability groups, a significant difference was found between the groups in terms of LDL-C and TC variability. A significant difference was also found between the groups with low and high UA variability in terms of albuminuria and albuminuria variability, which are indicators of CV risk. These findings revealed that the variability of uric acid was closely related to the variability of the lipid profile and glucose regulation indicators among the groups with equalized fasting blood glucose, HbA1c, gender and age values. In our detailed literature review, no study was found that revealed the relationship between uric acid variability and the variability of other risk factors. Interestingly, UA variability was statistically associated with more metabolic risk factors than the 5-year mean UA.

In our study, in accordance with the literature, the variability of UA was found to be associated with triglyceride and blood glucose regulation indicators. The significant relationship between UA variability and triglyceride, HbA1c, glucose variability was interpreted as that these parameters sometimes increase and decrease together, and thus their variability is related.

There is also literature information that can explain the link between UA variability and CVD risk factors. One study identified UA as an inflammatory molecule that promotes oxidative stress (29). Clinical observations showed the fluctuations in UA levels may trigger, exacerbate, and prolong the inflammatory process in gout (17). A rise in UA levels has been shown to enhance the crystallization rate of UA, triggering an immunological and inflammatory response (30). Consequently, variations in the UA levels may be associated with increased oxidative stress, which can contribute to increased CV risk. Another hypothesis is related to UA's anti-oxidant properties. Fluctuating UA levels may represent a compensatory mechanism to counteract oxidative stress, and may reflect CV disease risk factors. Additionally, UA variability is most likely correlated with the variability of CV risk factors, such as hypertension, DM, dyslipidemia, and renal failure (14-18). Therefore, it is suggested that UA variability reflects the development of other CV risk factors rather than stable hyperuricemia (15). Furthermore, in publications evaluating UA variability, patients with higher UA variability used more diuretics and more UA-lowering medications, and they had a lower eGFR and more comorbidities, indicating a high-risk category (17). Another interpretation of these results might be that the variability of UA probably reflects the variability of the quality and efficacy of treatment. Additional large-scale research concentrating on UA variability is required to better understand these issues.

Our research has some limitations as well as some strengths that should be highlighted. First and foremost, this is a retrospective study. Because of the nature of the retrospective analysis, the therapeutic significance of our investigation may be restricted. Another limitation of our study is that it only included a small number of patients. Furthermore, due to the retrospective nature of the study, we were unable to examine the medications taken by the patients or the changes in the drugs they were prescribed. However, we believe the strengths of this study include the length of the patient follow-up period (five years) and the measurement of UA variability and the variability of the other parameters.

CONCLUSION

This study demonstrated that UA variability is related to albuminuria, the atherogenic lipid profile, renal functions, and the variability of these parameters, irrespective of HbA1c and glucose levels. Thus, clinicians should consider uric acid variability in addition to basal UA levels. The therapeutic significance of UA variability and the use of more stable homogeneous metrics to represent UA variation must be examined.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Erzincan Binali Yıldırım University, School of Medicine, Non-invasive Clinical Researches Ethics Ethics Committee (Date: 28.01.2021, Decision No: 03/06).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The late-term results in our patients operated for lumbar spine fractures

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ABSTRACT

Aim: The current study aimed to evaluate the late-term results of patients operated for lumbar spine fractures in our clinic.

Material and Method: 134 patients from January 2012 to January 2020 were treated with "short-segment pedicle instrumentation" for lumbar fractures in our neurosurgery department. Patients with a burst fracture of a single lumbar vertebra were included. The final sample consisted of 67 patients who were followed up over the years with radiographs before and after surgery and CT scans at the final follow-up.

Results: The results showed that 60% of the patients were rated as Denis P1, 35% as P2, and 5% as P3. Screw breakage was observed in seven patients, and 67 patients underwent revision surgery. Furthermore, the fractured vertebral body's height was improved at the final follow-up stage, and an increase was witnessed from the preoperative figure of 16.4 mm to 25.8 at the final follow-up. At the final follow-up, the average Cobb angle was -11.6° preoperatively, and 6.3° after the operation and the correction loss was 12.1° which was severe in the middle part of the vertebra. By the final follow-up, disc spaces were narrowed below and above the fractured vertebra, and no correlation was found between clinical outcomes and adjacent disc degeneration.

Conclusion: We concluded that short-segment pedicle instrumentation produced satisfactory long-term results for lumbar fractures. To achieve adequate outcomes, correct management of complications and evaluation of various factors must be focused on.

Keywords: Lumbar, spinal fractures, spinal surgery

INTRODUCTION

Lumbar spine fractures result of major trauma, and it has been reported that over 765,000 new cases are reported of traumatic spinal fractures per year worldwide (1). New developments in research have shown with a population of over 84 million (2), Turkey observes 650 to 1700 new cases of injury to the spinal region every year. Furthermore, several individuals with spinal fractures rehabilitated account for 15 to 42% of the new cases (3).

Spinal injuries can be caused by a direct shock of a moving item bumping into the spine or incidental impact caused by movements of the spine (4,5). In the older population, lumbar spinal fractures occur due to falls, whereas young individuals have lumbar spine fractures due to road accidents (6). The main cause of spinal injury reported in Turkey is falling, which causes significant damage to the thoracic and lumbar regions (3). It has been reported that lumbar fractures are more common among adult women (59.8%) compared to adult men, as women have lower bone density (7,8).

Lumbar spinal fractures regarded as a major concern in the matter of public health, which causes a significant burden on patients, both economically and physically (9-11). Furthermore, high morbidity and mortality rates are linked to spinal fractures (9,11).

Different treatments for lumbar fractures are available based on the patient's severity, injury classification, and demographic characteristics (12). For lumbar spine trauma, the usage of pedicle screw and implants are common in treating thoracolumbar and lumbar fractures (13). The operative care involving surgical treatment, such as pedicle screw implants, is targeted to generate stability and reduce pain (14). Turkey reported a higher number of surgical interventions than other regions (3). The late results of surgical procedures have not been extensively studied in Turkey; however, studies

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in different regions have shown that post-operative back pain is a common complaint, and some patients may also experience vertebral height loss in the long-term which hinder the recovery of spinal stability (15,16).

Removal of pedicle screw may result in infection, degeneration of disc, osteopenia, and allergic reaction. Second surgical procedure, which is performed to remove the implant, increases the risk of site infection and neurovascular injury (17,18). Furthermore, it has been revealed that inactivity can lead to muscle weakness and negative outcomes of surgery (19-21). Most individuals with lumbar spine surgeries who opt for surgical treatment require narcotics post-operatively, and the usage extends beyond one month (16). Opioids are commonly used to manage pain, recovery can be costly, and analgesia use can have negative impacts (16). Other drugs utilized to manage back include nonsteroidal anti-inflammatory drugs (NSAIDs) and calcitonin (22). Individuals experience back pain that affects day-to-day functioning, and post-operative patients sometimes have to change their jobs due to lumbar surgery (23).

Lumbar surgeries are associated with acute post-surgical pain and affect the patient's recovery, directly impacting their quality of life (24,25). There is a lack of updated and extensive research on the long-term outcome of surgeries for lumbar spine fractures. The late-term results of such surgeries must be evaluated to provide better patient care. Hence, the present study aims to determine the late-term results in patients operated on for lumbar spine fractures and to add significant theoretical knowledge to the limited literature on late-term outcomes in patients operated on for lumbar spine fractures.

MATERIALS AND METHOD

The study was carried out with the permission of KTO Karatay Medical Faculty Non-Pharmaceutical and Non-Medical Device Researches Ethics Committee (Date: 30.12.2022, Decision No: 50512). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. For the present retrospective study, the data of all patients were collected from Meram Medicine Faculty.

Inclusion and Exclusion Criteria for Patients

From January 2012 to January 2020, 134 patients were treated with "short-segment pedicle instrumentation" for lumbar fractures in Meram Medicine Faculty neurosurgery department. According to Denis classification, 88 patients had a burst fracture of a single lumbar vertebra, and they were included in this study. However, the patients with severe intrusion in their spinal canal and who had neurological issues were not included in this study. The patients with a vertebral collapse of more than 60% were also not included in this study because they underwent anterior surgery. At the final follow-up, 3 patients died due to different medical issues, and 18 patients didn't show up, so the final sample for the present study included 67 patients.

Surgical Treatment

All selected patients were treated within 12 days of injury under general anesthesia. Standard trans-pedicular fixation was performed via a "posterior midline approach." Two types of pedicle implants (short-segmented) were utilized for fixation and reduction. The first one included "posterior short-segment fixation" (PSSF), which was used in 26 patients, and the other was "screw-rod angle pedicle fixation" (APF) which was used in 41 patients. However, 35 patients were found to be neurologically compromised, so laminectomy was performed on them. The facet's lateral part was preserved, and the dural sac's laceration was sutured. The pedicle screws were connected with the help of the rods. Later, a reduction force was applied using an instrument for distraction and lordosis. The segmental lordosis and body height of the vertebra were restored, and intraoperative fluoroscopy was used to check them. However, in 35 patients who went through a laminectomy, grafting was done. The patients were recommended to wear a lumbar corset to carry out different activities for at least three months. Revision surgery was recommended within the first year of operation for implant removal.

Follow-up Evaluation and Data Analysis

67 patients were followed-up for an average of 8 years. The clinical evaluation of these patients was done by the outpatient department. Lateral and anterior-posterior (AP) radiographs were also taken pre and post-surgery. A CT scan was also advised at the final follow-up; only 16 patients gave the green signal. The measurements in the context of lateral plain radiograph include the fractured vertebral body's height in the middle and posterior, the Cobb angle, and the fractured vertebra's sagittal angulation. The adjacent vertebra's (present under the fracture) height was taken as the reference, and reduction was determined as the difference between before and after surgery in lordosis and height. Correction loss was also determined as the difference in lordosis and height between pots-operative and pre-implant removal. The smallest distance between the lower and upper screw tips was also determined on the lateral radiograph just before the removal of the implant and after the operation. The shortening of this distance was considered implant deformation. The Mimura method (26) (**Table 1**) was used to assess the discs which were adjacent to the fractured vertebra and to compare them between "pre-operative and final follow-up" with lateral and AP radiographs.

Table 1. Discs' radiographic grading

DH (AD %)	OF (SOP on 8 edges: "<3 mm 1 pt., >3 mm 2 pts.")	ES
0=nor.	0=0 pt.	0=none
1=mil. (>75%)	1=1 to 4 pt.	1=either EP
2=mod. (>50%)	2=5 to 8 pt.	2=both EP
3=sev. (>25%)	3=9 to 12 pt.	
4=v. sev. (<25%)	4=13 to 16 pt.	

DH= disc height; AD= adjacent discs; nor.= normal; mil.= mild; mod.= moderate; sev.= severe; v. sev.= very severs; pt.= points; EP= endplates; ES= endplate sclerosis; OF= osteophyte formation; SOP= sum of points

RESULTS

Demographics of Patients

Table 2 shows that the total number of selected patients was 67.23.8% of these were male, while 76.1% were female. The average age of the patients was 32.9 years. The fractured levels were found to be T11 (2.9%), T12 (17.9%), L1 (40.2%), L2 (51.8%), L3 (14.9%), and L4 (2.9%). 37.3% of patients had fracture type Denis A (37.3%), B (56.7%), and C (5.9%). 35 patients were neurologically compromised integrating Frankel A (17.1%), B (14.2%), C (20%) and D (48.5%). Pre-operative CT and radiographs were taken in all selected patients.

Table 2. Demographics of patients

Characteristics	(n, %)
Gender	
Male	16 (23.8%)
Female	51 (76.1%)
Total	67 (100%)
Average age	32.9 years
Fracture level	
T11	2 (2.9%)
T12	12 (17.9%)
L1	27 (40.2%)
L2	14 (51.8%)
L3	10 (14.9%)
L4	2 (2.9%)
Total	67 (100%)
Fracture types	
Denis A	25 (37.3%)
Denis B	38 (56.7%)
Denis C	4 (5.9%)
Total	67 (100%)
Neurological compromise (pre-operative)	
Frankel A	6 (17.1%)
Frankel B	5 (14.2%)
Frankel C	7 (20%)
Frankel D	17 (48.5%)
Total	35 (100%)

Clinical Results

Denis's evaluation scale is provided in **Table 3**. The results obtained from this study showed that 60% of the patients were rated as "P1," 35% were rated as P2, and 5% were rated to be P3. 46% of the patients changed their work habits, while 10% could not carry out their daily activities.

Table 3. "Denis evaluation scale" (47)

Grade	Criteria
P1	There is no pain
P2	Minimal pain and no medication required
P3	Occasional medication, moderate pain
P4	Pain ranges from moderate to severe
P5	Chronic medication, severe pain constantly

Failure of Implant

Screw breakage was observed in seven patients, and the smallest distance between the lower and upper screw tips was found to be 2.5 mm between immediately post-surgery and just before removal of the plant. 61 patients had revision surgery for plant removal at an average of 14 months. Screws were loosened in a single patient, while two patients had bent screws (**Figure 1**) and were broken in five patients (**Figure 2**). Six patients were not willing to revision surgery. One of these patients had a loosened nut at 7 years (**Figure 3**). A screw was found to be broken in two patients at 6 and 7 years (**Figure 4**), and a foreign reaction was observed in two patients at 7 and 9 years. All these patients later went through revision surgery.

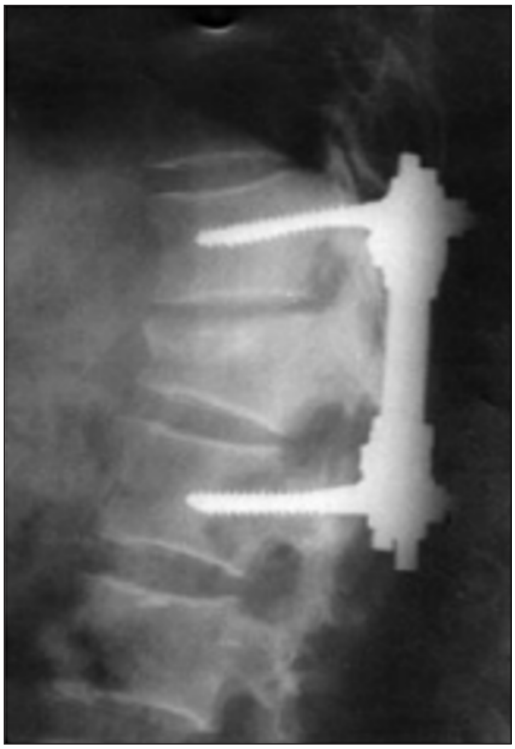

Figure 1. For a 51-year-old male with T12 burst fracture, PSSF was used for his treatment), post-operative radiograph (6 months) representing pedicle screws that were bent

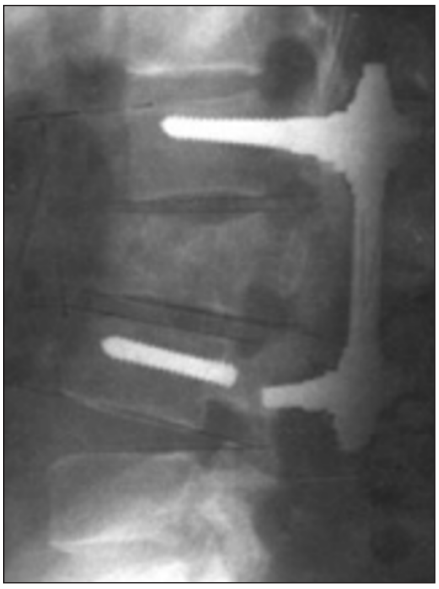

Figure 2. A 42-year-old male with L2 burst fracture, APF was used for his treatment), lower pedicle screws are broken

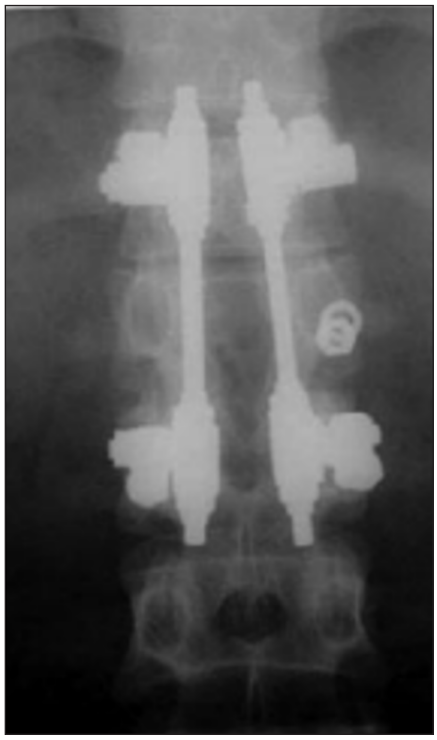

Figure 3. A 49-year-old male with L1 burst fracture, PSSF was used for his treatment), post-operative radiograph (8 years) representing loose nuts

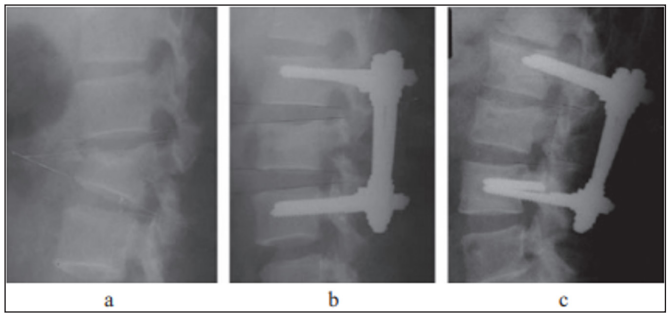

Figure 4. For a 47-year-old male with L2 burst fracture, APF was used for his treatment), (a) pre-operative radiograph, (b) post-surgery radiograph, (c) radiograph after 6 years of operation, showing broken pedicle screw and upper disc degeneration

Moreover, among 26 patients (who had PSSF fixation), implant failure was observed, which included a loose screw, nut, and screw breakage in one patient each, whereas a bent screw was observed in two patients. However, in 41 patients with APF fixation, implant failure was observed in six patients, and about 12 patients had implant failure with a loose screw and nut.

Correction Loss and Reduction

The fractured vertebral body's height was improved at the final follow-up compared to the pre-operative condition. The average height of the anterior vertebra was 16.4 mm preoperatively. At the final follow-up, it was found to be 25.8 mm. Therefore, a 9.4 mm average reduction was observed. The correction loss of the anterior and middle vertebra was 0.7 mm and 1.9 mm, as shown in **Table 4**. The average Cobb angle was -11.6° preoperatively and 6.3° after the operation (an average reduction of 17.8° and -5.8° was observed at the final follow-up), and the correction loss was 12.1°. The final reduction was 5.9°. Therefore, the correction loss was found to occur before implant removal, followed by implant deformation. The correction loss was found to be more severe in the middle part of the vertebra when checked at follow-up.

Table 4. Correction loss and reduction in adjacent discs and fracture vertebral body (mean±SD)

Index	PO	Red.	Loss before IR	Loss at F-U	Final F-U
ADH (mm)	6.1±2.5	3.2±2.6	4.2±4.4	6.2±3.6	2.8±2.2
AVH (mm)	16.5±4.8	9.8±6.2	0.5±1.4	0.7±1.2	25.7±5.6
ABH (mm)	9.7±3.6	1.4±1.6	3.3±2.8	5.2±3.8	6.3±4.2
MVH (mm)	19.2±5.6	6.3±5.8	1.6±3.2	1.7±3.2	23.2±5.7
PDH (mm)	3.3±1.8	0.6±2.3	1.5±1.7	1.8±2.2	1.8±1.8
PVH (mm)	34.2±2.5	0.8±2.8	−0.2±1.2	−0.5±1.3	35.2±1.8
PBDH (mm)	4.3±2.7	0.8±1.7	1.3±1.6	1.3±2.4	4.2±2.1
LD (degree)	3.8±3.5	3.5±4.5	4.5±4.8	6.2±3.5	1.1±2.6
LV (degree)	−22.4±10.3	13.4±9.3	0.5±3.7	1.5±3.7	−10.5±6.24
LLD (degree)	6.8±4.2	1.3±4.6	2.6±3.8	4.5±3.7	3.6±3.8

"ADH= anterior up disc height; AVH= anterior vertebra height; ABH= anterior below disc height; MVH= middle vertebra height; PDH= posterior up disc height; PVH= posterior vertebra height; PBDH= posterior below disc height; LD= lordosis in up disc; LV= lordosis in the vertebra; LLD= lordosis in the lower disc." Red= reduction; F-U= follow-up; PO= pre-operative; IR= implant removal

Adjacent Discs Changes

By final follow-up, the disc spaces were found to be narrowed both below and above the fractured vertebra. Fusion occurred spontaneously in 26 patients in upper disc space. At the same time, spontaneous fusion at lower disc space was observed in 13 patients (**Figure 5**). According to the Minura classification, the degeneration of lower and upper adjacent discs was significant at the time of final follow-up compared to the pre-operative situation, as the value of p was less than 0.01, as shown in **Table 5**.

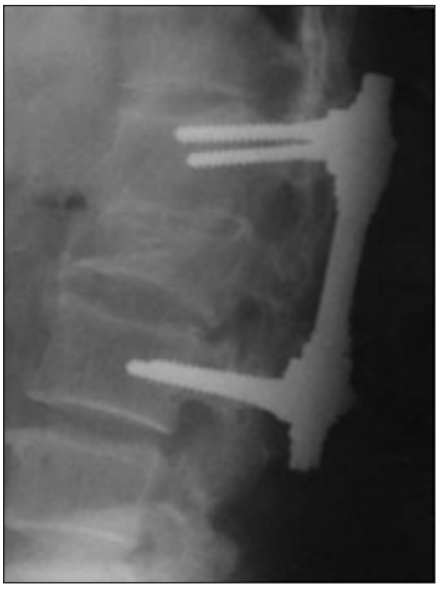

Figure 5. For a 52-year-old male with L2 burst fracture, PSSF was used for his treatment); the implant wasn't removed for 11 years, and good functioning instead of adjacent discs degeneration

Table 5. Discs degeneration pre-operation and at final follow-up

MG	UAD		LAD	
	PO (67 cases)	Final F-U (61 cases)	PO (67 cases)	Final F-U (61 cases)
1	21		45	
2	46		22	2
3		20		37
4		41		22

MG= Mimura Grade; UAD= Upper adjacent disc; LAD= Lower adjacent disc; PO= preoperative; F-U= follow-up, UAD (x^2= 67.11, v= 2, $p < 0.01$); LAD (x^2= 119.37, v= 2, $p < 0.01$)

Correlation between Radiological Findings and Long-term Clinical Outcomes

Table 6 shows no significant correlation between clinical outcomes and adjacent disc degeneration, as the value of p was greater than 0.05.

Table 6. Back pain comparison between patients with and without 20° kyphosis

Patients	D-P1	D-P2	D-P3
Wit. >20° kyphosis	39	21	1
WO >20° kyphosis	3	2	1
Tot.	42	23	2

D= Denis; wit= with; WO= without, Tot= total, (x^2= 16.8, v= 2)

DISCUSSION

Our results showed that "short-segment pedicle instrumentations" effectively reduced lumbar burst fractures and restored the body height of vertebrae and physical lordosis. It was also observed that instead of correction loss at the time of final follow-up, the spinal alignment was found to be improved significantly. According to Kim et al. (27) and Li et al. (28), posterior surgery effectively treats posterior injuries such as facet protruding or lamina into dural theca lancination. Verlaan et al. (29) has reported that surgical treatment of traumatic spine fractures is safe and effective. In their studies An et al. (30) and Smith et al. (31) has stated that short rigid fixation with pedicular instrumentation is more beneficial in surgical treatment of spine fractures. There are also different studies (32-35) in the literature that support the research results and draw attention to the safety of the use of short-segment pedicle instrumentation.

It has also been observed that neurological recovery was not satisfactory in patients with conus medullaris syndrome. Local kyphosis (greater than 20°) was found to be associated with back pain. This result was also advocated by Doğu (36). It has been observed that the patients who took extra care after the operation took less time to recover than those who kept on handling heavy objects . As indicated by Brown et al. (37) good postoperative care, can make the difference between success and failure of treatment.

Moreover, the late-term effects observed in patients treated with APF and PSSF showed that few of the patients suffered bent screws and loosened screws. They were recommended to undergo revision surgery to remove the plants and prevent further discomfort. This explains the efficiency of longer follow-ups for patients who have undergone surgery due to lumbar fractures. Similar to our results Xu et al. (38) concluded that short-segment pedicle instrumentation provided satisfactory reduction for thoracolumbar and lumbar burst fractures. It has also been shown in different studies that surgical intervention for lumbar spine fractures improves long-term quality of life.

The correction loss was found to be more obvious at the follow-up time due to the severely fractured vertebral body's preoperative collapse. Therefore, the correlation between reduction and correction was found to be positive, and collapse was found to be insignificantly correlated to reduction. This shows that minor collapse occurs post-sufficient reduction.

Research Implications

This research study has proven to be efficient in determining the association between back pain and local kyphosis. This study will also improve the information on the correlation between radiological findings and clinical outcomes of patients with lumbar fractures (treated with APF and PSSF). This study will also effectively promote awareness programs for patients with lumbar fractures who have undergone surgeries to take important measures to ensure proper healing. As a result, more rehabilitation management programs will be encouraged for such patients for effective outcomes.

Limitations and Future Research

The present study has some limitations which can be overcome in future studies. This study was limited to clinical outcomes of patients with lumbar fractures. In contrast, no focus was given to the patients' pre and post-operative personal or professional lives. Therefore, future studies can also be conducted in this context. This study only focused on APF and PSSF treatments due to researcher bias. In order to overcome this issue, future studies can also focus on other treatments such as laminectomy, balloon vertebroplasty, etc.

CONCLUSION

In Turkey, lumbar fractures among adults rapidly increase due to stress and accidents. These fractures are more commonly observed among older women as compared to men. This study was conducted to determine the later-term results in patients operated on for lumbar spine fractures. This study's main focus was on reduction, correction loss, and implant removal. For this study, a total of 67 patients (26 treated with PSSF and 41 treated with APF) were included, and the follow-up from January 2012 to January 2020 was one. The results obtained from this study showed that "short-segment pedicle instrumentations" are effective in providing successful reduction for lumbar burst fractures. Despite correction loss at the time of final follow-up, the spinal alignment was found to be improved significantly. However, the correlation between back pain and local kyphosis was significant.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of KTO Karatay University Medical Faculty Non-Pharmaceutical and Non-Medical Device Researches Ethics Committee (Date: 30.12.2022, Decision No: 50512).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Factors predicting the motivation to study abroad in Turkish medical students: a causal investigation into the problem of brain drain

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ABSTRACT

Aim: We aimed to examine the frequency of plans to practice medicine abroad in medical school students and the related variables, in relation to the recently increasing brain drain in physicians in our country.

Material and Method: A total of 82 volunteer students in the 5th and 6th grades were included in the study. Our study is a descriptive and cross-sectional study. A questionnaire was directed to the participants about sociodemographic data, attitudes towards the medical profession, the reasons that make it difficult to practice medicine in our country, the idea of working abroad, and the attractive features of abroad opportunities for students. In addition, the World Health Organization Quality-of-Life Scale (WHOQOL-Bref) to measure the quality of life of the students and the Perceived Stress Scale-14 (PSS-14) to measure the stress level were applied. The data were analyzed in SPSS (21.0) program.

Results: 56% Of the participants were female (n=46), 44% (n=39) were male, and the mean age was 24.07 ±1.65. Majority of the students (94%, n=77) stated that they thought of doing medicine abroad, and nearly half of them (46%, n=38) stated that they were determined on this issue. The answers given by the students to the question why they preferred medical school were as follows: Job guarantee (79%), income comfort (77%) and prestige (70%). Majority of the participants stated that they felt regret from time to time for choosing medical school (58.5%, n=48) and 45% (n=37) stated that they thought of leaving medical school in the past. The following answers were frequently given to the question of the most important reasons that make it difficult to practice the profession of medicine in our country: Heavy working conditions and long working hours (90%), verbal/physical violence against physicians (87%), mobbing and pressure applied by seniors/administrators in the workplace. (67%). The countries respondents considered to immigrate frequently were: Germany, UK and USA. The mean PSS-14 score of the participants was found to be 1.98±0.49, and there was no significant difference between those who thought to practice medicine abroad and those who did not. In the Pearson correlation test, it was determined that there was a significant and negative correlation between the WHOQOL-Bref and PSS-14 scores ($r=-0.620$, $p<0.05$).

Conclusion: The results show that most of the medical students have the idea of brain drain. Special attention should be given to the problems of physicians and medical students in the issue of physician brain drain, which causes the loss of qualified workforce in our country and has been increasing in recent years, and solution-oriented interventions should be implemented rapidly.

Keywords: Brain drain, medical students, quality of life, perceived stress, abroad

This research was presented as an oral presentation at the 1st International, 25th National Clinical Education Symposium, 19-22 May 2022, Çeşme.

INTRODUCTION

Brain drain is the migration of highly educated and qualified workforce to countries that offer better living and working opportunities (1). The movement of displacement, seen in every period of humanity, has generally been in the form of searching for resources and changing living conditions in order to meet the needs of people, although it has gained different qualities. Brain drain is the category of migration whose share has increased the most in international migration movements in recent years (1,2).

Brain drain has different meanings for developed and developing countries. While the developed countries can meet their increasing job and service demands because of the high population growth, expensive education and high demand for manufactured products, through immigrants, they can meet their demands more cheaply and profitably; In developing countries, immigrants contribute to the strengthening of their countries' human capital and economic development through ways such as business, trade, technology transfer, and academic cooperation (1,3). However, the International Labor

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Organization reports that in developing countries, where the number of highly qualified people is less than 5% of the total population and more than 20% of the skilled workforce migrates, the positive effects of migration on development are not valid (4).

Health workers are at the forefront of the occupational groups with the highest brain drain. Globalization, the disappearance of borders between countries, the increase in transportation-communication opportunities, the development of technology and the policies of developed countries that encourage migration have been effective in the increase of migration in both medical and other fields (2,5). In our country, it is thought that there has been an alarming increase in the rate of emigration of doctors and doctor candidates due to reasons such as increasing violent behavior towards physicians, harsh working conditions, low wages, and some health policies in recent years (6).

In this study, it was aimed to investigate the relationship between the perceived stress level and quality of life in medical school students, as well as their attitudes towards the profession of medicine, and their plans to practice the profession of medicine abroad. In addition, it was aimed to examine the sociodemographic data of the participants, the features that make it difficult to practice medicine in our country, and the attractive features of the opportunities abroad for students. It is thought that the results will be a guide for the necessary precautions and interventions against the increasing brain drain in medicine, which is one of the most qualified occupational groups in our country.

The hypotheses of our study: As the perceived stress level in medical students increases and their quality of life decreases, there is an increase in their plans to study abroad.

MATERIAL AND METHOD

The study was carried out with the permission of Mersin University Social and Human Science Ethics Comittee (Date: 30.03.2022, Decision No: 157). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The 5th and 6th grade students of the Faculty of Medicine were included in the study. Our research is a cross-sectional descriptive study. Our research was conducted between 01/04/2022-10/05/2022. A questionnaire was applied on the sociodemographic information of the participants and their attitudes towards the profession (including questions such as age, gender, marital status, what grade they are in, the attitudes of physicians about working conditions in our country and abroad, whether they are considering immigration). In addition, the Quality of Life Scale-Short form (WHOQOL-Bref) developed by the World Health Organization to measure the quality of life of the students and the Perceived Stress Level Scale to measure the stress level were applied. The Perceived Stress Scale is a 14-item scale developed by Cohen, Kamarck, and Mermelstein (7) in 1983, the validity and reliability study of which was conducted by Eskin et al. (8) in 2013. The scale we used in our study was obtained from the publication of the validity and reliability study. The validity and reliability study of the Quality of Life Scale-Short form was conducted in 1999 by Erhan Eser et al. (9). This scale used in our study was obtained from the website of the World Health Organization. The scales were delivered to the volunteers via an online questionnaire. The data were analyzed in the SPSS (21.0) program. Descriptive statistics, Kolmogorov-Smirnov, Student-T test, Chi-square and Pearson correlation analysis tests were applied.

RESULTS

Out of a total of 498 students attending the 5th and 6th grades of the medical faculty, 82 (16.4%) students volunteered to participate in the research. A total of 82 students were included in our study, of which 56% were female (n=46) and 44% (n=39) were male. The mean age was 24.07 ±1.65 years. 95% (n=78) of the students were single. The answers given by the students to the question why they preferred medical school were as follows: Job guarantee (79.3%), economic reasons (76.8%) and prestige (69.5%) (**Table 1**). The majority of the participants stated that they sometimes felt regret for choosing medical school (58.5%, n=48), and 45% (n=37) stated that they thought of leaving medical school (**Table 1**).

Table. Sociodemographic characteristics of students and some attitudes towards medical school

	Count (n)	Rate (%)
Gender		
Female	46	56
Male	39	44
Marital status		
Married	4	4.9
Single	78	95.1
Reasons for choosing medical school		
Job guarantee	65	79.3
Economic reasons	63	76.8
Prestige	57	69.5
İnterest in medical science	56	68.3
Willingness to help	47	57.3
Family pressure	15	18.3
Regret for choosing medical school		
Often	25	30.5
Sometimes	48	58.5
Never	9	11.0
Thoughts to drop out of medical school		
Yes	37	45.1
No	45	54.9

The following answers were frequently given to the question of the most important reasons that make it difficult to practice the profession of medicine in our country: Heavy working conditions and long working hours (90.2%), verbal/physical violence against physicians (86.6%), and the practice of senior/administrators in the workplace environment, mobbing and pressure environment (67.1%), performance system and the obligation to examine patients in a short time (56.1%), physicians' salaries (54.9%), high amount of malpractice lawsuits (48.8%), political pressures (% 25.6%), merit problems in academic units (17.1%), retirement conditions (17.1%) (**Figure 1**).

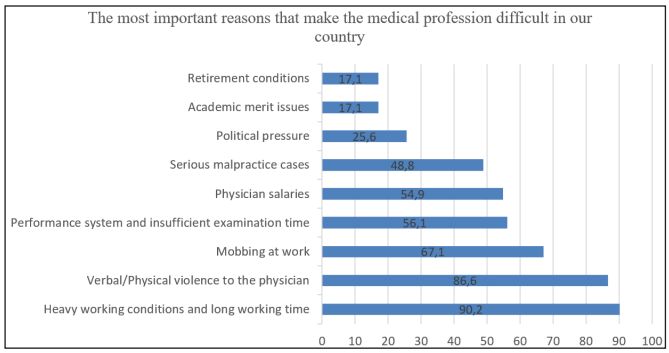

Figure 1. The most important reasons that make the medical profession difficult in our country

Majority of the students (94%, n=77) stated that they thought of doing medicine abroad, and nearly half of them (46%, n=38) stated that they were determined on this issue (**Figure 2**).

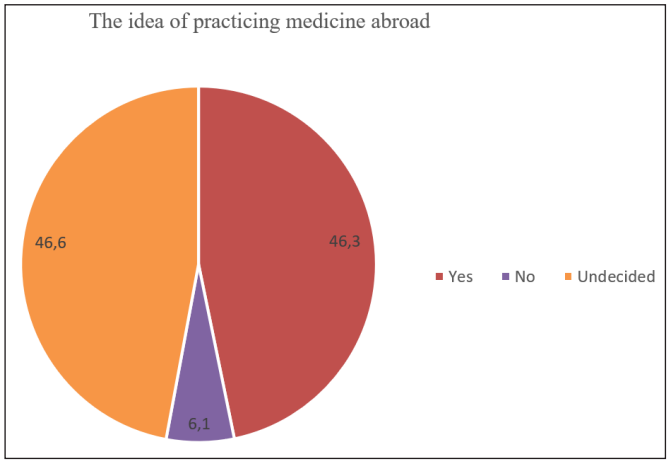

Figure 2. The idea of practicing medicine abroad among medical students

According to gender and marital status, there was no significant difference between the groups who thought to practice medicine abroad and the others. The answers given to the question of what are the most important reasons for students to consider practicing medicine abroad were as follows: Comfortable working conditions (89%), lifestyle and high living standards (77%), comprehensive laws and measures to protect physicians (71%) (**Figure 3**).

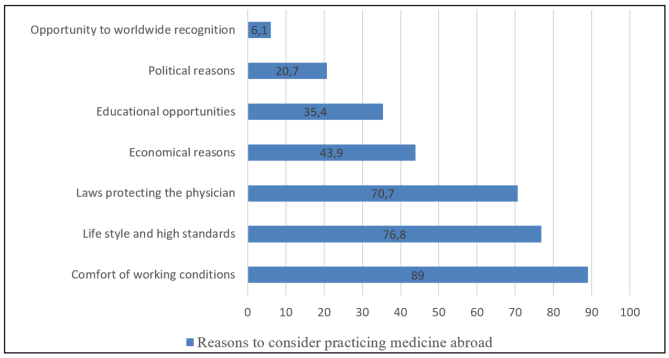

Figure 3. The most common reasons to consider practicing medicine abroad

The countries that respondents considered to migrate were, in order: Germany, UK, USA and other European countries. Participants considering immigration stated that they mostly prepared for the German and English language proficiency exams and the equivalence exams required to practice medicine in these countries. When asked about the reasons that prevent them from practicing medicine abroad, the participants frequently gave the following answers: Not wanting to stay away from family and friends (74%), foreign country exams and financial difficulties (62%), possible problems about immigration and fear of exclusion (44%) (**Figure 4**).

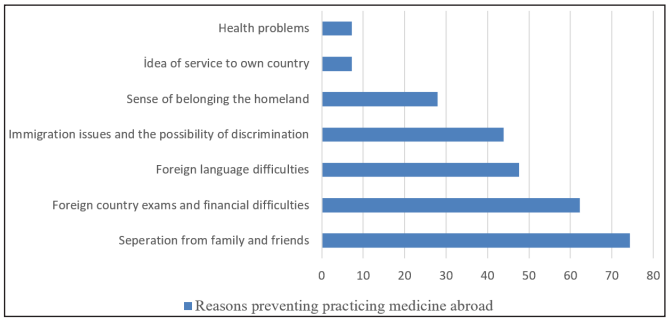

Figure 4. The most common reasons that prevent them from practicing medicine abroad

The students most frequently gave the following answers to the areas of specialization they intend to pursue after graduation: Psychiatry, Dermatology, Obstetrics and Gynecology.

The average quality of life percentile total score of the participants was 49%. The average field scores of the participants in the study on quality of life are as follows: General health status 47%, Physical health 47%, Psychological 55%, Social relations 61%, Environment 51%. While the social sub-score averages of the quality of life scale were higher for those who wanted to go abroad, their mental, physical sub-scores and total scale score averages were found to be lower. However, the findings are not statistically significant.

The mean score of the perceived stress level of the participants was determined as 1.98±0.49, and there was no significant difference between those who thought of practicing medicine abroad and the others.

The mean quality of life scores of the students who were considering dropping out of medical school were lower than the others. When the general health (p=0.037), physical health (p=0.019), psychological health (p=0.019) subgroups and total score (p=0.016) of the quality of life scale were evaluated, the difference between the groups was statistically significant.

Perceived stress scale mean scores of those who were considering dropping out of medical school were higher than the other group, but it was not statistically significant (p=0,125).

There was no significant difference in quality of life scale and perceived stress level scores according to gender, marital status and regret about choosing a medical school.

It was determined that there was a significant and strong negative relationship between Quality of Life and Perceived Stress (r=-0.620, p<0.05).

DISCUSSION

In this study, in which the thought of practicing medicine abroad and some related factors in the 5th and 6th grade students of the medical school was investigated, it was understood that the reasons for choosing the medical school were often the guarantee of profession, income comfort and prestige. More than half of the students (58%) stated that they felt regret from time to time for choosing medical school, and 45% stated that they thought of leaving medical school. According to the results obtained, the perceptions that make the medical profession attractive have changed due to the heavy working conditions and long working hours of the physicians, verbal/physical violence, mobbing in the workplace, performance system, malpractices and low economic standards. As a result of these conditions, it is seen that hopes for the future have decreased and some students regret that they chose medical school. The fact that psychiatry and dermatology are among the fields they want to specialize in after graduation may be due to the relatively low workload and malpractice risk. This suggests that branches with high risk of malpractice such as emergency medicine, surgery and cardiology may have problems in terms of the number of physicians in the future. The number of studies investigating the plans for brain drain in medical school students is not enough, and it has been observed that the tendency to this issue has increased both in our country and in the world in recent years (5,10,11). The difference of our research from the previous ones is that it examines the predictors such as perceived stress level and quality of life and contributes to the solution of the problems related to the underlying cause (12-14).

The fact that the idea of brain drain is widespread not only among medical students but also among students of nursing and other health professions shows that the negative effects of health policies on these groups should not be underestimated (15-17).

Medical faculties around the world have an education process that requires intense effort due to placement in the department and then challenging exams. Intense intellectual rumination and professional concerns about exams and the fields they will choose in the future are the results of these processes (18). In addition to all these, it does not seem easy at all to draw a new route to their education and professional life. Despite this, observed that there has been an increase in the number of students and physicians who consider practicing medicine abroad in better conditions as a way out, and the number of physicians who have migrated, especially in recent years. In our study, the majority of the students (94%) stated that they were considering practicing medicine abroad for reasons such as more comfortable working conditions, lifestyle and high living standards, comprehensive laws and measures to protect physicians. Half of the students stated that they were determined on this issue. This situation reveals that the concerns of medical students about their future are very serious in our country, so these concerns should be eliminated as soon as possible and precautions should be taken about brain drain in physicians. The countries that were considered to immigrate were Germany, England, the USA and other European countries, respectively. This result may be related to the laws, health system conditions, economic welfare and other living standards in these countries (19, 20).

In this study, it was thought that it would be useful to reveal the quality of life and perceived stress levels in order to embody the factors that predict brain drain. While the social sub-score averages of the quality of life scale were higher for those who wanted to go abroad, their mental, physical sub-scores and total scale score average scores were found to be lower. These results show that individuals who have a low quality of life but feel more socially secure are more motivated to go abroad. The lack of statistical significance of the findings may be due to the insufficient number of participants.

Intensive workload, care for severe and terminally ill patients, problems in relationship and task sharing in the workplace, disruption of sleep patterns, night shifts, dealing with patient relatives and economic problems cause work-related stress and tension (21-23). In this context, the scores of quality of life and perceived stress levels in physicians and physician candidates gain importance (23). The perceived stress level mean score perceived by the participants was determined

as 1.98±0.49, and there was no significant difference between those who intend to practice medicine abroad and others. This suggests that the factors causing brain drain are independent of the perceived stress level. While there are good aspects of practicing medicine abroad, there are also various difficulties such as adaptation to a foreign culture, language problems, social problems, preparation process and exams, which may be the reason for this situation.

On the other hand, the students stated that they mostly avoided practicing medicine abroad due to reasons such as not wanting to be away from their family and friends, foreign exams, lack of financial power for the migration process, possible immigration problems and fear of exclusion. These findings explain that although the idea of brain drain is very common in our country, it is less visible in practice due to various concerns.

The total quality of life scores and general health, physical health, psychological health subscale scores of those who were considering leaving the medical school were found to be significantly lower. According to this result, it is speculated that the students blame the medical faculty as the reason for feeling worse, they think that if they leave, they will feel better and their quality of life will increase. The idea of leaving medical school may be the result of more negative feelings in these areas.

Perceived stress scale mean scores of those who were considering dropping out of medical school were higher than the other group, but it was not statistically significant. Perceived stress may not directly affect the idea of dropping out of medical school, or the low number of participants may have prevented us from achieving significant statistical results. In addition, the fact that possible plans were very stressful after leaving the medical school due to the economic and social conditions in our country may have affected this result.

According to our study, the existence of a significant and strong negative relationship between students' quality of life and perceived stress can be explained by the negative effect of stress on their quality of life, and this result is expected.

The limitations of our study are the low number of participants, the inclusion of only medical school students in certain classes, and the inability to examine familial, environmental and other individual factors.

CONCLUSION

The results show that most of the medical students are intend to practicing medicine abroad. Heavy working conditions, violence at work and economic reasons make it difficult to practice medicine in our country and the other reasons strengthens the idea of brain drain among medical students. Special attention should be paid to the problems of physicians and medical students regarding the issue of brain drain in physicians, which has caused the loss of qualified workforce in our country and has been increasing recently, and solution-oriented interventions should be implemented rapidly.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Mersin University Social and Human Science Ethics Comittee (Date: 30.03.2022, Decision No: 157).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Investigation of the relationship between food consumption and emotions that show psychobiotic characteristics of healthcare professionals: Karabük province example

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ABSTRACT

Aim: The aim of this study was to examine the relationship between psychobiotic food consumption and moods in healthcare professionals.

Material and Method: The research was conducted on healthcare professionals in December 2022. The research sample consists of healthcare workers over the age of 18 and at least secondary school graduates (physician, nurses, midwives, laboratorians, anesthesia technicians, audiologists, radiology technicians, medical secretaries, nurses, civil servants, psychologists and physiotherapists). A questionnaire comprised three parts. In the first part, there are questions containing general information about the demographic characteristics of the participants (age, educational status, profession, etc.). In the second part, the nutritional habits of the participants and the food consumption frequency form including the foods showed psychobiotic properties were used. In the third part, Depression Anxiety Stress Scale (DASS-21) was used. Body Mass Indexes were calculated by measuring the body weight and height of the individuals. Statistical analyses were performed by using SPSS (IBM SPSS Statistics 24.0) package program.

Results: 88 (57.5%) of the participants were female and 65 (42.5%) of them were male. 57 participants (37.3%) were in the age range of 40-49. Negatively, weakly statistically significant relationship was found between the age and anxiety scale (rho=-0.208; p=0.010). A negatively significant relationship was found between the anxiety subscale and foods such as cauliflower, cabbage, broccoli and oats/oat bran consumption (rho=-0.231, p=0.004; rho=-0.387, p=0.000). Fish and fish oil consumption and depression and stress subscales have been positively statistically significant relationship (rho=0.166, p=0.040; rho=0.200, p=0.013).

Conclusion: The consumption of probiotics and psychobiotics is increasing day by day with the increase in the level of knowledge. Because psychobiotics have effects in alleviating anxiety, depression and psychological problems, it is thought that they may have positive effects, such as reducing the effects of factors that cause obesity, such as emotional eating. In this study, there are relationships between depression, anxiety and stress and consumption of psychobiotic foods, but there is a need for more detailed and large-scale studies as there are many factors that can affect the level of stress and anxiety.

Keywords: Mood, probiotics, prebiotics, phychobiotics, body mass index

INTRODUCTION

According to the World Health Organization, depression affects more than 300 million people around the world (1). Psychological disorders such as depression and anxiety disorders of individuals; It has a negative effect not only on health conditions but also on quality of life. Depression; sad and anxious mood, anxiety, pessimism, irritability, fatigue, changes in sleep patterns and suicide thoughts such as serious symptoms of emotional disorder. Mood disorders reduce productivity in the workplace of individuals and affect the economic welfare of all regions in welfare-health expenditures. Existing research; It shows that the interaction of psychological, environmental, genetic and biological factors and eating habits triggers the emotions of individuals. There are many multidisciplinary methods to treat these disorders (2,3).

Today, it is common for individuals to have both intestine and mood disorders together. This suggests that there is a strong connection between the central nervous system and the gastrointestinal tract (4). When the complex system between the intestine and the brain is analyzed, the relationship between these two organs goes further than the maintenance of homeostasis; It has been confirmed by studies that there is a relationship between intestinal microbiota and mental health (4-6). Psychobiotics have been defined as "living organisms that, when taken in adequate amounts, create health benefits in patients

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suffering from psychiatric illnesses" (7,8). It is therefore thought that all of the substances that affect psychology through the microbiome may be potential psychobiotics (9). The bacteria most commonly used as psychobiotics are probiotics, which show potential effects on psychological and physiological conditions such as improving anxiety, depression and appetite levels. Psychobiotics are probiotic microorganisms that affect the central nervous system and neurological functions of a host and can improve the quality of life of hosts with psychological disorders by balancing gastrointestinal function (10-13).

In recent years, clinical and animal studies have reported that one of the best ways to improve the microbiota is to supplement psychobiotic bacteria. It has been observed that the beneficial effects of psychobiotics are not only in the gut, but also reach the whole microbiota-gut-brain axis (8,9). Psychobiotics, when taken in appropriate formulations and in the right amounts, can have positive psychiatric effects on psychopathology (14,15). In an age where the tendency to eat ready-to-eat foods instead of traditional nutrition is increasing, access to and follow-up of up-to-date information by health professionals on the consumption of foods is an important component for increasing the quality of health (16). Exposure to tension and high stress due to intense work tempo can lead to both physical, behavioral, emotional and psychological problems of employees. The positive or negative emotions that people feel affect their decisions, choices, behaviors as well as their eating behaviors. Therefore, eating is a biological necessity and there is also a psychological dimension (16,20). While there are studies on the level and consumption of probiotic, prebiotic and synbiotic information of healthcare professionals in our country, there are few studies on psychobiotics. The hypothesis of this study is that health workers who consume more foods with psychobiotic properties have lower stress and anxiety levels. Therefore, the aim of this study was to examine the relationship between the consumption of foods showing psychobiotic properties and moods in healthcare professionals.

MATERIAL AND METHOD

The study was carried out with the permission of Karabük University, Non-invasive Clinical Researches Ethics Committee (Date: 19/12/2022, Decision No:1183). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Participants

This research was conducted in December 2022 on individuals who are health workers. This group was preferred because healthcare workers are under higher stress due to their working conditions. The sample size of the study was found to be 134 people by performing power analysis at 95% confidence interval and 0.05 significance level. The research sample consists of health workers over the age of 18 and at least secondary school graduates (physicians, nurses, midwives, laboratorians, anesthesia technicians, audiologists, radiology technicians, medical secretaries, nurses, civil servants, psychologists and physiotherapists). Before the research, the participants were informed about the research and the volunteer individuals who agreed to participate in the research were included in the research by signing the "Informed Consent Form". Those who did not volunteer to participate in the study, those with severe psychiatric illness, and those using regular probiotic supplements were excluded from the study.

Collection and Evaluation of Data

A questionnaire form containing multiple choice and open-ended questions was applied to the participants by the researcher with face-to-face interview technique. This questionnaire consists of three parts. In the first part, there are questions containing general information about the demographic characteristics of the participants (age, educational status, profession, etc.). In the second part, the nutritional habits of the participants and the food consumption frequency form including the foods showing psychobiotic properties were used (consumption of the relevant food for at least 3 months is based on regular consumption). In the third part, Depression Anxiety Stress Scale (DASS-21) was used. Researchers reached out to participants through personal connections. The survey was conducted face-to-face to the health personnel working in the Family Health Centers affiliated to the Safranbolu District Health Directorate of Karabuk Province by the researcher. It was completed in about 15 minutes.

The Depression, Anxiety, Stress Scale (DASS-21)

DASS-21 was developed by Lovibond et al. (18) and adapted to Turkish by Sarıçam. The scale has 21 items; There are seven items in the sub-dimensions of depression, anxiety and stress. The scale assesses symptoms of depression, anxiety and stress in the last week according to a quadruple rating between (0) never and (3) always. A score between 0 and 21 can be obtained from the sub-factors of the scale. Higher scores indicate higher levels of depression, anxiety and stress. In the clinical sample, Cronbach's alpha internal consistency reliability coefficient was found to be 0.87 for depression subscale, 0.85 for anxiety subscale and 0.81 for stress subscale (17).

Anthropometric Measurements

Anthropometric measurements were made by the researcher with the appropriate technique. Body length and body weight of the individuals included in the research were recorded in the questionnaire form. Body mass index (BMI) of patients was calculated by dividing body weight by square meters of height [body weight (kg)/

height²]. According to World Health Organization (WHO) standards, <18.5-<24.9 kg/m² is defined as normal, ≥25.0-<29.9 kg/m² is overweight, and ≥30.0 kg/m² is defined as obese (19).

Statistical Analysis

Statistical analyses were performed using a package program called SPSS (IBM SPSS Statistics 24.0). Frequency tables and descriptive statistics were used to interpret the results. Non-parametric methods were used for measurement values that were not suitable for normal distribution. In accordance with non-parametric methods, "Mann-Whitney U" test (Z-table value) method was used to compare two independent groups with their measurement values, and "Kruskal-Wallis H" test (χ2-table value) method was used to compare three or more independent groups with measurement values. The relationships between the scales and some variables were determined by correlation analysis. Interpretations of correlation coefficients rho=0; no relationship, rho=0.01-0.29; relationship at a weak level, rho=0.3-0.7; moderate relationship, rho=0.71-0.99; high level of relationship, rho=1; interpreted with excellent relationship levels (21). The results of the analysis were interpreted at the confidence level and 0.05 significance values for the comparison tests and at the significance values of 0.05 and 0.01 for the correlation tests and trust levels.

RESULTS

The demographic characteristics of the participants participating in the study are given in **Table 1**. Out of a total of 153 participants; 88 (57.5%) were female and 65 (42.5%) were male. 57 participants (37.3%) are between the ages of 40-49. 137 (89.5%) are married and 82 (53.6%) are undergraduates. The body mass index of 45.1 % of the participants is in the overweight group. The working time of 35.9 % of the participants is in the range of 10-15 years and 41.2 % are nurse.

Information on nutrition individuals is given in **Table 2**.

Table 3 includes the scores of individuals from the DASS-21 subscales and the relationships between age, body weight (kg) and height (cm) and body mass index. Negatively, weakly statistically significant relationship was found between age and anxiety scale (r=-0.208; p= 0.010). As age increases, the anxiety of individuals increases. A negative, weakly statistically significant relationship was found between height and stress (r=-0.193; p=-0.017). There was a moderate statistically significant positive relationship between anxiety, depression and stress scales (r=0.587; p=-0.000, r=-0.578; p=0.000). A very high degree of statistically significant positive relationship was found between depression and stress scales (r=0.921; p=0.000). Stress and depression scale scores tend to increase or decrease together.

Table 1. Demographic characteristics of individuals

Variable (n=153)	n	%
Gender		
Female	88	57.5
Male	65	42.5
Age (year)		
20-29	30	19.6
30-39	48	31.4
40-49	57	37.3
50 and over	18	11.8
Marital Status		
Married	137	89.5
Single	16	10.5
Education Level		
High School	50	32.7
University	82	53.6
Undergraduate	21	13.7
Body Mass Index (kg/m²)		
<18.5	1	0.65
18.5-24.9	42	27.5
25-29.9	69	45.1
>30	41	26.8
Have been working for		
0-5 years	20	13.1
5-10 years	19	12.4
10-15 years	55	35.9
15-20 years	47	30.7
20 years and over	12	7.8
Occupation		
Nurse	63	41.2
Physician	10	6.5
Midwife	20	13.1
Health officer	44	28.8
Other (Physiotherapist, Psychologist, Audiologist, Medical secretary)	16	10.5

Table 2. Distribution of participants' nutritional status and probiotic and prebiotic information

Variable (n=153)	n	%
Regularly using medication/food supplement		
Is not using	124	81.0
Vitamin B12	2	1.3
Vitamin D	14	9.15
Collogen	6	3.9
Multivitamin	7	4.6
Foods of choice when stressed, nervous or irritable		
Don't want to eat	78	51.0
Chocolate, wafer, biscuit, cake	47	30.7
Salted foods like crackers, snacks	5	3.3
Sugar drinks	23	15.0
Foods of choice when you are happy and cheerful		
Don't want to eat	87	56.9
Chocolate, wafer, biscuit, cake	42	27.5
Salted foods like crackers, snacks	5	3.3
Sugar drinks	19	12.4
Does your emotional state affect nutrition		
Effective	85	55.6
Not effective	68	44.4
Believing that probiotics are useful for health		
Beneficial	106	69.3
Not beneficial	20	13.1
Has no idea	27	17.6
Believing that prebiotics are useful for health		
Beneficial	106	69.3
Not beneficial	20	13.1
Has no idea	27	17.6

Table 3. Test of correlation between anthropometric measurements of individuals and DASS-21 scale scores

Variable (n=153)		Age (year)	Body mass index (kg/m²)	DASS-21 anxiety subscale	DASS-21 depression subscale	DASS-21 stress subscale
Age (year)	rho	1.000	0.048	-0.208**	-0.104	-0.061
	p		0.554	0.010	0.201	0.454
Body weight (kg)	rho	0.050	.828**	-0.087	0.009	0.029
	p	0.539	0.000	0.285	0.907	0.720
Length (cm)	rho	-0.008	-0.236**	-0.154	-0.145	-0.193*
	p	0.921	0.003	0.057	0.074	0.017
Body mass index (kg/m²)	rho	0.048	1.000	-0.029	0.093	0.133
	p	0.554		0.720	0.253	0.102
DASS-21 anxiety subscale	rho	-0.208**	-0.029	1.000	0.587**	0.578**
	p	0.010	0.720		0.000	0.000
DASS-21 depression subscale	rho	-0.104	0.093	0.587**	1.000	0.921**
	p	0.201	0.253	0.000		0.000
DASS-21 stress subscale	rho	-0.061	0.133	0.578**	0.921**	1.000
	p	0.454	0.102	0.000	0.000	

*p<0.05. **p<0.01, Spearmen Correlation Analyses (rho,p)

In **Table 4**, the results of the analysis of the comparison of the sub-dimensions of the DASS-21 scale and some characteristics of the individuals were included. It was analyzed that there were statistically significant differences between the gender of the individuals and the anxiety scale (Z=4.360, p<0.05). It was analyzed that there were statistically significant differences between the age groups of the individuals and the stress scale ($\chi 2$=7.872, p<0.05).

In **Table 5**, the consumption of foods with psychobiotic characteristics and the correlation of BMI and DASS-21 subscales are given. Negatively, weakly statistically significant relationship was found between dark chocolate consumption and anxiety subscale (r=-0.291; p=-0.000). Negatively statistically significant relationship between Kombucha tea and water kefir consumption and stress subscale was found to be weakly statistically (r=-0.193; p=-0.017). A negatively significant relationship was found between the anxiety subscale and foods such as cauliflower, cabbage, broccoli and oats/oat bran consumption (r=-0.231, r=0.040; r=-0.387 p=0.000). Fish/fish oil consumption and depression and stress subscales have been positively statistically significant relationship (r=0.166, r=0.040; r=0.200 p=0.013).

DISCUSSION

The recent development of the concept of psychobiotics is important in addition to traditional probiotic and prebiotic supplements. Animal and clinical studies in recent years report the potential of microorganisms for psychobiotics that alter the gut microbiota, improve cognitive function, and control anxiety and stress levels. However, due to the complexity of the gut-brain-microbiota axis, the elucidation of the specific mechanisms by which bacterial and yeast strains exert their activity and the identification of a systemic procedure for assessing the psychobiotic effects of a particular strain, formulation, or food product is still underway (21). In this sense, awareness is still low and there is no consensus in general. In a study conducted on university students, it was determined that 45.2% of the students had knowledge about the concepts of probiotics and prebiotics, but did not have clear information about the concept of psychobiotics (22). In a study aimed at measuring probiotic-prebiotic consumption, it was found that 38.4-46.0% of individuals consumed probiotics (22-24). It has been observed that individuals' knowledge can increase their probiotic-prebiotic food consumption. On the other hand, the low level of knowledge of individuals about psychobiotics did not reduce their consumption of probiotic foods. In our study, 60.1% of the participants knew the concept of probiotics, 69.3% knew the concept of prebiotics, 26.8% knew the concept of psychobiotics. 69.3% of the participants think that probiotics and prebiotics are beneficial for health. Although the number of individuals who have knowledge about probiotic-prebiotics is higher, the number of people who know the concept of psychobiotics in our study is lower. The reason for this is thought to be that the concept of psychobiotics is a relatively new concept and is still being studied.

Made works; It shows that lifestyle changes such as increasing physical activity, healthy nutrition, nutritional supplements when necessary, and the use of probiotic-prebiotic supplements improve the living conditions of individuals and reduce perceived stress. Healthy eating has been proven to successfully reduce symptoms even in non-clinical depression (25-27). Stress not only increases food consumption in some cases, but it can also shift individuals' food choices from lower-fat options to high-fat ones. Socio-demographic factors (gender, age, country) and lifestyle characteristics (nutritional behaviors, quality of life, social support, etc.) affect body perception, the content of food consumed and perceived stress level (28). Although improvements in stress have been observed before through

microbiota-targeted studies (probiotics, fermented drinks); future studies should investigate the hypothesis that the psychobiotic diet leads to a more stable microbiota, resulting in greater changes in perceived stress. Nishida et al. (27) investigated the psychobiotic potential of *Lactobacillus gasseri CP2305* to improve chronic stress-related symptoms in medical students. As a control and intervention group; each student was given psychobiotic supplementation for 12 weeks; The sleep quality index scores of students who used psychobiotic supplements were low in the Persistent Anxiety Inventory and their stress factors were lower. In this study, the foods preferred by the participants who woke up from sleep at night and ate were; It was analyzed that there were statistically significant differences between the foods preferred when stressed, nervous and irritable, and the rate of eating, the emotional state affecting nutrition and the anxiety subscale. It was determined that the emotional state of the participants affected their nutrition in general, and when they were stressed, nervous, irritable and happy, cheerful, they generally ate chocolate, wafers, biscuits and cakes.

In clinical and animal studies, it has been observed that psychobiotic supplementation provides similar effects to traditional antidepressant treatments, relieves symptoms and beneficial effects reach the whole microbiota-gut-brain axis, not only in the gut. When animal studies were examined, it was seen that the antidepressant effect of psychobiotics was closely related to the regulation of the microbiota-gut-brain axis (28). Another study found that psychobiotic food consumption can positively affect anxiety, depression, and mood swings (29,30). In our study, it is thought that the reason why the expected effect could not be achieved compared to other studies is due to the low level of knowledge of health professionals about psychobiotic foods.

Table 4. Comparison of Some Characteristics and Nutritional Preference of Individuals with DASS-21 Scale Scores

	DASS-21 Anxiety Subscale					DASS-21 Depression Subscale					DASS-21 Stress Subscale				
	x̄	SD	Median	Analysis	p	x̄	SD	Median	Analysis	p	x̄	SD	Median	Analysis	p
Gender				Z=-4.360	0.000				Z=-1.068	0.285				Z=-0.352	Z=0.725
Female	10.3	2.0	10.0			8.2	2.5	7.0			8.1	2.6	7.0		
Male	8.9	1.9	8.0			8.0	2.4	7.0			8.0	2.4	7.0		
Age (year)				χ^2=5.021	0.170				χ^2=7.547	0.053				χ^2=7.872	0.047
20-29	10.3	1.9	10.0			7.8	2.1	7.0			7.7	2.1	7.0		
30-39	10.0	2.1	10.0			8.8	3.0	7.0			8.8	3.1	7.0		
40-49	9.5	2.0	9.0			7.5	1.8	7.0			7.5	1.8	7.0		
50 and over	9.2	2.3	8.0			8.6	3.0	7.0			8.6	3.0	7.0		
Body Mass Index (kg/m²)				χ^2=3.842*	0.146*				χ^2=2.638*	0.267*				χ^2=2.879*	0.237*
<18.5	11.0					7.0					7.0				
18.5-24.9	10.2	2.2	10.0			8.2	2.6	7.0			8.2	2.6	7.0		
25-29.9	9.4	1.9	9.0			7.7	2.1	7.0			7.7	2.1	7.0		
>30	9.9	2.2	10.0			8.6	2.9	7.0			8.5	2.9	7.0		
Marital status				Z=-1.661	0.097				Z=-2.692	0.007				Z=-1.912	0.056
Married	9.6	2.0	10.0			7.9	2.4	7.0			7.9	2.4	7.0		
Single	10.6	2.2	10.0			9.3	3.3	7.0			9.2	3.4	7.0		
Foods of choice when stressed, nervous or irritable				χ^2=11.182	0.011				χ^2=0.265	0.966				χ^2=0.249	0.969
Don't want to eat	9.4	2.0	9.0			8.0	2.4	7.0			8.0	2.5	7.0		
Chocolate, wafer, biscuit, cake	10.2	1.9	10.0			8.0	2.5	7.0			8.0	2.5	7.0		
Salted foods like crackers, snacks	8.2	2.2	7.0			8.4	3.1	7.0			8.4	3.1	7.0		
Sugar drinks	10.3	2.1	10.0			8.3	2.7	7.0			8.2	2.7	7.0		
Foods of choice when you are happy and cheerful				χ^2=3.009	0.390				χ^2=2.671	0.445				χ^2=3.500	0.321
Don't want to eat	9.6	2.1	10.0			8.2	2.6	7.0			8.1	2.6	7.0		
Chocolate, wafer, biscuit, cake	10.0	1.8	10.0			7.7	2.1	7.0			7.7	2.1	7.0		
Salted foods like crackers, snacks	8.8	2.5	7.0			9.6	3.6	7.0			9.8	3.8	7.0		
Sugar drinks	10.1	2.1	10.0			8.2	2.6	7.0			8.1	2.6	7.0		
Does your emotional state affect nutrition				Z=-3.076	0.002				Z=-0.227	0.821				Z=-0.555	0.579
Effective	10.2	2.0	10.0			8.2	2.6	7.0			8.2	2.6	7.0		
Not effective	9.2	2.0	9.0			8.0	2.4	7.0			7.9	2.4	7.0		

In the comparison of two independent groups in data that do not have normal distribution with the measurement values, the "Mann-Whitney U" test (Z-Table value); In the comparison of three or more independent groups, "Kruskal-Wallis H" tests (χ^2-Table value) statistics were used. *One participant with a Body Mass Index <18.5 was not included in the analyses.

Table 5. Correlation of foods with psychobiotic properties with consumption status with BMI and DASS-21 subscales

Foods with Psychobiotic Properties	Correlation	BMI	DASS-21 anxiety subscale	DASS-21 depression subscale	DASS-21 stress subscale
Kefir	rho	-0.037	-0.085	0.070	0.047
	p	0.646	0.298	0.388	0.567
Milk with probiotics	rho	-0.072	0.084	-0.056	-0.003
	p	0.377	0.304	0.494	0.967
Yogurt with probiotics	rho	0.125	0.037	-0.035	-0.035
	p	0.123	0.650	0.667	0.667
Banana	rho	-0.086	-0.102	-0.048	-0.109
	p	0.293	0.208	0.554	0.182
Apple	rho	-0.035	0.100	0.012	0.015
	p	0.668	0.217	0.879	0.852
Dark chocolate	rho	0.084	-0.291**	-0.127	-0.072
	p	0.302	0.000	0.118	0.380
Kombucha tea	rho	0.090	-0.075	-0.148	-0.193*
	p	0.269	0.355	0.069	0.017
Water kefir	rho	0.090	-0.075	-0.148	-0.193*
	p	0.269	0.355	0.069	0.017
Boza	rho	0.092	0.006	-0.070	-0.054
	p	0.257	0.939	0.387	0.505
Tarhana	rho	0-.062	-0.045	0.084	0.057
	p	0.448	0.582	0.305	0.486
Fermented pickle	rho	0.071	-0.132	-0.105	-0.148
	p	0.386	0.104	0.197	0.067
Turnip	rho	0.065	0.076	-0.005	-0.008
	p	0.424	0.351	0.950	0.926
Vinegar	rho	-0.067	-0.025	0.092	0.067
	p	0.407	0.758	0.256	0.410
Pomegranate sour sauce	rho	-0.105	0.020	0.078	0.043
	p	0.195	0.804	0.337	0.595
Brine foods	rho	-0.114	0.027	0.110	0.084
	p	0.161	0.743	0.176	0.301
Whole grain products	rho	0.026	0.019	0.002	0.007
	p	0.749	0.817	0.977	0.928
Green leafy vegetables	rho	0.038	-0.036	-0.116	-0.104
	p	0.640	0.656	0.155	0.202
Vegetables such as cauliflower, cabbage, broccoli	rho	0.003	-0.231**	-0.064	-0.100
	p	0.975	0.004	0.434	0.217
Oats/oatmeal	rho	0.148	-0.387**	-0.125	-0.049
	p	0.067	0.000	0.123	0.551
Fish/fish oil	rho	0.002	0.103	0.166*	0.200*
	p	0.977	0.207	0.040	0.013

*p<0.05. **p<0.01, Spearmen Correlation analysis (rho,p)

The effects of psychobiotic supplementation on depressive symptoms were investigated in another systematic review. In the seven studies examined; in the intervention group compared to placebo; psychobiotic interventions have been found to be effective in improving the depressive symptoms of diseases such as hypertension and diabetes (31). In interpreting the different results of various studies, the anti-depressant effects of psychobiotics, the types of probiotic strains or prebiotics administered, the dosage and also the duration of supplementation should be taken into account. Some types have been shown to be effective in relieving symptoms. In our study, when the relationships between the scores they received from the DASS-21 subscales and age, body weight (kg) and height (cm), body mass index were examined; negative direction between age and anxiety, negative direction between height and stress; A very high degree of statistically significant relationship was found between anxiety and depression and stress in a positive direction and between depression and stress in a positive direction. As the age increases, the anxiety of individuals increases.

Today, the effects of foods containing psychobiotic organisms on mental health are mentioned. Some psychobiotics have been found to produce neuroactive compounds, showing behavioral effects, especially in stress-related disorders such as depression and anxiety.

Fermented foods such as yogurt, kefir, boza, which are among the fermented milk products, and foods such as bananas, apples and cocoa with prebiotic content have been shown to be related to mental health by supporting the proliferation of beneficial gut bacteria (32). In a randomized double-blind placebo-controlled study, individuals given probiotic yogurt and probiotic capsules showed improvements in their depression status (33). In another study, the relationship between the consumption of probiotic and prebiotic foods and happiness was discussed and a positive relationship was found between the consumption of probiotic milk and yogurt, apple, fermented yogurt and turnip juice and happiness status (34). In our study, a statistically significant relationship was found between the participants' dark chocolate consumption and the anxiety al scale, in a negative way between the consumption of kombucha tea and water kefir and the stress subscale and between the anxiety subscale and the consumption of foods such as cauliflower, cabbage, broccoli and oat/oat bran.

In a study, it was found that yoghurt (90.9%), ayran (59.6%) and pickles (55.6%) were consumed from foods with psychobiotic properties (35). In our study, kefir (68.0%), banana (98.0%), apple (100.0%), green leafy vegetables (100.0%) were consumed the most. It was found that boza, water kefir and kombucha tea are the least consumed psychobiotic products. This may be due to the fact that individuals do not like or do not try boza, water kefir and kombucha tea, as well as the lack of knowledge. In a similar study to determine the frequency of probiotic consumption of adult individuals, it was found that probiotic added foods are less frequently consumed in parallel with our study (36). In another study, it was found that 61.8% of the individuals participating in the study did not consume probiotic milk and that the probiotic yogurts were more preferable (37). Probiotic foods and consuming habits they consume according to the cultures and nutritional habits of the countries may vary (36). Probiotic and psychobiotic consumption is increasing day by day with the increase in the level of knowledge. It is thought that psychobiotics have positive effects such as reducing the effects of obesity such as emotional eating because of the effects of anxiety, depression and psychological problems. As far as we know, our study is the first study to investigate the relationship between psychobiotics and mood in health workers in our country. Healthcare workers are a group that is under serious stress. Adding psychobiotic foods to their diet can improve their mood.

CONCLUSION

Our study has some limitations. The study is limited to Safranbolu district of Karabük province. It cannot be attributed to the general. As a result of the literature review, the researchers determined the foods that are described as psychobiotic. If there is a scale to be developed for this purpose in the future, data will be collected more objectively. In addition to these, it has not been questioned how long the psychobiotic foods have been consumed regularly.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karabük University, Non-invasive Clinical Researches Ethics Committee (Date: 19/12/2022, Decision No:1183).

Informed Consent: All participants included in the study were informed and their consent was taken before filling the questionnaire.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Complications of total knee arthroplasty and the development of late deep infection in patients with rheumatoid arthritis

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ABSTRACT

Aim: This study aimed to assess complications and the presence of late deep infection in patients with rheumatoid arthritis (RA) who underwent primary and revision total knee arthroplasty (TKA).

Materıial and Method: Between June 1997 and October 2022, cemented TKA that cut the posterior cruciate ligament (PCL) was applied to 50 knees of 34 patients with RA, and posterior-stabilized (PS) revision TKA was applied to 7 knees of 5 patients. All the patients enclosed in this study were adults diagnosed with RA by a rheumatology or physical therapy physician according to the RA diagnostic criteria recommended by the American College of Rheumatology in 1987. The diagnosis of infection was based on the Periprosthetic Infection Diagnostic Criteria of the 2018 International Periprosthetic Joint Infections Consensus Meeting.

Results: Complications were found in 9 (18%) of the 50 knees who underwent primary TKA. Postoperative serous discharge was observed in 3 (6%) knees, serous discharge and late partial rupture of the quadriceps tendon in 1 (2%), early deep infection in 1 (2%), late deep infection in 3 (6%), and hematoma in 1 (2%). Revision surgery was performed on 3 (6%) knees due to infection and on 4 (8%) knees due to aseptic loosening. Complications developed in 2 of these knees who underwent revision TKA, 1 (14.3%) knee with periprosthetic fracture in the femur in the first postoperative year, and 1 (14.3%) knee with early deep infection. Deep vein thrombosis (DVT), pulmonary emboli (PE) and heterotopic ossification (HO) were not observed in any patient.

Conclusion: In patients with rheumatoid arthritis, total knee arthroplasty increased chronic late deep infection and the associated need for revision surgery, and decreased the rates of DVT, PE, HO.

Keywords: Rheumatoid arthritis, total knee arthroplasty, complications

INTRODUCTION

It is stated that more complications are expected in patients with rheumatoid arthritis (RA) who underwent total knee arthroplasty (TKA) compared to patients with osteoarthritis (1,2). It is noted that this situation occurs due to the surgical risk factors stated below.

1. Nature of the disease (autoimmune) (1,2),
2. Long duration of disease and number of comorbidities (1,2),
3. Use of immunosuppressive and nonsteroidal anti-inflammatory drugs (NSAIDs) (1,2);
   - Glucocorticoids cause poor bone quality, weakened immune system, and impaired wound healing,
   - Delay in wound healing caused by traditional disease-modifying anti-rheumatic drugs (DMARD), wound dehiscence, and the risk of opportunistic infection, especially by biological agents,
   - Bleeding side effects of NSAIDs,
   - Bone stock insufficiency (periarticular bone osteopenia, osteoporosis, and osteonecrosis),
4. Severe joint deformities due to soft tissue involvement and additional difficulties due to other joint involvements (knee, hip, shoulder, ankle) (1-3),
5. Cervical spine involvement in 80% of patients and atlantoaxial instability in 30% pose a risk for general anesthesia (Additional medical anesthesia issues) (4),

It is stated that RA is a risk factor for infection (2), and deep wound infections are the most critical complication concerning TKA results in patients with RA (5-8). It has been reported that the preponderance of periodontal disease is increased in patients with RA, and the possibility of enclosing staphylococcus aureus colonization in these patients is higher than in healthy controls (6,7). It has been reported that the need for blood transfusion increases in patients with RA due to anemia, contributing to the risk of infection (9).

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While some similar studies reported that TKA complication rates are higher in patients with RA (8,10), some studies convey that the complication rates are not different (11,12).

It is stated that the nature of the disease and the drugs used affect the duration of the disease, its treatment, surgery, and intricacies (1,2,9,13). Nevertheless, meticulous preparation of the patients for the operation, good timing of the procedure, and proper application (surgical experience) have been ascertained to increase the quality of life and functions in patients with RA (1,5).

This study aimed to assess complications and the presence of late deep infection in patients with RA who underwent primary and revision TKA.

MATERIAL AND METHOD

The study was conducted with the permission of Near East University Scientific Researches Ethics Committee (Date: 29.12. 2022, Decision No: 109-1648). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This Level III, therapeutic, retrospective study included 50 knees of 34 patients applied with posterior cruciate ligament (PCL)-sacrificing cemented primary TKA, and 7 knees of 5 patients applied with posterior-stabilised (PS) revision TKA between June 1997 and October 2022. All approaches were made with a standard anterior prepatellar incision followed by medial parapatellar arthrotomy. Total synovectomy was performed in all knees maintaining the fatty tissue between the synovium and the anterior femur. The distal femur cut was completed with an intramedullar guide and the proximal tibia cut with an extramedullar guide. Varus/valgus deformities were balanced with medial and lateral release.

At one hour before operation, first-generation cephalosporin (cefazolin sodium) was administered intravenously as prophylaxis at a dosage of 1gr for patients <70 kg and 2 gr for those >70 kg. In all patients, venous thromboembolism (VTE) prophylaxis was provided with low molecular weight heparin (LMWH) starting at 8 hours after operation. The operations were performed under spinal anaesthesia in 27 knee and under spinal-epidural anaesthesia in 23 knee. In all knees, bleeding was controlled and the operation area was washed. All patients were mobilised with full weight-bearing using a walker on the morning of postoperative day 1. After the drain was extracted at postoperative 24 hours, 30 mins of movement, 3-4 times a day, was routinely provided with a continuous passive movement (CPM) device.

All patients enclosed in this study were adults diagnosed with RA by a rheumatology or physical therapy physician by the RA diagnostic criteria recommended by the American College of Rheumatology in 1987 (14).

The drugs utilized by the patients were oral glucocorticoids by 26 (76.5%) and the conventional synthetic disease-modifying anti-rheumatismal drugs (csDMARD) of methotrexate by 10 (29.4%), sulfasalazine by 10 (29.4%), leflunomide by 10 (55.9%), and hydroxychloroquine by 6 (17.6%). Biological DMARDs (bDMARD) and targetted synthetic DMARDs (tsDMARD) were not used by any patient in this study.

A rheumatology or physical therapy specialist managed the anti-rheumatismal drug regimens (stopping preoperatively and/or continuing, and time of re-starting postoperatively). The diagnosis of infection in patients was based on the Periprosthetic Infection Diagnostic Criteria of the 2018 International Periprosthetic Joint Infections Consensus Meeting (15). The patients were followed up postoperatively at 1, 3, 6, and 12 months, and annually thereafter.

Inclusion Criteria

- Based on the criteria of the American rheumatology association, patients who were diagnosed with RA (>18 years old) and used treatment in the Physical Therapy and/or Rheumatology department were included in the study.

Exclusion Criteria

- Secondary inflammatory rheumatic osteoarthritis causes other than RA,
- Metabolic and malignant disease,
- Having a history of patellectomy, fracture around the knee, and infection,
- Patients who underwent high tibial osteotomy and did not respond to the invitation were excluded from the study.

Statistical Analysis

Data acquired in the study were analyzed statistically utilizing SPSS version 23 software. Continuous variables were stated as mean ± standard deviation (SD) or median (minimum-maximum) values, and categorical values as number (n) and percentage (%). Correlations between drug use and infection were examined using the Chi-square test. A value of $p < 0.05$ was accepted as the level of statistical significance.

RESULTS

The demographic data of the patients in the study are presented in **Table 1**.

Table 1. Demographic data

Parameters	Primary total knee arthroplasty		Revision totalknee arthroplasty	
	mean ± SD/n (%)	median (min-max)	mean ± SD/n (%)	median (min-max)
Age (years)	59.56 ± 11.2	61 (31-80)	60.2 ± 3.5	64 (59-67)
BMI (Kg/m²)	32.25 ± 4.54	32.4 (20.3-40)	32.7 ± 6.5	30.1 (25.8-39.9)
Gender				
Female	31 (91.2)		4 (80)	
Male	3 (8.8)		1 (20)	
Total number of patients	34		5	
Total number of knees	50		7	
Side				
Right	10		3 (42.9)	
Left	8		4 (57.1)	
Right/Left in separate sessions	11 (22knees)			
Bilateral in the same session	5 (10knees)			
Follow-up period (months)				
General	132.49 ± 56.38	132.8 (48-304)	83.1 ± 29.1	85.5 (55-126)
Right	114.87 ± 54.45	116 (48-216)	148 ± 53.3	154 (92-198)
Left	140.43 ± 66.98	144 (46-304)	45.8 ± 19.2	54.5 (17-57)
Bilateral	157.67 ± 42.1	161 (114-198)		
Duration of drug use (years)	22.35 ± 8.91	23.5 (7-41)		

SD: standard deviation, BMI: body mass index

Of the 50 knees on which primary TKA was conducted, revision TKA was performed on 7 (14%). The revision was conducted due to infection in 3 (6%) knees, and due to the use of aseptic loosening in 4 (8%). Complications were found in 9 (18%) of 50 knees who underwent primary TKA. Serous discharge was observed in 3 (6%) knees, serous discharge and late (postoperative 8 years) quadriceps tendon partial rupture in 1 (2%) knee, early deep infection in 1 (2%) knee, late deep infection in 3 (6%) knees, and hematoma in 1 (2%) knee (**Table 2**).

Table 2. The complications and revision data of the primary total knee arthroplasty cases

	n	%
Total number of knees	50	
Number of revisions	7	14
Revision due to infection	3	6
Right	2	4
Left	1	2
Revision due to aseptic loosening	4	8
Right	1	2
Left	3	6
Overall complications	9	18
Serous discharge, allergy, bullae.	4	8
Deep infection	4	8
Early deep infection	1	2
Late deep infection	3	6
Quadriceps tendon rupture	1	2
Hematoma	1	2

In the knees applied with revision TKA, periprosthetic fracture in the femur developed in 1 (14.3%) knee, and early deep infection in 1 (14.3%) knee (**Table 3**).

Table 3. The data and complications of the revision total knee arthroplasty cases

	n	%
Revision	7	
Revision due to infection	3	42.9
Revision due to aseptic loosening	4	57.1
Revision due to femoral loosening	0	0.0
Revision due to tibial loosening	7	100.0
Revision due to loosening in the femur+tibia	0	0.0
Revision due to patellar loosening	0	0.0
Overall complications	2	28.6
Periprosthetic fracture (Femur)	1	14.3
Deep early infection	1	14.3
Antibiotic in cement (2 gr Vancomycin) right	2	28.6
Antibiotic in cement (2 gr Vancomycin) left	0	0.0
Antibiotic in cement-Gentamicin right	1	14.3
Antibiotic in cement-Gentamicin left	4	57.1

There was no significant relationship between infection and drugs used (p=0.156) (**Table 4**). The rate of infection was determined to be 10% in methotrexate users, 30% in insulfasalazine users, 21.1% in leflunomide users, 33.3% in hydrocychloroquine users, and 11.5% in those using oral glucocorticoids.

Table 4. Relationships between the drugs used and infection rates

	Infection		P*
	Absent	Present	
Methotrexate	9 (90)	1 (10)	
Sulfasalazine	7 (70)	3 (30)	
Leflunomide	15 (78.9)	4 (21.1)	0.156
Hydroxychloroquine	4 (66.7)	2 (33.3)	
Oral glucocorticoids	23 (88.5)	3 (11.5)	

*Chi-square test

DISCUSSION

Following TKA, major complications (deep surgical site infection, wound opening, pulmonary embolism, fracture, reoperation) have been reported at rates between 5.55% and 14.4%, and minor complications (superficial surgical site infection, deep vein thrombosis, bleeding, peripheral nerve injury) at 2.86%-46.6% (16,17). Previous some studies reported that TKA complication rates are higher in patients with RA compared to OA cases (10), while some studies have reported no significant difference. (11). In the current study, complications were found in a total of 9 (18%) knees of primary TKA cases, including major complications (deep infection) in 4 (8%) knees, and minor complications in 5 (10%) (serous discharge, hematoma, quadriceps tendon partial rupture). The rate of complication in the primary TKA cases was found to be at a similar level to OA cases within the limits noted in literature. Following revision TKA in RA patients, the rate of complication has been reported to be 19-28% (18). In the current study, only major complications (deep infection and periprosthetic femur fracture) developed in 2 (28.6%) knees applied with revision TKA.

Following primary TKA, the rates of overall infection have been reported to be 1-2%, superficial infection 10%, and deep infection 0.3-3.9% (12,19,20), whereas in revision cases, the rate of overall infection has been stated to be 0-10% (21-23). For patients with RA, the general infection rate has been reported to be 1.4-4.2% (12,19,20), increasing to 5.9% in revision (21-23). In previous studies, infection rates following primary TKA have been seen to be 2-3-fold greater in patients with RA compared to patients with OA (6-8). However some studies have reported similar rates (12). Lee et al. (22) reported that a significantly higher rates of deep surgical site infection in patients with RA after TKA compared to patients with OA, but the superficial infection rates were similar. Rodriguez et al. (20) found that a delayed infection (mean 7 years) in 4.1% of patients with RA applied with primary TKA. In a study by Mortavazi et al. (21), the infection rate in revision patients was reported to be 19%. In the current study of primary TKA cases, findings of superficial infection, such as postoperative serous discharge, allergy and bullae, were determined in 4 (8%) knees and recovery was obtained in all of these with medical treatment. In 1 (2%) knee determined with early deep infection at one month postoperatively, treatment was applied with debridement, antibiotherapy, insert change and implant preservation. Late (delayed) deep infection was determined in 3 (6%) knees, at 4, 5, and 6 years respectively, and all were treated with single-stage revision. Early deep infection developed in one (14.2%) of the knees applied with revision. Recovery was obtained with treatment of debridement, antibiotherapy, insert change and implant preservation. The rate of superficial infection in the current study was similar to OA cases, and the rate of deep infection was determined to be higher than OA cases.

Corticosteroids suppress the inflammatory phase of wound healing and change the re-shaping of the wound, but it has been stated that the doses used in RA are not of a high enough level to create these problems (1,3,6). Methotrexate reduces the stretching power of the wound, but the doses given in RA have been reported to not generally affect this and therefore healing is not affected (24). The use of tumour necrosis factor alpha (TNF-α) inhibitors has been reported to create more wound separation and infection (6,7). Previous studies have stated that doses of corticosteroids should be altered preoperatively and continued during the operation if necessary; methotrexate should not be stopped but used continuously, and this aids in healing and does not increase the risk of infection, and biological agents should be stopped preoperatively due to increased infection rates (1,3). The current study found no significant relationship between infection and the use of corticosteroids, methotrexate, sulfasalazine, leflunomide, or hydroxychloroquine.

The incidence of periprosthetic fracture (PPF) after TKA has been reported to be 0.3-5.5%. Previous studies have shown that PPF after TKA usually tends to occur in the femur supracondylar region 2 years after the operation, and the reason is usually anterior femoral notching (25,26). It has been stated that in 35.3% of revisons, PPF occurs within two years, and the reason for failure is associated with aseptic loosening (27). The risk of PPF in patients with RA has been shown to increase due to the nature of disease, and poor bone quality associated with chronic use of steroids and DMARDs (1,28). A study by Choi et al. (1) in RA who underwent TKA reported that a significant increase in supracondylar PPF incidence after mean 11.9 years (range, 9-14 years). Lee et al. (29) indicated that patients with RA were at risk of PPF occurring after mean 11.4 years postoperatively. PPF was not detected in any of the primary TKA cases in the current study. This was thought to be due to the support provided for the patients in respect of osteoporosis, that care was taken during the operation not to create notches in the femur, and that the mean age of the patients was 59.6±11.2 years. However, PPF developed following a fall at 1 year postoperatively in one patient who underwent revision TKA, and this was treated with open reduction and internal fixation with a locking plate.

In TKA patients not administered with thromboprophylaxis, deep vein thrombosis (DVT) has been reported at rates of 50-70%, pulmonary thromboemboli (PTE) at 5%, and fetal PTE at 1-4%. In patients who have been administered thromboprophylaxis, these rates have been reported to

be DVT 0.9-5%, PTE 0.27-1.1%, and fetal PTE 0.1-0.5% (30). In patients with RA who have undergone TKA, RA has been noted to be protective against VTE (8), and the VTE incidence is 3-10-fold lower than OA patients, which has been attributed to the patients being younger and the use of NSAIDs (31). However, in some studies reported that no difference in terms of VTE (32), while there are some studies t reported that RA to be a risk factor for VTE (13). Besides, it has been reported that the incidence of VTE is 2.4% higher in patients with RA than OA patients (33). In a study of RA patients applied with TKA, the risk of VTE was lower, but in patients treated with biological DMARDs the VTE incidence was determined to be 5-fold higher compared to RA patients not treated with biological DMARDs (6). In the current study, none of the patients were treated with biological DMARDs or targetted synthetic DMARDs. Pulmonary embolism or DVT were not determined in any of the current study patients. This was considered because VTE prophylaxis was administered with LMWH starting from 8 hours postoperatively, followed by oral anticoagulants for 14 and/or 35 days, and antithrombocyte activity occurred because of the long-term use of NSAIDs in RA.

Quadriceps tendon rupture following TKA is uncommon, and has been reported to be observed at rates between 0.1% and 1.1% (34,35). In the current study, late (postoperative 8 years) quadriceps tendon partial rupture was seen in 1 (2%) knee due to a fall. As the patient had no evident loss of extension, treatment was non-operative. Dobbs et al. (34) reported satisfactory results and fewer complications with non-operative treatment of quadriceps tendon partial rupture.

The formation hematoma around the knee after TKA is frequently observed and can cause patients discomfort and concern about the operation's success. This condition has been reported to be associated with intraoperative tourniquet use, postoperative drainage methods, VTE prophylaxis, and male gender. However, the underlying specific mechanisms generally remain uncertain (36). In addition to the conditions present in patients with RA, long-term use of NSAIDs can increase the risk of bleeding. Hematoma developed in 1 (2%) knee of one male patient in the current study and this was successfully treated with removal of the sutures, drainage and dressings.

Heterotopic ossification was not determined in any patient in the current study. This was thought to be due to the use of corticosteroids and NSAIDs, which were continued postoperatively. In TKA cases, the rate of heterotopic ossification has been reported as 0-42% (37). It has been reported that this rate is lower in RA patients and this may be due to the use of NSAIDs and corticosteroids (38). No neurovascular injury, instability, or dislocation was reported in any of the current study patients.

Limitations

The main limitations of this study are its retrospective design, relatively low sample size, and lack of an OA control group for comparison.

CONCLUSION

RA is a chronic, systemic, autoimmune disease, and because of comorbidities a relative increase is observed in chronic late deep infection and associated revision, and a decreased in DVT, pulmonary embolism and heterotopic ossification due to the long-term use of NSAIDs and glucocorticosteroids. There was no significant relationship between the drugs (oral glucocorticoids and DMARDs) used by our patients and the infection. We did not detect an increase in PPF rates.

In patients with RA who undergo TKA, although complication rates have been reported to be higher than in OA cases, TKA can be performed safely and complications can be reduced with the following steps;

1. A multidisciplinary approach,
2. Adjustment of the time of stopping and re-starting drugs by establishing good direct communication with the rheumatologist (to provide a balance between reducing the risk of infection and suppression of disease activity),
3. Preparing the patient for the operation in respect of comorbidities,
4. Correct timing of the operation,
5. Preoperative prophylaxis,
6. An experienced surgeon,
7. Correct surgery under sterile conditions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Near East University Scientific Researches Ethics Committee (Date: 29.12.2022, Decision No: 109-1648).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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The relationship between levels of apolipoprotein A1 and B in aqueous and serum with stage of diabetic retinopathy

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ABSTRACT

Aim: To determine the association between serum and aqueous apolipoprotein (Apo) A1 and Apo B levels and Apo B/A1 ratio in diabetic retinopathy.

Material and Method: This cross-sectional prospective study included 63 diabetic patients with or without retinopathy and 38 control subjects who underwent cataract surgery. The study groups were as follows; healthy subjects (Group 1), diabetic patients without retinopathy (Group 2), with non-proliferative diabetic retinopathy (Group 3), and with proliferative diabetic retinopathy (Group 4). Serum and aqueous Apo A1 and Apo B levels were determined by using an enzyme-linked immunosorbent assay.

Results: The amount of Apo B was determined in aqueous samples of all (100%) patients in Group 4 and 77.7% of patients in Group 3.The mean serum Apo B/A1 ratio was significantly higher in Group 2, Group 3 and Group 4 compared with Group 1 ($p=0.002$, $p=0.037$ and $p<0.001$, respectively). The aqueous Apo B level, aqueous and serum Apo B/A1 levels were significantly correlated with the severity of retinopathy in diabetic patients (all $p<0.001$).

Conclusion: Higher serum and aqueous Apo B/A1 ratio were significantly associated with the stage of diabetic retinopathy.

Keywords: Aqueous humor, apolipoprotein A1, apolipoprotein B, diabetic retinopathy

INTRODUCTION

Diabetic retinopathy (DR) is one of the major cause of morbidity in diabetic patients. The prevalence of DR increases with the duration of diabetes (1). Diabetes duration, glycemic control, microalbuminuria and hypertension are well-known modifiable major risk factors for the progression of DR (2,3). The role of dyslipidemia as a potential risk factor for DR is of interest. There was no consensus on the relation with DR and dyslipidemia that some studies have interpreted the role of dyslipidemia with traditional lipid markers like total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides on the development and progression of DR (4,5) while several studies have reported no association (6).

Though the association of traditional lipid parameters with the initation or progression of DR is contraversial, there is evidence that the severity of DR is associated with the precursors of soluble lipoproteins apolipoprotein A1 (Apo A1) and apolipoprotein B (Apo B) levels in diabetic patients (4,7-9). Apo A1 is a HDL constituent and Apo B is found in very low density lipoprotein (VLDL), intermediate-density lipoprotein and LDL. Unlike traditional lipid parameters, these apolipoproteins are not affected by the prandial status (10). Apo A1 is a good indicator of lipid accumulation in peripheral tissues (8) and also has anti-inflammatory and antioxidant properties (11,12), it specifically inhibits oxidation of LDL which may damage vascular endothelial, anti-platelet and anti-inflammatory functions. Apo B is present as an extravasated form and was detected in the retinal layers of human eyes with DR (13) which may play a potential role in the pathophysiology of DR. Also, serum Apo B/A1 ratio was also shown to be related with the severity of DR in several studies (14-18).

To the best of our knowledge, there have been no studies published about Apo B levels and ApoB/A1 ratio in aqueous samples of diabetic patients. In this study, we aimed to determine the Apo A1 and B levels

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and the Apo B/A1 ratio in aqueous humor and serum of diabetic patients with or without retinopathy and compared with healthy controls.

MATERIAL AND METHOD

The study was carried out with the permission of Kırıkkale University Medical Faculty Clinical Researches Ethics Committee (Date: 2012, Decision No: 12/58). All research procedures were performed in accordance with the Declaration of Helsinki.

This cross-sectional prospective study included 63 patients with type 2 diabetes mellitus (DM) and 38 healthy age and gender matched control subjects who admitted for decreased vision due to cataract. Informed consents which included serum and aqueous sampling were obtained from all subjects before study participation.

Patients with macular edema, vitreous hemorrhage and retinal detachment, previous laser photocoagulation or intravitreal therapy within six months, previous vitreoretinal or glaucoma surgery history, dense cataract obscuring visibility of retina, systemic diseases other than DM and vitreoretinal disorders other than DR were excluded from the study. Patients scheduled for cataract surgery with no systemic or ocular diseases were recruited in the study as control group.

The classification of DR was made using the Airlie House Classification system[19]with seven-field retinal photograph by two experienced ophthalmologists. Patients groups were divided as follows; those without retinopathy as Group 2, with non-proliferative DR (non-PDR) as Group 3 and with proliferative DR as Group 4. Healthy control subjects were assigned as Group 1.

Each study participant underwent a detailed ophthalmological examination including best-corrected visual acuity using Snellen chart, Goldman applanation tonometry, slit-lamp anterior segment evaluation and dilated fundus examination. Fundus fluorescein angiography (FFA; Topcon TRC; Topcon Co, Tokyo, Japan) and spectral domain optical coherence tomography (SD-OCT; RetinaScan Advanced RS-3000; NIDEK, Gamagori, Japan) imaging were also performed when indicated.

Venous blood samples for Apo A1 and B levels were obtained preoperatively and stored at - 80°C after centrifuged. All cataract surgeries were performed under topical anesthesia using 2% lidocaine. About 0,1-0,2 ml of aqueous humor was aspirated with a sterile injector capped with an anterior irrigation tip. The aqueous samples of all patients were collected and stored at -80°C until testing in the same batch. Inefficient amount of samples were not recruited in the study.

Serum and aqueous Apo A1 and B levels were determined by using an enzyme-linked immunosorbent assay (ELISA) kit (USCNlife, USCN life Science Inc., PRC) according to the manufacturer's instructions. Sensitivity of Apo A1 and Apo B kits were 55 ng/mL and 4.27 ng/mL. Serum concentration of triglyceride, cholesterol, LDL and HDL were evaluated by an automated analyzer using commercially available kits and serum HbA1c levels of diabetic patients were measured with high-performance liquid chromatography.

Statistical Analysis

Statistical analyses were performed using the SPSS program software (Version 21, International Business Machines Co,Armonk, NY). Demographic characteristics and aqueous and serum apo A1 and B concentrations of the patients among the 4 groups were compared. One-way analysis of variance, the Wilcoxon rank-sum test, and the Kruskall-Wallis test were used to compare numerical data, and the Fisher exact test was used to compare categorical variables. Correlations were analysed by using Spearman's correlation coefficient. All data were expressed as mean±Standard deviation (±SD). A p value less than 0.05 was considered as statistically significant.

RESULTS

In Group 1, the mean age was 68.11±9.5 years and 55.3% of 38 patients were male. The mean age and the percentage of male patients were, 68.76±8.65 years and 52.9% in Group 2, 68.74±8.42 years and 51.9% in Group 3, and 65.42±8.33 years and 52.6% in Group 4, respectively. There were no significant differences among the groups in terms of age and gender (p=0.994 and p=0.594) (**Table 1**).

The mean HbA1c level was 8.9±2.29% in Group 2, 8.53±1.76% in Group 3 and 8.87±2.24% in Group 4, respectively and no statistically significant difference was observed between the groups (p=0.876). The mean duration of DM was 11.4±4.7 years in Group 2, 12.2±7.9 years in Group 3 and 18.9±6 years in Group 4. There were statistically significant differences between groups for DM duration (p<0.001) and DM duration was longer in Group 4 than Group2 and 3 (p< 0.001 and p=0.001) (**Table 1**).

The mean serum triglyceride level was 140.12±20.65 mg/dL in Group 2, 124.56±26.99 mg/dL in Group 3, 131±35.48 mg/dL in Group 4 and 114.16±31.68 mg/dL in Group 1. Serum triglyceride level was lower in Group 1 than Group 2 and Group 4 (p=0.002 and p=0.020). The mean serum total cholesterol, LDL and HDL levels were 195.24±4.67 mg/dL, 128.12±15.84 mg/

dL and 48.82±11.29 mg/dL in Group 2; 185.11±19.65 mg/dL, 120.26±32.42 mg/dL and 51.04±12.09 mg/dL in Group 3; 192.16±18.06 mg/dL, 113.58±26.62 mg/dL and 44.37±9.96 mg/dL in Group 4; 178.74±25.6 mg/dL, 112.03±27.78 mg/dL and 48.05±6.88 mg/dL in the control group. There were no statistically significant differences in total cholesterol, LDL and HDL levels among all groups (p=0.194, p=0.182 and p=0.124).

Apo B was determined in aqueous samples of 40 (63.5%) diabetic patients that were 21 of 27 patients in group 3 (33.3%) and all patients in group 4 (30.2%). The mean aqueous Apo B level was significantly higher in Group 4 than in Group 3 (p<0.001). Nevertheless Apo A1 level was detected in aqueous samples of all diabetic patients and healthy subjects.

The mean serum Apo A1 levels were significantly decreased in Group 4 compared with Group 1 and Group 3 (p=0.002 and p=0.001). The mean serum Apo B levels were significantly increased in Group 2, 3 and 4 compared with Group 1 (p values; 0.001, 0.002 and 0.008, respectively). Aqueous Apo A1 level was significantly higher in Group 3 and Group 4 in comparison to patients in Group 2 (p=0.001 and p=0.005). Aqueous Apo A1 level was also decreased in Group 1 when compared with Group 2, Group 3 and Group 4 (p=0.004, p<0.001 and p<0.001).

The mean serum Apo B/A1 ratio was higher in Group 2, Group 3 and Group 4 than control group (p=0.002, p=0.037 and p<0.001). The mean serum and aqueous Apo B/A1 ratios were higher in Group 4 compared with Group 3 (p=0.013 and p<0.001). (**Table 2**)

Serum LDL and cholesterol levels were significantly correlated with serum Apo B levels (p<0.001, Spearman correlation: 0.503, CI:0.328-0.662 and p<0.000, Spearman correlation: 0.602, CI:0.422-0.745). Aqueous Apo B levels were significantly correlated with the duration of DM and the severity of retinopathy (p<0.001, Spearman correlation: 0.478, CI:0.263-0.669 and p<0.001, Spearman correlation: 0.861, CI:0.816-0.908).

Higher aqueous Apo B levels and Apo B/A1 ratios had significant strong correlation with the severity of diabetic retinopathy (p<0.001, Spearman correlation: 0.809, CI:0.758-0.856 and p<0.001, Spearman correlation: 0.816, CI:0.754-0.867). Lower serum Apo A1 levels, higher serum Apo B levels and Apo B/A1 ratios had significant moderate correlation with the severity of diabetic retinopathy (p<0.001, Spearman correlation: -0.534, CI:-0.424-0.199, p=0.001, Spearman correlation: 0.417, CI:0.147-0.382 and p<0.001, Spearman correlation: 0.457, CI:0.307-0.599). Serum and aqueous humor Apo A1 and B levels and B/A1 ratios were not significantly correlated with HbA1c levels (p>0.05, in each comparison).

DISCUSSION

This study demonstrated that serum Apo B levels and Apo B/A1 ratio were increased in all diabetic patients with and without retinopathy than in control group. Serum Apo A1 levels were decreased in patients with PDR in comparison to patients with non-PDR and control subjects. Serum Apo B/A1 ratio was also higher in patients with PDR than in patients with non-PDR.

Table 1. Demographic features and serum lipid parameters in diabetic patients and control subjects

Parameters	Group 1 (control group)	Group 2 (without DR)	Group 3 (non-PDR)	Group 4 (PDR)	P value
Number, n	38	17	27	19	
Gender (F/M)	17/21	8/9	13/14	9/10	0.994
Age (years)	68.11±9.5	68.76±8.65	68.74±8.42	65.42±8.33	0.594
Total cholesterol (mg/dL)	178.74±25.6	195.24±4.67	185.11±19.65	192.16±18.06	0.194
Triglyceride (mg/dL)	114.16±31.68	140.12±20.65	124.56±26.99	131±35.48	0.005*
LDL (mg/dL)	112.03±27.78	128.12±15.84	120.26±32.42	113.58±26.62	0.182
HDL (mg/dL)	48.05±6.88	48.82±11.29	51.04±12.09	44.37±9.96	0.124
DM duration (years)		11.4±4.7	12.2±7.9	18.9±6	<0.001
HbA1c (%)		7.9±1.29	7.53±1.76	7.87±1.24	0.876

DM: Diabetes Mellitus, DR: diabetic retinopathy, F: female, HbA1c: hemoglobin A1c, HDL: high-density lipoprotein, LDL: low-density lipoprotein, M: male, PDR: proliferative diabetic retinopathy, *p< 0.05

Table 2. Comparison of serum and aqueous Apo A1 and B levels in diabetic patients and control subjects

Parameters	Group 1 (control group)	Group 2 (without DR)	Group 3 (non-PDR)	Group 4 (PDR)	P value
Serum Apo A1(mg/dL)	125.11±19.81	126.76±23.42	130.78±20.85	109.74±14.78	0.004*
Serum Apo B (mg/dL)	92.89±19.71	113.53±17.6	110.78±22.49	110±20.81	0.001*
Serum Apo B/A1	0.74±0.13	0.91±0.18	0.85±0.18	1.01±0.19	<0.001
Aqueous Apo A1 (ng/mL)	210.82±170.34	324.12±175.25	559.44±289.19	519.95±243.53	<0.001
Aqueous Apo B (ng/mL)	-	-	99.19±42.91	280.53±83.85	<0.001
Aqueous Apo B/A1	-	-	0.20±0,10	0.57±0.14	<0.001

Apo A1: apolipoprotein A1, apo B: apoliprotein B, DR: diabetic retinopathy, PDR: proliferative diabetic retinopathy, *p< 0.05

There were no studies investigating Apo B in human aqueous samples whereas prior studies demonstrated Apo A1 in aqueous samples of diabetic patients and healthy subjects. Apo A1 and B were detected as an extravasated form in vitreous samples and also in the retinal layers of human eyes with DR (8,9,13).

When considering the molecules involved in the pathogenesis of DR simultaneously appear in aqueous and vitreus samples of the same eyes (20), Apo B, detected in the aqueous samples of non-PDR and PDR patients, may serve as a biomarker to show the severity of DR. Aqueous humor does not make a direct contact with the retina whereas functional barriers between vitreus humor and aqueous humor are also not strict. Thus Apo B detected in aqueous samples should be released from retina and may leak into cilio-retinal circulation through the disrupted blood-retinal barrier or enter aqueous humor through blood aqueous barrier by diffusion.

Apo B was not identified in all aqueous samples of diabetic patients while Apo A1 was detected in all aqueous samples of both diabetic patients and control group. Apo B was detected in 63.4% of diabetic patients including 77.7% of non-PDR patients and all PDR patients whereas detected in none of the diabetic patients without retinopathy and healthy controls. Previous studies have found that large molecules can be exchanged between the vitreus and aqueous humor through vitreus-aqueous humor barrier (21-23). Apo A1 and B have different molecular weights; Apo A1 has a lower molecular weight of 28.1 kD, the molecular weight of Apo B is 540 kD. The higher molecular weight Apo B particules leaking into the aqueous were detected in severe forms of diabetic retinopathy but in none of the patients without retinopathy. Wu et al. (13) measured Apo B levels in postmortem retinas of diabetics and non-diabetics; found that the amount of extravasated Apo B was correlated with the severity of DR.These findings were consistent with our study and suggest that the severity and duration of diabetes may be significantly and positively correlated with existence and detection of Apo B in aqueous samples.

Intraocular Apo A1 was investigated by different methods in ocular tissues. Kawai et al. (24) detected Apo A1, the major component of HDL particles by Western blot in the tear films of healthy individuals and diabetic patients and the presence of Apo A1 was associated with leakage from the capillary vessels of the main lacrimal glands as a result of vascular damage in diabetic angiopathy and the increased amount of Apo A1 was related to the severity of DR. Simo et al. (8) determined overexpresion of Apo A1 in the retinas of diabetic patients without microvascular abnormalities in the two years preceeding the death, not only in its mRNA levels, but also in terms of protein content in their postmortem study and overexpression of Apo A1 was considered as an early finding in the retina of diabetic patients before the initiation of DR. Over-production and higher mRNA expression of Apo A1 in the retinas of PDR patients than in non-diabetics were also reported by using fluid proteomic analysis of human vitreus fluid (9,25). Apo A1 levels in aqueous were not significanly different in diabetic patients with or without retinopathy and healthy controls in our study. It may be related with sample size in the study, homogeneity of DR groups, and DM regulation that HbA1c levels were similar between the groups.

The Apo B/A1 ratio is of interest that the ratio reflects vascular endothelial damage in vascular disorders. Hu et al. (14) and Ankit et al. (17) exhibited a significant correlation between severity of DR and lower Apo A1 levels and decreased Apo A1/B ratio in serum samples. Sasongko et al. (15) determined a negative correlation between the development and the severity of DR and serum Apo A1 levels and a positive correlation with serum Apo B levels and Apo B/A1 ratio. Crosby-Nwaobi et al. (26) reported that an increase in serum Apo B and higher Apo B/A1 ratio may be associated with increased risk of PDR and clinically significant diabetic macular edema (CSME). Chung et al. (18) reported the association of serum Apo A1 and the ApoB/A1 ratio with presence of diabetic retinopathy. These findings were in agreement with our study and suggest that lower serum Apo A1, higher serum Apo B level and Apo B/A1 ratio were related with the severity of DR.

Though the effects of lipids on the initation or progression of DR were controversial in literature, our study suggested that higher serum Apo B levels and higher Apo B/A1 ratio had a significant moderate correlation and higher aqueous Apo B level and Apo B/A1 ratio had significant strong correlation with the severity of DR. Miljanovic et al. (27) observed an association between the serum lipid levels and increased risk of CSME and hard exudates, but not with progression of DR and PDR formation. In the Fenofibrate Intervention and Event Lowering in Diabetes Study (FIELD) no associations were declared between the serum lipid levels and the formation and the progression of DR (28). Several studies emphasized that the mechanisms of intraretinal lipid transport may be more prominent than the serum lipid levels in pathogenesis of DR (29,30). Aqueous humor exchanges substances, proteins and ions through capillaries by direct and indirect contact with ocular tissues. The contents of aqueous humor including proteins were used to determine the health status of blood vessels and/or ocular tissues. Aqueous humor and vitreus were evaluated for determining the formation or progression of DR (31). All these findings indicate that the mechanisms regulating the aqueous

lipid transport, rather than serum lipid levels, may have a more significant role in the pathogenesis of DR and Apo A1 and Apo B should be an ocular fluid biomarker for predicting progression of DR.

CONCLUSION

To conclude, in this study, higher aqueous Apo B/A1 ratios and higher aqueous Apo B levels in diabetic patients may help to detect and monitor the severity of DR and can be used as a potential biomarker. As best we know, this is the first study to investigate Apo B in aqueous samples of diabetic patients with any stages of DR. Further population-based longitudinal studies are needed to evaluate the role of various apolipoproteins in the pathogenesis of DR and the origin of them in intraocular fluids.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Medical Faculty Clinical Researches Ethics Committee (Date: 2012, Decision No: 12/58).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article

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Predictive value of inflammatory markers in gastric cancer

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ABSTRACT

Aim: Many recent studies are increasingly shedding light on the nature of the relationship between cancer and inflammation. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) platelet/neutrophil ratio (PNR), and Mean Platelet Volume (MPV) are proinflammatory markers, and their prognostic importance has been investigated in many solid cancers. In this study, we discussed the association of these derivative inflammatory markers, obtained from a cheap and simple peripheral blood test, with clinicopathologic variables in patients undergoing gastrectomy for gastric cancer.

Material and Method: The retrospective database of a total of 148 patients who were operated for gastric cancer in the Diyarbakır Gazi Yaşargil Training and Research Hospital Department of Surgery was analyzed. All blood results and pathology reports of the patients were reviewed retrospectively. Demographic characteristics of the patients and pathological features of the tumor were extracted from the database. NLR, PLR, PNR and MPV values were calculated from peripheral blood cell counts. Data were analyzed using SPSS version 24.0.

Results: PNR and MPV values were statistically significant according to N and T stage of the tumor, respectively (p=0.035, p=0.011). In MPV, this difference was statistically observed between T1 and T2 tumors (p=0.029). PLR and NLR values did not show a significant difference according to the size of the tumor (p>.05).

Conclusion: MPV values are significantly associated with tumor T stage. PNR values are significantly associated with tumor N stage. However, the clinical implications and the added value to clinical practice require further research.

Keywords: Inflammatory marker, gastric cancer, NLR, PLR, T stage

INTRODUCTION

The term biomarker originated in the 1950s and was defined by the National Institute of Health as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological responses to a therapeutic intervention (1). Inflammatory biomarkers have widespread clinical use postoperatively after gastrointestinal procedures due to their success in predicting postoperative complications and mortality (2-4).

Cancer-related inflammation is defined as the 7th hallmark of cancer (5), and the systemic inflammatory response has cellular and humoral (Procalcitonin, C-reactive protein, albumin) components. The cellular-mediated inflammatory response (lymphocytes, neutrophils and monocytes) is increasingly recognized as having an important role in tumorigenesis and carcinogenesis. Therefore, diagnostic biomarkers such as free circulating tumor cells, DNA, miRNA, and exosomes in serum have been used to screen and detect cancer at an early stage; however, their clinical use is still limited due to their instability and high cost (6).

Derivative biomarkers (neutrophil-to-lymphocyte ratio (NLR) (7) , platelet-to-lymphocyte ratio (PLR), platelet-to-neutrophil ratio (PNR) (8) , and modified Glasgow prognostic score (mGPS) (9)) have also been described and reported to be associated with poor survival in patients undergoing potentially curative surgery. It is now recognized that cancer-related inflammation is closely related to the cancer development process (10, 11). High NLR is associated with larger tumor size (12), and both PLR and NLR have been shown to be closely associated with poor prognosis, recurrence and shorter survival (13,14).

Globally, gastric cancer is the fourth (7.7 %) leading cause of cancer-related death (15). Surgery remains

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the only potentially curative treatment. However, approximately 40% of patients develop recurrence and there is no definitive standard of care for medical treatment in these patients. Therefore, it is highly valuable for clinicians to identify biomarkers that can improve prognostic modeling, independent of contemporary staging, which may encourage new therapeutic targets.

Since these parameters obtained from peripheral blood tests are cheap, simple and easily accessible, their predictive value is very valuable for clinicians. Such studies in patients with gastric cancer will help clinicians in terms of diagnosis, treatment and survival prediction. In this study, we aimed to evaluate the clinical implications of NLR, PNR, PLR and MPV values obtained from peripheral venous blood test results at the time of diagnosis in patients undergoing curative gastrectomy by revealing their relationship with tumor characteristics.

MATERIAL AND METHOD

Data of 167 patients were analyzed and 19 patients were excluded from the study due to insufficient data. This study includes retrospective data of a total of 148 patients who met the inclusion criteria at the surgery clinic of Diyarbakır Gazi Yaşargil Training and Research Hospital following local ethics committee approval (Date: 30.12.2022, Decision No: 286). The study includes newly diagnosed cases of primary and metastatic gastric cancer who did not receive any treatment likely to affect hematologic parameters. Exclusion criteria for this study were as follows: residual gastric cancer, neoadjuvant chemotherapy, concurrent and metachronous malignancies, emergency surgery, recent blood transfusion, liver cirrhosis, evidence of any inflammatory condition, presence of concomitant hematologic malignancies or disorders, autoimmune disorders, recent steroid therapy, and incomplete/incorrect medical records.

Data on demographic characteristics and laboratory values of the patients were retrospectively reviewed through the hospital's medical database records. Clinicopathologic characteristics including age, gender, clinical TNM stage, histopathology report were collected. Patients were staged according to the TNM staging system of the American Joint Committee on Cancer (AJCC 7th edition, 2010). Medical blood records including neutrophil, platelet, lymphocyte counts and mean platelet volume (MPV) were obtained from recent preoperative peripheral whole blood analysis. Neutrophil to lymphocyte ratio (NLR) was calculated by dividing the absolute number of neutrophils by the absolute number of lymphocytes, Platelet to neutrophil ratio (PNR) was calculated by dividing the absolute number of platelets by the absolute number of neutrophils. Similarly, platelet/lymphocyte ratio (PLR) was defined as the absolute number of platelets divided by the absolute number of lymphocytes. Albumin values were also recorded from biochemical tests.

Patients' pathology reports were reviewed and type of operation, tumor localization and size, histopathological diagnosis, grade, lymph node status (total, metastatic), lymphovascular invasion (LVI) , perineural invasion were obtained.

Statistical Analysis

All data were presented as mean±standard deviation (SD) and minimum-maximum values. Parametric test assumptions were examined before the difference analysis was performed. Normality was checked by Shapiro-Wilk test. Homogeneity of variances was tested with Levene. If the assumptions were met, difference analysis was performed with one-way analysis of variance (ANOVA) and if not, with Kruskal-Wallis test. Pairwise comparisons were made with Mann-Whitney U test. Statistical analyses were performed at 95 percent confidence intervals. A P value less than 0.05 was considered statistically significant.

RESULTS

Of the remaining 148 patients, 38 (25.7%) were female and 110 (74.3%) were male. The mean age was 63.2±12.7 years. Preoperative diagnostic tests revealed primary carcinoma of the stomach in 148 patients. The tumor was located proximally in 47 patients (31.8%) and distally in 101 patients (68.2%). The clinicopathologic characteristics of the patients included the study are shown in **Table 1**. The PLR, and NLR values of the patients did not differ statistically significantly with the T and N stages of the tumor (p>.05). However, the PNR value was found to be statistically significant with the N stage (p=0.035). Similarly, the preoperative albumin values of the patients were not statistically significant according to the T and N stages (p>.05).

Preoperative MPV value showed a statistically significant difference according to the T stage of the tumor (p=0.011). However, this differentiation was not observed in N stage (p>.05) . This difference was statistically observed between T1 and T2 tumors (p=0.029). As a result, it was observed that the MPV value increased statistically significantly as the diameter of the tumor increased. The continuous data of the patients and the differentiation of the tumor according to T and N stage are shown in **Table 2**.

Table 1. Variables of gastric cancer	
Variables	**Total**
	148
Surgery Type	
Subtotal Gastrectomy	57 (38.5%)
Total Gastrectomy	91 (61.5%)
Cancer Type	
Adenocarcinoma	139 (93.9%)
GİST	4 (2.7%)
Neuroendocrine Tumor	5 (3.4%)
Histopathologic Feature	
Vascular Invasion	72 (48.6%)
Neural Invasion	79 (53.4%)
Staging (TNM Classification)	
I	25 (16.9%)
II	46 (31.1%)
III	77 (52%)
T Category	
I	17 (11.5%)
II	14 (9.5%)
III	87 (58.8%)
IV	30 (20.3%)
N Category	
0	35 (23.6%)
I	42 (28.4%)
II	31 (20.9%)
III	40 (27%)

Table 2. Correlation of inflammation markers and T/N category			
İnflammation Markers	**Mean (SD)**	**P-value**	
		T category	**N category**
Preoperative Albumin	7.39±10.47	.26	.231
Preoperative MPV	8.70±1.42	.011*	.159
NLR	4.46±3.69	.333	.893
PNR	54.67±28.71	.161	.035*
PLR	185.67±86.09	.31	.808
*ANOVA, MPV: Mean Platelet Volume			

DISCUSSION

The inflammatory reaction triggered by tumor-related tissue damage is a critical factor in the tumor cell microenvironment (16). As components of the systemic inflammatory response; lymphocytes, neutrophils and platelets, are increasingly recognized to have an important role in carcinogenesis and tumor progression (10,15).

It is known that neutrophils, by secreting circulating growth factors and proteases, predispose circulating tumor cells to metastasize to distant organs (14,16,17). Cytokines and chemokines produced by both tumor and inflammatory cells have been shown to contribute to the development of distant metastasis and recurrence (18). Neutrophilic response has been associated with poor prognosis as it suppresses the cytotoxic activity of T cells (19). On the contrary, the presence of lymphocytes in the environment has been associated with better response to cytotoxic therapy and prognosis in oncologic patients (20). Lymphocytes generally represent the immune response in the fight against cancer by increasing tumor cell apostosis with the cytokines they provide (21). Inflammation results in thrombocytosis, lymphocytopenia, neutrophilia, and leukocytosis (10, 22). Platelets can participate in the inflammatory reaction by increasing angiogenesis or releasing growth factors (21-23).

We examined several factors reflecting the systemic inflammatory response. Among these factors, preoperative albumin, NLR and PLR values were not significantly associated with the TNM stage of the tumor. However, MPV values were associated with T stage in gastric cancer patients. This relationship was significant between T1 and T2 stages. In our study, the PNR value was found to be associated with the N stage. Based on these findings, we found that the association of MPV in early stage gastric cancers (T1-2) and PNR in locally advanced gastric cancers (N1-3) is more significant. The complete blood count test is a simple, low-cost and repeatable parameter of inflammatory response, as it is routinely performed in all cancer patients without any additional effort. The concept of inflammation-based scores such as NLR and PLR has been introduced in many other cancer types. NLR has been reported to be a negative prognostic factor in hepatocellular carcinoma, colorectal cancer and breast cancer (21, 24). Although both PLR and NLR can reflect prognosis, NLR is superior to PLR in predicting overall survival (29). The Glasgow prognostic score, like the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), is an inflammation-based prognostic score derived from peripheral blood-based inflammatory components. The Modified Glasgow Prognostic Score (mGPS) has been reported to be the only SIR-related prognostic biomarker independently associated with both DFS and OS in gastric cancer (7).

Several studies have also shown that inflammation-based scores are associated with prognosis in gastric cancer (25,26). PNR is an easily measurable, reproducible and inexpensive marker of subclinical inflammation. This suggests that the cytokine microenvironment provided by neutrophils contributes to tumor growth. Inflammation-based scoring systems are derived from peripheral blood-based inflammation components and have been proposed by various authors, but their clinical applications have not yet been used in routine practice and there is no consensus on optimal cut-off levels (27,28). In summary, these results suggest that components of inflammation are important triggers of tumor growth. According to Proctor, this is consistent with the 'seed and soil' nature of cancer growth (8).

The major limitation of our study is that it is observational and single-center, and the comparison of clinicopathological features of the tumor requires larger patient series. Before the clinical implications of proinflammatory markers as cancer markers, more prospective studies are required and there is a need to determine precise cut-off values and optimal limits. In particular, the NLR value has been reported to be a sensitive prognostic marker.

CONCLUSION

The ability to predict a patient's exact prognosis is critical for choosing the optimal treatment plan and follow-up strategies. Although tumor, node, metastasis (TNM) stage is the only reliable prognostic factor, heterogeneous clinical presentations are often observed even within the same tumor stage. Therefore, further studies should be performed to provide a more credible prognostic factor. As proinflammatory markers can be easily determined from a complete blood count, a potentially simple and inexpensive test can provide cancer prognosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee (Date: 30.12.2022, Decision No: 286).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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This is the article that the author of the article sends to the editor of the journal. In this section, it should be noted that part or all of the article is not published elsewhere and is not in the process of being evaluated in another journal at the same time, "**Material Support and Interest Relationship**" status, language and statistical checks are made.

2. Title Page

The category of the article submitted at the beginning of the page should be indicated (clinical analysis, research article, experimental study, case report, review, etc.). The names and surnames of all authors should be numbered after the superscript and numbered from 1, and they should be added under the names of the institutions, clinics, cities and countries. On the title page, each author's **Orcid ID** should be his/her e-mail address. This page should include the Authorized Author (s), name, full address, telephone and **e-mail** (address information should be indicated in English. Oral or Poster presentations presented at congresses should be indicated on the title page by giving the name, place and date of the congress.

3. Article File

There should be no names of authors and institutions, only this information should be on the title page.

Title: There should be a short and clear title. It should not contain abbreviations.

Abstract: English abstracts should be written. In research articles; It should be divided into sections of Aim, Material and Method, Results, Conclusion and should not exceed 400 words. In the review, case reports and the like.

Keywords: A minimum of 3 and a maximum of 6 keywords should be written. Words should be separated by semicolons. Keywords should be submitted in accordance with Subject **Medical Subject Headings (MESH)** (www.nlm.nih.gov/mesh/MBrowser.html).

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Research Article: Prospective-retrospective and all kinds of experimental studies can be published. Introduction, Materials and Methods, Results, Discussion, Conclusion. Abstract (approximately 400 words; aim, material and method, results and conclusion sections), Introduction, Material and Method, Results, Discussion, Conclusion, Acknowledgments, References.

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WHAT SHOULD BE INDICATED BEFORE THE RESOURCES

ETHICAL CONSIDERATIONS

Ethics Committee Approval: The study was carried out with the permission of …….... Ethics Committee of ……. (Date: ……., Decision no: ……).

Informed Consent: All patients signed the free and informed consent form. (If retrospective study; **Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.)

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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SOURCE WRITING EXAMPLES

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Excerpt from the book;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Excerpt from the book, which is the only author and editor;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams & Wilkins; 1996: 46-60.

Excerpt from the book with multiple authors and editors;

Schulz JE, Parran T Jr.: Principles of identification and intervention. In: Principles of Addicton Medicine, Graem AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams & Wilkins; 1998: 1-10.

If the editor is also the author of the chapter in the book;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag; 1988: 45-67.

Excerpt from PhD/Undergraduate Thesis;

Kilic C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Excerpt from an internet site;

Site name, URL address, author names, access date should be given in detail.

Giving a Doi number;

Joos S, Musselmann B, Szecsenyi J. Integration of complementary and alternative medicine into the family market in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi: 10.1093/ecam/nep019).

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Authors should declare, if any, the roles of sponsors of the study:

1. Design of the study 2. Data collection, analysis and interpretation of the results 3. Writing the report

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—Editor to Presentation Page

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- Ethical Status,
- "Conflict of Interest"
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