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The stress and happiness levels of gastroenterologists in Turkiye and factors influencing them

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ABSTRACT

Aims: This study aimed to investigate the stress and happiness levels of gastroenterologists in Turkiye and the factors affecting them.

Methods: The authors designed a 25-question questionnaire to investigate gastroenterologists' stress and happiness levels and the reasons that may affect them. Documents containing the questions were sent to 405 gastroenterologists working in Turkiye between October and December 2023 by phone or email via Google Forms.

Results: A total of 126 participants, 65.1% of whom were male and 52.4% of whom were under 40 years of age, took part in our study. A median score of 4 on a 5-point Likert scale was obtained when participants were asked about their general level of stress. When the general happiness status was analysed, it was concluded that this median value was below the stress values with 3. The general happiness had the strongest positive correlation with workload satisfaction and career planning happiness ($r=0.56$, $p<0.001$ and $r=0.46$, $p<0.001$, respectively). The general stress level was most negatively correlated with happiness from work intensity satisfaction and support from hospital management ($r=-0.43$, $p<0.001$ and $r=-0.30$, $p<0.001$, respectively).

Conclusion: Our study showed that gastroenterologists in Turkiye have a significant level of stress and a neutral level of happiness. It was observed that the most important stress factor is workload, which has a direct effect on the level of happiness and stress. Some participants in our study considered leaving the country due to stress, posing a risk to the future provision of gastroenterology services in Turkiye.

Keywords: Gastroenterologist, stress, happiness, workload, emotional health

INTRODUCTION

The mental health of medical doctors has become a subject of increasing research in recent years, and it is increasingly recognised that stress and burnout, especially in doctors, are among the main determinants of patient care.[1,2] Although stress can be beneficial to a certain extent, heavy working conditions can lead to undesirable physical and psychological consequences. This can result in lost working days, reduced work performance and personal problems.[3] In addition, previous studies have reported problems such as increased risk of medical and decision-making errors, reduced doctor-patient interaction and early retirement.[4,5]

Gastroenterology is a demanding speciality with an increasing demand for endoscopy, which can require unplanned out-of-hours working and involves many invasive procedures.[6] Therefore, studies investigating the stress and burnout levels of gastroenterologists have started to be published in recent years. In a recent national study conducted in Portugal, it was found that burnout was higher in gastroenterologists who were younger, worked on weekends and performed a high volume of endoscopic procedures. In another nationally based study, it was similarly reported that young gastroenterologists were at risk of burnout.[7] Studies investigating the stress levels and causes of gastroenterologists are more limited in number.[6]

It is thought that burnout among doctors in Turkiye has increased in recent years due to various reasons, including workload, economic problems and fear of violence.[8] It has been reported in the literature that there has been an increase in the number of doctors leaving Turkiye for other countries in recent years due to these and similar reasons.[9]

To the best of our knowledge, there is no study on the stress levels and causes affecting gastroenterologists in Turkiye. In this study, we aimed to investigate the stress and happiness levels of gastroenterologists in Turkiye and the reasons affecting them.

METHODS

Study Design and Participants

The authors designed a 25-question questionnaire to investigate gastroenterologists' stress and happiness levels

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and the reasons that may affect them. The survey was sent via Google Forms by phone or email to 405 gastroenterologists working in Turkiye between 15 October and 15 December 2023. Participants were initially informed that the survey was voluntary, and that no identifying information would be included in the survey. Lokman Hekim University Faculty of Medicine Akay Hospital Ethics Committee (Date: 06.09.2023, Decision No: EK1-2023-290) and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

Data Collection and Questions

Participants were presented with a total of 25 questions designed by the authors. Some questions were modified from questions found in a similar study in literature.[6] The first ten questions collected demographic and occupational data about the participants. The following four questions were based on the respondents' level of emotional health, such as stress level (graded 0-5; 0=none, 5=very stressfull), happiness level (graded 1-5; 1=very unhappy, 5=very happy), daily sleep duration and frequency of sleep interrupted by work. Questions 15-22 were possible morale-related factors (graded 1-5; 1=very unhappy, 5=very happy) that could potentially affect stress and happiness levels. The remaining three questions consisted of the main causes of stress, the thought of leaving due to stress and solutions.

The survey forms with the questions can be found in the attached file.

Statistical Analysis

SPSS 25 and R Studio 2023.03.0 (with packages "corrplot 0.92" and "ggplot 2 3.4.3") were used in our study. Descriptive statistics were expressed as frequencies, percentages, means and medians (Q1-Q3). The relationship between scale items was analysed using Spearman rank correlation analysis. Univariate logistic regression (LR) was used to analyse whether the identified categories were risk factors for stress and happiness. The chi-squared ratio test was used for pairwise ratio comparisons of scale items. For all analyses, the significance level was set at 0.05.

RESULTS

A total of 126 participants took part in our study, of whom 65.1% were male and 52.4% were under 40 years of age. The majority of the participants were married (80.2%) and actively working (96%). The study concluded that the institution of employment was generally a training-research hospital (34.9%), followed by city hospitals (27.8%). Additionally, it was found that 61.9% of the participants, who reported that their interest in gastroenterology was primarily in advanced endoscopy (53.2%), had been professionals in the field of gastroenterology for less than 5 years. Other detailed information is presented in Table 1.

When the participants were asked about the general stress level, the median value was 4 on a 5-point Likert scale. In contrast, the median value for general happiness was 3, indicating that happiness levels were lower than stress levels. Although 61.1% of the participants had a sleep level of around

Table 1. Demografic and occupational characteristics of the study group

Gender	
Female	44 (34.9)
Male	82 (65.1)
Age	
<40	66 (52.4)
40-50	45 (35.7)
50>	15 (11.9)
Marital status	
Single	17 (13.5)
Married	101 (80.2)
Divorced	8 (6.3)
Current work status	
Working	121 (96)
Retired then returned	5 (4)
Type of hospital	
University hospital	22 (17.5)
Training and research hospital	44 (34.9)
City hospital	35 (27.8)
Public hospital	12 (9.5)
Private hospital	13 (10.3)
Subspecialty	
Advanced endoscopy	67 (53.2)
Inflammatory bowel diseases	24 (19)
Hepatology	20 (15.9)
Functional diseases	8 (6.3)
Other	7 (5.6)
Stage/status	
Education person	29 (23)
Specialist physician (Compulsory national duty)	30 (23.8)
Specialist phsician	30 (23.8)
Trainee/Fellow	37 (29.4)
Duration of work as a gastroenterologist (years)	
<5	78 (61.9)
5-10	22 (17.5)
10-20	13 (10.3)
20<	13 (10.3)
Number of gastroenterologists working in the same hospital	
0	25 (19.8)
1	12 (9.5)
2-5	33 (26.2)
>5	56 (44.4)
Total number of out of hours in 1 month (days)	
0	25 (19.8)
1-5	34 (27)
6-10	33 (26.2)
10>	34 (27)
Variables are expressed as n (%)	

6-8 hours, the number of gastroenterologists who experienced 1 to 5 sleep interruptions due to out-of-hours work in a month constitutes a significant amount (48.4%) (Table 2).

Table 2. Emotional health indices of the study group

Stress levels	4 (3-4)
Happiness levels	3 (2-4)
Sleep duration (hours)	
<4 h	3 (2.4)
4-6 h	40 (31.7)
6-8 h	77 (61.1)
>8 h	6 (4.8)
Number of sleep interruptions per month (days)	
0 day	13 (10.3)
1-5 day	61 (48.4)
6-10 day	36 (28.6)
10> day	16 (12.7)

The general level of stress and happiness is expressed as mean and median (Q1-Q3), others n (%)

When the relationship between general happiness and stress levels and morale-related factors was analysed, it was concluded that general happiness had the strongest positive correlation with workload satisfaction and career planning happiness (r=0.56, p<0.001 and r=0.46, p<0.001, respectively) and the weakest correlation with happiness from medical supplies/equipment (r=0.21, p=0.026). It was concluded that general stress level was most negatively correlated with happiness from work intensity satisfaction and support from hospital management (r=-0.43, p<0.001 and r=-0.30, p<0.001, respectively) and least correlated with happiness from career planning (r=-0.14, p=0.137) (Figure 1).

Figure 1. Correlations of general happiness and stress levels with factors associated with morale. A: Workload, B: Support from hospital management, C: Support from clinical colleagues, D: Hospital buildings/facilities, E: Medical supplies and devices, F: Salary adequacy, G: Career planning, H: Home Life. X: Non-significant

Taking into account the 4th and 5th categories of general stress level and the 1st and 2nd categories of general happiness on a Likert scale, the logistic model was used to analyse whether demographic and occupational variables were risk factors. Although the variable total number of working hours in 1 month seemed to be a candidate risk factor for stress level (p=0.06), it did not reach a significant level of significance. No significant result was found for general level of happiness (Table 3).

Table 3. Logistic regression analysis for stress (likerts 4 and 5) and unhappiness (likerts 1 and 2)

Variables	Stress (LR for categories 4. and 5.)		Unhappiness (LR for categories 1. and 2.)	
	OR (95% CI)	p	OR (95% CI)	p
Gender	1.5 (0.4-6.5)	0.561	0.8 (0.08-9.3)	0.882
Age	1.4 (0.5-4.1)	0.494	1.3 (0.2-6.9)	0.760
Marital status	0.5 (0.1-2.4)	0.455	0.3 (0.1-5.5)	0.453
Type of hospital	1.1 (0.6-1.8)	0.888	1.4 (0.5-4)	0.573
Current work status	0.9 (0.5-1.6)	0.723	0.9 (0.4-2.6)	0.950
Subspecialty	0.9 (0.5-1.9)	0.903	2.8 (0.6-13.9)	0.209
Duration of work as a gastroenterologist (years)	1.1 (0.6-2.2)	0.757	1.9 (0.4-9.8)	0.431
Number of gastroenterologists working in the same hospital	0.8 (0.4-1.3)	0.351	0.8 (0.3-1.9)	0.628
Total number of out of hours in 1 month (days)	2.3 (0.9-5.6)	0.061	0.3 (0.1-1.6)	0.174

LR: Logistic regression, OR: Odds ratio, CI: Confidence interval

The results of the analyses in which all the responses of the participants to the morale-related factors are evaluated in general and the ratios of the 1st-2nd categories and the 4th-5th categories are compared are presented in Table 4. It is seen that there is a significant difference between the groups with high and low happiness levels in almost all factors. It was concluded that only satisfaction with hospital buildings/facilities did not make a difference (p=0.208) in terms of the respondents' attitude.

When the participants were asked about the factors causing stress, excessive work ranked first with 17.24%. However, the least important factor causing this situation was confidence with 4.4%. When asked about the unit or location they would consider leaving due to stress, current hospital and country of resindece shared the same percentage (30.1%). In response to the factors that may be effective in reducing the level of stress, the most common answer (27.6%) was to increase the national assosiciation-bureaucracy relations. In addition, training programmes (26.4%) and mentoring by experienced (25.7%) are also considered to be solutions for the participants with high rates (Figure 2).

DISCUSSION

Our study investigated the stress and happiness levels of gastroenterologists in Turkiye and the reasons for them. The study found that a significant proportion of gastroenterologists in Turkiye were in the stressful category and their happiness levels were not in the happy or unhappy classification, but in the neutral range. In our study, it was observed that the morale-related factor affecting both stress and happiness levels is satisfaction with workload, which is directly proportional to happiness and inversely proportional to stress. Among the stress factors, workload was most frequently mentioned by the participants, and the most common solution suggestion was to increase the relations of the national gastroenterological association with the bureaucracy and management units.

Table 4. Participants' responses to morale-related factors								
	L1	L2	L3	L4	L5	L1-L2	L4-L5	p
Workload	14 (11.1)	36 (28.6)	45 (35.7)	28 (22.2)	3 (2.4)	39.7	24.6	0.015
Support from hospital management	33 (26.2)	39 (31)	34 (27)	16 (12.7)	4 (3.2)	57.2	15.9	<0.001
Support from clinical colleagues	6 (4.8)	19 (15.1)	46 (36.5)	49 (38.9)	6 (4.8)	19.9	43.7	<0.001
Hospital buildings/facilities	17 (13.5)	30 (23.8)	43 (34.1)	30 (23.8)	6 (4.8)	37.3	28.6	0.180
Medical Supplies and devices	24 (19)	49 (38.9)	31 (24.6)	20 (15.9)	2 (1.6)	57.9	17.5	<0.001
Salary adequacy	42 (33.3)	35 (27.8)	38 (30.2)	9 (7.1)	2 (1.6)	61.1	8.7	<0.001
Career planning	9 (7.1)	48 (38.1)	40 (31.7)	23 (18.3)	6 (4.8)	45.2	23.1	<0.001
Home life	4 (3.2)	9 (7.1)	27 (21.4)	66 (52.4)	20 (15.9)	10.3	68.3	<0.001

Variables are expressed as n (%), L1: It represents the first category of the Likert-Type Scale

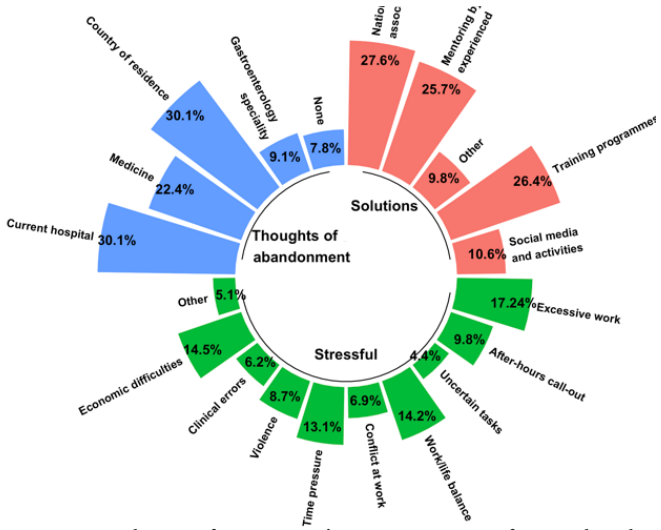

Figure 2. Distribution of participants' responses to stress factors, thoughts of abandonment and solutions

Stress and burnout among physicians have been an important research topic in recent years. Although these studies have been conducted in different countries[10,11] and on different specialities[12,13] the common feature of most of them is that physicians have significant stress and burnout. In 2018, an online survey of 15,000 U.S. physicians showed that 50% had stress and burnout. It was stated that the significant level of these participants was between the ages of 45-54, the group with high work efficiency.[14] A year later, a similar rate of burnout was observed. It was suggested that 14 per cent of participants had suicidal thoughts.[15]

Studies on gastroenterologists have shown that doctors in the specialist group also have high stress levels.[6] In a study conducted among gastroenterologists in the UK, it was found that the most important cause of stress was excessive workload. Undoubtedly, many reasons such as the nature of gastroenterology requiring both working hours and after hours, requiring emergency patient examination and management, and having many invasive procedures may be effective in this. In another study, it was reported that gastroenterologists had moderate stress and burnout, and that this stress level was mostly related to invasive procedures, and that operators with less experience and operators performing invasive advanced endoscopic procedures experienced more stress.[16] In our study, 57.9% of participants rated themselves in the stressful and very stressful category. Workload was found to be the most stressful factor. It is known that the total population of Turkiye will exceed 85 million by 2023. It has been published that more than 70% of this population is the adult population.[17] In a recent study investigating the awareness of gastroenterologists about obesity in Turkiye, it was reported that a total of 1117 gastroenterology specialists were reached via e-mail registered to the National Gastroenterology Association.[18] Considering these ratios, there is 1 gastroenterologist per 50,000 adult population in Turkiye. Considering that some of these registered gastroenterologists are retired, this can give us an idea of the work intensity of the remaining gastroenterologists who are still working. In addition, the fact that workload satisfaction correlated correctly with happiness level and inversely with stress level emphasizes the importance of this issue more clearly in our study. We think that the problems in work-life balance, which stand out among the stress factors, may also be related to this intense workload.

In some studies, it was reported that gastroenterologists in the younger age group were more at risk of stress and burnout. In the same study, it was reported that burnout was higher in those who worked on weekends and performed a higher number of endoscopic procedures.[19] Although the study included 52 gastroenterologists and used a burnout scoring system, it is comparable to our study in terms of key findings. In our study, multivariate analysis was performed on stress and no significant risk factor was found when the high stress groups were examined for both demographic and occupational risk factors. Although we found a statistical result close to the significant finding of gastroenterologists working overtime after working hours, we could not determine that there was a risk factor.

In our study, economic problems and salary levels were found to be one of the prominent stress factors and low levels of morale-related happiness. In a recent study conducted in the USA, it was stated that gastroenterology was the subspeciality of internal medicine with the highest number of applicants compared to the positions offered in the last 12 years. This demand rate was found to be correlated with salary adequacy.[20]

Another notable finding in the participants' responses was that the most common reasons for leaving the hospital and the country of residence were the current hospital and the country of residence. A recent study found that the main reasons for doctor migration in Turkiye were economic difficulties, intensive working conditions and increasing violence.[9] In our

study, it is noteworthy that similar factors came to the fore and the idea of travelling to other countries was considered at any time in approximately one third of the participants. Considering that more than half of the participants were under the age of 40, it can be said that these data may pose a risk in the capacity to provide gastroenterological health services.

Among the solutions identified by the participants, increasing the activities of the national association, particularly in relation to bureaucracy and management units, increasing training programs and mentoring by experienced gastroenterologists came to the fore. In this regard, the American Gastroenterological Association (AGA) recently highlighted the high stress levels of gastroenterologists, especially fellows and less experienced gastroenterologists, and the importance of mentoring and training programs.[21]

Limitations

This study has some limitations. First, the relatively low number of participants may affect the generalizability of the findings. The number of participants could have been higher if the researcher's reached gastroenterologists through the national gastroenterological association. Another limitation was that the participants determined their stress and happiness levels according to their own subjective evaluations.

CONCLUSION

Our study showed that gastroenterologists in Turkiye have a significant level of stress and a neutral level of happiness. It was observed that the most important stress factor is workload, which has a direct effect on the level of happiness and stress. In addition, the fact that some of the participants in our study had thoughts of leaving the country and the profession due to stress is a risk in terms of limiting the activities of providing health services in the field of gastroenterology in Turkiye in the future.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval was obtained from the Lokman Hekim University Faculty of Medicine Akay Hospital Ethics Committee (Date: 06.09.2023, Decision No: EK1-2023-290).

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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Investigation of the effect of implant crown ratio and material type on the force transmitted to the implant in implant-supported restorations: a finite element analysis study

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ABSTRACT

Aims: The crown implant ratio may pose a problem, especially when short implants are used. This condition is associated with marginal bone loss. Therefore, in this study, it was aimed to evaluate the stresses arising from the bone, implant and its parts and the restoration by finite element analysis (FEA), as a result of comparing a situation with ideal bone support and a similar situation with vertical bone loss. The null hypothesis is that the type of material and crown length chosen for implant-supported restorations will not make a difference in terms of stress on implants of different sizes. **Methods:** For this study, 8 mm implants were placed in the 44-46 region and a group with a 3-unit 12 mm length fixed prosthesis and a group with 12 mm implants and a 3-unit 8 mm length fixed restoration were designed. The data of the implant parts were obtained from a implant company (Bilimplant, İstanbul, Turkiye) and placed in the appropriate position within a bone data drawn in the Solidworks 2013 software (Solidworks Corp., USA). Appropriate multi-unit parts were then added and 3-unit restorations were designed with exocad. Necessary arrangements were made in the Geomagic Design X 2020 (3D systems, Morrisville, NC, USA) program, the restorations were given the characteristics of 2 different materials (lithium disilicate and zirconia). Applying a force of 200 N on the occlusal direction, the maximum principal stress values occurring in the bone, implant, multi-unit, restoration and occlusal screw were recorded. **Results:** Principal stress (Pmax) values recorded on the implant for the 1st premolar were higher on the 12 mm implant (B1 and B2 groups) and lower on the 8 mm implant. For the implant applied to the 1st molar region, higher stress values were observed in the groups with 8 mm implants (A1 and A2 groups), while lower values were observed with 12 mm implants (B1 and B2 groups). **Conclusion:** As the crown/implant ratio increases in favour of the implant, the survival of the unit decreases. In addition, it is more appropriate to prefer rigid materials in implant restorations.

Keywords: CAD/CAM, finite element analysis, implant

INDRODUCTION

Advancing technology has made the use of implants appropriate for tooth deficiencies.[1] One of the most important factors in the success of implants is their strong connection with the bone tissue during the osseointegration process. As a result of successful osseointegrated implants, patients being rehabilitated both functionally and aesthetically.[2,3]

Another important factor affecting the success of the implant is the way the stress that the implant is exposed to is transmitted to the bone. This condition, also called implant biomechanics, is related to the shape, length, diameter and design of the implant. It is also known that the groove design observed in screw implants affects biomechanics. The contact of the implant with the surrounding bone is directly related to the stress factor that will occur in the bone.[4,5] The force generated by the transmission of stress to the bone is related to the design of the implant, its biomechanical properties and the destruction reactions that occur as a result of the strain reflected by the implant to the bone.[6] Due to anatomical limitations such as insufficient bone area, proximity to the maxillary sinus or inferior alveolar nerve, it may become impossible to place the implant in the ideal diameter and length. In order to eliminate these problems, additional surgeries such as bone grafting or sinus lift operations are required. In such cases, short (<10 mm) implants may be considered as an alternative.[1,3,7]

Implant restorations are divided into two parts: artificial tooth (crown) and implant. The crown part is defined as the area outside the alveolar bone and the implant part is

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defined as the area inside the alveolar bone. Crown-implant separation is defined as the physical relationship determined by radiography. In radiographic terms, the crown-to-implant ratio refers to the relationship between the length of the crown visible on radiographic images and the length of the implant. It is a measure of the ratio between the height of the crown and the portion of the dental implant embedded in the jawbone. This ratio gives preliminary information about the prognosis of implant treatment.[8,9] Disproportionate crown-to-implant ratios and reduced implant root surface can make the implant more vulnerable to trauma caused by occlusal forces. As a result of the literature review, it was found that excessive crown-to-implant ratios reduce the long-term survival rate of the implant.[8] Non-axial loading, which increases in direct proportion to the anatomical crown length, creates a significant lateral moment. This leads to stress concentration at the implant neck, which may result in technical complications of the prosthetic components.[10]

Two recent systematic reviews investigated the long-term success of implant-supported single crowns and fixed dental prostheses in relation to survival and complication frequency, regardless of the difference between ceramics and metal ceramics. The systematic review by Jung et al.[11] found that the 5-year survival rate of implant-supported single crowns was 96.3% (95% CI: 94.2-97.6%).[11] Another result concluded that zirconia implant abutments have been considered successful over the past decade and that the survival results are on par with metal abutments.[12] However, whether the prognosis of zirconia implant-supported restorations is similar to that of metal ceramic implant restorations has not been fully elucidated to date.[11-13] Lithium disilicate and monolithic zirconia materials are increasingly being used due to their high biocompatibility and mechanical properties.[14] In a study conducted by De Angelis et al.[15] monolithic lithium disilicate and monolithic zirconia crowns showed comparable clinical results with a 100% survival rate in both groups.[15] No significant difference was found between the technical complications and the opposing teeth. Another review showed that double-layered lithium disilicate restorations are a viable treatment alternative to monolithic zirconia implant restorations with similar biological complications and fewer aesthetic issues. In terms of fracture strength, lithium disilicate shows similar properties to zirconia material.[16,17]

Finite element analysis (FEA) is used to evaluate the mechanical behavior of complex structures and to support in vitro experiments. It is basically a computational technique used to simulate and predict how materials will react when subjected to different forces. A working hypothesis can be simulated to evaluate the stress exerted on teeth under varying masticatory conditions. However, issues such as material properties, limitations, mesh distribution and calculation can easily affect the result of FEA. In order to create a virtual model and to have confidence in the FEA results, the data should be supported by in vivo and in vitro studies.[18-20]

The aim of this study was to evaluate the stresses on different materials at different implant crown length ratios using FEA and to diagnose the possible risks of using short implants. The null hypothesis was that there would be no difference in stress distribution between restorations created with monolithic zirconia and lithium disilicate materials with different implant crown ratios.

METHODS

The study was carried out with the permission of Necmettin Erbakan University Dentistry Non-drug and Non-medical Device Researches Ethics Committee (Date: 25.07.2024, Decision No: 2024/463). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The bone tissue model was created with Solidworks 2013 software (Solidworks Corp., USA). Based on the data from Bilimplant®, the model was created using short (8 mm) and long (12 mm) implants. Then, multi-unit parts compatible with the gingival height were selected and 3-unit restorations were designed using Exocad (Dental Cad3.1 Rijeka, EXOCAD, Darmstadt, Germany). For group A, implants with a length of 8 mm were placed in the bone model corresponding to the 44 and 46 regions and restorations with a crown length of 12 mm were designed on them. As a control group, group B was formed by placing implants with a length of 12 mm into the bone and restorations with a crown length of 8 mm were designed on them, shown in Table 1. The data obtained were then exported as Standard Tesselation Language (STL) files. The models were edited using Geomagic Design X 2020 (3D systems, Morrisville, NC, USA). To simplify the complexity of the three-dimensional finite element models, bone was assumed to have isotropic and linear elastic properties. The implants were assumed to be fixed in the bone.

Table 1. Describing the subgroups

Length of the implant	Lithium disilicate	Zirconia
8 mm	A1	A2
12 mm	B1	B2

With the Exocad program, A1, A2, B1, B2 groups were formed by making the necessary arrangements in the design of 3-membered multi-unit restorations with monolithic zirconia and lithium disilicate materials on a 12 mm long crown in group A and 8 mm long crown in group B (Table 1). Additional modifications were also made in Geomagic Design X 2020 (3D systems, Morrisville, NC, USA) program, then transferred to Solidworks 2013 software (Solidworks Corp., USA). All parts were merged. The data were transferred to the ABAQUS 2020 finite element analysis program (ABAQUS, 2020 Dassault Systems Simulation Corp., Johnston, RI, USA) and the restorations were characterized by 2 different materials (lithium disilicate and zirconia). An isotropic linear elastic simulation was performed for the restorative materials. A load of 200 N was applied to the model in each group in accordance with the oral environment and the required pressure was calculated. FEA was then done using ABAQUS software to evaluate the stress distribution. A force of 200 N was applied in the occlusal direction. The maximum principal stress (Pmax) values occurring in the bone, implant, restoration and occlusal screw were recorded.

RESULTS

The distribution of the basic maximum stress values of all components over the complements is shown in Table 2. The maximum stress value of the cortical bone was observed in the lithium disilicate material designed on an 8 mm implant in group A1, while the minimum value was seen in the zirconia material applied on a 12 mm implant in group B2 (Figure 1). The values seen on the occlusal screw were independent of the implant site (1st premolar and 1st molar), shown in Figure 2, 3. The maximum principal stress (Pmax) was seen in group B1 (lithium disilicate material designed on a 12 mm implant), and the minimum stress values were seen in the group with zirconia material designed on an 8 mm implant (Figure 4).

Table 2. Distribution of principle maxium stress values on complements, (MPa value)

	A1	A2	B1	B2
Cortical bone	93.56	92.85	48.62	46.56
Occlusal screw 1st premolar	9.43	5.56	20.43	13.37
Occlusal screw 1st molar	8.04	5.05	10.03	5.99
Implant 1st premolar	46.16	45.63	220.8	213.5
Implant 1st molar	87.07	86.19	43.93	40.86
Restoration	32.35	40.37	12.92	12.40

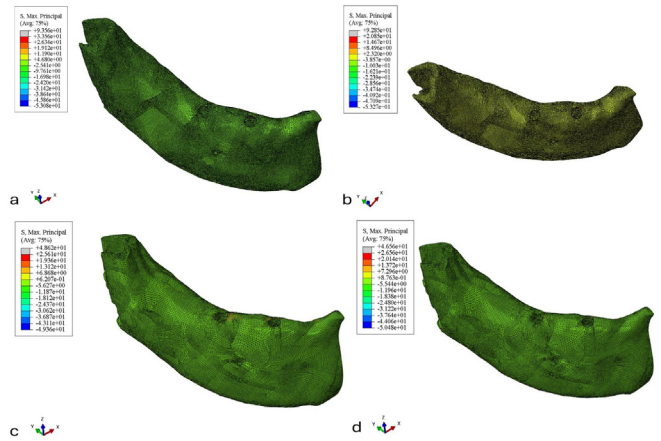

Figure 1. Stress values in cortical bone, a; 8 mm implant lithium disilicate restoration, b; 8 mm implant zirconia restoration, c; 12 mm implant lithium disilicate restoration, d; 12 mm implant zirconia restoration stress distribution in cortical bone

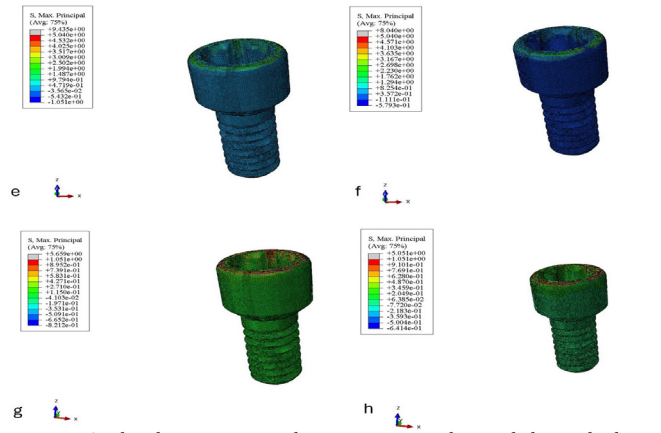

Figure 2. Occlusal screw stress values on 8 mm implant, e; lithium disilicate rest, 1st premolar, f; lithium disilicate rest, 1st molar, g; zirconia rest, 1st premolar, h; zirconia rest, 1st molar occlusal screw stress distribution

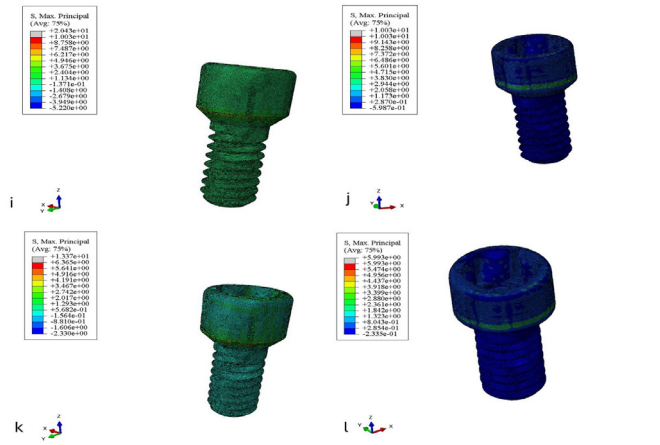

Figure 3. Occlusal screw stress values on 12 mm implant, i; lithium disilicate rest, 1st premolar, j; lithium disilicate rest, 1st molar. k; zirconia rest, 1st premolar, l; zirconia rest, 1st molar occlusal screw stress distribution

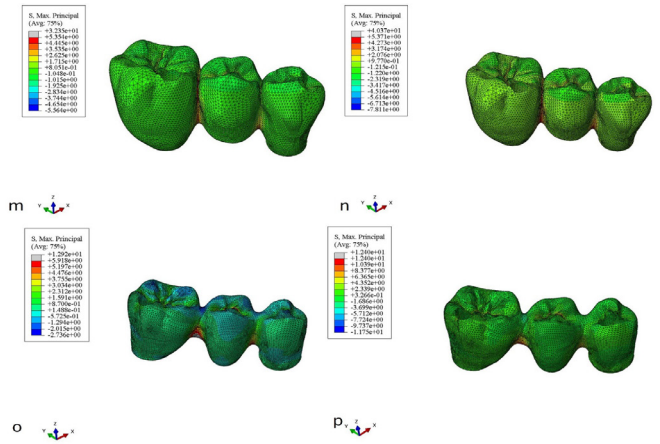

Figure 4. Stress values in restoration, m; 8 mm implant lithium disilicate restoration, n; 8 mm implant zirconia restoration, o; 12 mm implant lithium disilicate restoration, p; 12 mm implant zirconia restoration stress distribution in restoration

Principal stress (Pmax) values on the implant for the 1st premolar were higher on the 12 mm implant (B1 and B2 groups), shown in Figure 5 and lower on the 8 mm implant. For the implant applied to the 1st molar region, higher stress values were observed in the groups with 8 mm implants (A1 and A2 groups) shown in Figure 6, while lower values were observed with 12 mm implants (B1 and B2 groups).

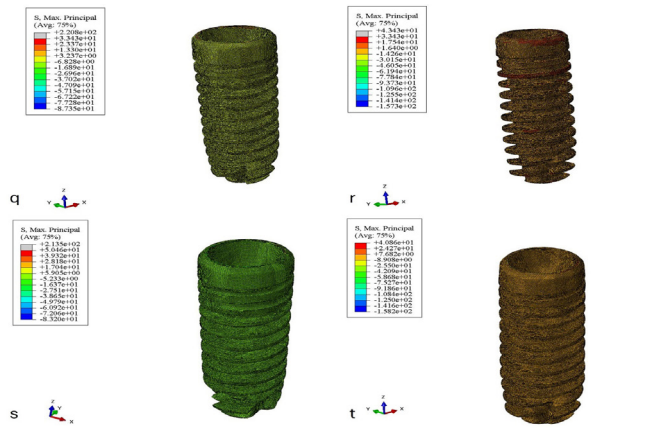

Figure 5. Stress values on 12 mm implant, q; lithium disilicate rest, 1st premolar, r; lithium disilicate rest, 1st molar, s; zirconia rest, 1st premolar, t; zirconia rest, 1st molar 12 mm implant stress distribution

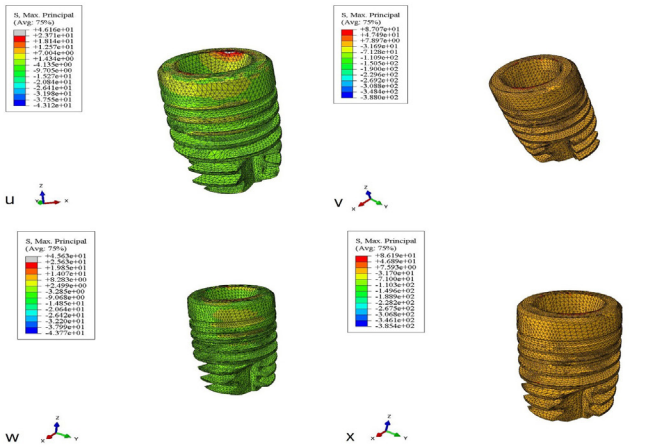

Figure 6. Stress values on 8 mm implant, u; lithium disilicate rest, 1st premolar, v; lithium disilicate rest, 1st molar, w; zirconia rest, 1st premolar, x; zirconia rest, 1st molar 8 mm implant stress distribution

In the restoration, the maximum principal stress value (Pmax) against the applied force was recorded in the zirconia material applied on the 8 mm implant (40.37 MPa), while the minimum value was recorded in the zirconia restoration designed on the 12 mm implant.

DISCUSSION

The flexural strength of zirconia material is higher than that of lithium disilicate and the transformation toughness effect due to the stress it is exposed to increases the strength of the material. Known et al.[21] reported a difference in strength between 3 y-tzp, 5 y-tzp and lithium disilicate.[21] Roberts et al.[17] reported that lithium disilicate material may be an alternative to zirconia hybrid abutment material due to its high fracture strength. The fact that the value between groups B1 and B2 is close to the maximum stress (Pmax) values seen in the restoration with a crown length of 8 mm may be related to this.[17]

De Angelis et al.[14] reported a high survival rate (100%) for implant-retained restorations in both groups of monolithic lithium disilicate and monolithic zirconia crowns. The importance of a reduced occlusal table, reduced load and load direction to prevent overloading of the restoration is also related to the survival of the implant restoration. Therefore, it can be said that the high presence of crowns and the maximum stress on them in groups A1 and A2 are related to each other.[14]

Patients with bruxism can apply a force of up to 700 N to the fixed prostheses in their mouths. Therefore, the treatment plan for posterior implants should be carefully considered when the crown length is high (12 mm) in patients with high occlusal forces.[22]

Malchiodi et al.,[23] conducted a study using 5 mm high implants, stated that the crown/implant ratio is the main parameter that can affect the success of the restoration and the loss of crestal bone from a biomechanical point of view. High stress applied to the implant can lead to crestal bone resorption and loss of the implant. Therefore, it is important that the forces applied to the restoration should not be too much.[23]

In some cases, the bone-implant interface can tolerate occlusal forces without adverse effects on bone tissue. The increase in occlusal forces causes crestal bone loss, and if the increase in force is continuous, implant loss may occur.[24,25]

Blanes et al.[26] it has been suggested that a higher clinical crown/implant ratio causes less crestal bone loss, and this is due to splinting of implant restorations. In conclusion, it can be said that the use of implant restorations with a crown-to-implant ratio of 2/3 in the posterior region can provide successful results.[26]

In our study (Table 2), the correlation between restoration and stress sources on the cortical bone was determined.The high stress on the cortical bone in the A1 and A2 groups with high crown/implant ratio can be explained by the high crown length and the use of short implants (8mm). Accordingly, the null hypothesis that there would be no difference in stress distribution between restorations created with monolithic zirconia and lithium disilicate materials with different implant/crown ratios was rejected.

Nissan et al.[27] they stated that screw fracture was more common in 15 mm crowns and the complication rate was less in short crowns.[27]

The stress distributions of restorations made from different materials differ from each other. Screw loosening is more common in implant-supported single crowns. Implant-supported fixed bridge components are predicted to be more stable under force and able to move more integrally against anti-rotation.[28-30]

Yilmaz et al.[22] found that the survival of the implant complex with a crown length of 14 mm was lower than that of 10 mm. Despite the excessive height of the crowns, a crown-to-implant ratio of 1/1 and 1.4/1 was found in the 10 and 14 mm groups. However, the crown implant ratio is important, since the crown screw is the primary unit that stabilizes the crown in the implant.[22] The reason why the stress on the occlusal screw was less in the A1 and A2 groups and more in the B1 and B2 groups may be due to the distribution of stress to other elements in the implant system.

Limitations

Limitations of this study include the fact that only two different sized implants were used. It is thought that more accurate results will be obtained by working with more implant groups. With finite element analysis, material properties are considered linear isotropic and elastic, but this may not reflect the clinical situation accurately. Therefore, it would be appropriate to support future studies with more groups and material studies.

CONCLUSION

As the crown/implant ratio increases in favor of the implant, the survival of the unit decreases. In addition, the use of more rigid materials in the application of over-implant restorations has produced better results.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Necmettin Erbakan University Dentistry Non-drug and Non-medical

Device Researches Ethics Committee (Date: 25.07.2024, Decision No: 2024/463).

Informed Consent
No biological material was used in the study, informed consent is not required as it is a laboratory study on dental implant material.

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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Oral health attitudes and behaviors of the dental students in a state university in İstanbul

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ABSTRACT

Aims: Dental students have a critical role in educating their patients and relatives regarding oral health. The aim of the present study is to evaluate the changes in attitude and behavior of dental students' during their education from preclinical to clinical classes using the Hiroshima University Dental Behavioral Inventory (HU-DBI).

Methods: The Turkish translation of HU-DBI was distributed to the 537 students studying at the Faculty of Dentistry, University of Health Sciences, in the 2023-2024 academic year.

Results: A total of 416 students completed the survey. The total mean HU-DBI score was 6.3±1.54. The mean HU-DBI scores were significantly higher in clinical classes (6.51±1.48) compared to preclinical classes (5.82±1.61) (p=0.001; p<0.01). Compared to the clinical students, preclinical students reported a significantly higher percentage of bleeding when they brush their teeth (p=0.001); they were bothered about their teeth color (p=0.0119; they thought that their teeth were getting worse even though they brushed them every day (p=0.006); and they postponed going to the dentist until their teeth hurt (p=0.001). Moreover, a significantly higher percentage of clinical students stated that their dentist has told them that they brush their teeth very well compared to the preclinical students (p=0.044).

Conclusion: Initiating oral health education programs at the start of dental education may be beneficial for improving students' oral health awareness and knowledge.

Keywords: Inventory, dental students, Turkiye

INTRODUCTION

Periodontal disease with more than 50% prevalence is a general health problem all around the world, which is also associated with numerous systemic problems such as diabetes mellitus and atherosclerozis.[1,2] Understanding the link between periodontal disease and systemic health increased the importance of periodontal status for systemic homeostasis. Therefore, trained and motivated oral-health care providers have an important role in the dissemination of true knowledge and attitudes regarding the subject.[2,3] Dental students are the future of oral healthcare, and they serve as role models for their families, friends, and patients with the responsibility of oral health promotion. In order to appropriately guide their patients, they must develop correct oral health attitudes and behaviors during their early years of education.[4] The setting in which dental students experience behavioral and motivational shifts about their oral self-care routines, has received less attention.[5] Although some studies have shown that, dental students' attitudes and behaviors are different in the preclinical and clinical years;[3,5-7] the others failed to show any differences.[8,9]

Hiroshima University Dental Behavioural Inventory (HU-DBI) is a validated and reliable instrument to facilitate assessment of health attitudes and behaviors among dental students in different educational systems developed by Kawamura.[10] This inventory has been translated into several languages to evaluate the oral health awareness of different countries. The original HU-DBI had good test-and-retest reliability in both Japanese and English versions.[11,12] Additionally, a previous study indicated that the Turkish translation of the HU-DBI matched the English form linguistically.[5] Due to variances in dental faculty curriculum and educational systems between faculties, the HU-DBI is a useful tool for characterizing oral health attitudes among dental students of different countries and different faculties.[6] Regarding the Turkish dental student population, only a few studies have examined the attitudes and behaviors of dental students and possible gender variations of different faculties.[3,5,6] In Turkiye, the duration of the dentistry faculty is five years. In our faculty, preclinical classes comprise years 1 and 2, whereas clinical classes are years 3, 4, and 5. Preclinical students take both preclinical laboratory and basic science courses, while the clinical students supervise and treat the patients under the supervision of academic staff.

In the recent decade, there has been a global trend towards the standardization of dental education.[13] To measure the

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progress of this trend, comparative studies will become more important to assess dental students' oral health behaviors and attitudes in different dental faculties. Moreover, recent studies have suggested that oral health behaviors may demonstrate gender differences, with men having poorer oral hygiene practices and fewer dental visits compared to women.[14,15]

The aim of this study is to evaluate the attitude and behavioral changes of dental students during their education using the HU-DBI survey. The hypotheses of the study were that students' attitudes and habits regarding oral health would change positively when shifting from preclinical to clinical classes, and their HU-DBI scores would increase. Additionally, HU-DBI scores would not differ between genders.

METHODS

The study was performed in compliance with the Helsinki Declaration and approved by the University of Health Sciences Hamidiye Scientific Researches Ethics Committee (Date: 13.06.2024, Decision No: 7/14). In order to evaluate students' attitudes and habits regarding oral health, the Turkish translation of the HU-DBI was used.[5] HU-DBI is a 20-question survey with two-choice answers (agree/disagree). 1st, 2nd, 3rd, 4th, and 5th grade students studying at the Faculty of Dentistry at the University of Health Sciences in the 2023-2024 academic year (a total of 537 students) were invited to the research. On the day the surveys administered, all students were informed about the content of the study at the end of the class period, and the access link of the survey were sent online to the class groups. The first part of the survey included an information form about the study's content, asking students who agreed to participate voluntarily to tick the relevant box on the form's first page.

Inclusion Criteria

1) Acceptance of participating in the study voluntarily,

2) Answering all questions,

3) Declaring birth dates and genders.

Exclusion Criteria

Incomplete filling out of questions and age-gender sections.

In calculating HU-DBI values; those who answered "I agree" to questions 4, 9, 11, 12, 16, 19 were given 1 point, and those who answered "I disagree" were given 0 points; Points will be collected by giving 1 point to those who answer "I disagree" to questions 2, 6, 8, 10, 14, 15, and 0 points to those who answer "I agree". The maximum HU-DBI value that could be obtained was 12, and a higher value indicated better oral health-related attitudes and behaviors.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used when evaluating the study data. Pearson Chi-square and independent sample t tests were used for group comparisons. Significance was evaluated at $p<0.05$ level.

RESULTS

A total of 416 students participated in the study. 47.5% of the students were males (n=198), and 52.5% were females (n=218). Preclinical students constituted (1st, 2nd grade) 29.8% (n=124), whereas clinical students (3rd, 4th, and 5th grades) constituted 70.2% (n=292). Table 1 displays the percentage of responses and p values for all students.

15 out of 20 questions revealed no significant differences between preclinical and clinical students.

The answers to the questions "My gums have a tendency to bleed when I brush my teeth," "The color of my teeth bothers me," "I think my teeth are getting worse even though I brush them every day," and "I postpone going to the dentist until my tooth hurts" revealed a statistically significant difference($p=0.001$; $p=0.011$; $p=0.006$; $p=0.001$). The agree rate was found to be higher in preclinical classes compared to clinical classes. The answers to the question "My dentist says I brush my teeth very well" revealed a statistically significant difference ($p=0.044$; $p<0.05$). Clinical classes showed a higher agree rate (Table 1).

Total mean HU-DBI score was 6.3±1.54. The mean HU-DBI scores were significantly higher in clinical classes (6.51±1.48) compared to preclinical classes (5.82±1.61) ($p=0.001$; $p<0.01$) (Table 2).

DISCUSSION

The multifactorial nature of periodontal diseases underscores the significance of behavioral interventions.[7] Proper oral hygiene techniques and use of appropriate products according to individual needs', brushing duration, frequency, and regular professional visits have utmost importance for the sustainment of healthy oral conditions. Therefore, starting dental students' education about preventive dentistry in their early years is critical for the dissemination of true knowledge. The results of the present study revealed that preclinical students had worse self-reported oral health behaviors and dental visit habits than their clinical counterparts. Clinical students had a significantly higher overall mean HU-DBI score than preclinical students, with no gender differences. These findings were in line with the previous studies assessing the behavioral changes of dental students from preclinical to clinical classes and could be explained by the fact that education broadens students' knowledge of oral health, which may result in more positive attitudes and behaviors.[3,4,6,7]

Regarding gender differences, previous cross-sectional studies reported that while women attended the dentist more regularly for scheduled treatments or routine checks, men were less likely to visit the dentist and more likely to seek care for immediate issues like discomfort. In addition, men were less likely to seek preventative care and used healthcare services less frequently.[14,15] As a result, the present study also aimed to investigate the possible effect of gender on dental students' health attitudes and behaviors. Riad et al.,[8] reported no differences between gender and clinical-preclinical students in Estonian students, even though the total mean HU-DBI score was the highest to be reported in the literature. Also, Surme and Akman[6] reported gender as an influencing

Table 1. The analysis of the responses according to clinical and preclinical classes

		Groups				
		Clinical		Preclinical		
		n	%	n	%	[a]p
1. I don't worry much about visiting the dentist.	Disagree	224	76.7	104	83.9	0.102
	Agree	68	23.3	20	16.1	
2. My gums tend to bleed when I brush my teeth.	Disagree	244	83.6	78	62.9	0.001**
	Agree	48	16.4	46	37.1	
3. I worry about the color of my teeth.	Disagree	194	66.4	66	53.2	0.011*
	Agree	98	33.6	58	46.8	
4. I have noticed some white sticky deposits on my teeth.	Disagree	234	80.1	102	82.3	0.616
	Agree	58	19.9	22	17.7	
5. I use a child-sized toothbrush.	Disagree	280	95.9	116	93.5	0.307
	Agree	12	4.1	8	6.5	
6. I think that I cannot help having false teeth when I am old.	Disagree	268	91.8	116	93.5	0.536
	Agree	24	8.2	8	6.5	
7. I am bothered by the color of my gums.	Disagree	268	91.8	112	90.3	0.628
	Agree	24	8.2	12	9.7	
8. I think my teeth are getting worse despite my daily brushing.	Disagree	264	90.4	100	80.6	0.006**
	Agree	28	9.6	24	19.4	
9. I brush each of my teeth carefully.	Disagree	70	24.0	24	19.4	0.303
	Agree	222	76.0	100	80.6	
10. I have never been taught professionally how to brush.	Disagree	174	59.6	64	51.6	0.133
	Agree	118	40.4	60	48.4	
11. I think I can clean my teeth well without using toothpaste.	Disagree	244	83.6	106	85.5	0.624
	Agree	48	16.4	18	14.5	
12. I often check my teeth in a mirror after brushing.	Disagree	36	12.3	8	6.5	0.075
	Agree	256	87.7	116	93.5	
13. I worry about having bad breath.	Disagree	104	35.6	46	37.1	0.774
	Agree	188	64.4	78	62.9	
14. It is impossible to prevent gum disease with toothbrushing alone.	Disagree	102	34.9	38	30.6	0.397
	Agree	190	65.1	86	69.4	
15. I put off going to the dentist until I have a toothache.	Disagree	166	56.8	40	32.3	0.001**
	Agree	126	43.2	84	67.7	
16. I have used a dye to see how clean my teeth are.	Disagree	276	94.5	122	98.4	0.076
	Agree	16	5.5	2	1.6	
17. I use a toothbrush that has hard bristles.	Disagree	238	81.5	102	82.3	0.856
	Agree	54	18.5	22	17.7	
18. I don't feel I've brushed well unless I brush with strong strokes.	Disagree	220	75.3	86	69.4	0.205
	Agree	72	24.7	38	30.6	
19. I feel I sometimes take too much time to brush my teeth.	Disagree	210	71.9	96	77.4	0.245
	Agree	82	28.1	28	22.6	
20. I have had my dentist tell me that I brush very well.	Disagree	124	42.5	66	53.2	0.044*
	Agree	168	57.5	58	46.8	

[a]Pearson Chi-square test, **p<0.001, *p<0.05

Table 2. Comparison of HU-DBI scores between clinical and preclinical classes

	Groups		Total	
	Clinical	Preclinical		
	Mean±SD (Median)	Mean±SD (Median)	Mean±SD (Median)	[b]p
Total score	6.51±1.48 (7)	5.82±1.61 (6)	6.3±1.54 (6)	0.001**

[b]Independent samples test, **p<0.001, HU-DBI: Hiroshima University dental behavioral inventory, SD: Standard deviation

factor, with female dental students presenting with better responses to the questionnaire than male colleagues. We can attribute these controversial results to the different curricula of the countries, as well as potential cultural and gender differences. Regarding the dental students in Turkiye, present study revealed the mean HU-DBI score 6.3±1.54, which is comparable to the findings of Yildiz and Dogan[3] (6.53±1.99) and higher than the findings of Surme and Akman[6] (5.95±1.65) and Peker et al.[5] (6.25 clinical students; 5.59 preclinical students). When HU-DBI scores of the different

countries were examined from high to low are presented as: Estonia (8.09±1.22),[8] Switzerland (8.02±1.27),[16] Germany (7.67±1.32),[7] Finland (7.15±1.13),[11] Greece (6.86±1.83),[17] Japan (6.64±2.47),[11] Croatia (6.62±1.54),[18] Lithuania (6.35±1.43),[19] and China (5.07).[12] According to Komabayashi et al.,[12] cultural orientations could induce insightful findings in national comparisons of oral health attitudes and behaviors. Self-reported oral health behaviors appeared to differ significantly among the nations, which may have been caused by variations in student health education programs or cultural norms.

Clinical students more frequently disagreed with item 2, "My gums tend to bleed when I brush my teeth," compared to preclinical students. The enhanced understanding of periodontal disease prevention and the improvement of oral hygiene measures in clinical years can explain this finding.[2,3,6,7,18] Study results showed that preclinical students' oral health attitudes mirrored those of the Turkish population, where aesthetic appearance and lack of pain are major motivational factors.[5] With the progression from preclinical to clinical years, health attitudes and behaviors improve, which was seen as a decrease in worrying about the color of teeth, thought of the worsening of teeth despite daily brushing, and putting off going to the dentist until having a toothache. Moreover, over time, results revealed an increase in students' self-confidence, as evidenced by item 20 (I have had my dentist tell me that I brush very well). Clinical and preclinical students agreed with this item 57.5% and 46.8%, respectively, and the difference was statistically significant. This finding was in line with the previous studies conducted in Turkiye;[3,5,6] however, some of them reported no differences between the years.[7,18]

Limitations

The present study presented valuable data regarding the shifts in attitudes and behaviors of dental students during their education, with the following limitations: Although the response rate was high (77.49%), findings should be interpreted cautiously, since there are many other dental schools in İstanbul and the results may not reflect the general population. Furthermore, the possibility of giving better responses by the students than their actual status might have masked the real results, and study findings should be supported with a clinical assessment, which may be a topic of an another study.

CONCLUSION

Initiation of properly designed oral health promotion education programs at the beginning of dental education may be beneficial to improving preclinical students' oral health awareness. Further studies with increased participation are required to investigate the behaviors and attitudes of dental students throughout the different regions of Turkiye to evaluate the possible differences in curriculum.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the University of Health Sciences Hamidiye Scientific Researches Ethics Committee (Date: 13.06.2024, Decision No: 7/14).

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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The relationship between lipid levels and clinical outcomes in sepsis patients in the intensive care unit: a retrospective study

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ABSTRACT

Aims: This study aimed to investigate the relationship between serum cholesterol levels (HDL-C, LDL-C, and triglycerides) and clinical outcomes in sepsis patients in an intensive care unit (ICU).

Methods: This retrospective study included patients aged >18 years diagnosed with sepsis who were admitted to the Internal Medicine ICUs of Konya City Hospital between June 15, 2021, and March 6, 2024. All data were obtained from routine blood tests of the patients in the ICU.

Results: The study included 477 patients (median age, 73 years; females, 45.9%). The median levels of APACHE-II and SOFA scores were 27 (range, 5-55) and 7 (range, 2-19) points, respectively. The survived patients were younger and had lower median APACHE and SOFA scores compared to the non-survived patients ($p<0.05$ for all). The survived patients had higher levels of platelets, albumin, and HbA1c ($p=0.001$, $p<0.001$, and $p=0.022$, respectively), but significantly lower levels of HDL-C, triglycerides, and C-reactive protein (CRP) compared to the non-survived patients ($p=0.026$, $p=0.011$, $p=0.034$, respectively). In multivariable regression analyses to document independently related parameters, it was found that age (HR: 1.030), SOFA score (HR: 1.891), HDL-C (HR: 1.054), and triglyceride (HR: 1.007) levels were positively and independently related, while acute pancreatitis (HR: 0.057) and albumin levels (HR: 0.428) were inversely related to in-hospital mortality in the study population (all had p-value <0.05).

Conclusion: The findings highlight the potential utility of lipid biomarkers in risk assessment and prognostication in critically ill patients, emphasizing the need for further prospective research to elucidate underlying mechanisms and optimize therapeutic strategies for sepsis management in intensive care settings.

Keywords: Sepsis, lipid levels, intensive care unit, lipid metabolism, prognosis, critically ill

INTRODUCTION

Variations in serum total cholesterol (TC) concentrations, deviations from the expected normal range of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), are recognized features associated with chronic inflammatory conditions.[1] It has been demonstrated that in immunity and host defense, cholesterol metabolism is directly regulated by interferon cytokine response, and additionally, it has been shown that metabolites both upregulate and downregulate the pathway directing immune effector functions and anti-infective activity.[2] In terms of lipoprotein levels, it has been observed that HDL-C neutralizes infections or supports the clearance of toxins both in gram-negative bacteria (lipopolysaccharide) and Gram-positive bacteria (lipoteichoic acid) infections.[3] It has been noted that there is a positive correlation between sepsis and its severity with clinically significant cytokines, including tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interleukin 10 (IL-10).[4,5] In patients with sepsis and septic shock, these cytokines exhibit a reverse correlation with serum cholesterol levels.[6,7]

There are numerous clinical observational studies, primarily focusing on sepsis, which report a reverse relationship between serum cholesterol levels and mortality rates in critically ill adults.[8,9] Despite limitations in population size and scope, these studies consistently report associations between low cholesterol levels (HDL-C, LDL-C, triglycerides, and TC) and mortality in sepsis.[10,11]

The current study aimed to investigate the relationship between serum cholesterol levels (HDL-C, LDL-C, triglycerides) and clinical outcomes in patients with sepsis hospitalized in intensive care unit (ICU).

METHODS

The study was approved by KTO-Karatay University Medical Faculty Ethics Committee for Non-drug and Non-medical Device Trials (Date: 07.03.2024, Decision No: 2024/042). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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The present retrospective study included patients aged ≥18 years diagnosed with sepsis who were admitted to the Internal Medicine ICUs (from emergency department or wards in the hospital) of Konya City Hospital between June 15, 2021, and March 6, 2024. Patients with hypothyroidism, those receiving lipid-lowering medications, with trauma, immune-deficiency, and applied cardiopulmonary resuscitation before ICU admissions were excluded from the study. A total of 477 patients were included in the study. All data were obtained from routine blood tests of the patients, and the initial day blood results of the patients in the ICU were scanned and recorded. Acute Physiology and Chronic Health Evaluation (APACHE)-II scores indicating mortality and Sequential Organ Failure Assessment (SOFA) scores used as diagnostic criteria for sepsis were calculated using the worst clinical and laboratory findings of the patients at the end of the 24th hour of ICU admission. The APACHE-II scores of the patients who died within the first 24 hours of ICU admission were also calculated by the worst clinical and laboratory findings of them (n=14). The Sepsis-3 criteria were used to diagnose sepsis in this study.[12] Additional blood samples were not taken from the patients for this study. General demographic properties, co-morbidities, and ICU and hospital admission and discharged dates of the patients were recorded. Length of hospital and ICU stays were calculated using the mentioned dates. The patients were divided into two groups according to the hospital last status (survived or non-survived). Primary end-point was accepted as in-hospital mortality in this study.

Statistical Analysis

The data were analyzed using the IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp, Armonk, NY, USA). Descriptive statistical methods were used to express categorical variables as numbers and percentages. Whether numerical parameters exhibited a normal distribution was determined using the Kolmogorov-Smirnov test, histogram, and coefficient of variation. Numerical parameters exhibiting a normal distribution were presented as mean ± standard deviation, while non-normally distributed numerical parameters were expressed as median (minimum-maximum). For comparisons of medians between groups, the Mann-Whitney U test was used for two independent groups, while student's t-test was used for comparing means between two independent groups. Spearman's correlation test was applied for correlation analyses. Binary logistic regression analysis was used to find out independently associated factors for in-hospital mortality. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 477 patients with sepsis were enrolled in the study. Demographic and clinical characteristics of the patients are summarized in Table 1, 2; respectively. Among the patients, 45.9% were female, and the median age of the overall cohort was 73 years (range: 18-97 years). Of the patients included in the study, 47.6% survived. The most prevalent comorbidities included hypertension (47.4%), acute kidney failure (45.1%), and diabetes mellitus (40.5%), respectively. The median APACHE score was 27 (range: 5-55), and the median SOFA score was 7 (range: 2-19).

Table 1. Demographic data of the patients

	n=477
Sex, n (%)	
Female	219 (45.9)
Age, Median (minimum-maximum)	73 (18-97)
Hospital end state, n (%)	
Death	250 (52.4)
Comorbidities, n (%)	
Hypertension	226 (47.4)
Acute kidney failure	215 (45.1)
Diabetes mellitus	193 (40.5)
Malignancy	136 (28.5)
Coronary artery disease	136 (28.5)
Congestive heart failure	90 (18.9)
Chronic obstructive pulmonary disease	86 (18.0)
Chronic kidney disease	82 (17.2)
Dementia	78 (16.4)
Hematological disease	43 (9.0)
Asthma	33 (6.9)
Gastrointestinal bleeding	19 (4.0)
Acute pancreatitis	15 (3.1)

Table 2. Clinical data of the patients

	n=477
Clinical scores, median (minimum-maximum)	
APACHE-II	27 (5-55)
SOFA	7 (2-19)
Laboratory parameters, median (minimum-maximum)	
WBC, 103/µL	11575 (50-172240)
Hb, g/dL	10.5 (3.4-20.9)
PLT, 103/µL	191 (3-1714)
Glucose, mg/dl	142.5 (58-996)
CRE, mg/dl	1.42 (0.2-8.05)
ALT, IU/L	21 (5-5787)
Total cholesterol, mg/dl	119 (27.2-307.2)
LDL-C, mg/dl	61 (3.87-218)
HDL-C, mg/dl	28 (3-88)
Triglyceride, mg/dl	140 (34-722)
Albumin, g/dl	2.8 (1.4-5.2)
CRP, mg/L	119.18 (0.6-550)
TSH, mU/L	1.39 (0.01-5.94)
HbA1c, %	6.40 (4.40-18.80)
Length of stay (days), median (minimum-maximum)	
Hospital	16 (0-745)
Intensive care unit	7 (0-126)

APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; WBC: white-blood-cell count; Hb: hemoglobin; PLT: platelet count; CRE: creatinine; ALT: alanine transaminase; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; TSH: thyroid-stimulating hormone

Table 3, 4 present a comparison of demographic, clinical, and laboratory parameters between the survived and non-survived patients, respectively. The survived patients were significantly younger compared to the non-survived patients (p=0.001), and their median APACHE-II and SOFA scores were significantly lower (p<0.001, for both). Additionally, the survived patients exhibited significantly higher levels of platelets (PLT), albumin, and HbA1c (p=0.001, p<0.001, and p=0.022, respectively) while their levels of HDL, triglycerides, and C-reactive protein (CRP) were significantly lower than those of the non-survived patients (p=0.026, p=0.011, p=0.034 respectively). Furthermore, the length of stay in the ICU was significantly shorter in the survived patients than in the non-survived patients (p=0.019).

Table 3. Comparison of demographic data between the survived and non-survived patients

	Survived (n=227)	Non-survived (n=250)	p
Sex, n (%)			
Female	107 (47.1)	112 (44.8)	0.609
Age, median (minimum-maximum)	69 (18-97)	75 (21-95)	0.001
Comorbidities, n (%)			
Diabetes mellitus	98 (43.2)	95 (38.0)	0.250
Hypertension	112 (49.3)	114 (45.6)	0.414
Dementia	38 (16.7)	40 (16.0)	0.827
Chronic kidney disease	36 (15.9)	46 (18.4)	0.463
Acute kidney failure	96 (42.3)	119 (47.6)	0.244
Gastrointestinal bleeding	9 (4.0)	10 (4.0)	0.984
Acute Pancreatitis	11 (4.9)	4 (1.6)	0.042
Chronic obstructive pulmonary disease	39 (17.2)	47 (18.8)	0.646
Asthma	17 (7.5)	16 (6.4)	0.640
Coronary artery disease	66 (29.1)	70 (28.0)	0.795
Congestive heart failure	47 (20.7)	43 (17.2)	0.329
Malignancy	52 (22.9)	84 (33.6)	0.010
Hematological disease	25 (11.0)	18 (7.2)	0.146

Table 5 illustrates the correlation of TC, HDL-C, LDL-C, and triglyceride levels with various clinical parameters. According to the data, TC showed positive correlations with hemoglobin (Hb), blood glucose (GLU), LDL-C, HDL-C, triglycerides, albumin, and HbA1c, while exhibiting a negative correlation with CRP. LDL-C was positively correlated with Hb, PLT, GLU, TC, HDL-C, albumin, and HbA1c, but negatively correlated with SOFA score, and creatinine (CRE), and CRP levels. HDL-C demonstrated positive correlations with Hb, PLT, TC, LDL, and albumin levels, while negatively correlated with SOFA score, and CRE, triglycerides, and CRP levels. Triglyceride levels showed positive correlations with APACHE and SOFA scores, and GLU, CRE, TC, CRP, and HbA1c levels, but were negatively correlated with age and HDL and albumin levels. The significant correlation results had rho coefficient levels lower than 0.30, which indicated weak correlations. No correlation was found between lipid parameters and the duration of hospital or ICU stay.

Table 4. Clinical and laboratory parameters between the survived and non-survived patients

	Survived (n=227)	Non-survived (n=250)	p
Clinical scores, median (minimum-maximum)			
APACHE-II	24 (5-53)	29 (12-55)	<0.001
SOFA	5 (2-15)	9 (2-19)	<0.001
Laboratory parameters, median (minimum-maximum)			
WBC, 103/µL	11055 (110-90460)	12035 (50-172240)	0.433
Hb, g/dL	10.8 (3.4-18.2)	10.3 (5.6-20.9)	0.093
PLT, 103/µL	212.5 (8-613)	160.5 (3-1714)	0.001
Glucose, mg/dl	147 (64-996)	139.5 (58-755)	0.210
CRE, mg/dL	1.35 (0.21-7.35)	1.46 (0.2-8.05)	0.070
ALT, IU/L	20 (5-1470)	22 (5-5787)	0.066
Total cholesterol, mg/dl	115.2 (27.8-307.2)	123.1 (27.2-265.4)	0.131
LDL, mg/dl	60 (3.87-218)	61 (3.87-167)	0.872
HDL, mg/dl	25 (6-64)	30 (3-88)	0.026
Triglyceride, mg/dl	134 (34-722)	149 (46-718)	0.011
Albumin, g/dl	2.9 (1.4-5.2)	2.6 (1.4-4.2)	<0.001
CRP, mg/L	110.97 (0.6-458)	127.73 (1.21-550)	0.034
TSH, mU/L	1.39 (0.01-5.53)	1.37 (0.01-5.94)	0.913
HbA1c, %	6.6 (4.7-18.8)	6 (4.4-11.1)	0.022
Length of Stay (days), median (minimum-maximum)			
Hospital	14 (0-670)	17 (0-745)	0.601
Intensive care unit	6 (0-108)	7 (0-126)	0.019

APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; WBC: white-blood-cell count; Hb: hemoglobin; PLT: platelet count; KRE: creatinine; ALT: alanine transaminase; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; TSH: thyroid-stimulating hormone

In multivariable regression analyses to document independently related parameters with hospital mortality (Table 6), it was found that age (HR: 1.030), SOFA score (HR: 1.891), HDL-C (HR: 1.054), and triglyceride (HR: 1.007) levels were positively and independently related to in-hospital mortality, while acute pancreatitis (HR: 0.057) and albumin levels (HR: 0.428) were inversely related to in-hospital mortality in the study population.

DISCUSSION

Sepsis constitutes a leading cause of mortality in critical care units globally and consumes substantial healthcare resources. According to the current study results, older age, higher APACHE and SOFA scores, as well as elevated CRP and triglyceride levels, were identified as risk factors for mortality in sepsis patients, consistent with previous findings.[1,4,5,7,9] Notably, the HDL-C levels of survivors were lower compared to those of non-survivors in this study, contrary to some previous research indicating lower HDL-C levels as a risk factor for sepsis-related mortality.[9-11,13] Conversely, one study proposed that low serum HDL levels may serve as a poor prognostic indicator for severe sepsis, suggesting an association between day 1/2 HDL-C levels and survival.[14] Another study reported that lipoprotein concentrations lack discriminatory ability between survivors and non-survivors,[15] and a separate

Table 5. Correlation analysis between study parameters and lipid levels

	Total cholesterol		LDL-C		HDL-C		Triglyceride	
	rho	p	rho	p	rho	p	rho	p
Age	-0.019	0.671	0.023	0.623	0.082	0.073	-0.153	0.001
Clinical scores								
APACHE-II	-0.029	0.533	-0.080	0.091	-0.088	0.064	0.166	<0.001
SOFA	-0.071	0.121	-0.116	0.011	-0.124	0.007	0.155	0.001
Laboratory parameters								
WBC, 103/µL	-0.067	0.196	-0.050	0.333	-0.056	0.281	-0.037	0.471
Hb, g/dl	0.268	<0.001	0.272	<0.001	0.219	<0.001	0.000	0.993
PLT, 103/µL	0.065	0.211	0.103	0.047	0.106	0.040	-0.095	0.064
Glucose, mg/dl	0.138	0.003	0.121	0.008	0.043	0.353	0.140	0.002
CRE, mg/dl	-0.089	0.053	-0.142	0.002	-0.149	0.001	0.121	0.008
ALT, IU/L	0.025	0.590	0.048	0.297	-0.053	0.248	0.064	0.164
Total cholesterol, mg/dl	1.000		0.897	<0.001	0.671	<0.001	0.289	<0.001
LDL-C, mg/dl	0.897	<0.001	1.000		0.643	<0.001	-0.005	0.910
HDL-C, mg/dl	0.671	<0.001	0.643	<0.001	1.000		-0.210	<0.001
Triglyceride, mg/dl	0.289	<0.001	-0.005	0.910	-0.210	<0.001	1.000	
Albumin, g/dl	0.284	<0.001	0.293	<0.001	0.348	<0.001	-0.112	0.014
CRP, mg/L	-0.148	0.001	-0.212	<0.001	-0.224	<0.001	0.163	<0.001
TSH, mU/L	-0.053	0.249	-0.020	0.663	-0.072	0.114	-0.019	0.685
HbA1c, %	0.175	0.030	0.180	0.025	-0.050	0.535	0.177	0.028
Length of stay								
Hospital	0.072	0.114	0.054	0.242	0.046	0.314	0.045	0.326
Intensive care unit	-0.019	0.684	-0.020	0.663	-0.002	0.964	-0.038	0.405

APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, WBC: White-blood-cell count, Hb: Hemoglobin, PLT: Platelet count, CRE: Creatinine, ALT: Alanine transaminase, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, CRP: C-reactive protein, TSH: Thyroid-stimulating hormone

Table 6. Multivariable binary logistic regression analyses results that show the independently related factors for hospital mortality

Parameters	HR	95% CI	p-value
Age, years	1.030	1.006-1.054	0.015
Acute pancreatitis	0.057	0.005-0.687	0.024
SOFA score	1.891	1.645-2.173	<0.001
HDL-C level	1.054	1.026-1.083	<0.001
Triglyceride level	1.007	1.003-1.011	<0.001
Albumin level	0.428	0.237-0.774	0.005

HR: Hazard ratio, CI: Confidence interval, SOFA: Sequential Organ Failure Assessment, HDL-C: High-density lipoprotein cholesterol

The significantly related parameters (p<0.05) with hospital mortality in univariable analyses were included in multivariable analyses (age, acute pancreatitis, malignancy, APACHE-II, SOFA scores, platelet, HDL-C, triglyceride, albumin, C-reactive protein, and length of ICU stay). HbA1c level was not added to the regression model due to significantly correlation between triglyceride levels and high missing data (HbA1c level was measured in 154 patients). Binary logistic regression analysis was done using backward method. The last step (step-6) was shown in the table. The Omnibus test p-value was <0.001, Nagelkerke R square was 0.670, and the Hosmer and Lemeshow test p-value was 0.118 for this step.

study found no significant relationship between HDL-C and hospital mortality.[16] In another study conducted by Aydemir et al.,[17] low HDL and LDL levels may be useful in predicting mortality. The etiology of the reported low HDL-C levels on the first day of severe sepsis remains unclear, with possible influences from baseline HDL-C levels preceding sepsis, heightened endotoxin production during severe infection, or suppression of production by pro-inflammatory cytokines.[14] Due to lack of data in this subject, further studies are needed and warranted to clarify causality between mentioned parameters. Additionally, variations in comorbidities, age, CRP, and APACHE II values within the patient population may have affected the current HDL-C profiles.[9] A previous retrospective cohort study in sepsis patients suggests that intra-sepsis HDL-C levels are more critical than baseline values and may be related to the different types of HDL present during inflammation.[16] Additionally, a prospective cohort study analyzing dysfunctional HDL in sepsis patients demonstrated a significant association between dysfunctional HDL levels and in-hospital mortality, as well as between early cholesterol levels and the severity of organ failure and sepsis-related death.[18] Therefore, the functionality of HDL particles is as crucial as their quantity or size.[13] These findings may also explain the current study's observation of higher HDL-C levels in non-survivors. Future studies are needed to explore other potential mechanisms.

Previous studies have extensively investigated changes in serum cholesterol levels in sepsis patients, primarily examining associations with illness severity and mortality.[10,11,13,16,18,19] In the present study, we conducted a comprehensive analysis to elucidate correlations between serum cholesterol levels (HDL-C, LDL-C, Triglycerides) and various clinical parameters, including blood counts and medical scores in sepsis patients, potentially contributing to future research endeavors. In a prior study, researchers analyzed correlations

at different time points and compared them between survivors and non-survivors,[9] revealing dynamic relationships influenced by patient population and time points. Another study reported correlations between APACHE III scores and CRP levels on days 4-7 in sepsis patients.[20] Additionally, several studies investigating cytokine levels and clinical parameters such as albumin, CRP, and APACHE scores,[5,21] as well as cholesterol and cytokine concentrations,[6] and cholesterol and monocyte/platelet activation,[8] have contributed to the understanding of sepsis pathophysiology.

In the current study, no correlation was found between lipid parameters and the duration of hospital or ICU stay. To our knowledge, no other studies have investigated the correlation between lipid profiles and the length of hospital or ICU stay in sepsis patients. In addition, we found that low HbA1c level might be related to in-hospital mortality in the study population. This finding supports the knowledge that intensive glycemic control (targeting HbA1c level <6%) especially in older and critically ill patients might be dangerous.[22]

Limitations

The biological mechanisms underlying lipid levels in sepsis remain incompletely understood, leading to limited and conflicting data regarding sepsis's impact on cholesterol synthesis.[23] Further research is warranted to expand our comprehension of these mechanisms and the role of cholesterol in sepsis.

This study has several limitations. Firstly, its retrospective nature precludes additional tests and interventions. Additionally, the lack of serum cholesterol levels at different time points during hospitalization due to the retrospective setup limits our insights. Although the population size is considerable, data were collected from a single institution, limiting the generalizability of the findings. Moreover, the heterogeneous patient group regarding infection types, comorbidities, and ages directly influences mortality rates and laboratory parameters.

CONCLUSION

This study sheds light on the significant role of serum cholesterol levels, particularly HDL-C, LDL-C, and triglycerides, in the clinical outcomes of sepsis patients. The observed associations between cholesterol levels and mortality rates underscore the prognostic relevance of lipid metabolism in sepsis. The current findings highlight the potential utility of lipid biomarkers in risk assessment and prognostication in critically ill patients, emphasizing the need for further prospective research to elucidate underlying mechanisms and optimize therapeutic strategies for sepsis management in intensive care settings.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of KTO-Karatay University Medical Faculty Ethics Committee for Non-drug and Non-medical Device Trials (Date: 07.03.2024, Decision No: 2024/042).

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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Evaluation of the views of family physicians on radiological anatomy course

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ABSTRACT

Aims: The feedback obtained from surveys administered to healthcare professionals working as physicians, in addition to students, is highly valuable for improving anatomy education. In our study, we aimed to contribute to the enhancement of anatomy education in medical faculties by obtaining the opinions of family physicians regarding the radiological anatomy course.

Methods: In our study, the opinions of family physicians regarding the radiological anatomy course were obtained through a survey prepared by the researchers, consisting of 12 questions, and conducted on a voluntary basis. A total of 387 family physicians participated, with 50.4% (n=195) being female and 49.6% (n=192) male, who responded to the survey form sent to Kocaeli and İstanbul family physician associations via email accounts.

Results: Only 19.4% (n=75) of the family physicians who participated in our study had taken a radiological anatomy course during their undergraduate education, and they stated that besides its contribution to theoretical and practical courses before graduation, it was also beneficial in their postgraduate medical careers. Of those who had taken the radiological anatomy course during their undergraduate education, 94.7% (n=71) believed that this course should be included in medical school curricula, compared to 91.9% (n=284) of those who had not taken this course during their undergraduate education.

Conclusion: We believe that to improve and enhance anatomy education, and thus contribute to the development of more qualified physicians and their professional careers, the radiological anatomy course should be added to the curriculum of medical faculties.

Keywords: Family physicians, medical faculty, anatomy

INTRODUCTION

In Turkiye, medical education generally follows a six-year structure, consisting of three years of basic sciences, followed by two years of clinical sciences, and then, one year of internship training.[1] Anatomy education, which is a fundamental component of basic medical sciences, serves as a cornerstone in medical school education.[2] Anatomy is the oldest medical discipline that studies the normal shape, structure, organs and relationships between these organs of the human body.[3] In medical faculties, anatomy education is provided through theoretical and practical courses. The theoretical courses usually involve slides, while the practical courses involve the utilization of various models and cadavers. Making changes in anatomy education can enhance both the teaching and learning processes, leading to greater success for students. It has been demonstrated that the radiological anatomy course enhances students' understanding of anatomy from a theoretical aspect.[4] Due to the lack of cadavers in medical faculties in our country, the time for dissection is limited.[5] The addition of radiological anatomy courses not only contributes to the theoretical aspect but has also been found to enhance the efficiency of dissection time in practical classes.[6]

A family physician is a specialist in family medicine who provides primary care, preventive health services for families and individuals, and provides first-line diagnosis, treatment, and rehabilitation services. They may also provide mobile healthcare services when necessary.[7] It is extremely important for physicians to receive a high-quality education in basic medical sciences to enhance their clinical practices throughout their professional careers.[8] Physicians should have a good knowledge of anatomy to conduct a proper physical examination and to make an accurate diagnosis of the patient.[9] In conclusion, to produce competent physicians, medical faculties should provide a solid education in anatomy. As in many other fields, feedback obtained from surveys given to graduates and practicing physicians is valuable in assessing the achievement of targeted outcomes in anatomy education. The aim of this study is to contribute to the improvement and development of anatomy education by evaluating family physicians' opinions about the radiological anatomy course through a survey.

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METHODS

The study was carried out with the permission of the Kocaeli University Non-interventional Researches Ethics Committee (Date: 02.11.2023, Decision No: 2023/18.25). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The opinions of family physicians regarding the radiological anatomy course were collected using a Google Forms survey, consisting of 12 questions. The questions in the survey regarding the radiological anatomy course were prepared based on the survey questions from the study conducted by Rathan et al.,[16] which had a Cronbach's alpha value of 0.92, as well as the study conducted by Gülekon.[30] A power analysis conducted using the PASS 11 program for a 95% confidence interval and a 5% margin of error yielded a sample size of 385. The survey form was sent to the Kocaeli and İstanbul family physician associations via email accounts, and ultimately, 387 family physicians participated in the study. The surveys were conducted entirely on a voluntary basis, and at the beginning of the survey, a brief explanation about the study was provided. To ensure the confidentiality of the responses, personal information such as the names, surnames, and phone numbers of the family physicians was not collected. In the first three questions of the survey, family physicians were asked to specify their gender, age, and the medical faculties from which they graduated. For the remaining nine questions, they were expected to respond with "yes," "no," or "I don't know."

RESULTS

Out of the 387 family physicians who participated in our study, 50.4% (n=195) were female, and 49.6% (n=192) were male. In terms of age distribution, 57.4% (n=222) were in the 24-34 age range, 37.2% (n=144) were in the 35-45 age range, and 5.4% (n=21) were in the 46-56 age range.

11.4% (n=44) of the family physicians were graduates of Marmara University, 8.8% (n=34) were graduates of Uludağ University, and 5.4% (n=21) were graduates of Kocaeli University's medical faculty. The remaining 74.4% were graduates of medical faculties from other universities (Figure 1).

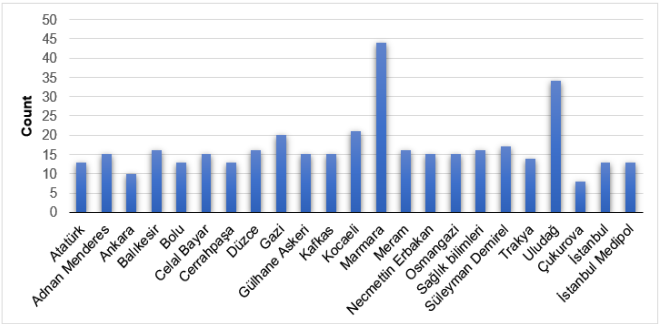

Figure 1. Medical faculties from which family physicians graduated

79.8% (n=309) of the family physicians answered "no," 19.4% (n=75) answered "yes," and 0.8% (n=3) answered "I don't know" to the question 4: "Have you taken the radiological anatomy course?". The responses of the 75 individuals who took the radiological anatomy course to question 5: "Did this course increase your interest in learning anatomy?" question 6: "Did this course make learning anatomy easier and more understandable?" question 7: "Have you seen any contribution of this course in your professional life?" and question 8: "Did this course increase the efficiency of your cadaver dissection time?" are shown in Figure 2.

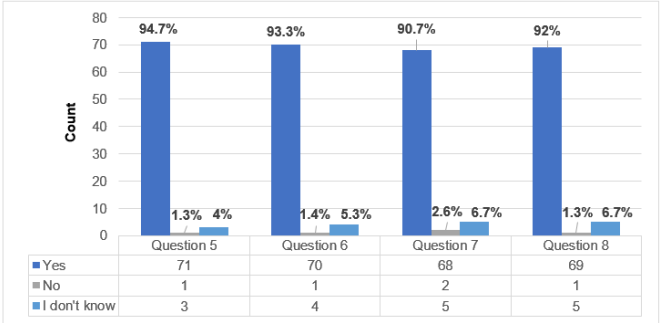

Figure 2. Opinions of family physicians who took the radiological anatomy course

The responses of family physicians who took the radiological anatomy course to question 9: "Do you think the radiological anatomy course should be included in the medical school curriculum?" question 10: "Would you prefer to have a radiological anatomy course in your medical school curriculum in the preclinical period?" question 11: "Would you prefer to have a radiological anatomy course in your medical school curriculum in the clinical period?" and question 12: "Would you prefer to have a radiological anatomy course in your medical school curriculum in both preclinical and clinical periods?" are shown in Figure 3. The answers given to the 9th, 10th, 11th, and 12th questions by family physicians who did not take the radiological anatomy course are shown in Figure 4.

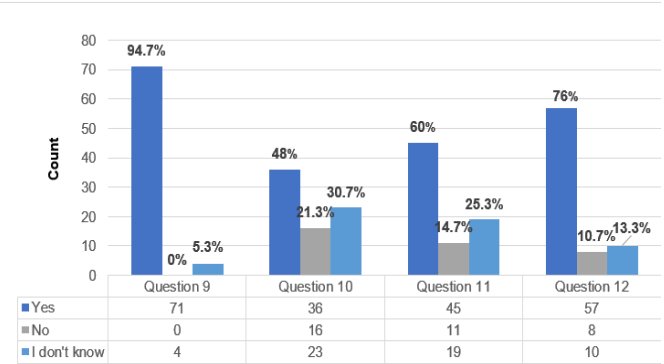

Figure 3. Responses of family physicians who took the radiological anatomy course regarding the medical school curriculum

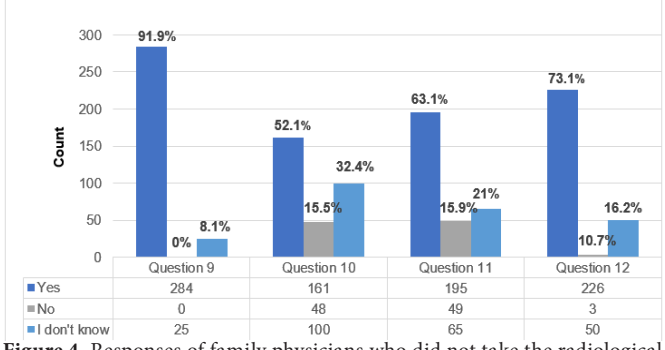

Figure 4. Responses of family physicians who did not take the radiological anatomy course regarding the medical school curriculum

DISCUSSION

The most effective and highest quality method for anatomy education is still a topic of debate.[10] Consulting both students and faculty members, as well as clinicians, for their opinions is a method commonly used to improve anatomy education in medical faculties. As a result of the survey conducted by Yilmaz et al.[11] on 212 research assistants working at the faculty of medicine, it was stated that there was a need for improvement in anatomy education. The first study assessing the need for basic anatomy in clinical practice was conducted by Hankin et al.[12] on 50 participants consisting of family medicine and internal medicine residents, revealing the importance of basic anatomy knowledge in clinical practice. In conclusion, the opinions of family physicians working in primary care, who provide health services to patients of all age groups with discomfort throughout the body, are also important for the improvement of anatomy education.[13]

Recognizing and interpreting a radiological image is highly important in medical education. However, radiological anatomy is a grey area that is not comprehensively taught in either anatomy or radiology disciplines.[14] The use of radiological and cross-sectional images in pre-graduate anatomy education provides in vivo visualization of anatomical structures and provides insight into pathological processes.[15] The use of radiological images in anatomy courses has been observed to not increase the difficulty of the subject; on the contrary, simultaneous teaching of radiological anatomy alongside dissection courses has been found to enhance the retention of knowledge.[16,17] It also allows students to interpret theoretical anatomical knowledge in two-dimensional sectional images and relate it to clinical information.[18] Furthermore, it has been shown that there is an increasing benefit of radiological images in the diagnosis and management of patients in clinical settings during postgraduate medical practice.[19] Consistent with the literature, in our study, 93.3% of family physicians who took the radiological anatomy course during their undergraduate education stated that it increased their interest in learning anatomy, and 90.7% stated that it made learning anatomy easier and more understandable.[20] In a study by Hammoudi et al.,[21] students indicated that the radiological anatomy course they took would definitely be beneficial in their future careers, and similarly, in our study, 92% of family physicians who took the radiological anatomy course during their undergraduate education stated that they saw its contribution in their professional careers.

Anatomy education is an essential yet costly component of medical school curricula, and many countries around the world have limited financial resources in this regard. Over the past 15 years, a total of 432 articles related to anatomy education have been examined in the literature, particularly focusing on researching the most effective anatomy education methods for countries with limited financial resources. Economic and technical aspects of radiological imaging and courses have been found to demonstrate the highest operational feasibility compared to the less feasible dissection method.[22] In our country, due to the ongoing shortage of cadavers in anatomy education, dissection cannot be performed in some medical faculties, and in many faculties, the time allocated for dissection is limited.[23] In the study conducted by Sadegi et al.[24] on students in the 4th semester of medical education, it was observed that the group who took a radiological anatomy course in addition to practical anatomy knowledge was more satisfied with the course and their practical anatomy knowledge was more permanent. Pascual et al.[25] emphasized the integration of atlases used in practical dissection courses with radiology in their study. During the period when dissection was not possible due to the COVID-19 pandemic, Anatomy Departments of two universities in Brazil prepared a digital radiology atlas e-book, which was widely accepted. Even after face-to-face classes resumed, it was observed that students continued to use the e-book and their exam scores increased.[26] Our study is like the literature in terms of the contribution of radiological anatomy courses to practical lessons. 92% of family physicians who took the radiological anatomy course during their undergraduate education reported that this course increased the effectiveness of dissection time.

Radiological images can be incorporated into anatomy education through various approaches such as self-directed learning, viewing in the dissection room, e-learning, or blended learning. The discussion has shifted from whether the radiological anatomy course should be included in the curriculum to when and how it should be taught in the curriculum.[27,28] In a study conducted on 150 clinicians working at the Fırat University Medical Faculty Hospital, approximately 90% of them stated that anatomy education in medicine is fundamental and important. Furthermore, it is suggested that for the permanence of anatomical knowledge, anatomy education should not be limited to the pre-clinical period but should also continue during the clinical period.[29] In a study conducted on students at Gazi University Faculty of Medicine, the percentage of those who wanted to take the radiological anatomy course increased from around 65% in the second year to around 95% in the sixth year. Approximately 60% of the students expressed their preference to take this course both in high school and in medical school, spanning both pre-clinical and clinical years.[30] Our results, in parallel with previous studies, show that a large majority, such as 76% of family physicians who took the radiological anatomy course and 73.1% of those who did not, expressed their desire to take this course both in pre-clinical and clinical years before graduation.

CONCLUSION

The fact that only 19.4% of the family physicians in our study had taken the radiological anatomy course during their undergraduate education indicates that this course is included in the curriculum of only a few medical faculties. However, most family physicians who took the radiological anatomy course during their undergraduate studies stated that this course contributed to both pre-graduation and post-graduation periods, with 94.7% of those who took the course and 91.9% of those who did not take the course expressing that this course should be included in the medical school curriculum. In conclusion, upon examining the responses from family physicians, we believe that including the

radiological anatomy course in the medical school curriculum and providing it in the most comprehensive manner possible would be beneficial. When we look at the literature, we come across studies conducted on students questioning whether adding radiological anatomy to the medical school curriculum for improving anatomy education leads to benefits only in the pre-graduation period. We believe that our study, conducted on family physicians, contributes to the existing literature by questioning the impact of radiological anatomy course both in the pre-graduation period and in the post-graduation medical career.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kocaeli University Non-interventional Researches Ethics Committee (Date: 02.11.2023, Decision No: 2023/18.25).

Informed Consent

All family physicians signed a 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 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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Exploring the causes of kinesiophobia in patients with breast cancer-related lymphedema: a comprehensive study

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ABSTRACT

Aims: Breast cancer is the most common cancer in women worldwide. Breast cancer survivors often experience arm and shoulder pain, limited shoulder range of motion, and lymphedema as the most common post-treatment morbidities. All these morbidities can be considered as the main causes of the fear of movement, called kinesiophobia. This is the first study aims to evaluate the biological and psychological causes of kinesiophobia in breast cancer-related lymphedema (BCRL), the relationship between kinesiophobia and BCRL, and the impact of kinesiophobia on patients' upper extremity function and quality of life. The biological and psychological causes of kinesiophobia in women with breast cancer-related lymphoedema were investigated for the first time in the literature.

Methods: Patients with BCRL were included in the study. Demographic and clinical information including age, educational status, body-mass index (BMI), and dominant upper extremity were recorded. BCRL stage (International Society of Lymphology (ISL) Scale), Quality of Life Scale [European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLO-C30)], upper extremity functional status [Quick-Disabilities of the Arm, Shoulder and Hand Score (Quick-DASH)], Tampa Kinesiophobia Scale (TKS), Kinesiophobia Causes Scale (KCS) were assessed.

Results: The mean age of the 114 patients included in the study was 58.25±9.41 years. A total of 100 patients exhibited a TKS score above 37, indicative of kinesiophobia. There was a statistically significant positive correlation between age and BMI and total TKS score ($p<0.05$). The TKS score (46.18±6.61) was significantly higher in 66 patients with a dominant limb affected by BCRL ($p<0.05$). No significant correlation was found between the lymphedema stage (ISL) and quick-DASH ($p>0.05$). However, the relationship between the Quick-DASH score and the TKS score was significant ($p<0.05$). A strong significant positive correlation was observed between the TKS score and the KCS score ($p=0.0001$).

Conclusion: In our study, the severity of kinesiophobia was higher in patients with more limited upper limb function. Psychological (self-acceptance, self-assessment of motor predispositions, body care) and biological causes (morphological, individual need for stimulation, energetic substrates, power of biological drivers) increased the severity of kinesiophobia. Biological causes were found to cause more kinesiophobia and affect upper limb function in MKBL. In particular, impairment in the strength of biological impulses was found to be one of the main causes of kinesiophobia. Understanding the causes of kinesiophobia in MDL may improve rehabilitation programs and lead to the development of new strategies to help patients support treatment to reduce fear of movement.

Keywords: Breast cancer, Kinesiophobia Causes Scale, Tampa Kinesiophobia Scale, lymphedema, EORTC QLO-C30

INTRODUCTION

Breast cancer is the most common cancer in women worldwide.[1] Breast cancer survivors often experience arm and shoulder pain (30-40%), shoulder range of motion limitation (15-30%), and lymphedema (10-40%) as the most common post-treatment morbidities.[2] Lymphedema is the accumulation of protein-rich interstitial cells in tissue as a result of impaired lymphatic function.[3] Breast cancer-related lymphoedema (BCRL) affects approximately one in five women with breast cancer.[4]

Kinesiophobia is defined as the fear and anxiety that develop about activity and physical movement, arising from a sense of sensitivity to injury.[5] Cancer patients are reluctant to exercise due to physical and mental illness.[6] The addition of kinesiophobia may have a negative impact on oncology rehabilitation.[7] A study demonstrates that following the recognition of survivors, the decline in activity level is as minimal as 3%.[8] There has been a high incidence of kinesiophobia in women after mastectomy, and a similar incidence of impairment of upper extremity function has been observed in these patients.[9]

Breast cancer survivors may develop shoulder pain, reduced shoulder range of motion, and avoid physical activity due

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to the risk of BCRL and kinesiophobia.[10] The fair avoidance model posits that the experience of pain directly causes avoidance behaviour, which in turn increases the risk of decreased activity, functional decline, and anxiety.[11] This situation, which is particularly evident in BCRL patients over the long term, represents a significant underlying factor in the development of kinesiophobia. Kinesiophobia, which has both biological and psychological origins, is a factor contributing to the development of shoulder pain and limited range of motion in breast cancer survivors,[12,13] yet its impact on BCRL has been minimally explored in the literature.[14]

The objective of this study is to examine the biological and psychological causes of kinesiophobia in BCRL using the Causes of Kinesiophobia Scale (KSC), which is a validated tool in our country. Furthermore, the relationship between kinesiophobia and BCRL is measured in conjunction with global health status (EORTC-QLQ-C30) in patients, to investigate its impact on quality of life.

METHODS

Study Design

The present study is a prospective investigation that included BCRL patients aged 18-75 years at the Oncological Rehabilitation Clinic of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between July 2022 and January 2023. The study was approved by the Ankara Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Ethics Committee (Date: 27.07.2022, Decision No: 2022-07/1960). Informed consent forms were obtained from the patients. The study was conducted by generally accepted ethical principles for the conduct of research stemming from the 1975 Declaration of Helsinki.

Participant Characteristics

Inclusion criteria; patients diagnosed with breast cancer and presenting with breast cancer-related lymphoedema (tissue changes such as swelling, oedema, stiffness in the unilateral upper extremity) who have undergone treatment for breast cancer (total/subtotal mastectomy and/or chemotherapy and/or radiotherapy) at least three months ago.

Exclusion criteria for the study were multiple metastases, a history of orthopedic, neurological, or infectious disease affecting the function of the upper limb, acute pain anywhere in the body, paralysis, or loss of sensation in the limb with lymphedema.

Demographic and clinical information such as age, educational status, body-mass index (BMI), and the upper extremity affected by the dominant limb were recorded.

Measures (Patient Assessment Methods)

Lymphedema stage: The International Society of Lymphology Scale is used to stage lymphedema and Each patient is graded according to the following stages:[15]

- **Stage 1:** reversible edema is present,
- **Stage 2:** irreversible edema exists without tissue changes,
- **Stage 3:** Irreversible tissue changes, such as hyperkeratosis and papillomatosis.

Global Health Status (EORTC-QLQ-C30): The EORTC QLO-C30 (European Organisation for Research and Treatment of Cancer (EORTC) quality of life C-30), a cancer-specific quality of life scale, was applied to the patients. The scale is evaluated in 3 subgroups: a) functional scale, b) symptom scale, and c) general health status (global quality of life). In the QOL questionnaire; in the first 28 questions, including the functional scale and symptom scale, it is stated that the quality of life deteriorates as the number of scores increases. In the 29th and 30th questions, which express general health status, it is stated that the quality of life increases as the number of scores increases.[16] The effects of kinesiophobia and upper extremity function on general health were assessed.

Upper extremity functional status: The quick-disabilities of the arm, shoulder, and hand score (Quick-DASH), a disability questionnaire developed for the arm, shoulder, and hand, was used to assess patients' upper extremity function. The questionnaire is a five-point Likert-Type Scale with a total score of 100, with higher scores indicating a lower level of function, and consists of a total of 11 questions. It has been adapted into Turkish by Düger et al.[17]

Kinesiophobia: The Tampa Kinesiophobia Scale (TKS) is a 17-item tool used to measure fear of movement and re-injury. It includes parameters related to injury and fear avoidance in work-related activities. A Turkish validity and reliability study was conducted in 2016 by.[14] Patients with TKS scores above 37 are considered highly kinesiophobic.[7,18] The validity and reliability of the scale have been shown to measure the level of kinesiophobia in cancer patients.[19]

Causes of kinesiophobia: The Kinesiophobia Causes Scale (KCS) assesses an individual's fear of movement and consists of two domains: the biological domain (BD) and the psychological domain (PD). The total score of the KCS is the mean of the BD and PD. A high score on the questionnaire indicates a greater fear of movement. A validity and reliability study was conducted in Turkiye in 2020.[12]

The BD includes morphology, individual need for stimulation, energetic substrates, and power of biological drivers.

The PD includes self-acceptance, self-assessment of motor predispositions, and body care.

The total score of KCS is the mean value of BD and PD, and a high score on the questionnaire indicates that the individual has a greater fear of movement.[20]

Statistical Analysis

Descriptive statistics were presented using mean±standard deviation for normally distributed variables, median (min-max) for non-normally distributed variables, and the number of cases and percentages for nominal variables. The paired sample t-test was used for normally distributed, dependent numerical data, while the independent samples t-test was used to analyze independent data. The Chi-square test was applied to assess the difference between two categorical variables. Pearson correlation analysis was used to determine correlations. Results were considered statistically significant if $p<0.05$.

RESULTS

The STROBE flow diagram of our study is shown in Figure 1.

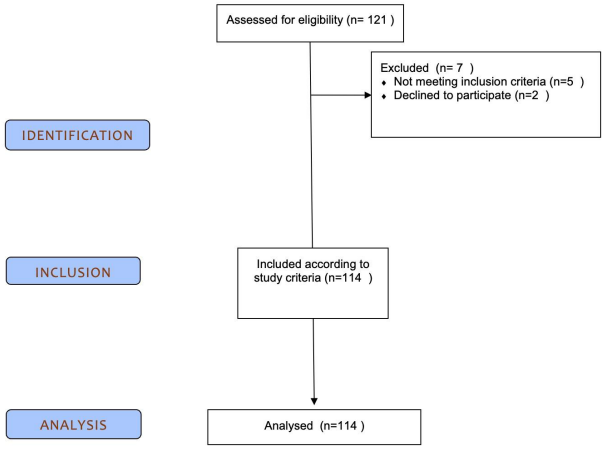

Figure 1. STROBE flow diagram

The mean age of the 114 patients included in the study was 58.25±9.41 years. Of the patients, 87% (100) had kinesiophobia based on having TKS total scores above 37. The sociodemographic and clinical characteristics of the 114 patients included in the study are summarized in Table 1.

Table 1. Sociodemographic and clinical characteristics of patients (n: 114)

Age, mean±SD (min-max) years	58.25±9.41 (37-75)
BMI, mean±SD (kg/m²)	30.25±4.77
Education level, n (%)	
Literate	4 (3.5)
Primary education	70 (61.4)
High school	17 (14.9)
University	23 (20.1)
Breast cancer subgroups, n (%)	
Hormone positive	75 (65.7)
Her-2 positive	26 (22.8)
Triple negative	13 (11.4)
Surgery, n (%)	
Total mastectomy	97 (85.0)
Subtotal mastectomy (breast conserving surgery)	17 (14.9)
The affected arm is dominant, n (%)	66 (57.8)
Stage of lymphedema, n (%) (ISL)	
Stage 1	14 (12.3)
Stage 2	68 (59.6)
Stage 3	32 (28.1)
Tampa Kinesiophobia Scale total score, mean±SD	44.78±7.54
Tampa Kinesiophobia Scale total score 37£ n (%)	100 (87.7)
Quick DASH, mean±SD	52.41±19.74
EORTC-QLQ-C30	
Physical function (EORTC-QLQ-C30), mean±SD	59.72±21.05
Symptom Scale (EORTC-QLQ-C30), mean±SD	34.73±22.05
Global Health Status (EORTC-QLQ-C30), mean±SD	54.33±21.40

SD: Standard deviation, min: Minimum, max: Maximum, BMI: Body-mass index, ISL: lymphedema stage, Quick-DASH: Quick-disabilities of the arm, shoulder, and hand score, EORTC-QLQ-C30: Global health status

The correlation between total TKS and increasing age was statistically significant (p=0.003, r: 0.2753).

There was no significant relationship found between education level and total TKS score (p=0.833) when analyzed.

In the study, 59.6% of patients had mild lymphedema and 28.1% had severe lymphedema. The relationship between lymphedema stages (ISL) and quick-DASH (p>0.05, r=0.01), as well as the total TKS score (p>0.05, r=0.06), was not significant.

The total TKS score of 66 (57.8%) patients whose limb affected by lymphedema was dominant (46.18±6.61) was higher than that of non-dominant patients (42.85±8.36) and was found to be statistically significant (p=0.019). There was a statistically significant relationship between BMI and total TKS score (p=0.018, r=0.28). The relationship between the quick-DASH score and the total TKS score was significant (p= 0.018, r=0.27) (Table 2).

Table 2. Correlation between lymphedema stages and quick-DASH, BMI, total tampa score, physical function score (n: 114)

		Stage of lymphedema	Quick DASH	BMI	Total tampa score	Physical function (EORTC-QLQ-C30)
Stage of lymphedema	r	1.0000	0.0106	0.1392	0.0606	-0.0130
	p		1.0000	0.7295	1.0000	1.0000
Quick DASH	r	0.0106	1.0000	0.1458	0.2790	-0.7223
	p	1.0000		0.7295	0.0185	<.0001
BMI	r	0.1392	0.1458	1.0000	0.2833	-0.1230
	p	0.7295	0.7295		0.0181	0.7697
Total tampa score	r	0.0606	0.2790	0.2833	1.0000	-0.3572
	p	1.0000	0.0185	0.0181		0.0009
Physical function (EORTC-QLQ-C30)	r	-0.0130	-0.7223	-0.1230	-0.3572	1.0000
	p	1.0000	<.0001	0.7697	0.0009	

Pearson correlation, Quick-DASH: Quick-disabilities of the Arm, Shoulder, and Hand score, BMI: Body-mass index, EORTC-QLQ-C30: Global Health Status

The statistical distribution of the total TKS score; biological domain and psychological domain subgroups are shown in Table 3. In the study, the mean of biological reasons was found to be higher than the mean of psychological reasons.

Table 3. Results of the Kinesiophobia Cause Scale (n: 114)

Components of kinesiophobia factors	mean±SD (min-max)
Morphologic	66.05±26.39 (20.0-100.0)
Individual need for stimulation	65.27±22.53 (20.0-100.0)
Energetic substrates	65.00±25.34 (20.0-100.0)
Power of biological drivers	69.08±24.33 (20.0-100.0)
Biological domain	65.61±19.46 (20.0-100.0)
Self-acceptance	65.17±25.83 (20.0-100.0)
Self-assessment of motor predispositions	39.45±24.37 (20.0-100.0)
Body care	65.42±18.24 (20.0-100.0)
Psychological domain	60.73±43.06 (20.0-95.6)
KCS total score	60.11±16.91 (26.45-93.6)

SD: Standard deviation, min: Minimum, max: Maximum, KCS: Kinesiophobia Causes Scale

When the correlation between quick-DASH and general health status and KCS total score, biological domain, and psychological domain was evaluated; a statistically significant positive correlation was observed between the quick-DASH and the KCS total score (p<.0001, r=0.47). Likewise, a statistically significant positive correlation was observed with the biological domain (p<.0001, r=0.51). The same statistical significance was not observed between quick-DASH and the psychological domain (p=0.35, r=0.08). A statistically significant negative correlation was observed between general health status and KCS total score (p=0.02, r=-0.25). The same statistical significance was not observed between general health status and biological domain (p=0.05, r=-0.21) and psychological domain (p=0.29, r=-0.13). However, the correlation between general health status and the biological domain was close to statistical significance. The association of KCS total score with quick-DASH and general health status is shown in Table 4.

Table 4. Correlation between quick dash, global health status, KCS total score, biological domain, psychological domain (n: 114)

		Quick-DASH	EORTC-QLQ-C30
KCS total score	r	0.4755	-0.2599
	p	<.0001	0.0261
Biological domain	r	0.5169	-0.2198
	p	<.0001	0.0564
Psychological domain	r	0.0879	-0.1366
	p	0.3521	0.2945

Pearson correlation, KCS: Kinesiophobia Causes Scale, Quick-DASH: Quick-Disabilities of the Arm, Shoulder, and Hand score, EORTC-QLQ-C30: Global Health Status

The study analyzed the correlations between the TKS total score and the KCS total score, in addition to the biological and psychological domains, using data from 114 patients. The results showed a positive and statistically significant correlation between the TKS total score and the KCS total score, as well as the biological domain (p=0.0001, r=038) (Table 5).

Table 5. Correlation between TKS total score and KCS total score, biological domain, psychological domain (n: 114)

		KCS total score	Biological domain	Psychological domain
TKS total score	r	0.3814	0.3656	0.1359
	p	0.0001	0.0003	0.1494

TKS: Tampa Kinesiophobia Scale, KCS: Kinesiophobia Causes Scale

DISCUSSION

Our study included 114 patients diagnosed with BCRL; 87.7% (n=100) were kinesiophobic (TKS total score 37£). In another study with a much smaller number of patients, the rate of kinesiophobia was found to be 30.8%.[14] It is important to remember that many social, psychological, and economic factors can be associated with the development of kinesiophobia.

In a study of fear of movement after breast cancer treatment, an increase in levels of kinesiophobia was found with age.[21] In line with the literature, it was observed in our study that the severity of kinesiophobia increased with increasing age.

In our study, no significant relationship was found between educational level and severity of kinesiophobia, supporting the findings of Gencay et al.[14] Karadibak et al.[22] found increased fear of exercise in lymphedema patients with higher levels of education in a study with a much smaller number of patients.

There is evidence that high BMI and severe physical inactivity may be associated with an increased risk of breast cancer.[23] Overweight women are known to report significantly more fear of exercise than women of normal weight.[7,21] Supporting the literature, our study found that women with breast cancer and a high BMI had high levels of kinesiophobia.

A comprehensive study that followed women for 11 years after mastectomy showed that 24% had developed BCRL.[24] Only a few studies have shown that BCRL affects the adduction, internal rotation, and flexion of the shoulder and is an important cause of disability in the upper extremities.[25-27] In a study by Dawes et al.,[28] it was found that the patient population, consisting of participants with only mild BCRL, had significantly higher Quick-DASH scores and limitations in upper extremity function. Supporting the findings of Smooth et al.,[26] our study found that the stage of BCRL did not affect upper limb function limitations. There are two reasons for this. Firstly, our study included patients with varying degrees of severity, from mild to severe. Secondly, patients may choose to avoid using the affected upper limb as part of their lymphedema treatment, regardless of the available limb volume.

Kinesiophobia is reported to increase BCRL risk in breast cancer patients, and women with BCRL have higher rates of kinesiophobia.[14] Based on the limited literature available, our study found that patients with BCRL affecting their dominant limb exhibited higher levels of kinesiophobia.

There was no correlation between the severity of kinesiophobia and the stage of lymphoedema in our study. This suggests that patients may experience fear of movement regardless of the stage of lymphedema, even in the early stages. While Gencay et al.[14] supported our study, Karadibak et al.[22] found a positive correlation between the stage of lymphedema and the severity of kinesiophobia in a smaller study. It is important to note that this correlation was observed in a smaller number of patients.

There are few studies in the literature on the relationship between kinesiophobia and upper extremity function.[29] In our study, the severity of kinesiophobia was higher in patients with more limited upper extremity function, supporting a small number of studies in the literature.

The significant correlation between the TKS, which is the gold standard for assessing kinesiophobia in breast cancer patients, and the KCS total score was evaluated in our study for the first time in the literature. Psychological and biological causes of kinesiophobia have been found to significantly increase the severity of kinesiophobia.

In breast cancer-related lymphoedema, biological causes (Morphologic, individual need for stimulation, energetic substrates, power of biological drivers) seem to cause more

kinesiophobia and affect upper extremity function. In particular, impairment of the power of biological drives is seen as one of the main causes of kinesiophobia.

While psychological causes of kinesiophobia were not found to be related to upper extremity function and general health status, it is seen that inadequate body care is the most common cause of kinesiophobia among psychological causes.

In our study, we found that the total score for kinesiophobia (KCS total score) was higher in patients with worse general health. It was observed that psychological and biological causes as a whole affected the general health status of the patients.

Limitations

The strength of the study is that it is the first study to examine the biological and psychological causes of kinesiophobia, its severity, and its effect on upper extremity functional status in a group of BCRL. A further strength of the current study is that it is the first time that the Kinesiophobia Causation Scale has been used in cancer survivors.

It should be noted that the study is not without limitations. Although kinesiophobia is a highly prevalent phenomenon among patients with BCRL, a multitude of economic, social, and psychological factors may interact with one another to influence kinesiophobia.

CONCLUSION

Fear of movement in cancer patients can have a negative impact on disease progression and can lead to reduced quality of life and even disability through increased mobility limitations. With lymphedema affecting one in five women who have had breast cancer, examining the causes of kinesiophobia may improve rehabilitation programs and lead to the development of strategies to help patients support treatment to reduce movement anxiety. Given the increasing number of breast cancer survivors, much more work is needed in the area of kinesiophobia to improve the overall well-being of patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Ethics Committee (Date: 27.07.2022, Decision No: 2022-07/ 1960).

Informed Consent

All patients signed and 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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Correlation of hemogram parameters with acute phase reactants in subacute thyroiditis

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ABSTRACT

Aims: Subacute thyroiditis is a painful, inflammatory thyroid gland disease. It manifests clinically with thyrotoxicosis and an increase in acute-phase reactants. In our study, we aimed to investigate the correlation between hemogram parameters (neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), pan-immune inflammatory value (PIV), and systemic immune-inflammatory index (SII)) and elevated acute phase reactants during the diagnosis of this disease where inflammation is prominent.

Methods: Our study is a retrospective analysis involving 48 subacute thyroiditis (SAT) patients and 48 healthy control subjects. Thyroid function tests (TSH, FT4, and FT3), complete blood count values including white blood cell, neutrophil, monocyte, lymphocyte, and platelet counts, and C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were recorded for the patients. The relationship between hemogram parameters, acute phase reactants, and thyroid function tests at the time of diagnosis and six months after starting treatment was analyzed.

Results: The female count in the patient group was 34 (70.8%), and in the healthy group, it was 29 (60.4%) in our study. There was no statistically significant difference in gender distribution between the groups. NLR, PLR, PII, and SII were significantly higher in SAT patients at the time of diagnosis. We found a positive correlation between CRP levels and SII and PIV and between ESR levels and PLR and PIV at the time of diagnosis.

Conclusion: As a practical biomarker, PIV was significantly higher in patients with SAT compared with the control group. Our study is the first to show that PIV may be a new diagnostic tool for SAT.

Keywords: Subacute thyroiditis, pan-immune inflammatory value, systemic immune-inflammatory index

INTRODUCTION

Subacute thyroiditis is the most common cause of painful thyroid gland diseases that occur after viral infections or post-viral infections. Viral infections experienced two to six weeks earlier are the main factors triggering SAT in genetically predisposed individuals. Viruses such as Coxsackie virus, Echovirus, adenovirus, mumps virus, measles, and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) lead to the development of SAT.[1] Positivity for HLA-B35, HLA-B 18:01, DRB1, and HLA-C 04:01 in SAT patients indicates the genetic aspect of the disease. The cytotoxic T-cells of cellular immunity become active and damage follicular cells. This inflammation can persist for weeks and months.[2] 75-80% of SAT patients are middle-aged women.[3]

Patients present with symptoms resembling upper respiratory tract infections, such as sore throat, fatigue, weakness, myalgia, arthralgia, and a mild to moderate increase in body temperature. Severe pain and tenderness are observed in the thyroid gland. The thyroid gland is sensitive and painful upon palpation.[4] Laboratory analysis of patients shows moderate leukocytosis, while CRP and ESR are significantly elevated. Since all cases present with thyrotoxicosis lab, a phrase such as the vast majority thyroid function tests reveal decreased TSH and elevated FT4 and FT3. In typical cases of subacute thyroiditis (SAT), from a clinical and laboratory perspective, thyroid scintigraphy is unnecessary. However, during the thyrotoxic phase, scintigraphy reveals a decreased radioactive iodine uptake. The ultrasound appearance is typical.[5] In the areas of the gland affected by inflammation, there are localized or generalized hypoechoic, heterogeneous areas, and the parenchyma in these areas has almost no blood supply. Nodular appearance can be observed in the areas of inflammation. Approximately a quarter of cases have transient hypothyroidism, and permanent hypothyroidism develops in 10% of cases.[6,7]

A hemogram is a simple test used in the evaluation of patients without specific symptoms. In the literature, the data obtained from hemogram have started to be used as prognostic factors in the diagnosis of acute and chronic diseases, hematologic

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and solid malignancies, cardiologic and respiratory diseases, and in the evaluation of the response to treatment. The effect of neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) obtained from hemogram parameters on prognosis, survival, and morbidity parameters in many inflammatory diseases and malignancies has been researched and significant correlations have been found in these studies.[8-10] The pan-immune inflammation value (PIV), calculated from a complete blood count, is a marker used to assess the severity of inflammation. It is obtained by calculating the values of neutrophils, platelets, monocytes, and lymphocytes.[11] PIV has become an important marker used to predict survival in esophageal cancers, colorectal cancers, and breast cancers.[12-14] Similarly, the systemic immune-inflammatory index, another parameter obtained from hemogram, has gained importance in the evaluation of diseases, such as hepatocellular cancer, where inflammation plays a role in pathophysiology.[15-17]

In our study, we aimed to examine the relationship between acute phase reactants indicating the inflammatory status at the time of diagnosis and after treatment in SAT patients and hemogram parameters (NLR, PLR, PIV, and SII).

METHODS

This research received approval from the Hitit University Clinical Researches Ethics Committee (Date: 26.12.2023, Decision No: 2023-164). All procedures involving human subjects were conducted in strict compliance with ethical guidelines, as outlined by the institutional and/or national research governing body, the 1964 Declaration of Helsinki, and its subsequent revisions or analogous ethical criteria.

Our study is a retrospective investigation that included 96 patients, consisting of 48 subacute thyroiditis patients and 48 healthy individuals, who applied to the Hitit University Internal Medicine Clinic between 2020 and 2023. The patients were diagnosed with subacute thyroiditis based on anamnesis, physical examination, high ESR and CRP, low TSH, high T4 and T3 levels, and ultrasound findings supporting thyroiditis. Patients between the ages of 18-85 without a history of thyroid disease, and acute or chronic infections were included. The patient group excluded patients with acute or chronic infections, a history of malignancy, medication history affecting hemogram parameters, acquired immunodeficiency, and pregnant individuals. The healthy group was composed of patients without chronic diseases who came to the Internal Medicine polyclinic for routine examination. Hemogram parameters [white blood cell (10^9/L), hemoglobin (g/dl), platelet (10^9/L), neutrophil (10^9/L), lymphocyte (10^9/L), monocyte (10^9/L)], thyroid function tests (TSH, FT4, FT3), CRP (mg/L), and ESR (mm/h) were recorded at the time of diagnosis and six months after the initiation of treatment. Samples for complete blood count (CBC) analysis were collected in EDTA anticoagulant Monovette tubes (Sarstedt, Leicester, United Kingdom). Hemoglobin level, Neutrophil count, Monocyte count, platelet count, lymphocyte count were obtained from CBC analysis. Neutrophil/lymphocyte ratios (NLR), platelet/lymphocyte ratios (PLR), pan-immune inflammatory index (PIV = platelet × neutrophil × monocyte/lymphocyte), and systemic inflammatory index (SII = platelet × neutrophil/lymphocyte) were calculated and recorded. The ESR(1-20 mm/h) was assigned using the Westergren technique, and the CRP (0-5 mg/L) was determined by nephelometry. Thyroid stimulating hormone (TSH) (reference range: 0.27-4.2 uU/ml), free thyroxine (fT4) (reference range: 0.93-1.7 ng/dl), free triiodothyronine (fT3) (reference range: 2-4.4-3.71 pg/ml) were measured with a chemiluminescence immunoassay. Hemogram parameters of patients at the time of diagnosis and after treatment were analyzed by comparing them with acute phase reactants and TFT.

Statistical Analysis

Data were analyzed using the IBM SPSS Statistics Standard Concurrent User V 29 (IBM Corp., Armonk, New York, USA) statistical package program. Summary statistics were provided as unit numbers (n) and percentages (%) for categorical variables. For numerical variables, summary statistics, including mean, standard deviation, and standard error, were calculated based on the distribution of the data. The normal distribution of numerical variables was evaluated using the Shapiro-Wilk normality test. The homogeneity of variances between groups was analyzed using the Levene test. An independent sample t-test was employed for group-wise comparisons of age variables. The Yates chi-square test was used for comparisons of the gender variable among groups. Linear mixed effect models were utilized for comparing the biochemical values of the patient group at the time of diagnosis and at the 6th month, both within the patient group and with the healthy group. A Bonferroni correction was applied to all pairwise comparisons. An independent sample t-test was used to compare the values at the time of diagnosis between patients with normal and high TSH levels in the 6th month in the patient group. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

The patient group and the healthy group were matched in terms of age and gender. Descriptive characteristics of participants are given in Table 1.

Table 1. Descriptive characteristics of participants

	Groups		Test statistics	
	Patient n=48	Healthy n=48	Test value	p value
Gender, n (%)				
Female	34 (70.8)	29 (60.4)	0.739	0.390$^{\Phi}$
Male	14 (29.2)	19 (39.6)		
Age, (years)	46.5±9.3	44.3±10.8	1.087	0.280†
Complaint, n (%)				
None	9 (18.8)			
Pain	27 (56.3)			
Pain+tenderness	6 (12.5)			
Pain+fever	4 (8.3)			
Pain+tenderness+fever	2 (4.2)			

n: Patient number, %: Column percent, age is summarized as mean±standard deviation, $^{\Phi}$: Yates chi-square test, †: Independent samples t-test

In Table 2, the diagnostic and 6-month values of the patient group were compared both within their group and with the healthy group. The NLR, PLR, SII, and PIV values of the patients at diagnosis are statistically higher than those of the healthy group, and their values at 6 months are statistically similar to those of the healthy group. However, the 6-month NLR, PLR, SII, and PIV values of the patients are statistically lower than those at diagnosis.

According to Table 3, there is a statistically significant weak negative correlation between TSH values at diagnosis and PIV values in the patient group. The 6th-month T4 values of patients have a statistically significant weak negative correlation with SII and PIV values. At the time of diagnosis, there is a statistically significant moderate positive correlation between CRP values and SII values; there is also a statistically significant weak positive correlation between CRP values and PIV values. ESR values at the time of diagnosis have a statistically significant weak positive correlation with PLR, SII, and PIV values. The other correlation coefficients in Table 3 are not statistically significant.

According to Table 4, there is a statistically significant weak positive correlation between the decrease in CRP values and the decrease in SII values. Similarly, there is a statistically significant weak positive correlation between the decrease in CRP values and the decrease in PIV values. The other correlation coefficients in Table 4 are not statistically significant.

According to Table 5, there is a statistically significant weak negative correlation between T4 values and PLR values in the healthy group. The other correlation coefficients in Table 5 are not statistically significant.

According to Table 6, the descriptive cut off value of PIV was >238.7 (96.4% sensitivity and 92.9% specificity), and of SII was >530.6 (100% sensitivity and 96.4% specificity) for the acute inflammatory phase of the disease.

DISCUSSION

The present study showed that NLR, PLR, PIV and SII were significantly higher in the SAT group compared to the control

Table 2. Comparisons between groups

	Groups			Test statistics¥	
	Patient-diagnosis moment	Patient-6th month	Healthy	f value	p-value
TSH	0.169±0.106[a]	4.504±0.733[b]	1.773±0.106[c]	32.569	<0.001
T4	2.660±0.290[a]	1.105±0.043[b]	1.228±0.290[c]	14.023	<0.001
T3	5.168±0.212[a]	2.794±0.076[b]	3.083±0.212[c]	55.348	<0.001
CRP‡	62.40±4.61[a]	5.47±0.53[b]	3.46±0.53[c]	280.510	<0.001
SEDIM	59.71±2.27[a]	13.18±0.91[b]	9.38±2.27[c]	181.006	<0.001
WBC (10^3)‡	9.28±3.24[a]	7.84±2.26[b]	6.88±3.24[b]	7.455	0.007
HGB	12.56±0.21[a]	13.40±0.19[b]	14.10±0.21[c]	4.275	0.040
PLT	346.31±11.35[a]	264.47±7.72[b]	269.71±11.35[b]	17.772	<0.001
IG-p*	0.319±0.025[a]	0.238±0.023[b]	0.337±0.025[a]	5.908	0.016
IG-c**	0.032±0.002[a]	0.019±0.002[b]	0.025±0.002[c]	9.337	0.003
NLR	4.096±0.443[a]	2.097±0.206[b]	1.806±0.443[b]	8.368	0.004
PLR	0.231±0.030[a]	0.145±0.022[b]	0.120±0.030[b]	6.756	0.010
SII‡	1406.5±167.4[a]	556.56±63.85[b]	477.69±63.85[b]	30.349	<0.001
PIN (10^3)‡	943.4±100.1[a]	278.9±29.1[b]	259.6±100.1[b]	30.046	<0.001

¥: In linear mixed model analysis, data are given as estimates of mean±standard error. The a, b, and c superscripts indicate differences between groups in each row. There are no statistical differences between groups with the same superscripts. ‡: Groups were compared using logarithm-base-10 transformed data. *IG-p: Percentage of immature granulocytes, **Immature granulocyte count, TSH: Tiroit stimulating hormone, CRP: C-reaktif protein, WGB: White blood count, HGB: Hemoglobin, PLT: Platelet, IG: Immunoglobulins, NLR: Neutrophil lymphocyte ratio, PIN: Personal identification number

Table 3. Correlation of NLR, PLR, IGY-Y, IG-S, SII, and PIV values with TSH, T4, T3, CRP, and sedimentation values at diagnosis and 6th month in the patient group

	TSH		T4		T3		CRP‡		SEDIM	
	Diagnosis	6th month	Diagnosis	6th month	Diagnosis	6th month	Diagnosis	6th month	Diagnosis	6th month
NLR	-0.064	0.049	-0.038	-0.111	0.018	-0.023	0.060	-0.129	0.196	0.001
PLR	-0.052	0.038	-0.056	0.012	-0.015	0.007	0.067	-0.062	0.284*	-0.006
IG-p	-0.115	-0.106	-0.128	0.092	-0.052	0.044	0.273	0.279	0.132	0.182
IG-c	-0.025	0.041	-0.105	-0.008	-0.041	-0.095	0.260	0.222	-0.009	0.173
SII‡	-0.190	0.091	-0.034	-0.336*	0.134	-0.040	0.421*	-0.050	0.342*	0.101
PIV‡	-0.328*	0.098	0.104	-0.322*	0.228	-0.121	0.376**	-0.001	0.314*	0.133

The values in the table are Pearson correlation coefficients, ‡: Correlation coefficients were calculated on logarithm-base 10 transformed data. *: p<0.05, **: p<0.01, NLR: Neutrophil lymphocyte ratio, PIV: Particle image velocimeter, CRP: C-reaktif protein, PLR: Public lending right, IG: Immunoglobulins

Table 4. Correlation of TSH, T4, T3, CRP, and sedim values with NLR, PLR, IGY-Y, IG-S, SII, and PIV values according to the values at the time of diagnosis and the 6th month difference (difference = 6th month diagnosis) in the patient group

	TSH	T4	T3	CRP‡	SEDIM
NLR	-0.025	-0.020	0.114	0.099	0.178
PLR	-0.028	-0.009	0.088	0.043	0.153
IG-p	-0.050	-0.150	-0.057	0.278	0.146
IG-c	0.152	-0.180	-0.112	0.109	0.007
SII‡	0.110	0.016	0.205	0.300*	0.180
PIV‡	0.105	0.051	0.215	0.323*	0.218

The values in the table are Pearson correlation coefficients.‡: Correlation coefficients were calculated on logarithm-base 10 transformed data. *: p<0.05, TSH: Tiroit stimulating hormone, CRP: C-reaktif protein, NLR: Neutrophil lymphocyte ratio, PLR: Public lending right, IG: Immunoglobulins, PIV: Particle image velocimeter

Table 5. Correlation of TSH, T4, T3, CRP, and sedim values with NLR, PLR, IGY-Y, IG-S, SII, and PIV values in the healthy group

	TSH	T4	T3	CRP‡	SEDIM
NLR	-0.012	-0.134	0.222	-0.127	-0.227
PLR	-0.098	-0.390**	0.065	-0.125	-0.081
IG-p	-0.004	0.038	0.087	-0.136	-0.107
IG-c	0.020	0.070	0.035	-0.128	-0.007
SII‡	-0.013	-0.241	0.065	-0.129	-0.112
PIV‡	0.100	-0.170	0.102	-0.072	-0.151

The values in the table are Pearson correlation coefficients, ‡: Correlation coefficients were calculated on logarithm-base 10 transformed data. **: p<0.01, TSH: Tiroit stimulating hormone, CRP: C-reaktif protein, NLR: Neutrophil lymphocyte ratio, PLR: Public lending right, IG: Immunoglobulins, PIV: Particle image velocimeter

Table 6. AUC values for the PIV and SII parameters

	AUC (95.0% for AUC)	p	Cutoff	Sensitivity (95.0% for sens.)	Specificity (95.0% for spec)
PIV	0.987 (0.913-1.000)	<0.001	>238.7	96.4 (81.7-99.9)	92.9 (76.5-99.1)
SII	0.999 (0.934-1.000)	<0.001	>530.6	100.0 (87.7-100.0)	96.4 (81.7-99.9)

AUC: Area under the curve

group. This is the first study to evaluate the diagnostic and prognostic significance of PIV, a new inflammatory marker, in patients with SAT.

Subacute thyroiditis is an inflammatory disease of the thyroid that presents with increased thyroid hormones and acute-phase reactants. Patients typically complain of thyroid tenderness and pain in the thyroid region, resembling symptoms of an upper respiratory tract infection. Some studies also note that a small number of patients present with painless or minimally painful subacute thyroiditis following viral causes.[18] In our study, 56.3% of patients presented to the clinic with pain complaints, while 18.8% had no symptoms. Epidemiological studies on SAT show a higher incidence in women compared to men (19.1 and 4.1 per 100,000/year respectively), with a higher incidence in young adults and middle-aged women.[19] In our study, 70.8% of diagnosed SAT patients were women, with an average age of 46.5±9.3.

During the acute phase of the disease, significantly elevated acute-phase reactants such as ESR and CRP are commonly observed, often in conjunction with subclinical hyperthyroidism. Thyrotoxicosis develops over 2-4 weeks due to the inflammatory damage of thyroid follicles, resulting in the release of large amounts of thyroid hormones.[20] In our study, patients had low TSH and high T4 and T3 levels at the time of diagnosis, indicative of thyrotoxicosis (p<0.001, p<0.001). High CRP and ESR levels were also present, consistent with thyrotoxicosis (p<0.001, p<0.001). Biopsy results from cases where the full diagnosis could not be established showed follicular and thyroid cell destruction during the acute phase and widespread polymorphonuclear leukocyte infiltration, extensive lymphocyte and mononuclear cell infiltration, and giant cell granulomatous inflammation during the subacute phase.[21] In the immune system, neutrophils cause the release of chemokines, cytokines, and growth factors and platelets contribute to the increase of cytokines that emerge in inflammation. During inflammatory events, neutrophil, monocyte, and platelet levels increase while lymphocyte levels decrease.[22] It is clear that various cytokines from platelets and neutrophils cause tissue destruction by activating the innate and acquired immune system caused by the vicious cycle with more and more neutrophil and platelet activation. This plays a role in the pathogenesis of many acute and chronic inflammatory and autoimmune conditions.[23,24] Looking at the pathophysiology of SAT, it is evident that it has a high inflammatory burden. In our study, we considered hematologic parameters (NLR, PLR, SII, and PIV) as potential indicators for diagnosing SAT cases.

A review of the literature reveals studies on hemogram parameters in the diagnosis and follow-up of SAT patients. The study by Calapkulu et al.[25] has shown significantly elevated levels of CRP, ESR, NLR, and PLR at the time of diagnosis. In a study conducted by Cengiz et al.,[26] in the acute phase of the disease, cut-off values were 2.4 (80% sensitivity and 51% specificity) for NLR and 146.84 (83% sensitivity and 54% specificity) for PLR, while correlation analysis revealed a significant correlation between NLR and PLR with acute phase reactants. Bahadır et al.[27] found that the optimum cut-off values for NLR and PLR for SAT were respectively 1.84 (specificity 85.9% and sensitivity 90.1%; p<0.001; AUC=0.934; 95% CI: 0.905-0.964) and 140.2 (specificity 83.5% and sensitivity 77.1%, p<0.001, AUC=0.821, 95% CI: 0.767-0.874) and NLR, PLR, CRP and ESR levels at the time of diagnosis were significantly higher than post-treatment levels (all p<0.001). In the correlation analysis of this study, a positive linear relationship was observed between PLR and CRP at the time of diagnosis (p=0.002, r=0.220), PLR and ESR before treatment (p=0.018, r=0.171), NLR and CRP before treatment (p<0.001, r=0.330) and NLR and ESR before treatment (p=0.001, r=0.242). Besides these studies, in contrast, it has been observed that NLR decreased in diseases accompanied by autoimmune and inflammatory conditions. Turan et al.[28] found that NLR was low at the time of diagnosis in Graves' patients with thyrotoxicosis. This study indeed suggests that NLR might help differentiate Graves' patients from SAT patients in cases of thyrotoxicosis. Our study also found significantly elevated NLR (4.096±0.443) and PLR

(0.231±0.030) values at the time of diagnosis in SAT patients (p<0.004; p<0.010). A statistically weak positive correlation was observed between ESR values at the time of diagnosis and PLR.

Pan-immune inflammatory value (PIV), obtained from complete blood count parameters, has been used more as a prognostic biomarker in cancer diseases.[29] In a meta-analysis by Guven et al.,[30] it was stated that PIV may be a prognostic biomarker in cancer. One study conducted on peritoneal dialysis patients found that pan-immune inflammation at baseline was significantly associated with an increased risk of death from all causes, cardiovascular disease, and infection.[31] No study on pan-immune inflammation value (PIV) in SAT patients was found in the literature. In our study, PIV values at the time of diagnosis were statistically higher than the healthy group (943.4±100.1, p<0.001), while the values at 6 months were statistically similar and lower than the healthy group. We found a statistically significant weak negative correlation between TSH values at the time of diagnosis and PIV values. While a statistically significant weak positive correlation was observed between CRP and PIV values at the initial application of the patients, there was a statistically weak positive correlation between ESR values and PIV values. A statistically significant weak positive correlation was found between the decrease in CRP values six months after the diagnosis and the decrease in PIV values.

Systemic immune-inflammatory index (SII), calculated easily with neutrophil, platelet, and lymphocyte counts, is a biomarker indicating systemic inflammatory activity. A high level of this index indicates the presence of relatively high neutrophil and platelet counts and low lymphocyte counts. This is indicative of a strong inflammatory response. SII has been associated with mortality and prognosis in many types of cancer, including breast, stomach, esophageal, pancreatic, and gastrointestinal stromal tumors.[32-35] In addition, a study by Pakoz et al.[36] showed that SII is a strong activation marker in ulcerative colitis patients. When we examine the literature, there are studies examining the relationship between SAT and SII. In the study conducted by Keskin and et al.,[37] SII was found to be high in SAT patients at the time of diagnosis. In our study, SII values at the time of diagnosis were statistically higher than the healthy group (1406.5±167.4, p<0.001), while the values at 6 months were statistically similar and lower than the healthy group. A statistically important moderate positive correlation was observed between CRP values at the time of diagnosis and SII values, and there was a statistically weak positive correlation between ESR values and SII values. A statistically important weak positive correlation was observed between the decrease in CRP values six months after the diagnosis and the decrease in SII values.

In order to support the diagnosis of subacute thyroiditis, high acute phase reactants accompanied by thyrotoxicosis are needed. As we have seen from the available studies, hemogram parameters are now also guiding in acute infections. In this study, we think that hemogram parameters (NLR, PLR, PIV, and SII) can guide the diagnosis and follow-up of subacute thyroiditis patients.

Limitations

There are several limitations to our study. One of these is that our study is retrospective. The second is that the treatments given at the time of diagnosis could not be clearly reached.

CONCLUSION

We showed that indices such as the NLR, PLR, SII and PIV which can be easily derived from routine blood tests, may be good predictors in the diagnosis of SAT. We also found, for the first time, that PIV (a new inflammatory index) may be a diagnostic tool in patients with SAT. According to our findings in this study, we think that hemogram parameters will guide clinicians in the diagnosis and follow-up of SAT together with acute phase reactants. There is a need for studies to find simple, cheap and easily obtained indexes such as this one to facilitate the diagnosis of diseases such as SAT.

ETHICAL DECLARATIONS

Ethics Committee Approval

This research received approval from the Hitit University Clinical Researches Ethics Committee (Date: 26.12.2023, Decision No: 2023-164).

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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Clinical research for low back pain in Turkiye: analysis of pubmed-indexed randomized controlled trials

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ABSTRACT

Aims: Low back pain (LBP) is a prevalent condition and a major contributor to disability worldwide. Despite bibliometric analyses of LBP literature, no study has specifically explored Turkiye's contribution to this field through randomized controlled trials (RCTs). This study aims to examine the characteristics of Turkiye-based RCTs on LBP, utilizing PubMed, the most frequently used biomedical search engine.

Methods: A comprehensive search was conducted on PubMed using the terms "low back pain [Title]" and "(Turkiye) OR (Turkiye)." Only interventional RCTs were included. Data points such as publication year, open-access status, first author's specialty, study content, journal quartile (Web of Science), and citation count (Google Scholar) were analyzed.

Results: Most publications are authored by Physical Medicine and Rehabilitation (PMR) specialists (26) and physiotherapists (24), with emergency medicine specialists (6) in third place. The number of publications increased over time, peaking in 2021 (10). Most publications appeared in Q1-Q2-Q3 journals (67). The average citation count is 46.9, median is 29, ranging from 0 to 305, with citation counts strongly influenced by publication year ($p<0.001$). The most common research topics are Complementary and Alternative Medicine (CAM) (15), Physical Therapy Agents (14), and Injections (10). PMR specialists have more citations than other groups ($p=0.001$). Open access status did not significantly affect citation counts ($p=0.277$).

Conclusion: Turkiye-based RCTs on low back pain have steadily increased, with PMR specialists and physiotherapists leading the field. Publications are primarily found in high-impact journals. Key research topics include CAM, physical therapy agents, and injections.

Keywords: Low back pain, randomized controlled trial, Turkiye, bibliometric analysis, PubMed

INTRODUCTION

Low back pain (LBP) is one of the most prevalent musculoskeletal disorders, affecting a substantial portion of the global population.[1] Most individuals experience at least one episode of acute low back pain during their lifetime, and although the condition often resolves on its own, it frequently develops into a chronic issue for many.[2] Research indicates that over 60% of individuals with mechanical low back pain continue to suffer from pain or experience recurrences within a year of the initial onset.[3] Furthermore, low back pain is recognized as a leading cause of global productivity loss and is the primary cause of years lived with disability in numerous countries.[4] Prevalence estimates indicate that LBP affects around 11.9% of the population at any given time, with a one-month prevalence of 23.3%, particularly in middle-aged and older women.[5] These figures emphasize the substantial personal and societal burden associated with this condition.

PubMed, a widely used database for biomedical literature, plays a crucial role in disseminating research findings. It provides access to citations and abstracts from over 5000 life science journals, with coverage extending back to 1948. Serving as an indispensable tool for researchers and clinicians worldwide, PubMed enables millions of searches daily, allowing users to stay updated on the latest scientific developments and contribute to new discoveries.[6,7] Despite the extensive body of LBP literature indexed in PubMed, few studies have specifically addressed Turkiye's academic contribution to this field.

Although several bibliometric analyses have examined the global and national LBP research landscape, there has been limited focus on Turkiye's specific contributions.[8-11] This study seeks to fill this gap by analyzing the clinical research on low back pain in Turkiye, as indexed in PubMed, with a focus on randomized controlled trials (RCTs). The aim is to provide a comprehensive overview of Turkiye's research output, including details such as the publishing trends, journal impact, and citation performance of these studies.

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METHODS

This study did not involve human or animal subjects, as it is a bibliometric analysis of existing literature. Therefore, no formal ethical approval was required. However, the research was conducted in accordance with general ethical principles, ensuring research integrity and data confidentiality.

This bibliometric analysis focused on RCTs related to LBP indexed in PubMed and conducted by first authors affiliated with institutions in Turkiye. A systematic search of PubMed was performed using the advanced search query "low back pain [Title]" AND "(Turkiye) OR (Turkiye)," with a filter applied to include only clinical trials. Only interventional randomized controlled clinical trials were included in the analysis. Non-RCT publications such as letters to the editor, case reports, narrative reviews, and observational studies were excluded from the analysis. Data collected included the year of publication, open-access status, the first author's medical specialty, the study's primary research question, the journal's quartile ranking according to Web of Science, and the citation count from Google Scholar. For some journals, quartile rankings were unavailable in Web of Science.

The studies were grouped based on their primary research question into the following categories: exercise, oral-IV-IM medications, injections, Complementary and Alternative Medicine (CAM), physical therapy agents, balneotherapy, kinesiotaping, patient education, telerehabilitation, and virtual reality. Different massage techniques, manual therapy techniques, vagal stimulation, diet, neural therapy, and mesotherapy techniques were categorized under CAM. Studies primarily focusing on prevalence, risk factors, pain-related factors, disease duration or severity, painkiller usage, and pain assessment methods were outside the scope of this analysis and were not included. Our focus was limited to interventional RCTs addressing treatment approaches.

Some studies were counted in multiple groups due to overlapping content. For example, mesotherapy (1 study) and neural therapy (1 study) studies were included in the "CAM" and also in the "Injections" group. ESWT (1 study) was categorized under physical therapy agents.

Most studies recommended exercise programs for both the intervention and control groups as part of standard care. Studies where the primary focus was to compare exercise methods or specifically evaluate the effectiveness of exercise were categorized separately under the "Exercise" group. Studies that used exercise as part of a standard treatment in both groups were also recorded.

Since the majority of publications were authored by physiatrists and physiotherapists, some comparisons were conducted based on three groups for statistical reasons: physiatrists, physiotherapists, and others (this group includes various medical specialties as well as a small number of nurses and occupational therapists).

Statistical Analysis

It was performed using SPSS (Statistical Package for the Social Sciences) Version 21.0 (IBM Corp., Armonk, NY), with statistical significance defined as $p \leq 0.05$. Descriptive statistics (mean, standard deviation, median, and range) were used to summarize the data. Non-parametric tests were applied due to the nature of the data distribution. The Kruskal-Wallis test was used to compare citation counts and publication ages among the three groups of authors (physiatrists, physiotherapists, and others). Post-hoc analysis was conducted using the Mann-Whitney U-test where appropriate. Spearman's rank correlation test was applied to assess the relationship between publication year and citation count.

RESULTS

There are 72 unique publications in total, spanning from 2003 to 2024. These publications show a gradual increase over the years, peaking in 2021 with 10 publications (Figure 1). The majority of publications are authored by Physical Medicine and Rehabilitation (PMR) specialists (26), followed by physiotherapists (24), and emergency medicine specialists (6) (Figure 2). Physiatrists and physiotherapists had more publications than other groups, but there was no significant difference between these two groups.

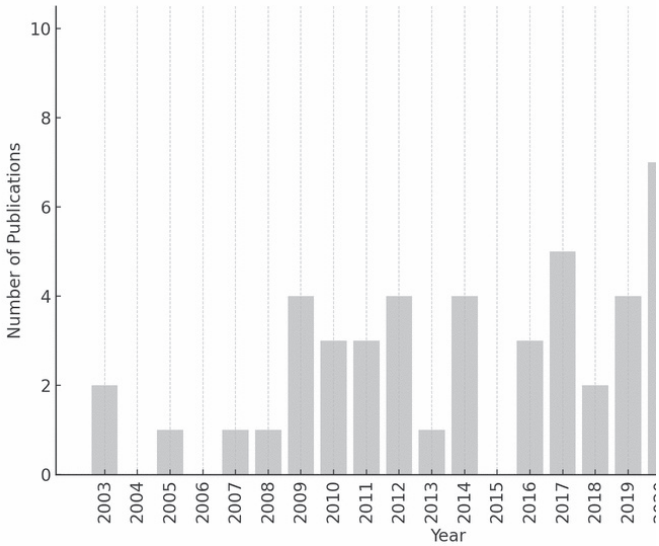

Figure 1. Number of publications by year

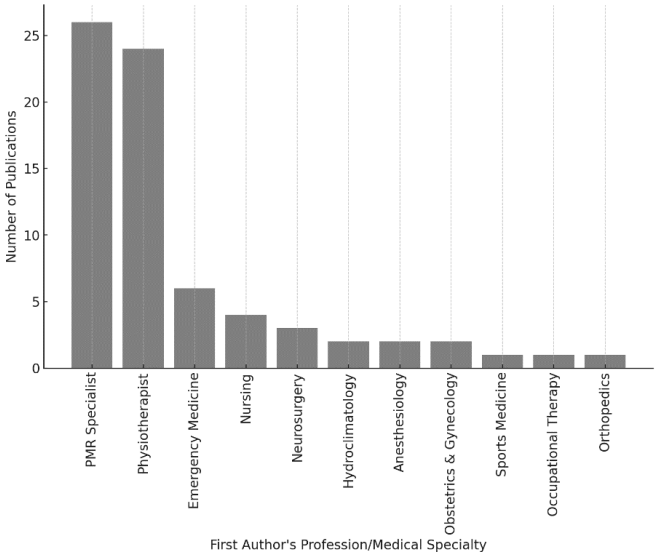

Figure 2. Distribution of publications by first author's profession/medical specialty

Out of the six studies conducted by emergency medicine specialists, five focused on acute low back pain, while one study included both acute and chronic low back pain patients. Among the other studies analyzed, only six involved patients with acute low back pain. In one of these six studies, both acute and chronic low back pain patients were included.

The majority of the publications appeared in Q1-Q2-Q3 journals (67 publications). Only a few (5) were published in Q4 or non-classified journals (Figure 3).

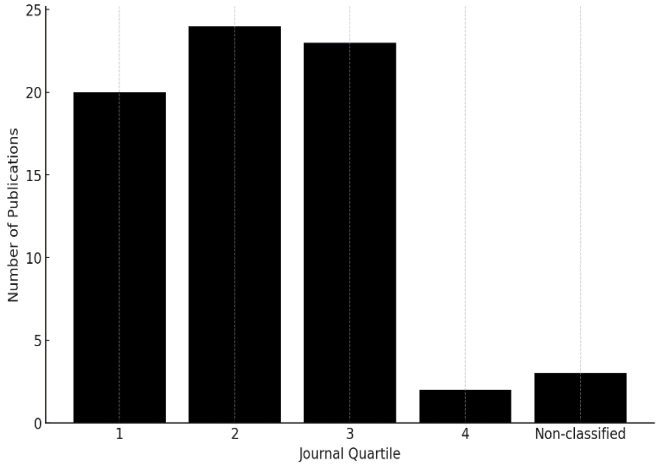

Figure 3. Distribution of publications by journal quartile

The most common research topics were Complementary and Alternative Medicine (15 publications), Physical Therapy Agents (14 publications), Injections (10 publications), Oral-IV-IM Medications (9 publications), and Exercise (8 publications). 36 studies included exercise as a treatment modality, while 36 did not. Among the studies that included exercise, 8 focused exclusively on exercise interventions, while the other 8 incorporated an exercise program alongside the primary treatment being studied (Figure 4).

The average citation count across all publications is 46.9, with a median of 29, ranging from 0 to 305 citations. A Spearman correlation test showed a strong negative correlation between citation count and publication year (p<0.001), indicating that older publications tend to have more citations.

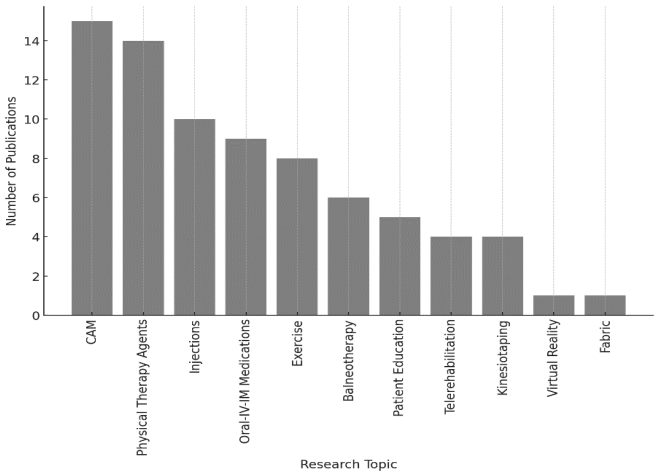

Figure 4. Distribution of publications by research topic

Dividing the publications into three groups (PMR specialists, physiotherapists, and others) and analyzing citation counts using the Kruskal-Wallis test revealed significant differences (p=0.002). Post-hoc analysis showed that PMR specialists had significantly higher citation counts than both physiotherapists (p=0.002) and the other groups (p=0.046), while there was no significant difference between physiotherapists and the other groups (p=0.726) (Table 1).

The analysis of publication years among the three groups (PMR specialists, physiotherapists, and others) also revealed a statistically significant difference in publication age (p<0.001). PMR specialists had the oldest publications, with a significantly higher publication age than both physiotherapists (p<0.001) and the other groups (p=0.008). There was no significant difference between physiotherapists and the other groups (p=0.403) (Table 1).

The 10 most cited studies cover topics such as physical therapy agents, exercise, patient education, and injections, with citation counts ranging from 139 to 305.

Out of the 72 publications, 11 are open access, and 61 are not. The Mann-Whitney U test revealed no statistically significant difference in citation counts between open access and non-open access publications (p=0.277).

Table 1. Citation analysis and years since publication by groups

	Median (min-max)	Mean±SD	p	Post-hoc
Number of citations				
Total	29 (0-305)	46.9 ± 55.0	0.002	0.002(a-b) 0.046(a-c)
Physiatristsa	44 (1-305)	75.6 ± 70.2		
Physiotherapistsb	16 (0-117)	25.7 ± 29.9		
Othersc	18.5 (0-136)	36.2 ± 41.6		
Publication age (2024-publication year)				
Total	5 (0-21)	6.9 ± 5.6	<0.001	<0.001 (a-b) 0.008(a-c)
Physiatristsa	11 (2-21)	10.6 ± 5.9		
Physiotherapistsb	2.5 (0-14)	3.3 ± 3.4		
Othersc	5.5 (0-15)	6.6 ± 4.4		

SD: Standard deviation

DISCUSSION

The analysis of RCTs related to LBP in Turkiye reveals several key insights. First, there has been a steady increase in the number of RCTs over the years, with a notable peak in 2021. Physiatrists and physiotherapists were the primary contributors to these studies. The most common research topics included CAM, physical therapy agents, and injections. Older publications had higher citation counts, open-access status did not significantly impact citation performance.

In line with the conclusions from previous bibliometric studies, our analysis shows a clear upward trend in the number of RCTs on LBP in Turkiye over the years.[8,9,12] Similar to Weng et al.'s[9] analysis, which identified a consistent annual growth in nonspecific LBP publications from 2000 to 2018, and Huang et al.'s[12] findings that LBP research has gained increasing global attention in the last two decades, our study demonstrates a rising interest in LBP research in Turkiye, peaking in 2021. However, despite this growth, Turkiye has not yet emerged as one of the top countries contributing to LBP-related academic literature, a point that underscores the need for further enhancement of research output and global visibility. Moreover, unlike previous studies, which often did not provide detailed breakdowns by study types, our analysis offers a focused examination of RCTs, providing a unique contribution.

Additionally, as highlighted by Šajnović et al.,[8] thematic analyses of chronic LBP research have identified six primary themes, including complementary methods in physiotherapy. This finding parallels the results of our study, where CAM emerged as a significant research focus in Turkiye's LBP-related RCTs. The attention given to CAM in the Turkish literature reflects the broader global interest in exploring non-conventional therapies for managing LBP. Our analysis shows that CAM-related trials were among the most frequently studied topics, further underscoring the relevance of this approach within both Turkish and international LBP research.[13]

Considering the publication numbers in 2019, 2020, and 2021, it appears that the COVID-19 pandemic did not negatively affect RCTs related to low back pain in Turkiye. Research activity in this field continued to grow, indicating that clinical trials persisted despite the challenges posed by the pandemic.

The dominance of physiatrists in terms of citation counts could be attributed to their longer history of academic involvement in Turkiye.[14,15] PMR is an established and longstanding specialty in the country, which may explain why these professionals receive higher citation counts, as they have had more time and experience to contribute to the scientific literature.

The fact that open access status does not significantly affect citation counts may be due to the availability of certain restricted-access publications through alternative platforms. Researchers may still access non-open access articles via academic networks or institutional libraries, which might explain why open access does not have a marked influence on citation performance in this context.

Limitations

One limitation of this study is that the search was restricted to publications indexed in PubMed, which may have excluded relevant studies available in other databases. However, it is important to note that numerous studies have similarly evaluated the contributions of different specialties at a national level using PubMed as the sole database.[16,17] A second limitation is that only studies with the term "low back pain" in the title were included, potentially omitting studies related to the topic but not explicitly mentioning it in the title. Future research involving more databases and including studies focused on specific diagnoses and causes of low back pain could validate, expand, and provide different perspectives on the preliminary findings of this study.

CONCLUSION

This bibliometric analysis highlights the steady growth of Turkiye-based RCTs on low back pain, particularly led by PMR specialists and physiotherapists. The increasing number of publications, especially in high-impact journals, reflects the country's growing academic contribution to this field. Key research areas, including CAM, physical therapy agents, and injections, align with global trends in LBP research. While citation counts are strongly influenced by the publication year, open access status does not appear to impact citation performance significantly. Future research should expand to include a broader range of databases and study types to offer a more comprehensive understanding of Turkiye's role in the global LBP research landscape.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study did not involve human or animal subjects, as it is a bibliometric analysis of existing literature. Therefore, no formal ethical approval was required. However, the research was conducted in accordance with general ethical principles, ensuring research integrity and data confidentiality.

Informed Consent

This study did not involve human or animal subjects, as it is a bibliometric analysis of existing literature. Therefore, no informed consent was 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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Evaluation of burnout and job satisfaction among family physicians working in the earthquake region

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ABSTRACT

Aims: The study aims to determine and evaluate the levels of professional burnout and job satisfaction among family physicians working in Adıyaman. We aimed to evaluate the factors affecting these levels.

Methods: This research is a descriptive cross-sectional study. 185 family physicians (86%) agreed to participate in the survey. The survey was added to Google Forms, and the link to the survey was sent to individuals' personal emails after obtaining verbal consent via cell phones. After verbal verification, data were collected via Google Forms between March 15, 2024, and May 15, 2024.

Results: Family physicians working in towns and villages experience lower levels of burnout and higher job satisfaction($p<0.001$). Additionally, we found that physicians with lighter work demands($p<0.001$), those who perceive the payment system as fairer ($p=0.003$, $p<0.001$), those who feel less stressed ($p<0.001$), and those who maintain a hopeful outlook on the future($p<0.001$), also experience reduced burnout and increased job satisfaction.

Conclusion: The study identified that factors such as the geographical location where family physicians practice, their workload, and the physical condition of their work environment, alongside psychosocial factors like their sense of security, professional satisfaction, and perceived stress levels, significantly impact occupational burnout and job satisfaction. To enhance the effectiveness and longevity of the family medicine system, which is pivotal in primary health care, it is crucial to consider improvements in physical conditions and psychological and social well-being.

Keywords: Family medicine, burnout, professional satisfaction

INTRODUCTION

Family physicians' job satisfaction and burnout significantly impact their personal and professional lives. Job satisfaction reflects individuals' overall attitudes toward their jobs and is influenced by various elements.[1] Identifying job satisfaction and burnout levels is crucial for improving the quality of healthcare services and ensuring the well-being of healthcare professionals.[2] The Maslach Burnout Inventory (MBI) is one of the most frequently used measurement tools in this field and is widely used to assess the burnout levels of healthcare workers.[3,4]

Family physicians' work environments and demands significantly impact their job satisfaction and burnout. Studies have shown that increased work demand and inadequate working conditions lead to high levels of burnout and low job satisfaction among healthcare professionals.[5,6] Notably, there are significant differences in job satisfaction and burnout levels between physicians working in rural and urban areas.[7] Physicians working in rural areas often experience higher job satisfaction and lower burnout due to lower population density and less complexity. In contrast, those in urban areas face higher work demands and stress.[8,9]

Other important factors affecting family physicians' job satisfaction and burnout include physical workplace conditions, performance evaluation systems, and professional expectations.[10,11] Well-equipped and ergonomic working environments enable physicians to perform their jobs more comfortably and efficiently.[12] Similarly, fair and transparent performance evaluation systems can increase physicians' motivation and job satisfaction.[13] Managing healthcare professionals' job-related expectations and providing a positive outlook for the future can enhance job satisfaction and reduce burnout.[14,15]

Recent studies also highlight the complex relationship between job satisfaction, burnout, and healthcare outcomes. High levels of burnout are associated with reduced job performance and patient care quality. In contrast, interventions aimed at

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improving workplace support and reducing job stress have been shown to enhance job satisfaction and lower burnout rates among healthcare workers.[16,17] Moreover, fostering a supportive work environment and encouraging work-life balance are essential strategies to mitigate burnout and enhance job satisfaction among physicians, as evidenced by recent literature.[18]

Determining family physicians' satisfaction and burnout levels working in earthquake zones and understanding the sociodemographic characteristics affecting these factors can improve healthcare professionals' general health and working conditions after a disaster. Improvements made in this regard can support healthcare professionals in providing more efficient and satisfying services, thereby positively contributing to public health. In Turkiye, primary health care services are delivered by two main groups of physicians: general practitioners, who undergo six years of medical education, and family physicians, who complete an additional three years of specialized training following their initial medical education.[19] This study aims to determine the working conditions, work demand, professional satisfaction, and burnout levels of family physicians working in earthquake-affected zones who experienced the 2023 Turkiye earthquake centered in Kahramanmaras and the factors affecting these aspects.

METHODS

This research is a descriptive cross-sectional study. Ethical approval for the study was obtained from the Ethics Committee of Ankara University (Date: 03.04.2024, Decision No: 06/29). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The aim was to reach all 215 family physicians in Adıyaman province, with no sampling calculated. However, 185 family physicians (86%) agreed to participate in the survey. The survey was added to Google Forms, and the link to the survey was sent to individuals' emails after obtaining verbal consent via cell phones. After verbal verification, data were collected via Google Forms between March 15, 2024, and May 15, 2024. No time limit was applied when answering the survey.

The survey consists of four sections: The first section, 'Demographic Information Form,' has 11 questions; the second section has 11 questions related to family medicine; the third section, MBI has 22 items; and the fourth section, 'Job Satisfaction Scale,' has 36 items.

To determine the job satisfaction of family physicians, a survey developed by Paul E. Spector in 1997 consisting of 9 dimensions (salary, promotion, supervisors, fringe benefits, contingent rewards, operating conditions, coworkers, nature of work, communication) and 36 items was used.[1] This survey was adapted to Turkish by Yelboğa[2] in 2009, with a Cronbach's alpha reliability coefficient of 0.78. The six-point Likert scale ranges from "strongly disagree" to "strongly agree." The minimum score from the scale is 36, and the maximum score is 216; there is no specific cut-off point for the scale, with higher scores representing higher job satisfaction. Negative item scores were reversed and combined with positive items.

The Burnout inventory, developed by Maslach and Jackson[3] in 1981, is a seven-point Likert-type scale. Translated into Turkish by Ergin in 1992, this scale adjusts the original seven-point response options to range from "0 never" to "4 always." The scale is divided into three sub-dimensions: emotional exhaustion (9 questions), depersonalization (5 questions), and reduced personal accomplishment (8 questions). Emotional exhaustion is scored between 0-36, depersonalization between 0-20, and reduced personal accomplishment between 0-32. The total scale score determines the level of burnout. Questions in the reduced personal accomplishment sub-dimension are reverse-scored, and the higher the scores in emotional exhaustion and depersonalization, the higher the level of burnout; the higher the score in the reduced personal accomplishment dimension, the lower the sense of personal accomplishment.[4]

Statistical Analysis

Analyses in the study were performed using SPSS for Mac 29 and Jamovi 2.4 (The Jamovi project, 2023). Descriptive statistics were summarized using mean ± standard deviation, median, number, and percentage values. Normal distribution was assessed with Shapiro-Wilk tests. Student's t-test, One Way ANOVA, or Welch's t-test were applied for the analysis of continuous variables with normal distribution. For continuous variables not normally distributed, the Mann-Whitney U test and the Kruskal-Wallis test were used. Bonferroni and Tamhane's T2 corrections were employed in post-hoc analyses. Correlation between scale scores was evaluated using Pearson and Spearman correlation tests, depending on the distribution. A p-value of <0.05 was considered statistically significant.

RESULTS

Most participants (83.8%) are general practitioners, and 69.7% are male. The average age of the participants is 38.9±8.9 years, while the average professional experience is 12.9±9.1 years, and the average professional experience in family medicine is 7.4±5.3 years. 80.5% of the participants are married, and 53.5% work in the city center. The average emotional exhaustion score of the participants is 20.3±7.7, the average depersonalization score is 6.8±3.6, the average personal accomplishment score is 19.3±4.1, and the average Maslach burnout score is 46.5±9.5. The average job satisfaction score is 111.2±25.8.

The Cronbach's alpha coefficient of the Maslach Scale is 0.91, and for the job satisfaction scale, it is 0.80.

According to the workplace, the Maslach burnout score of physicians working in towns was significantly lower compared to those working in provincial and district centers (town-provincial $p<0.001$, town-district $p=0.003$) (Table 1).

There was a statistically significant difference in the Maslach burnout score among those who found the physical conditions at their workplace sufficient, insufficient, or undecided. However, post-hoc analysis revealed no statistically significant differences between these three groups. The Maslach burnout score showed significant differences based on opinions about family medicine practice. Those who rated family medicine practice as poor or very poor had significantly different

Table 1. The relationship between the participants' Maslach burnout scale and job satisfaction and their sociodemographic characteristics

		n	%	Maslach burnout		Job satisfaction	
				Mean±SD	p-value	Mean±SD	p-value
Occupation	General practitioner	155	83.8	46.7±9.3	0.484	111.4±25.8	0.779
	Family medicine specialist	30	16.2	45.4±10.5		110±26.6	
Gender	Male	129	69.7	46.9±9.8	0.339	110.3±27.8	0.461
	Female	56	30.3	45.5±8.9		113.1±20.6	
Marital status	Married	149	80.5	46.5±9.7	0.874	110.8±25.7	0.438
	Single	33	17.8	46.6±8.7		114.2±26.6	
	Divorced/widowed	3	1.6	43.6±9.6		95±23.8	
	No	15	8.1	49.9±8.7		102.5±24.8	
Workplace	City center	99	53.5	47.5±8.9	<0.001	108.6±25.0	<0.001
	District center	49	26.5	48.3±10.9		105.1±26.1	
	Town/village	37	20.0	41.4±7.6		126.1±22.7	
Total years in profession	10 years or less	94	50.8	45.8±9.9	0.317	113.1±25.0	0.307
	More than 10 Years	91	49.2	47.2±9.1		109.2±26.7	
Years as family physician	6 years or less	96	51.9	45.2±9.6	0.064	113.7±25.7	0.174
	More than 6 Years	89	48.1	47.8±9.3		108.5±25.8	

SD: Standard deviation

burnout scores compared to those who rated it as good or very good (very good-poor p=0.010, very good-very poor p<0.001, good-very poor p<0.001, good-poor p<0.001, undecided-very poor p=0.003) (Table 2).

The burnout score also varied significantly with the physicians' work demands. Physicians who thought their work demands were too heavy had significantly higher burnout scores than those who found their work demands manageable (p<0.001). Similarly, those who perceived their job stress as higher than necessary had significantly higher burnout scores (p<0.001). Future expectations influenced burnout scores, with decreasing optimistic expectations leading to significantly higher burnout scores compared to unchanged or increasing expectations (unchanged-decreased p<0.001, increased-decreased p=0.002) (Table 2).

Job satisfaction scores differed significantly with workload, with lower scores for those feeling their workload was too heavy (p<0.001). Higher perceived job stress also led to significantly lower job satisfaction (p<0.001). Future expectations influenced job satisfaction, with decreasing optimism leading to lower scores (p<0.001) (Table 2).

DISCUSSION

Our study has detailed factors affecting family physicians' job satisfaction and burnout. The findings obtained from family physicians working in Adıyaman, Turkiye, which has just passed the one-year mark since experiencing a major earthquake, can mainly shed light on projects to be developed related to primary healthcare services post-disaster.

The present study found that physicians working in small towns had significantly lower emotional exhaustion scores, depersonalization scores, and Maslach burnout scores than those working in provincial and district centers; their job satisfaction scores were significantly higher. Physicians working in smaller and quieter settlements might be less affected by high work demand and stress. This finding is consistent with the literature, indicating that healthcare professionals working in areas with lower population density and less complexity may have higher job satisfaction.[7] The ability to establish closer and more personal relationships with the community in rural areas might increase professional satisfaction for physicians.

The present study found that those who considered the physical conditions at their workplace inadequate had significantly higher burnout scores and lower job satisfaction scores than those who found them adequate. These findings are consistent with a study conducted by Aras et al.[8] in 2018. Inadequate physical conditions can increase physicians' stress levels and decrease job satisfaction. It is known that well-equipped and ergonomic working environments enable physicians to perform their jobs more comfortably and efficiently. Increasing the operating expenses provided for the construction or rental of family health centers by the state could address this issue.

In the present study, those who rated the family medicine practice as poor or very poor had significantly higher burnout scores and lower job satisfaction scores than those who rated it as good or very good. As highlighted in Yılmaz's[9] study, these findings indicate the need to develop new projects to address the shortcomings of the family medicine practice by considering the demands of healthcare professionals.

In the present study, those who felt they could not handle the work demand had significantly higher burnout and lower job satisfaction scores than those who felt they could handle the work demand or found it manageable. Excessive work demands can negatively affect healthcare professionals' physical and mental health, reducing productivity and impacting the quality of patient care. These findings are consistent with the results presented by West et al.,[10] and Dyrbye et al.[11] Implementing new regulations to reduce the work demand of family physicians would increase satisfaction for both family physicians and their patients.

Table 2. The relationship between the participants' Maslach burnout scale and job satisfaction and several variables

		n	%	Maslach burnout		Job satisfaction	
				Mean±SD	p-value	Mean±SD	p-value
Are the physical conditions at your workplace adequate?	Yes	71	38.4	44.8±10.7	0.020	118.0±25.6	0.001
	No	98	53.0	48.3±8.5		104.7±24.9	
	Undecided	16	8.6	43.1±8.1		120.3±23.7	
How do you find the family medicine practice?	Very bad	18	9.7	56.6±6.0	<0.001*	80.7±12.9	<0.001
	Bad	42	22.7	50.7±7.7		94.7±21.0	
	Good	78	42.2	42.3±8.0		125.1±19.9	
	Very good	11	5.9	41.8±7.8		133.6±21.7	
	Undecided	36	19.5	46.9±10.5		108.7±22.6	
How do you assess your workload?	Less than you can handle	11	5.9	41.5±12.7	<0.001	133.0±29.2	<0.001
	As much as you can handle	73	39.5	42.0±7.5		122.8±19.9	
	More than you can handle	101	54.6	50.3±8.8		100.4±24.3	
How do you assess your job stress?	None	5	2.7	47.2±13.8	<0.001	141.4±34.1	<0.001
	As much as it should be in work life	87	47.0	41.1±7.3		123.0±20.9	
	Too much	93	50.3	51.5±8.4		98.5±23.1	
How have your future expectations changed since starting work as a family physician?	Decreased	107	57.8	49.8±9.2	<0.001	101.1±24.3	<0.001
	Unchanged	56	30.3	41.6±8.1		123.2±22.3	
	Increased	22	11.9	42.6±7.6		129.8±17.7	
Do you feel secure as a family physician?	Yes	26	14.1	37.4±9.2	<0.001	140.3±18.7	<0.001
	No	136	73.5	49.1±8.5		102.4±22.6	
	Undecided	23	12.4	41.2±6.9		130.0±14.7	
Do you think the performance evaluation system is fair?	Yes	16	8.6	40.9±12.8	0.003*	133.5±17.6	<0.001
	No	138	74.6	47.9±9.2		105.2±25.5	
	Undecided	31	16.8	43.2±7.0		126.2±17.5	
With which group do you face the most issues in your professional communication?	Patients and their relatives	127	68.6	47.4±9.6	0.085	110.6±26.5	0.057
	Supervisors	44	23.8	45.2±8.6		107.8±23.9	
	Colleagues	14	7.6	42.0±10.1		126.5±22.0	
Do you think working as a family physician has contributed to your medical notion?	Yes	98	53.0	44.1±9.1	0.001	119.5±24.9	<0.001
	No	59	31.9	49.6±10.3		97.9±21.9	
	Undecided	28	15.1	48.3±6.6		110.1±25.9	
If you were a new graduate from medical school, would you join the family medicine system under the current conditions?	Yes	77	41.6	42.1±8.7	<0.001	125.1±21.2	<0.001
	No	74	40.0	50.6±9.4		97.5±23.9	
	Undecided	34	18.4	47.4±7.3		109.2±23.5	
Are you considering leaving your current job?	Yes	69	37.3	52.5±8.1	<0.001	95.2±21.9	<0.001
	No	75	40.5	41.0±8.8		125.6±23.0	
	Undecided	41	22.2	46.2±6.7		111.5±21.1	
Do you think the medical profession suits your personality?	Yes	122	65.9	45.2±9.5	0.022	116.1±25.7	<0.001
	No	32	17.3	50.1±10.2		93.9±24.0	
	Undecided	31	16.8	48.0±7.7		109.5±20.2	

SD: Standard deviation

Consistent with the study by Selamu et al.,[12] the present study found that those who considered work stress to be more than it should be had significantly higher burnout scores and lower job satisfaction scores compared to those who found work stress to be at an appropriate level. Stress management and supportive working environments can help physicians experience less burnout and more job satisfaction.[10,11] Regular training and seminars organized by the Ministry of Health to help family physicians cope with stress would be beneficial, and including nurses and other staff working in the family health centers in these training sessions could improve efficiency.

Parallel to West's[13] study, the present study found that family physicians with decreased optimistic expectations for the future had significantly higher burnout scores and lower personal accomplishment and job satisfaction scores than others. Managing professional expectations and providing a positive outlook for the future can increase job satisfaction and reduce burnout for family physicians.[9] Special regulations for family physicians in earthquake-affected areas like Adıyaman, where the effects of the 2023 Turkiye earthquake are still evident, could provide a solution.

In the present study, family physicians who did not feel secure had significantly higher burnout scores and lower personal accomplishment and job satisfaction scores than others. These findings are similar to Rassolian et al.[14] Ensuring physicians feel secure at their workplace can help them perform better and experience less burnout. Preventing violence in healthcare can make healthcare professionals feel more secure and increase their productivity.

In the present study, those who found the performance system in family medicine unfair had significantly higher burnout scores and lower job satisfaction scores than others. These findings align with the results of a study conducted by Cagan et al.[15] Physicians who find the performance system unfair have higher burnout and lower job satisfaction scores, highlighting the impact of performance evaluation systems on healthcare professionals. A fair and transparent performance evaluation system can increase physicians' motivation and job satisfaction.[9]

In the present study, those who felt working in family medicine did not contribute to their medical notion had significantly higher burnout scores and lower personal accomplishment and job satisfaction scores than those who felt it contributed to their medical notion. A work environment where prioritizing professional meaning and personal contribution can increase physicians' job satisfaction. Our findings, in line with West et al.'s[10] study, indicate the need for new regulations for family medicine practice.

Consistent with the study by Altan and Şahin,[20] the present study found that those who would still choose family medicine if newly graduated had significantly lower burnout scores and higher job satisfaction scores than those who would not choose it again or were undecided. Our study shows that being satisfied with their career choice can make physicians more committed and motivated in their work. Creating opportunities for medical students to get to know different specialties better during their education could help them make informed choices for personal and professional satisfaction.[21]

Consistent with the study by Wang et al.,[22] those who considered quitting their job had higher burnout scores and lower job satisfaction scores compared to those who did not consider quitting or were undecided. Measures to increase job satisfaction in earthquake-affected areas could reduce the intention of physicians to leave their profession and prevent burnout.

In the present study, those who felt that the medical profession suited their personality had significantly lower burnout scores and higher personal accomplishment and job satisfaction scores than those who felt it did not suit their personality or were undecided. The alignment between personal skills and professional expectations can help physicians find more satisfaction in their work. Therefore, projects that help children and adolescents choose careers suited to their abilities and interests should be developed before university. The pre-university education curriculum could be revised to help students better understand themselves.[23]

Limitations

The survey was administered via a participation link sent to the participants' email addresses rather than through face-to-face interactions. Consequently, it is assessed that data security was adequately maintained. However, since the study was confined to the Adıyaman province, the results cannot be generalized to a broader population. Further research in this area is needed to provide insights that can lead to more effective and satisfactory practices for physicians.

CONCLUSION

The study identified that factors such as the geographical location where family physicians practice, their workload, and the physical condition of their work environment, alongside psychosocial factors like their sense of security, professional satisfaction, and perceived stress levels, significantly impact occupational burnout and job satisfaction. To enhance the effectiveness and longevity of the family medicine system, which is pivotal in primary health care, it is crucial to consider improvements in physical conditions and psychological and social well-being.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval for the study was obtained from the Ethics Committee of the Ankara University (Date: 03.04.2024, Decision No: 06/29).

Informed Consent

All individuals verbally consent to participate in the study.

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.

Data Availability Statement

Data will be available upon reasonable request from the corresponding author.

Author Contributions

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

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Original Article

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Is there a role of genetic tendency in post-COVID pulmonary thromboembolism?

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ABSTRACT

Aims: COVID-19 is a multisystemic disease characterized by endothelial dysfunction. The improper activation of the coagulation cascade may lead to thromboembolic events, which are presumed to contribute to the disease's overall high morbidity and mortality. This research examines the role of thrombophilia mutations in patients diagnosed with post-COVID pulmonary thromboembolism.

Methods: Between May 2020 and December 2020, 61 patients were diagnosed with pulmonary thromboembolism (PTE). Thirty-two patients were positive in COVID-19 -RT-PCR testing, and 29 patients were identified with non-COVID PTE. All PTE diagnoses were made by thorax computed tomographic angiography. Demographic characteristics, genetic mutation results, and laboratory values of the patients were retrospectively evaluated.

Results: The median age of patients was 56 years (25-81), and most patients (n=43,70.5%) were male. There was no difference between factor 5 Leiden mutation, while prothrombin 20210A mutation was more commonly observed in post-COVID patients ($p<0.05$). Between the two groups, no difference was observed regarding MTHFR gene mutation, anticardiolipin and antiphospholipid antibodies, protein S, and protein C values. D-dimer values were statistically higher in the post-COVID PTE group ($p<0.05$). As seen in the study, we may state that patients with post-COVID PTE had a higher diagnosed prothrombin 20210A and more elevated D-dimer values compared to non-COVID-related PTE patients.

Conclusion: In our study, we found that D-dimer values were higher in patients with post-COVID PTE than in patients with non-COVID PTE, and prothrombin 20210A mutation was more common in the post-COVID PTE patient group. We believe that further studies with a larger study group are needed to elucidate this issue.

Keywords: COVID-19, D-dimer, factor 5 Leiden mutation, post-COVID pulmonary thromboembolism, thrombophilia mutations

INTRODUCTION

The novel SARS-CoV-2 virus first appeared in Wuhan, China, in December 2019. SARS-CoV-2 expanded internationally despite efforts to stop it from doing so, creating a public health emergency. Thus, the World Health Organization (WHO) designated the novel coronavirus infection as a pandemic in March 2020.[1] SARS-CoV-2 was later defined as the Coronavirus of 2019, COVID-19, and was reported as a disease correlated to coagulopathies that may cause arterial and venous thromboembolic events.[2]

Among COVID-19 patients, thrombosis is one of the most severe complications that may occur and is reported as one of the most likely causes of sudden COVID-19 death.[3] Many causes, genetic or acquired, may lead to thrombosis, however, hypercoagulation and hypofibrinolysis are among the main common pathologies observed causing thrombosis. Patients with COVID-19 typically experience severe hypercoagulability in their lungs, and pulmonary arteries are the site of most vascular thrombotic complications. Severe coagulation abnormalities, in particular fibrin and platelet-rich thrombi, were seen in post mortem lungs from SARS-CoV-2 infected individuals. These abnormalities were not seen in non-COVID-19 autopsy controls.[4] Etiologically, thrombophilia may manifest in two different pathways, acquired and hereditary. However, a clear cut cannot be made in many cases, especially in patients with already known hereditary mutations.[5]

Three factors are required for hemostatic balance: an intact vessel wall, adequate blood coagulability, and a functioning hemostasis system. Hemostasis may decline as a result of pathologies that affect anticoagulant and fibrinolytic systems. The final outcome often presents itself as deep vein thrombosis (DVT) or pulmonary thromboembolism (PTE). Many thrombophilia risk factors have been defined, with Prothrombin G20210A and factor V Leiden gene mutation

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being accepted as the most common inherited ones for venous thromboembolism.[6] Other known risk factors are deficiencies in coagulation pathways, such as protein S, Protein C, and antithrombin 3 deficiencies. The mutant form of factor V is known as factor V Leiden (FVL), which disrupts the functional interaction between factor V and protein C.[7] This leads to resistance in activated protein C, which in turn increases the risk of thrombosis. FVL is the most frequent genetic cause of unexplained venous thrombosis. As it is very common and due to being the most frequent genetic cause, patients with COVID-19 could be evaluated for the mutation, and if observed, appropriate treatment may be utilized to reduce venous thromboembolic morbidity. G20210A, on the other hand, is caused by a point mutation and is used to define a prothrombin subtype. The presence of prothrombin G20210A increases the concentration of overall prothrombin, and as a result, this autosomal dominant disease predisposes the patient to both arterial and venous thrombosis.[8]

In this study, patients diagnosed with PTE with either post-COVID-19 infection or non-COVID-19-related were evaluated to investigate the role of mutations in PTE.

METHODS

The study was performed after the approval from the Ankara Oncology Training and Research Hospital Ethics Committee (Date: 05.09.2024, Decision No: 2024-09/128). This research was carried out in conjunction with the Helsinki Declaration (as revised in 2013). Sixty-one patients diagnosed with PTE between dates of May 2020 and December 2021 were evaluated in the study, with 32 patients being positive for COVID-19 RT-PCR and the remaining defined as non-COVID-related PTE. All PTE diagnoses were made by thorax computed tomographic angiography. Demographic characteristics, genetic mutation results, and laboratory values of the patients were retrospectively evaluated. Doppler ultrasonography of the lower extremity was performed on all patients to investigate possible deep vein thrombosis as an additional risk factor for PTE. All included patients were older than 18 years old.

Inclusion criteria for the study:

- Patients over the age of 18,
- Patients diagnosed with PTE and being followed up,
- Patients whose demographic information, additional disease information, laboratory values, genetic mutation results, tomography reports and 1-year prognosis information could be accessed from the hospital system or patient files were included in the study.

Exclusion criteria for the study:

- Patients whose investigated criteria could not be accessed from the patient file or hospital information system,
- Patients diagnosed with malignancy,
- Patients with active infection other than COVID-19 infection were not included in the study.

Statistical Analysis

The initial data were first evaluated by Kolmogorov-Smirnov test for distribution pattern, with histograms used when deemed necessary. Student's t-test was used for parametric variables, whereas Mann-Whitney U test was used for nonparametric analysis, with results being given as mean with standard deviation or median with maximum and minimum values, respectively. IBM SPSS (Statistical Package for the Social Sciences) statistics (version 22) was used for statistical analysis. It was stated that if there is a p-value below 0.05, it would be taken as statistically significant.

RESULTS

All sixty-one patients evaluated in the initial period was included into the study. The mean age of the patients was 56 (25-81) years and the majority of the patients (n=43, 70.5%) were male (Table 1). Half of all patients were diagnosed and hospitalized for COVID-19 pneumonia before PTE diagnosis. None of the patients had a diagnosis of malignancy, immobilization or surgery that could have predisposed them to venous thromboembolic events. DVT incidence was lower in patients diagnosed with post-COVID PTE compared to those without COVID-related PTE. Before the diagnosis, 53.1% of all patients had been on an anticoagulant prophylaxis.

Table 1. Demographic findings and general characteristics of the patients

Parameters (n, %)		Post-COVID PTE (n=32)	Non-COVID PTE (n=29)	Total (n=61)	p value
Age (median, min-max)		56.50 (25-81)	51 (27-67)	56 (25-81)	0.333
Gender	Male	21 (48.8)	22 (61.1)	43 (70.5)	0.381
	Female	11 (61.2)	7 (38.8)	18 (29.5)	
Hospitalization before PTE due to COVID-19	Yes	16 (50)	-	16 (26.3)	-
	No	16 (50)		45 (73.7)	
Deep venous thrombosis	Yes	2 (6.3)	8 (27.6)	10 (16.4)	0.025
	No	30 (93.7)	21 (72.4)	51 (83.6)	
Anticoagulation history before PTE	Yes	17 (53.1)	-	17 (27.9)	-
	No	15 (46.9)		44 (72.1)	
Survival	Exitus	1 (3.1)	0 (0)	1 (1.6)	0.130
	Alive	31 (96.9)	29 (100)	60 (98.4)	
Hospitalization days (median, min-max)		8 (4-28)	7 (0-25)	8 (0-28)	0.337

PTE: Pulmonary thromboembolism, min: Minimum, max: Maximum

No difference was observed between two groups regarding factor V Leiden mutation, while the prothrombin 20210A mutation was significantly more common in post-COVID PTE patients ($p<0.05$). For other thrombophilia mutations; including MTHFR gene mutation, anticardiolipin and antiphospholipid antibodies, and protein S and protein C values, no significant difference was seen between two groups. The D-dimer values were higher in patients with post-COVID PTE diagnosis compared to those without, and the difference was found statsistically significant ($p<0.05$) (Table 2, 3).

DISCUSSION

Complex interactions between varying processes partake in the thrombosis development in COVID-19 patients, however exact individual components causing these complicatinos have yet to be understood. With our study, we aimed to stimulate further research to clarify the biological and clinical implications of inherited thrombophilic conditions in SARS-CoV-2 infection and to promote the idea of an optimal approach to anticoagulation in these cases.

In a study conducted in Sweden, roughly one million patients who tested positive for SARS-CoV-2 infection between the dates of February 1, 2020, and May 25, 2021, were examined and compared with over 4 million control subjects. The study reported that there was an elevated risk for pulmonary thromboembolism in the acute phase following COVID-19, along with increased incidence for DVT within three months, PTE within six months, and bleeding risk within two months following infection history. Overall, the study reported that COVID-19 was a risk factor for DVT, PTE, and hemorrhage.[9]

In a meta-analysis consisting of 20 studies, a total of 1988 COVID-19 patients were evaluated, and 30% of the patients had VTE, 20% had DVT, and 18% had PTE. Similar rates were observed when patients in intensive care units and under antithrombotic prophylaxis were evaluated as a subgroup analysis. The study also reported that a higher body weight was linked to a higher incidence of PTE, and the elderly population was more suspectable to VTE, including PTE and DVT. Male gender was not found a risk factor.[10] Other studies reported that in patients with severe COVID-19 diagnosis, a longer prothrombin time (PT), higher D-dimer values, and lower platelet counts were observed.[11-14] Currently, available literature summarizes that coagulopathy seen in severe COVID-19 would be caused by a combination of localized thrombotic microangiopathy and low-grade disseminated intravascular coagulopathy (DIC).[15]

Many studies have reported that in viral infections, levels of coagulation molecules including factor XI, factor VIII,

Table 2. Mutation and thrombophilia factor comparison between two groups

Parameters (n, %)		Post-COVID PTE (n=32)	Non-COVID PTE (n=29)	Total (n=61)	p value
Factor V leiden mutation	Heterozygote	2 (6.3)	2 (6.9)	4 (6.6)	0.315
	Homozygote	0 (0)	2 (6.9)	2 (3.3)	
	Normal	30 (93.7)	25 (86.2)	55 (90.1)	
Prothrombin 20210A mutation	Heterozygote	5 (15.6)	0 (0)	5 (4.9)	0.032
	Homozygote	0 (0)	2 (3.3)	2 (6.9)	
	Normal	29 (84.4)	27 (93.1)	56 (91.8)	
MTHFR gene 1 mutation	Heterozygote	8 (25)	5 (17.2)	13 (21.3)	0.358
	Homozygote	5 (15.6)	2 (6.9)	7 (11.5)	
	Normal	19 (59.4)	22 (75.9)	41 (67.2)	
MTHFR gene 2 mutation	Heterozygote	6 (18.8)	5 (17.2)	11 (18)	0.534
	Homozygote	5 (15.6)	2 (6.9)	7 (11.5)	
	Normal	21 (65.6)	22 (75.9)	43 (70.3)	
Anticardiolipin IgM	Positive	0 (0)	0 (0)	0 (0)	-
	Negative	32 (100)	29 (100)	61 (100)	
Anticardiolipin IgG	Positive	0 (0)	0 (0)	0 (0)	-
	Negative	32 (100)	29 (100)	61 (100)	
Antiphospholipid IgM	Positive	0 (0)	0 (0)	0 (0)	-
	Negative	32 (100)	29 (100)	61 (100)	
Antiphospholipid IgG	Positive	0 (0)	0 (0)	0 (0)	-
	Negative	32 (100)	29 (100)	61 (100)	
Parameters (mean, SD)					
Protein C (IU/dl)		74.28 (±5.58)	73.51 (±7.02)	73.91 (±6.26)	0.639
Protein S (IU/dl)		71.9 (±8.12)	71.37 (±5.24)	71.65 (±6.85)	0.767
Antithrombin 3 (%)		71.65 (±4.75)	72.48 (±9.98)	72.04 (±7.64)	0.677
Fibrinogen (mg/dl)		308.46 (±46.83)	301.72 (±44.36)	305.26 (±45.42)	0.567

PTE: Pulmonary thromboembolism, MTHFR: Methylenetetrahydrofolate reductase, SD: Standard deviation, IgM: Immunoglobulin M, IgG: Immunoglobulin G, SD: Standard deviation

Table 3. Comparison of laboratory results between two groups				
Parameters (median, min-max)	**Post-COVID PTE (n=32)**	**Non-COVID PTE (n=29)**	**Total (n=61)**	**p value**
WBC (10^3/µl)	8.6 (2.82-18.26)	9.63 (5.36-24.85)	9.23 (2.82-24.85)	0.038
NLR	3.06 (0.91-16.8)	3.69 (1.36-20.69)	3.2 (0.91-20.69)	0.239
Hemoglobin (g/dl)	13.25 (8-16.8)	14.5 (11.1-17.3)	13.7 (8-17.3)	0.054
Platelet (10^3/µl) (mean, SD)	246.03 (±77.40)	248.03 (±88.54)	246.98 (±82.19)	0.925
Uric acid (mg/dl)	4.95 (3.3-9.7)	5 (1.7-7.7)	5 (1.7-9.7)	0.448
LDH (IU/L)	244.5 (147-558)	283 (151-1134)	270 (147-1134)	0.309
Albumin (g/L)	39.9 (18.7-47)	37.5 (27.4-48)	38.1 (18.7-48)	0.319
D-dimer (µg FEU/L)	2.88 (0.23-17.85)	1.51(0.22-9.13)	1.9 (0.22-17.85)	0.030

PTE: Pulmonary thromboembolism, WBC: White blood cell, NLR: Neutrophile lymphocyte ratio, LDH: Lactate dehydrogenase, SD: Standard deviation, FEU: Fibrinogen equivalent unit

Von Willebrand factor, soluble tissue factor, prothrombin fragment 1β 2 and thrombin-antithrombin complexes, platelet activation, and fibrin degradation products were found to be increased.[16,17] The link between the release of cytokines and the coagulation cascade was assumed to be the cause of these findings.[18] Patients with severe COVID-19 disease symptoms typically have high D-dimer, fibrin degradation products, fibrinogen, and low antithrombin levels.[19] These findings could be attributed to the discussed studies, and similarly, in our study, D-dimer values were significantly higher in patients with post-COVID PTE. The prolongation of the inflammatory process and the development of endothelial dysfunction due to cytokine storm may explain microthrombus formation in critically ill patients, and a similar process could be assumed for patients with post-COVID history and their higher D-dimer levels.

Setefely et al.[20] reported in a study with 102 hospitalized COVID-19 patients that Factor V activity was considerably higher in COVID-19 patients compared to concurrent controls. Patients with a Factor V activity over 150 IU/dl had a significantly higher DVT and PTE incidence rate than those lower than the reported value.

In a study examining the association between hereditary thrombophilia and VTE due to COVID-19, patients diagnosed with hereditary thrombophilia, prothrombin G20210A and factor V Leiden mutations were investigated. Patients with hereditary thrombophilia were found to have a higher risk of VTE after SARS-CoV-2 infection than those without thrombophilia, despite all other demographic results, medication history, and comorbidities being similar within two groups.[21] In our study, in our study, no difference was observed between post-COVID and non-COVID PTE patients regarding factor 5 Leiden mutation incidence, whereas the prothrombin 20210 A mutation was observed more commonly in post-COVID PTE patients and was statistically significant. No difference was present between the two groups regarding MTHFR gene mutation, anticardiolipin and antiphospholipid antibodies, and protein S and protein C values.

A case series that suggested previously unidentified inherited thrombophilias are likely a contributing factor to mortality in COVID-19 individuals suggested that COVID-19 infection was a factor in death. Consequently, it was underlined that more investigation is required to clarify the association between thrombotic risk factors and to demonstrate that SARS-CoV-2 patients with genetic thrombophilias are more susceptible to thrombotic consequences.[22]

CONCLUSION

It is not possible to distinguish which patients may develop PTE during the post-COVID period. The assumption that those with a history of thrombosis or with known thrombotic risk factors would cause post-COVID PTE also does not have any adequate supporting evidence, compared to the general population.

In our study, we found that D-dimer values were higher in patients with post-COVID PTE than in patients with non-COVID PTE, and prothrombin 20210A mutation was more common in the patient group with post-COVID PTE. Although we obtained significant results, we believe that because of our limited number of patients and the study's single-centre nature, further studies with a larger study group are required to illuminate this topic.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Oncology Training and Research Hospital Ethics Committee (Date: 05.09.2024, Decision No: 2024-09/128).

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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Functional outcomes of 26 patients surgically treated for talus fractures

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ABSTRACT

Aims: This study evaluates whether trauma mechanisms, fracture types, and surgical treatment choices in cases of operatively treated talus fractures have an effect on the clinical outcomes of patients.

Methods: Twenty-six patients over the age of 18 who were surgically treated between 2019 and 2022 were included in the study. The collected data included age at the time of injury, gender, trauma characteristics (affected side, trauma mechanism, associated injuries), treatment characteristics (surgical delay, operation time, length of hospital stay), rates and types of revision surgery, and last follow-up date. The American Orthopaedic Foot & Ankle Society (AOFAS) Ankle-Hindfoot Score and a Visual Analogue Scale (VAS) were used to measure patient-reported outcomes.

Results: The mean age of the cohort was 33.6±11.8 years and it included 8 women (30.7%) and 18 men (69.2%). The most common trauma mechanisms were falls from a height (10 patients) and injuries sustained during traffic accidents (6 patients). The most common surgery performed was cannulated screw osteosynthesis (20 patients, 76.9%), followed by plate osteosynthesis (5 patients, 19.2%) and K-wire and screw osteosynthesis (1 patient, 3.9%). The mean VAS score was 1.9±2.1 (range: 0-8) and the mean AOFAS score was 67.2±25.5 (range: 17-97).

Conclusion: This study revealed that the selected surgical method, fracture type, and trauma mechanism did not have significant effects on patient-reported functional outcomes. These results suggest that, although talus fractures are rare, the need for surgical intervention and the occurrence of postoperative complications make these fractures a significant type of trauma.

Keywords: Talus fracture, trauma mechanism, screw osteosynthesis

INTRODUCTION

The incidence of talus fractures has increased in recent years. Although they previously accounted for 0.85% to 1% of all fractures, recent epidemiological data suggest that talus fractures are now approximately 2% of all fractures.[1,2] Talus injuries are most commonly seen following high-energy trauma and they predominantly occur in male individuals under 40 years of age. Due to the high-energy mechanisms, the rates of associated fractures are high.[3] Although they are rare, talus fractures present significant challenges for trauma surgeons and can potentially lead to permanent disability in ankle and foot function.[4] Previous studies have highlighted fracture displacement and delayed surgery as risk factors for complications in cases of talus fractures. Historically, urgent open reduction and internal fixation (ORIF) has been recommended to reduce the incidence of complications.[5] However, more recent publications suggest no correlation between the timing of surgical fixation and the development of osteonecrosis.[6,7] Approximately 57% of the talar surface is covered by articular cartilage.[8] This unique anatomical feature presents three challenges in the treatment of talus injuries: relatively limited surface area is available for vascular entry, fracture displacement can easily disrupt the mechanics of nearby joints, and obtaining access for surgical treatment requires the management of tight constraints. Due to these anatomical characteristics, avascular necrosis (AVN) and post-traumatic arthritis (PTA) are common complications following traumatic talus fractures.[4-11] In this study, we evaluate whether the trauma mechanisms, fracture types, and surgical treatment choices in cases of operatively treated talus fractures have an effect on the clinical outcomes of patients.

METHODS

Upon receiving Ankara Bilkent City Hospital No. 2 Clinical Researches Ethics Committee approval (Date: 21.02.2024, Decision No: TABED 1-24-209), the records of 26 patients diagnosed with talus fractures and surgically treated between 2019 and 2022 in the Orthopaedics and Traumatology Clinic of Ankara Bilkent City Hospital were reviewed. The collected data included age at the time of injury, gender, trauma characteristics (affected side, trauma mechanism, associated injuries), treatment characteristics (surgical delay, operation

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time, length of hospital stay), rates and types of revision surgery, and the last follow-up date. All surgically treated patients over 18 years of age were included in the study. Patients with substance abuse, those who presented for revision surgery after external surgery, those with follow-up durations of less than 12 months, and those who were conservatively followed were excluded from the study. The American Orthopaedic Foot & Ankle Society (AOFAS) Ankle-Hindfoot Score[12] and a visual analogue scale (VAS) were used to measure patient-reported outcomes. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Surgical Technique

A surgeon specialized in lower extremity surgery evaluated the surgical indications. The definitive criteria for surgical treatment were open fractures and dislocation of the ankle joint with failed closed reduction. Surgical treatment was applied for all patients with displaced fractures. Operative treatment involved temporary external fixation in the case of major dislocations, followed by ORIF with screws, plates, or K-wires for osteosynthesis. In cases of closed talus fractures without dislocation and therefore with a lower risk of AVN, surgery was performed after soft tissue consolidation. The patient was positioned supinely, 1.5 g of prophylactic cefuroxime was administered, and a thigh tourniquet was applied and inflated to control bleeding. Fixation of talar neck and body fractures was typically achieved with K-wires, followed by definitive fixation with cannulated screws after radiographic control. For fragmented talar body fractures, for which screw osteosynthesis was unsuitable, plate osteosynthesis was performed via an anteromedial or anterolateral approach. Postoperative care included partial weight-bearing with a walking boot for 6 weeks using two crutches with 15 kg of weight-bearing together with antithrombotic therapy until full weight-bearing was achieved.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 22.0 for Windows. Descriptive statistics for numerical variables were expressed as mean, standard deviation, median, and minimum-maximum values. Descriptive statistics for categorical variables were expressed as percentages and frequencies. The Shapiro-Wilk test showed that the quantitative variables did not have normal distribution; therefore, non-parametric test procedures were employed. The Mann-Whitney U test and Kruskal-Wallis analysis of variance were used to identify the relationships between studied parameters. For the binary analysis of categorical data, the chi-square test was used. Results were evaluated with 95% confidence intervals at a significance level of $p<0.05$.

RESULTS

Between 2019 and 2022, a total of 32 patients were treated for talus fractures. Twenty-six of those patients underwent surgery and 6 were treated conservatively. The mean age of the study cohort was 33.6±11.8 years and it included 8 women (30.7%) and 18 men (69.2%). The average age of the female patients was 32 years, while the average age of the male patients was 34.2 years. Fifteen patients (57.6%) had right-side fractures and 11 (42.3%) had left-side fractures. The characteristics of the patients are summarized in Table. The most common trauma mechanisms were falls from a height (10 patients) and injuries sustained during traffic accidents (6 patients) (Table). Simultaneous lower extremity injuries were observed in 12 patients (46.1%). Three patients had open talus fractures. In total, 5 patients had dislocations in the talocrural, talocalcaneonavicular, and/or subtalar joints. Fractures with dislocations were treated with emergency ORIF in 2 cases, temporary external fixation involving the ankle joint in 1 case, and successful closed reduction followed by ORIF in 2 cases. The time between trauma and surgery was 4.4±5.8 days (range: 0-25 days). The most common surgery performed was cannulated screw osteosynthesis for 20 patients (76.9%), followed by plate osteosynthesis for 5 patients (19.2%) and K-wire and screw osteosynthesis for 1 patient (3.9%). Four patients (15.3%) required revision surgery due to postoperative infection (n=1), malreduction (n=2), or nonunion (n=1). The mean follow-up period for all patients was 30.3 months (range: 12-49 months). The mean VAS score was 1.9±2.1 (range: 0-8) and the mean AOFAS score was 67.2±25.5 (range: 17-97). No significant differences were found in VAS or AOFAS scores according to fracture types (p=0.91, p=0.40), trauma mechanisms (p=0.31, p=0.21), or surgical approaches (p=0.06, p=0.05).

Table. Demographic, clinical, and radiological characteristics of the patients

Demographics	Age		33.6±11.8
	Gender	Female	8 (30.7%)
		Male	18 (69.2%)
Fracture type	Neck fracture		16 (61%)
	Body fracture		7 (26%)
	Head fracture		3 (11%)
Trauma mechanisms	Fall of <3 m		5 (19.2%)
	Fall of >3 m		10 (38.5%)
	Road traffic accident		6 (23.1%)
	Ankle distortion during sports		5 (19.2%)
Type of definitive treatment	Screw osteosynthesis		20 (76.9%)
	Plate osteosynthesis		5 (19.2%)
	Screw osteosynthesis + K-wire		1 (3.9%)
Reintervention rate after definitive operation	Implant removal		4 (15.4%)
	Deep infection		1 (3.8%)
	Malreduction		2 (7.7%)
	Nonunion		1 (3.8%)
Time from trauma to surgery (days)			4.4±5.8
VAS score			1.9±2.1
AOFAS score			67.2±25.5

DISCUSSION

Talus fractures pose a significant challenge for trauma surgeons due to their rarity and the potential for serious complications. In our study, the outcomes of 26 cases of talus fracture were evaluated and the effects of trauma mechanism, fracture type, surgical delay, and treatment method on patient outcomes were analysed. Our findings largely align with the existing literature while providing new insights in some areas. Long-term PTA development is common after talus fractures, with recent studies reporting a high prevalence of up to 75%. It is noted that complex fractures, particularly in the neck and

body of the talus, significantly contribute to the development of PTA, as damage to the joint surface in these fractures increases the risk of post-traumatic arthritis.[13,14] In our study, dislocations in the talocrural, talocalcaneonavicular, and/or subtalar joints were observed in 5 patients, and 2 of those patients underwent emergency ORIF. There were no significant complications in these cases, but as the literature suggests, the potential risk of such complications in displaced fractures should always be considered.[6] Four patients in our study required revision surgery, supporting the higher complication risk associated with displaced fractures. Regarding AVN risk, some studies in the literature indicate that surgical timing and fracture displacement have direct effects on the development of AVN.[9] Recent studies suggest that the impact of surgical timing on the development of AVN is less significant than previously thought, and that the proper application of surgical technique plays a more critical role. Particularly in high-energy injuries, the risk of AVN increases; however, it has been observed that delaying surgical intervention does not necessarily lead to a heightened risk. This indicates that surgical techniques are a crucial factor in the optimal management strategies for talus fractures.[13,14] In our study, the mean time between trauma and surgery was 4.4 days, which is consistent with the recommended time intervals in the literature. This may be associated with the low incidence of AVN in our study. High-energy trauma is the most common cause of talus fractures, with such injuries frequently being associated with motor vehicle accidents or falls from a height.[12] In our study, 10 patients were injured in falls from a height and 6 patients were injured in traffic accidents. As noted in the literature, high-energy trauma typically results in more complex fractures and higher complication rates.[15] However, in our study, there was no significant difference between VAS or AOFAS scores according to trauma mechanisms. This suggests that the trauma mechanism may not always have a clear effect on functional outcomes in cases of talus fractures. As functional outcomes of our study, the mean VAS score was 1.9 and the mean AOFAS score was 67.2. The literature indicates that functional recovery after a talus fracture is slow, and many patients experience permanent pain and movement restrictions.[16] New research indicates that complex talus fractures have a negative impact on functional outcomes, with higher complication rates associated with these types of fractures. Accordingly, it is noted that simple fractures result in higher AOFAS scores after treatment, while complex fractures are associated with significantly lower scores.[13,14] Similarly, in our study, most patients did not achieve full functional recovery and the average scores indicated moderate functional losses. In particular, lower AOFAS scores were observed in cases involving complications; for example, patients undergoing revision surgery due to malreduction had more limited functional recovery. Regarding surgical treatment, our study showed that the most common method used in the treatment of talus fractures was cannulated screw osteosynthesis, applied for 20 patients. This surgical method has been noted in the literature for its effectiveness in restoring joint integrity.[17] In our study, the majority of patients who underwent cannulated screw osteosynthesis experienced a complication-free postoperative period. However, the literature also highlights plate osteosynthesis as an effective method for comminuted talus fractures.[18] In our study, 5 patients underwent plate osteosynthesis and successful outcomes were achieved. Particularly for comminuted fractures, the use of this technique in the present study aligns with the results in the literature. The timing of surgical intervention and the surgical technique significantly influence long-term recovery and complication risks in cases of talus fractures. The literature emphasizes that urgent surgical intervention and selection of a proper technique can reduce the risk of AVN and PTA.[19] In our study, although no significant relationship was observed between surgical delay and AVN development, the general findings are consistent with the complex data presented in the literature.

Limitations

The fact that this study was retrospective and did not incorporate long-term results was a limiting factor. In addition, due to the rarity of talus fractures, a small number of patients were included in the analysis and the subgroups for trauma mechanism, surgery type, and fracture location were accordingly very small. This was another limiting factor.

CONCLUSION

In this study, we concluded that the selected surgical method, fracture type, and trauma mechanism did not have significant effects on patient-reported functional outcomes after talus fractures. Our results demonstrate that, although talus fractures are rare, the need for surgical intervention and the rate of postoperative complications make these fractures a significant type of trauma. Surgical treatment methods should be selected carefully according to fracture type and trauma mechanism, and patients should be closely monitored postoperatively. While the outcomes of high-energy traumas are more complex than those of low-energy injuries, complications can be minimized with timely surgery and proper techniques.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Bilkent City Hospital No. 2 Clinical Researches Ethics Committee (Date: 21.02.2024, Decision No: TABED 1-24-209).

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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Chronic obstructive pulmonary disease and malnutrition: severity of the disease and controlling nutritional status (CONUT) score

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ABSTRACT

Aims: The definition for chronic obstructive pulmonary disease (COPD) is abnormalities of the or alveoli, that can cause chronic respiratory symptoms. A significant number of COPD patients have malnutrition. We aimed to demonstrate the correlation between the Control of Nutritional Status (CONUT) score and the severity of the disease, the number of hospitalizations, and emergency department visits due to acute exacerbations of COPD. **Methods:** Patients over 65 years of age diagnosed with COPD were included in this study. Smoking habits, systemic and pulmonary comorbidities, Modified British Medical Research Council (mMRC) survey score and COPD assessment test (CAT) score, number of COPD exacerbations, number of hospitalizations due to COPD in the last year were recorded. CONUT score was calculated by looking at blood albumin, total cholesterol and lymphocyte levels. **Results:** This study was carried out with 112 COPD patients. The mean age of our patients was 72.28±7.3 (64-96). Of the 112 patients, 26 (23.2%) were female and 86 (76.8%) were male. Forced expiratory volume in 1 second (FEV1%) was 42.31% (13.00-75.00%), CAT 17.83±6.8 (7-34), mMRC 2.19±1.1 (0-4), COPD attack count 2.30±2.1 (0-9) and 35 patients were hospitalized due to COPD attacks. The CONUT score determined as 2.71±2.3 (0-9), 45 (40.1%) patients were normal, 36 (32.1%) were light, 29 (25.9%) were moderate, and 2 (1.8%) patients were severe. There was a statistically significant, correlation between CONUT values and FEV1 (%), CAT and mMRC values. The patients were divided into 2 groups as low (values 4 and below) and high (values 5 and above). A statistically significant difference was found between the CONUTs high and low groups in terms of CAT, mMRC and FEV 1 (%). The number of high CONUT attacks was statistically significantly higher than the number of low CONUT attacks. High CONUTs hospitalization rates are significantly higher than low CONUTs hospitalization rates. **Conclusion:** The CONUT score is accepted as a promising tool for the assessment of malnutrition. In our study, CONUT scores were high in COPD patients over 65 years of age with low FEV1%, high CAT and high mMRC values. This high level suggests that the CONUT score may be a new prognostic predictor. And again, we found that the CONUT score was associated with a high number of attacks and hospitalizations. These results suggest that the use of the CONUT score may help adapt patients' follow-up and treatment strategies.

Keywords: COPD, CONUT, malnutrition

INTRODUCTION

The definition for chronic obstructive pulmonary disease (COPD) is abnormalities of the airways (bronchitis/bronchiolitis) or alveoli (emphysema), that can cause chronic respiratory symptoms (dyspnea, cough, sputum). It's a heterogeneous condition and causes persistent and often progressive airway obstruction.[1] COPD is a significant cause of mortality and morbidity worldwide and is the third leading cause of all deaths.[2] Worsening of symptoms of cough, sputum and/or dyspnea accompanied by tachypnea and/or tachycardia within the last 14 days as a result of local and systemic inflammation due to infection, air pollution or other exposure are defined as acute exacerbations in COPD.[1] COPD exacerbations cause an increase in the need for hospitalization and an increase in secondary mortality rates.[3] Exacerbation of COPD is the cause of a significant portion of health care costs attributable to COPD.

A significant number of COPD patients have malnutrition. Studies have reported a strong link between body weight and respiratory muscle mass, and have shown that progressive respiratory disorders develop with malnutrition.[4,5] Malnutrition is detected in 25% of COPD patients followed in outpatient clinics and 50% of COPD patients treated in hospitals.[6] This rate reaches 60% in critically ill COPD patients with acute respiratory failure.[7] COPD patients with protein energy malnutrition also have Weight loss. Weight loss and loss of lean body mass affect respiratory function capacity negatively and life expectancy in COPD patients.[8]

Monitoring of body weight reduction in COPD patients has been identified as a poor prognostic factor.[9] Weight loss in COPD patients is an independent risk factor and is caused by malnutrition, high metabolic rate and/or inappropriate

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nutritional intake.[10] Patients with advanced COPD often have a decrease in body weight. It is stated that there is a decrease in body weight in about half of all COPD patients; in particular, one-fourth of people with severe disease and one-third of patients with extremely severe disease also have losses in free fat mass index.[11] In COPD patients, normal daily respiratory energy expenditure increases 10-fold, and this increase in energy expenditure cannot be replaced by proportional energy intake and may lead to malnutrition.[12] Higher mortality in COPD patients has been associated with malnutrition.[10] A study based on the European Society of Clinical Nutrition and Metabolism (ESPEN) showed that malnutrition has a significant effect on prognosis at two years. In addition, this study stated that free fat mass index is more significant in the diagnosis of malnutrition and COPD prognosis.[13] According to data from many studies, it is seen that 30-60% of patients hospitalized with COPD have impaired nutritional status, which increases the risk of hospitalization, decreases exercise tolerance and has a negative effect on mortality.[14] Although a wide variety of therapeutic approaches can be used, malnutrition in COPD patients is underdiagnosed and undertreated.

The Control of Nutritional Status (CONUT) score is a simple nutritional marker that allows the assessment of a patient's nutritional status.[15] Although the CONUT score was initially developed to predict acute deterioration in surgical patients, it has a high prognostic value in certain populations such as the elderly, cancer patients, patients affected by gastroenterological or heart failure or ischemic stroke.[16]

The poor prognosis observed in elderly patients with COPD may be related to an impaired nutritional status. Therefore, as with many diseases, it is important to evaluate the nutritional status of the patient in COPD to take corrective measures. Malnutrition in COPD patients is underdiagnosed and therefore untreated. Based on this information, we wanted to evaluate our elderly patients with COPD with the Nutritional Status Control scale. We aimed to show the relationship between CONUT score and severity scores, the number of hospitalizations and emergency department admissions due to acute exacerbation of COPD.

METHODS

Ethical Approval

This study was approved by the Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (Date: 28.05.2024, Decision No: 2661). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population and Design

This cross-sectional retrospective study included patients diagnosed with COPD over 65 years of age. Patients who came to the Chest Diseases Outpatient Clinic of our hospital between 01.01.24 and 01.06.24 for control were included in our study.

All COPD patients over the age of 65 who applied to the outpatient clinic within the specified period were evaluated. Patients over the age of 65 whose diagnosis of COPD was confirmed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria, who did not have a known chronic disease other than COPD, and who had laboratory tests within the last 6 months were admitted to our study.[1] Patients under the age of 65, with missing file and laboratory information, with previously known chronic diseases other than COPD, with insufficient information for identification criteria, patients with sleep breathing disorder, patients with neurological diseases such as advanced dementia, Alzheimer's, cerebrovascular disease, and patients with a history of orthopedic or other surgical operations were not included in this study.

Data Collection

Detailed anamnesis, pulmonary function tests and posterior anterior chest radiographs are routinely performed in COPD patients admitted to the outpatient clinic. All COPD patients over the age of 65 who applied to the outpatient clinic within the specified period were re-evaluated by the physicians participating in the study. Patients whose diagnosis of COPD was confirmed and laboratory data were found in the system were recorded in the study excel file. Smoking habits, systemic and pulmonary comorbidities, Modified British Medical Research Council (mMRC) survey score and COPD Assessment Test (CAT) score, number of COPD exacerbations, number of hospitalizations due to COPD in the last year were recorded. Blood sampling was saved on all patients to determine glucose, albumin, total cholesterol, creatinine, hemoglobin, white blood cells (WBCs), lymphocytes, and C-reactive protein (CRP).

Scale

Nutritional status was evaluated using the the CONUT score. The CONUT score, first used by Ignacio de Ulíbarri et al.[15,] is a new nutritional marker based on serum albumin value, absolute lymphocyte count and serum cholesterol value. Values between 0-12 can be detected; 0-1: normal, 2-4: light, 5-8: moderate, and 9-12: severe are considered high.

Statictical Analysis

IBM SPSS 26.0 package program was used in the statistical analysis of the study. Descriptive statistics (frequency, percentage, min-max values, median, mean, standard deviation, etc.) of the demographic data, clinical values, laboratory results of the study participants were calculated. Before all statistical analyses, the normal distribution of the parameters was determined by the Shapiro-Wilk test. Parametric tests were used for the analysis of normally distributed variables, and non-parametric tests were used for the analysis of normally distributed variables. Accordingly, pearson correlation analysis was used for normally distributed parameters and Spearman correlation analysis was used for non-normally distributed parameters in relationship analysis. In the comparison of CONUT low/high groups in terms of related parameters, independent samples t test, which is one of the parametric tests, was used for the parameters that were not normally distributed, and Mann-Whitney U test, which was one of the nonparametric tests, was used for the parameters

that were not normally distributed. Chi-square test was used to compare categorical data. All statistical analyses were evaluated at 95% confidence interval and significance was evaluated at p<0.05.

RESULTS

Demographic Characteristics and Laboratory Findings

This study was carried out with 112 COPD patients without distinction between men and women. The mean age of our patients was 72.31±7.27 (65-96). Of the 112 patients, 26 (23.2%) were female and 86 (76.8%) were male. The body-mass index (BMI) of the patients was 29.75 (26.51-31.23). Smoking pack-year history 39.53±6.1 (25-56). The laboratory parameters were: glucose 102.4±19.7 (67-197) mg/dl, urea 42.63±19.5 (17-153) mg/dl, creatinine 1.1±0.4 (0.32-3.82) mg/dl, alanine aminotransferase 18.69±10.7 (7-71) U/L, aspartate aminotransferase 22.68±9.4 (6-62) U/L, albumin 3.81±4.7 (2.79-5.36) g/dl, total cholesterol 173±36.3 (114-316) mg/dl, C-reactive protein 10.47±13.9 (0.5-90.43) mg/L, hemoglobin 13.26±1.7 (8.6-17.5), hematocrit 40.35±4.9 (26.7-52.6), platelet 250.07±85.4 (108-713) 10^9/L, lymphocytes 1730±700 (490-3660) n/mm^3 (Table 1).

Table 1. Baseline demographic and laboratory findings of the study population

Characteristics	Patients (n=112)
Gender, n(%)	
Female	26 (23.2%)
Male	86 (76.8%)
Age, year, mean±SD (min-max)	72.31±7.27 (65-96)
BMI, year, mean±SD (min-max)	26.24±5.1 (15.7-44.44)
Smoking habit	
Pack-years (min-max)	39.53±6.1 (25-56)
Laboratory parameters, mean±SD	
White blood cell (10^9/ml)	8.33±2.1
Hemoglobin (g/dl)	13.26±1.7
C-reaktive protein (mg/L)	10.47±13.9
Lymphocytes (n/mm^3)	1.73±0.7
Albumin (g/dl)	3.81±0.47
Total cholesterol (mg/dl)	173.53±36.3

SD: Standard deviation, min: Minimum, max: Maximum, BMI: Body-mass index

Pulmonary Function Test, CAT, mMRC, CONUT

When the pulmonary function tests of one hundred and twelve patients were examined, forced expiratory volume in 1 second (FEV1%) was 42.31% (13.00-75.00%) and forced vital capacity (FVC%) was 46.50 (15.00-80.00). CAT 17.83±6.8 (7-34), mMRC 2.19±1.1 (0-4), COPD attack count 2.30±2.1 (0-9) and 35 patients were hospitalized due to COPD attacks. The CONUT score of all our patients was calculated and determined as 2.71±2.3 (0-9). When the CONUT score was evaluated according to severity, 45 (40.1%) patients were normal, 36 (32.1%) were light, 29 (25.9%) were moderate, and 2 (1.8%) patients were severe (Table 2).

Table 2. Pulmonary function test, CAT, mMRC, CONUT score data of all patients

Characteristics	Patients (n=112) Mean±SD (min-max)
Pulmonary function test	
FVC (L)	1.53±0.6 (0.42-3.07)
FVC (%)	46.5±14.6 (15-80)
FEV1 (L)	1.08±0.4 (0.29-2.14)
FEV1 (%)	42.31±13.1 (13-75)
FEV1/FVC	71.6±13.2 (38-100)
CONUT	2.71±2.3 (0-9)
Number of exacerbations	2.3±2.1 (0-9)
Hospitalization, n (%)	35 (31.25)
CAT	17.83±6.8 (7-34)
mMRC	2.19±1.1 (0-4)

SD: Standard deviation, min-max: minimum-maximum, FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, CONUT: Controlling nutritional status, CAT: COPD assessment test, mMRC: Modified medical research council

Patients' CONUT scores were compared with pulmonary function test, CAT, and mMRC values. There was a statistically significant, negative, low-level correlation between CONUT values and FEV1 (%) values of the participants (p=0.0001<0.01). When FEV1 (%) decreases, CONUT increases. There was a statistically significant, positive, low-level correlation between CONUT values and CAT and mMRC values of the participants (p=0.0001<0.01). CONUT increases or decreases along with CAT and mMRC (Table 3).

Table 3. Correlation of CONUT with FEV1 (%), CAT and mMRC

		CONUT	FEV1 (%)	CAT	mMRC
CONUT	r	1.000	-.310**	.357**	.365**
	p		0.001	0.0001	0.0001
	n	112	112	112	112
FEV1 (%)	r		1.000	-.748**	-.774**
	p			0.0001	0.0001
	n		112	112	112
CAT	r			1.000	.723**
	p				0.0001
	n			112	112
mMRC	r				1.000
	p				
	n				112

CONUT: Controlling Nutritional Status, FEV1: Forced expiratory volume in 1 second, CAT: COPD assessment test, mMRC: Modified Medical Research Council

The patients were divided into 2 groups as low (values 4 and below) and high (values 5 and above) according to the results of the CONUT score. There were 81 (72.3%) patients in the low CONUT group and 31 (27.7%) patients in the high group. The mean number of attacks was 1 (0-7) in the low CONUT group and 4 (0-9) in the high group.

According to the high and low CONUT levels, the groups were compared with CAT, mMRC and FEV1%. A statistically significant difference was found between the CONUTs high and low groups in terms of CAT, mMRC and FEV1% (Table 4) (Figure).

Table 4. Comparison of CONUT with CAT, mMRC and FEV 1 (%) according to high and low			
CONUTs	**Low CONUT(≤4) n=81**	**High CONUT (≥5) n=31**	**p**
Median (Min-max)			
CAT	16 (7-33)	21 (9-34)	0.001**[2]
mMRC	2 (0-4)	3 (1-4)	0.001**[2]
Mean±SD (Min-max)			
FEV 1 (%)	44.63±13.1 (15-75)	36.26±11.1 (13-58)	0.002**[1]

SD: Standard deviation, min-max: minimum-maximum, CONUT: Controlling Nutritional Status, FEV1: Forced expiratory volume in 1 second, CAT: COPD assessment test, mMRC: Modified medical research council, [1]: Independent samples t test; [2]: Mann-Whitney U test; **: p<0.01

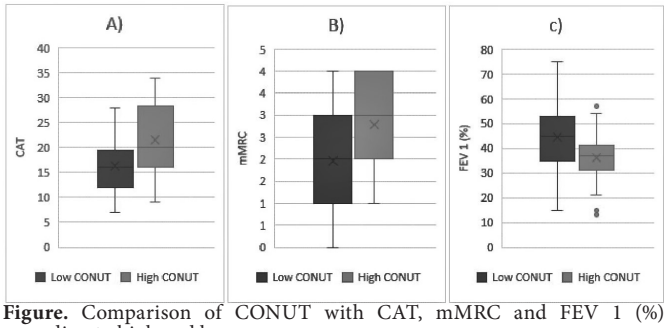

Figure. Comparison of CONUT with CAT, mMRC and FEV 1 (%) according to high and low

CONUT: Controlling nutritional status, CAT: COPD assessment test, mMRC: Modified medical research council, FEV1: Forced expiratory volume in 1 second

There is a statistically significant difference in the number of attacks between the CONUT high and low groups. (Mann-Whitney U test; U=594.5; Z=-4.383; p=0.0001<0.01). The number of high CONUT attacks was statistically significantly higher than the number of low CONUT attacks. There is a statistically significant difference between the CONUT high and low groups and the number of hospitalizations (Chi-square test; X^2=27.425; p=0.0001<0.01). High CONUTs hospitalization rates are significantly higher than low CONUTs hospitalization rates (Table 5).

Table 5. Comparison of the number of hospitalizations and the number of attacks according to CONUT high and low			
CONUTs	**Low CONUT (≤4) n=81**	**High CONUT (≥5) n=31**	**p**
n, median (min-max)			
Number of exacerbations n (%)	1 (0-7)	4 (0-9)	0.0001**[1]
Number of hospitalizations			
0	65 (80.2)	12 (38.7)	0.0001**[2]
1	13 (16)	7 (22.6)	
2	3 (3.7)	9 (29)	
3	0 (0)	2 (6.5)	
4	0 (0)	1 (3.2)	

min: Minimum, max: Maximum, CONUT: Controlling nutritional status, [1]: Mann-Whitney U test; [2]: Chi-square test; **: p<0.01

DISCUSSION

COPD is a heterogeneous disease characterized by persistent and often progressive air way obstruction.[1] Being an important cause of fatality all around the world, COPD ranks third among all deaths.[2] COPD exacerbations cause an increased need of hospitalization and an increased risk of death in patients with COPD.[3] It's been shown that a significant number of patients with COPD had malnutrition and progressive respiratory disorders developed due to malnutrition.[4,5] Although it was researched in many systemic diseases the CONUT score was not quite evaluated with COPD and its parameters. We think our study is important in this aspect.

In our study we compared the CONUT score, one of the indications of malnutrition and COPD parameters. The CONUT score was high in one third of our patients. Correlation existed between the CONUT score and FEV1%, CAT and mMRC values. As FEV1% value of our patients decreased, the CONUT score increased. Also, as CAT and mMRC values increased CONUT score increased. The second aim of our study was to assess the correlation between the COPD exacerbations and the numbers of hospitalizations along with the CONUT score. We found relation among these values.

Assessing malnutrition and supporting the assessment is vital for the management of patients with COPD.[17] There is no gold standard method to assess the nutritional status of patients with COPD. BMI is a simple method for assessing the nutritional status and a low BMI is related to a worse prognosis.[18] Along with this, BMI may not reflect the nutritional status of patients with COPD correctly.[19] In a very small portion of our patients too had low BMI. Therefore we did not use BMI to assess malnutrition.

Malnutrition causes negative effects on exercising and muscle function along with lung function, increases exacerbations, mortality and expenses.[20] In their studies Gea et al.[21] associated the status of inflammations with increased exacerbations in COPD, anorexia and increased work of breathing. They indicated that it had a direct effect on muscle dysfunction and caused an increased risk of hospitalization due to exacerbations. They added that in the end the loss of muscle mass would cause a negative functional effect by compromising the functioning of respiratory muscles. In a similar way Silvestre also indicated that malnutrition played an important role by reducing muscle mass, strength and durability of respiratory muscles in patients with COPD and also, malnutrition is related to the severity of illness and the duration of increased exacerbations, hospitalization and long-term hospitalization.[22] In a recently published article, it was stated that malnutrition in COPD caused frequent attacks in patients and it was shown that there was an increase in the number of hospitalizations and duration of stay.[23] Law et al.[24] researched malnutrition in patients hospitalized for AECOPD. They detected malnutrition in one fifth of the patients and wrote this group of patients had worse results compared to the patients without malnutrition, both during and after hospitalization. In a review article published in 2022 it was stated that malnutrition was common among patients with COPD and this existing malnutrition is associated with an increased number of attacks in COPD patients, an increased number of hospitalizations and longer hospitalization periods.[25] Similarly, in our study, we found an increase in the number of hospital admissions due to acute attacks and

therefore hospitalizations in our patients with high CONUT scores. This is related to the deterioration of the respiratory level scores (FEV1%, CAT and mMRC) of the patients due to malnutrition.

One of the three parameters of the CONUT score is albumin. Yamaya et al.[26] stated in their studies that malnutrition is associated with severe emphysema, airflow limitation, attacks related to infection and mortality. Also in this study total protein, serum albumin and lymphocyte levels were detected to be low. In a study examining malnutrition albumin level was found to be low in patients with severe COPD. It was shown that nutritional parameters of patients during exacerbation were related to length of hospital stay and duration of readmission.[27] Other than ours only one study examining the relation between malnutrition and COPD by using the CONUT score was encountered. In a study Lo Buglio et al.[28] conducted, they found the CONUT score to be high nearly in two third of COPD patients over 65 years old. In this study they detected correlation among the CONUT score and FEV1%, CAT and mMRC values. Again in this study, Lo Buglio et al. detected relation between the CONUT score and numbers of COPD attacks with the numbers of hospitalizations. We found the CONUT score to be high in nearly one third of our patients. We found negative correlation in our elderly patients' CONUT score and FEV1% value and positive correlation between CAT and mMRC values. We found a correlation between the number of exacerbations and the number of hospitalizations in our elderly COPD patients in the last year. The results of our and a limited number of other studies have shown that malnutrition, which can be prevented if attention is paid, is directly related to the respiratory scores of the patients and thus to the quality of life. Especially in the outpatient clinic, we can evaluate the patient's malnutrition and reduce the respiratory problems that may develop.

Limitations

This study was a relatively small-scale study with 112 patients. This may have influenced the statistical power to detect significant effects. In addition, since it was a single-center retrospective study, it covered a certain segment of the society. The results cannot be generalized to the entire population. Our study is the second study showing the relationship between malnutrition and COPD. Prospective and multicenter studies on more patients are needed to confirm our findings. In addition, malnutrition treatment studies with COPD can be performed to show improvements in respiratory scores.

CONCLUSION

The CONUT score is accepted as a promising tool for the assessment of malnutrition. By applying it easily in outpatient clinics, the risks that may develop in the patient can be predicted. In addition, treatment success can be increased by stopping malnutrition at an early stage. In our study the CONUT score was detected to be high in COPD patients over 65 years old who had severe symptoms, low FEV1%, high CAT and high mMRC values. This high level suggests that the CONUT score may be a new prognostic predictor. And again, we found the CONUT score to be related to the high numbers of attacks and hospitalizations in elderly patients affected by COPD. These results suggest that the use of the CONUT score may help tailor patients' follow-up and treatment strategies. We think that supporting the validity of the CONUT score in patients with COPD with studies involving a higher number of patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (Date: 28.05.2024, Decision No: 2661).

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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Enhancing morphological understanding of the lateral pterygoid muscle for orofacial pain treatment: a cadaveric study

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ABSTRACT

Aims: Injections to the lateral pterygoid muscle (LPM) have gained popularity for managing orofacial pain. Techniques like ultrasonography (USG), electromyography (EMG), and arthroscopy help prevent improper injections and tissue trauma during the procedure, but they require practitioner expertise and experience. Arthroscopy, while precise, is invasive. Blind injections are simpler and convenient for outpatient settings, but their safety is debated. This study examines the anatomical traits of the area of the injection to contribute to the safety and efficacy of these injections for temporomandibular-related orofacial pain.

Methods: The LPM consistently displayed two distinct bellies-superior and inferior-in 16 dissections of 8 cadavers. We measured lateral pterygoid plate (LPP) depth and length, pterygomaxillary angle, superior and inferior head vertical length, superior and inferior head thickness, distance between zygomatic arch and mandibular notch, and distance between superior border of inferior head and mandibular notch.

Results: Significant correlations were found between distances, thicknesses, and lengths of the muscle heads, indicating critical anatomical relationships relevant for safe injections. The mean age of cadavers was found as 79.00±1.78 years (In this article, the '±' notation corresponds to the standard deviation). The average depth and length of the LPP were 43.47±3.34 mm and 15.61±1.09 mm, respectively. The distance from the zygomatic arch to the mandibular notch was 10.76±0.39 mm, whereas the distance from the superior border of the inferior head to the mandibular notch was 6.74±0.29 mm. Significant associations were found between the distance from the zygomatic arch to the mandibular notch and both the thickness and length of the superior head ($p=0.011$ and $p=0.005$). Correlations were also observed between the distance from the superior border of the inferior head to the mandibular notch and the thickness of both heads ($p<0.001$ and $p=0.045$).

Conclusion: A greater distance from the zygomatic arch to the mandibular notch, as well as from the superior border of the inferior head to the mandibular notch, may potentially improve the safety and ease of injections into the LPM. Our study, therefore, provides insights to the anatomical traits of the region and contributes to safety of blind LPM injections to treat temporomandibular-related orofacial pain.

Keywords: Lateral pterygoid muscle, orofacial pain, temporomandibular joint, temporomandibular pain, cadaveric study

INTRODUCTION

The lateral pterygoid muscle (LPM) is essential for various temporomandibular joint (TMJ) movements, such as protrusion, depression, and mediotrusion, which facilitate TMJ opening and lateral motion.[1] Dysfunction of the pterygoid muscles can lead to TMJ dislocation,[2] mandibular issues such as restricted jaw movement and TMJ clicking, as well as temporomandibular pain. Temporomandibular disorders (TMD) encompass issues affecting the masticatory muscles and TMJ, with a prevalence of 12% to 17% in the general population.[3-5] Notably, hyperactivity of the LPM is linked to TMD, and targeted injections into this muscle can help manage associated pain. This hyperactivity may also contribute to degenerative changes in the TMJ[4] and is often associated with dislocation due to excessive forward condylar movement.[2,6] Patients frequently display habits like nocturnal clenching and grinding, leading to muscle tenderness and limited movement from increased masseter activity.[5,7] Hence, injections in these muscles have been a longstanding approach for the treatment of orofacial pain.

The success of the injection may serve for both as diagnostic and therapeutic measures for patients experiencing orofacial pain.[8] Administering the injection into the muscle is uncomplicated and can be performed on outpatient basis with minimal risk of complications. Injections can be delivered via intraoral.[8] or extraoral routes, although the deep location of the LPM can make this challenging. In the event of the inadvertent injection or unintentional spread of the drug to neighboring muscles, complications such as difficulties in

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swallowing or speaking may arise.[9] Hence, to ensure both safety and efficacy, guided techniques using ultrasound, MRI, CT, electromyography (EMG), nerve stimulation and arthroscopy are recommended, although blind application is also a viable option.[5,8-11] Similar to other interventional pain treatments, ultrasound guidance is essential for preventing tissue trauma and ensuring accurate needle placement with real-time imaging, minimizing unnecessary costs and pain for the patient.[12]

Ultrasound-guided (USG) techniques provide visualization of medication spread, allowing for precise administration and reduced local anesthetic dosages. Asking the patient to open their mouth creates space between the coronoid process and the zygomatic arch, facilitating effective visualization for experienced clinicians. Electromyography (EMG) assists by inducing muscle movement, confirming correct needle placement. However, EMG carries a risk of damaging nearby structures like the maxillary artery and long buccal nerve.[8] Therefore, clinicians must be proficient in USG and EMG techniques to ensure the safety of LPM injections. While arthroscopy offers real-time imaging, it is more invasive than other techniques and requires inpatient settings. It also envolves longer treatment durations and higher costs. Thus, arthroscopy should be considered only after other methods have proven ineffective.

The blind extraoral technique requires precise knowledge of the infratemporal fossa, particularly the inferior head of the lateral pterygoid muscle, which exhibits minimal anatomical variation.[13] For injection, the clinician palpates bony landmarks with the jaw opened at least 20-30 mm wide. The entry point is 35 mm from the external auditory canal and 10 mm below the zygomatic arch, with the needle angled 15° upward toward the upper molars to reach the inferior head of the lateral pterygoid.[13] The extraoral route is ideal for blind injections, providing a safe and effective method with a direct path to the muscle. This approach can also be done in an outpatient setting.[6] The aim of this study is to analyze the anatomy of the area to ensure safer injections for treating orofacial pain from the temporomandibular region.

METHODS

Ethics

Conducting scientific studies on cadavers or cadaveric body parts do not require ethical approval. The authors would like to express their sincere gratitude to the donors and their families for their contribution to education and science. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Anatomy

The extraoral technique requires a detailed understanding of the anatomical structures within the infratemporal fossa.[13] The medial and lateral pterygoid muscles are key contributors to orofacial pain, with the LPM playing a central role in both jaw opening and closing. Located laterally in the infratemporal region, the LPM cannot be palpated due to its position on the pterygoid plate.[13] Accurate knowledge of its origin (sphenoid bone and pterygoid plate) and insertion points (condylar process and TMJ capsule) is essential for effective injection. The muscle has two bellies-superior, responsible for TMJ closure, and inferior, involved in jaw opening and protraction (Figure 1, 2). Surrounding structures, including the maxillary artery, pterygoid venous plexus, and long buccal nerve, must be carefully considered to prevent complications such as bleeding during injection.[8]

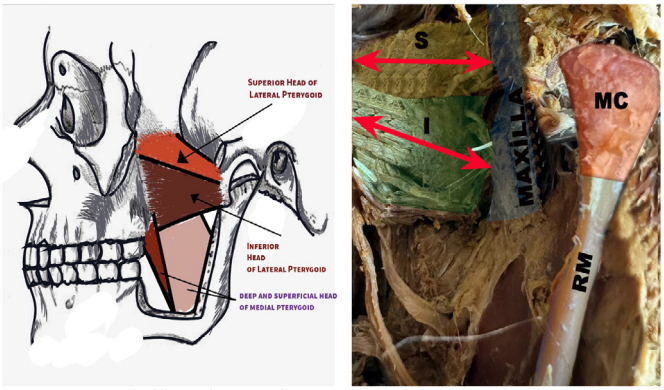

Figure 1. Two bellies of LPM; the superior and inferior head. a) illustrates the superior and inferior head. b) illustrates the length of superior and inferior heads

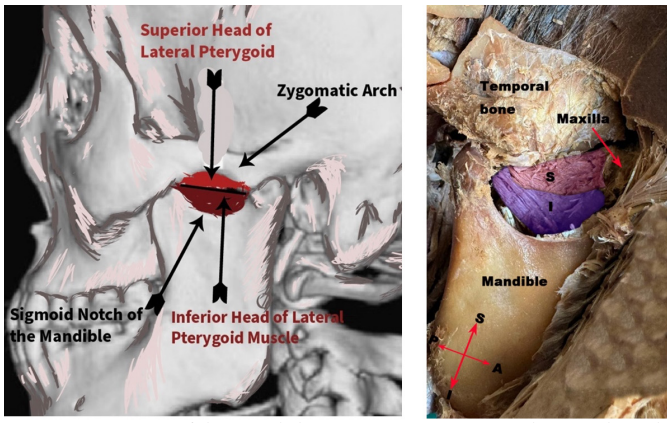

Figure 2. Location of the muscle between zygomatic arc and sigmoid notch of the mandible

To achieve a safe injection for orofacial pain patients, we dissected 8 cadaver heads, examining 16 LPM and surrounding structures, including the LPP, maxillary artery, long buccal nerve, and external auditory meatus. We thoroughly examined the LPM and its surrounding structures to identify anatomical variations that could affect injection safety. Key structures assessed included the LPP, mandibular condyle, sphenoid bone, maxillary artery, and pterygoid venous plexus, particularly due to the bleeding risks in blind injections.

This study was performed on 16 side of eight formalin-fixed cadaver heads. There was no history of surgery or trauma in the dissected area of the used cadavers. All measurements were obtained using a digital caliper (Digimatic caliper, model no: CD-15APXR; Mituyoto Corporation, Kanagawa, Japan) and by aid of a Kirshner-wire. Measurement of each parameter was performed twice and the mean results were calculated. In order to reduce variability, the first and second measurements were performed consecutively with minimal time between them.

To optimize extraoral (blind) injections, we measured the mean depth and width of the LPP and noted the locations of the maxillary tuberosity and tragus. We also assessed the LPM, focusing on the thickness and length of its superior and inferior heads. Measurements were taken from the midpoints of each belly, with the lengths determined by the origin (sphenoid bone) and insertion (condylar process) points.

Statistical Analysis

For the statistical analysis of the dry bone measurements, SPSS software version 23.0 (IBM Corp., Armonk, NY, USA) was used. Descriptive data were summarized as means and standard deviations (Stds). The Mann Witney U test was used for side comparison and $p<0.05$ was considered statistically significant. Correlation analysis between measurements was performed using the Spearman correlation test, and $p<0.05$ was considered statistically significant.

RESULTS

In all dissections conducted on both sides of 8 cadavers (totally 16 dissection), the LPM consistently displayed two distinct bellies-superior and inferior. The mean age of the cadavers found as 79.00±1.78. We measured the minimum, maximum and mean measurements for the following parameters and the data obtained are presented in Table:

Table. Descriptive statistics for the 16 dissections of the lateral pterygoid plate

	n	Min	Max	Mean	SD
LP plate depth	16	36.82	47.89	43.47	3.34
LP plate length	16	14.65	18.02	15.61	1.09
Superior head thickness	16	6.01	7.09	6.63	0.43
Inferior head thickness	16	10.98	12.96	12.00	0.54
Superior head length	16	12.01	12.96	12.53	0.37
Inferior head length	16	17.45	19.63	18.54	0.58
Distance between zygomatic arch and mandibular notch	16	10.30	11.63	10.76	0.39
Distance between superior border of inferior head and mandibular notch	16	6.23	7.02	6.74	0.29
Pterygomaxillary angle	16	168.00	181.00	174.37	4.33
%Age	16	76.00	81.00	79.00	1.78
Valid n (listwise)	16				

Min: Minimum, Max: Maximum, SD: Standard deviation

- Depth of the LPP
- Length of the LPP
- Pterygomaxillary angle
- Thickness of the two heads of the LPM
- Lengths of the two heads of the LPM
- Distance between zygomatic arch and mandibular notch
- Distance between superior border of inferior head and mandibular notch

The mean depth of the LPP from the skin surface was 43.47±3.34 mm, while its mean length was 15.61±1.09 mm. The mean vertical lengths of the superior and inferior heads at their insertion to the sphenoid bone were 12.53±0.37 mm and 18.54±0.58 mm, respectively. Additionally, at the midpoint of the muscle, the mean thicknesses of the superior and inferior heads were 6.63±0.43 mm and 12.00±0.54 mm, respectively.

The distance between the zygomatic arch and the mandibular notch (Figure 2, 3, 4a) was 10.76±0.39 mm, while the distance between the superior border of the inferior head and the mandibular notch was recorded as 6.74±0.29 mm.

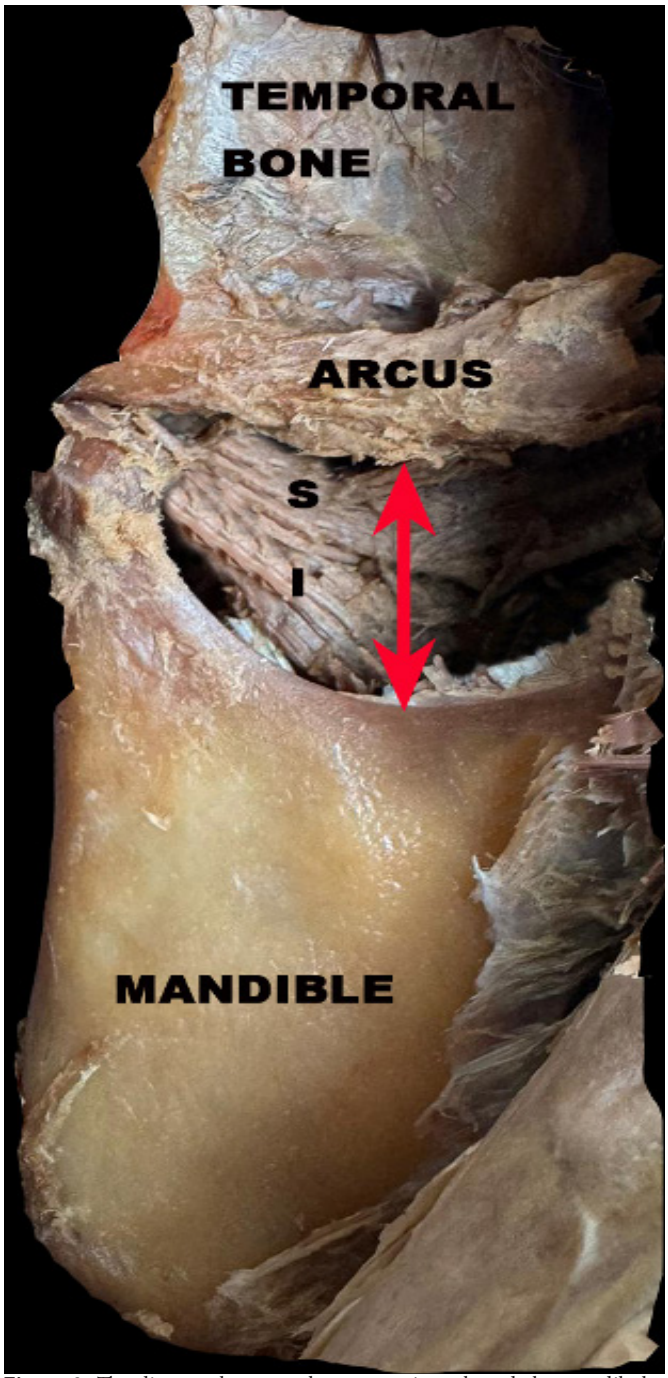

Figure 3. The distance between the zygomatic arch and the mandibular notch

There were statistically significant associations between the distance from the zygomatic arch to the mandibular notch and

both the thickness and length of the superior head (p=0.011 and p=0.005, respectively). Similarly, significant correlations were observed between the distance from the superior border of the inferior head to the mandibular notch and the thickness of both the superior and inferior heads (p=0.000 and p=0.045, respectively). Furthermore, a notable correlation was seen between the pterygomaxillary angle and the thickness of the inferior head (p=0.016).

DISCUSSION

It is well-established fact is that dysfunction of the pterygoid muscle is directly correlated with pain, significantly impacting patients' quality of life and causing functional disability.[14] Pain influences muscle function by reducing agonist activity and increasing antagonist muscle activity.[15] These alterations in muscle activity represent a protective adaptive mechanism aimed at preventing potential further injury. These changes in muscle activity are the protective adaptation mechanism for preventing possible advanced injury. Pain typically involves the masticatory muscles and the preauricular region. In case of the presence of adjacent muscles, symptoms may be accompanied by headache and neck pain.[5,16]

The abnormal activity of LPM is often associated with orofacial pain, a common occurrence in TMD patients.[4] TMD patients are characterized not only by pain but also by symptoms such as joint limitation and joint clicking, which are prominent features of the condition.[4,5,17] While LPM injection is considered to be generally safe, similar to any pain management injection, it carries a risk of bleeding. This is due to the proximity of the LPM to the maxillary artery (Figure 4b) and the pterygoid venous plexus. Inadvertent diffusion of the drug to closely located muscles may result in transient dysphagia, pain during chewing, nasal regurgitation, and dysarthria.[6] There are known recommendations for ensuring safe injections, including practices, such as aspirating during injection and promptly halting the procedure if blood is observed during aspiration.[6,17] The primary goal of this study is to conduct a thorough examination of the anatomical features within the specified region. This analysis aims to guarantee the safe administration of injections for alleviating orofacial pain stemming from the temporomandibular area.

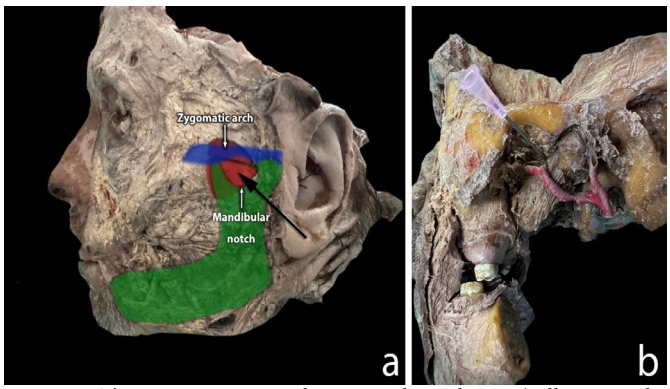

Figure 4. The injection site is shown on the cadaver. a) illustrates the injection area on the cadaver's face, while b) provides a more detailed view of the same region

The LPM is unique among the masticatory muscles as it is the sole muscle capable of depressing the mandible. The LPM also plays a role in controlling protrusion and unilateral movement of the lower jaw. Functionally, the upper head of the LPM serves as an effective stabilizer for the condyle during the closing phase.[13] The other masticatory muscles contributing to chewing and speech include the medial pterygoid, masseter, and temporalis muscles.[18] As the safe injection of the LPM involves targeting its main muscle bulk, this procedure may pose challenges for clinicians due to its deep-seated location. To address concerns regarding muscle depth, it is worth noting that our study determined the mean depth of the LPP from the skin surface to be 43.47±3.34 mm. In several studies, the LPM was found to be located at a depth of 3-4 cm consistent with our results.[6,17] Kucukguven et al.[17] reported the average depth of the LPP from the skin surface as 49.9±2.2 mm in a total of 20 cadaver half-heads. Given that over 50% of TMD patients have musculoskeletal issues as a significant source of the disease, the success of LPM injection can serve as a valuable diagnostic tool for identifying the source.[19]

The superior head of LPM primarily functions in TMJ closure, while the inferior head LPM is chiefly responsible for jaw opening and protraction. Prior research regarding the two bellies of the LPM reveals the predominance of the inferior head over the superior head in terms of size.[1] Consistent with existing data, our study confirms that both the thickness and length of the inferior head exceed those of the superior head. Specifically, we measured the thickness of the superior and inferior heads at 6.63±0.43 mm and 12.00±0.54 mm, respectively. Similarly, the length of the superior and inferior heads was recorded at 12.53±0.37 mm and 18.54±0.58 mm, respectively.

Our results revealed a mean typical pterygomaxillary angle of 174.37±4.33 degrees. Another study demonstrated comparable results, showing a mean typical pterygomaxillary angle measurement consistent with ours, at 168.3±15.8 degrees.[17] This average measurement may assist clinicians in gauging needle alignment along the LPP for accurate extraoral injections. Given the significant correlation observed between the pterygomaxillary angle and the thickness of the inferior head, we conclude that using the correct injection angle can improve the safety of the procedure.

Since muscle abnormalities associated with TMDs impact the function of the LPM, it is important to recognize that the muscle thickness may be altered as a consequence. Muscle contraction due to spasm, edema, or both could theoretically result in increased muscle belly thickness, while atrophy might lead to a relative decrease in thickness.[20] Our findings indicate that the thickness of the superior and inferior heads are 6.63±0.43 mm and 12.00±0.54 mm, respectively. In another study, the reported thickness for the superior and inferior heads were 3.1±1.2 mm and 10.2±1.8 mm, respectively.[17] Differences in the mean measurements of LPM head thickness across studies suggest the presence of the aforementioned issues, such as spasm, edema, and atrophy. Clinicians should be mindful of this potential variability when administering injections.

Our findings reveal that the mean distance from the zygomatic arch to the mandibular notch is 10.76±0.39 mm. We observed significant associations between this distance and both the

thickness and length of the superior head. Moreover, the average distance from the superior border of the inferior head to the mandibular notch measures 6.74±0.29 mm. As previously stated, significant correlations exist between this distance and the thickness of both the superior and inferior heads. Therefore, an increase in both distances-specifically, the mean distance from the zygomatic arch to the mandibular notch and the distance from the superior border of the inferior head to the mandibular notch-could potentially enhance the safety and accessibility of injections into the LPM.

Limitations

While this study discusses the advantages and disadvantages of various injection techniques (ultrasound-guided, EMG, arthroscopy, and blind injections, it lacks experimental data that directly compares these techniques, as we focused on the results of cadaver examinations. Such comparative studies are essential for determining which technique is the safest and most effective. The advanced age of the cadavers and their formalin fixation may partially limit the clinical applicability of the findings obtained from the cadaver morphological structures in living tissues, which should be taken into consideration as an additional limitation. Thus, this limitation highlights the need for future research to include direct comparisons to provide clearer guidance on best practices in clinical settings.

CONCLUSION

The blind injection technique has advantages of being simple, fast, and convenient to be applied in outpatient clinic. Yet, similar to other injections administered with a blind technique, the blindly performed LPM injection is also subject to controversy regarding its safety. However, the notable advantages warrant a detailed discussion of its safety in this study. LPM injection is a minimally invasive treatment option for orofacial pain management. Our study demonstrates that blind LPM injections can be safe for treating TMDs, particularly when clinicians possess a thorough understanding of the region's anatomy. Furthermore, we believe that designing prospective clinical studies should provide practical guidelines for clinicians to implement these findings in their practice, ensuring that our research translates effectively into clinical applications.

ETHICAL DECLARATIONS

Ethics Committee Approval

Conducting scientific studies on cadavers or cadaveric body parts do not require ethical approval. The authors would like to express their sincere gratitude to the donors and their families for their contribution to education and science.

Informed Consent

Since this was a cadaver study, written informed consent was not required.

Conflict of Interest Statement

The authors declared no conflicts of interest.

Financial Disclosure

The authors stated that this study 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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Parameters effective on survival in connective tissue disease-related interstitial lung disease

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ABSTRACT

Aims: Connective tissue diseases (CTD) are systemic diseases that most commonly cause lung involvement. To examine how the disease will progress and survival at the time of diagnosis in connective tissue disease related interstitial lung disease (CTD-related ILD).

Methods: Patients with radiological diagnosis of CTD-related ILD were included in this retrospective study. Seventy-five patients aged over 18 years, who were diagnosed as having ILD radiologically and rheumatoid arthritis, Sjögren's syndrome, polymyositis/dermatomyositis, systemic sclerosis, ankylosing spondylitis, systemic lupus erythematosus. Patients who underwent high-resolution computed tomography, pulmonary function test, carbon monoxide diffusion capacity test, and 6-minute walk test were included in the study. During the 1-year follow-up period, the data of the patients who died and survived were compared.

Results: Of the 75 patients included in the study, 55 were women and 20 were men. There were comorbidities in 56 (74.66%) patients. There was no statistical difference between the patients' CTD subtype and FEV1, FVC, FEV1/FVC, DLCO, 6MWT distance, and 6MWT baseline oxygen saturation. At the end of the 1-year follow-up period, four patients died. Age, sex, smoking, CTD subtype, presence of comorbidities, and chronic obstructive pulmonary disease were not associated with survival, but it was determined that non CTD duration, the presence of CHF, DM, and a fibrosis rate of >10% were statistically significantly associated with survival. Among the serologic markers, ESR (60.25±17.72 vs. 24.52±18.96) and CRP (81.12±80.53 vs. 6.36±7.53) were found to be statistically significantly higher in patients who died; the levels of other markers were similar to patients who survived. FEV1, FVC, and 6MWT distances were significantly lower in patients who died. The presence of emphysema, air cysts, nodule, atelectasis, septal thickening, parenchymal bands, air trapping, honeycomb, opacity, ground-glass, mosaic attenuation, and bronchiectasis was not found to be associated with survival in HRCT. However, calcific nodules, pleural effusion, bronchial wall thickening, and fibrotic change were found to be statistically significantly associated with survival.

Conclusion: We suggest that patients with CTD-related ILD with comorbidity, low baseline respiratory function parameters, a fibrosis rate of >10% on HRCT, calcific nodule, pleural effusion, bronchial wall thickening, and fibrotic changes should be followed more closely in terms of disease progression and mortality.

Keywords: Connective tissue diseases, interstitial lung diseases, survey

INTRODUCTION

Connective tissue diseases (CTD) are systemic diseases that most commonly cause lung involvement. Connective tissue diseases (CTDs) that show features of interstitial lung disease (ILD) include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), dermatomyositis (DM) and polymyositis (PM), ankylosing spondylitis (AS), Sjögren syndrome (SS), and mixed connective tissue disease (MCTD).[1] The frequency of interstitial lung disease (ILD) in patients with CTD has been reported as 40-50% and is the main cause of mortality and morbidity in these patients.[1] The frequency of lung involvement, clinical findings, prognosis, and response to treatment vary depending on both the histologic subtype and the underlying rheumatic disease. The prevalence of CTD-related ILD varies according to the classification criteria for specific diagnoses and study registries, with higher frequencies in SSc and idiopathic inflammatory myopathies (DM and PM) and lower frequencies in SLE.[1] The presence of ILD in CTD patients has been identified as an important

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risk factor for poor prognosis. Previous guideline[2] and some studies[3,4] highlight the prognostic relevance of CTD-related ILD with prognosis. However, it is challenging to compare studies and apply study findings to clinical practice because different ILD criteria are utilized in clinical trials. Moreover, due to the complexity of CTD diagnosis, there are insufficient data on parameters that can predict prognosis in patients with CTD-related ILD.

Understanding the factors that may be associated with the prognosis of CTD with ILD may help physicians select more appropriate treatments and improve the prognosis of patients.

This study aimed to investigate clinical-radiologic parameters related to survival in patients with CTD-related ILD.

METHODS

Ethics Approval

Approval was received Fırat University Ethics Committee (Date: 17.10.2019, Decision No: 15/01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

Seventy-five patients aged over 18 years, who were diagnosed as having ILD radiologically and RA, SS, PM/DM, SSc, AS, SLE in accordance with the guidelines.[1,5-9] Patients with lung malignancy, tuberculosis, chronic obstructive pulmonary disease, and drug or occupation-related ILD were not included in the study.

Study Design

This retrospective study was conducted between 2010-2015. Complete blood counts, blood levels of creatinine, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), transaminases, C-reactive protein (CRP), and the erythrocyte sedimentation rate (ESR) were studied.

Interstitial lung disease was diagnosed through clinical findings, HRCT (Philips Brillance CT 64-slice) and pulmonary function tests (PFT).[1] Patients with septal thickening, air trapping and mosaic appearance, parenchymal bands, subpleural curvilinear lines, bronchial wall thickening, ground-glass appearance, centrilobular opacity, consolidation, honeycomb appearance, nodules, bronchiectasis and emphysematous changes were included in the study. The intensity of fibrosis was recorded on HRCT (lower/higher than 10%).

Pulmonary function tests, carbon monoxide diffusion capacity measurement (DLCO), and the six-minute walk test (6MWT) were performed. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and FEV1/FVC were evaluated in the respiratory function test. Carbon monoxide diffusion capacity was measured using the single breath method. With the 6MWT, the maximum walking distance of the patient in 6 minutes, who walked at the fastest speed they could along a 55-meter corridor, was evaluated.

The patients received their routine treatments in accordance with the guidelines.[5-9]

At the end of 1 year, the survival status of the patients was recorded.

Statistical Analysis

The results are presented as mean±standard deviation, and the IBM SPSS Statistics 21 statistical program (authorization code: d91314f638c364094170; Armonk, NY, USA) was used to evaluate the data. The Chi-square test was used to compare categorical data, and student's t-test was used to compare paired groups. For all statistical analyses, $p<0.05$ was considered statistically significant.

RESULTS

Seventy-five patients who were diagnosed as having CTD-related ILD were included in the study. Of the patients, 55 (73.3%) were women. The age, sex, and disease duration of the patients according to the subtype of CTD are presented in Table 1. Patients with SLE were significantly younger than patients with RA (p=0.02), patients with RA were significantly older than patients with AS (p<0.001), patients with SS were significantly older than patients with AS (p=0.016), and patients with AS were significantly younger than patients with SSc (p=0.003). There were comorbidities in 56 (74.66%) patients.

There was no statistical difference between the patients' CTD subtype and FEV1, FVC, FEV1/FVC, DLCO, 6MWT distance, and 6MWT baseline oxygen saturation (SpO_2) (p =0.100, p=0.117, p=0.798, p=0.183, p=0.051, and p=0.131, respectively). Only the 6MWT end SpO2 of patients with SLE was significantly lower than that of patients with AS (p=0.021). Pulmonary function test results of the patients are presented in Table 2 (mean±SD).

Table 1. Age and gender distribution of patients according to connective tissue disease subtype

Connective tissue disease subtype	Age	Gender (F/M)	Disease duration (year)
Systemic lupus erythematosus (n=3)	43±19.15	2/1	7.66±2.51
Rheumatoid arthritis (n=29)	59.20±10.05	22/7	7.13±2.21
Sjögren's syndrome (n=3)	59.00±6.08	3/0	10.03±0.11
Ankylosing spondylitis (n=11)	43.45±8.98	2/9	6.63±1.74
Polymyositis/dermatomyositis (n=3)	47.66±15.14	3/0	9.0±1.73
Systemic sclerosis (n=25)	56.64±12.51	22/3	6.92±2.81
Reynaud (n=1)	47	1/0	3

At the end of the 1-year follow-up period, four patients died. The patients who died were observed to be older than surviving patients, although this did not reach statistical significance (63.50±2.64 vs. 54.26±12.57, p=0.083). All patients who died were female, and two were found to have SSc, one had SS, and one had RA.

Age, sex, smoking, CTD subtype, presence of comorbidities, and chronic obstructive pulmonary disease were not associated with survival (p=0.083, p=0.215, p=0.284, p=0.398, and p=0.231, respectively), but it was determined that non CTD duration, the presence of CHF, DM, and a fibrosis rate of >10% were statistically significantly associated with

Table 2. Pulmonary function test, DLCO and 6MWT results according to CTD subtypes

CTD subtype	FEV1 (%)	FVC (%)	FEV1/FVC	DLCO (%)	6MWT (m)	6MWT baseline SpO_2 (%)	6MWT end of SpO_2 (%)
Systemic lupus erythematosus (n=3)	77.33±14.74	77.66±15.01	81.66±4.50	60.50±24.74	283.75±136.11	94.00±4.24	91.50±4.94
Rheumatoid arthritis (n=29)	87.75±18.09	80.42±14.40	83.85±8.85	78.25±30.79	360.68±120.73	95.24±2.06	94.17±2.92
Sjögren's syndrome (n=3)	75.66±12.85	72.00±11.26	79.66±3.51	93.01±32.12	385.00±76.97	94.66±1.15	92.66±2.51
Ankylosing spondylitis (n=11)	89.00±9.41	83.20±10.20	85.10±4.25	81.66±15.19	491.09±94.07	96.45±1.21	96.27±1.84
Polymyositis/ dermatomyositis (n=3)	65.66±3.05	66.66±2.30	79.00±4.35	54.66±19.13	403.33±63.50	96.33±2.08	92.33±7.23
Systemic sclerosis (n=25)	79.29±17.80	73.45±13.64	84.33±7.16	63.21±18.53	356.09±125.76	93.31±4.46	91.22±6.15
Reynaud (n=1)	59	55	87	49	330	96	84

DLCO: Carbon monoxide diffusion capacity, 6MWT: Six-minute walk test, CTD: Connective tissue disease, FEV1: Forced expiratory volume in the first second, FVC: Forced vital capacity, SpO_2: Oxygen saturation

Table 3. PFT, DLCO and 6MWT findings of survival, non survival patients

	FEV1 (%)	FVC (%)	FEV1/FVC	DLCO (%)	6MWT (m) (m)	6MWT baseline SpO_2 (%)	6MWT baseline SpO_2 (%)
Survival (n=71)	84.69±15.25	78.41±12.69	84.36±6.36	71.80±23.23	386.66±119.32	94.91±3.14	93.3 9±4.68
Non survival patients (n=4)	51.50±18.43	54.75±13.12	73.50±13.77	25.26±24.21	221.66±92.24	93.0±1.00	89.33±1.15

PFT: Pulmonary function tests, FEV1: Forced expiratory volume in the first second, FVC: Forced vital capacity, DLCO: Carbon monoxide diffusion capacity, 6MWT: Six-minute walk test

survival (p=0.021, p=0.027, p=0.001, p=0.02, and p=0.017, respectively). Among the serologic markers, ESR (60.25±17.72 vs. 24.52±18.96) and CRP (81.12±80.53 vs. 6.36±7.53) were found to be statistically significantly higher in patients who died (p=0.002 and p=0.001, respectively). As shown in Table 3, FEV1, FVC, and 6MWT distances were significantly lower in patients who died (p<0.001, p=0.001, p=0.054, and p=0.034, respectively). Calcific nodules, pleural effusion, bronchial wall thickening, and fibrotic change in HRCT were revealed to be statistically significant predictors of survival (p=0.019, p=0.001, p=0.016, and p=0.012, respectively).

According to the results of univariate analysis, the effect of statistically significant clinical and radiologic parameters in predicting survival was evaluated using logistic regression (model p=0.001, Cox and Snell R2=0.223). It was found that none of the variables included in the model (FEV1, FVC, FEV1/FVC, 6MWT, DM, CHF, duration of CTD, fibrosis rate >10%, calcific nodule, bronchial wall thickening, presence of fibrotic change) predicted survival (p=0.061, p=0.622, p=0.776, p=0.704, p=0.816, p=0.904, p=0.240, p=0.375, p=0.845, p=0.987, and p=0.295, respectively).

DISCUSSION

We found that, at the end of 1 year of follow-up in patients with CTD-related ILD, it was determined that the presence of DM, CHF, high ESR, CRP, low FEV1, FVC, FEV1/FVC, 6MWT, a fibrosis rate of >10% on HRCT, the presence of calcific nodules and pleural effusion, bronchial wall thickening, and fibrotic changes on HRCT were associated with survival.

It is thought that serologic markers used in the diagnosis and follow-up of CTD may be useful in predicting the development or progression of ILD.[10] In the current study, serum CRP values were significantly higher in patients with fibrosis rates >10% than in those with fibrosis rates <10%, and there was no relationship between other markers (antiCCP, antidsDNA, RF, antiRo, antiScl) and fibrosis rates. Patients with mixed CTD, it was found that the increase in basal anti-RNP antibody titer and the presence of anti-ro-52 antibodies were strong markers predicting the progression of ILD.[10] In recent study, Chiu et al.[4] reported that the positivity of various rheumatologic factors was not associated with poor prognosis. Since the literature is inconsistent, further research should be done on serological markers and prognosis.

It has been reported that the presence of RA-ILD is the second cause of death in patients with RA.[11] The present study, it was observed that patients with RA-ILD were generally aged over 60 years, the majority were women, and 37% were smokers. It has been shown that the risk of developing ILD is high in patients with RA who are aged over 65 years, those with a disease onset age over 65 years, smokers, and those with high anti-CCP titers.[12] In another study, older age, late disease onset, male sex, and high RF levels were found to be risk factors for the development of RA-ILD.[13]

Certain lung function test parameters are frequently used to assess the progression of CTD-related ILD. The current research, it was observed that the basal FEV1, FVC, FEV1/FVC, 6MWT distances of patients who died were significantly lower than those of survivors. Additionally, it was found that the FVC, DLCO, and 6MWT results of those with fibrosis rates >10% were significantly lower than those with fibrosis rates <10%. In a study in which patients with SS-ILD were followed for 15 years, it was stated that a one year decrease in FVC and DLCO values were the best indicators of mortality.[14] In RA-ILD, low DLCO and FVC values measured at the time of diagnosis were associated with the risk of ILD progression.[15] In another study Chiu et al.[4] reported that involving various CTD patient groups, low DLCO level at baseline was associated with poor prognosis in CTD-related ILD patients. Chan et al.[16] reported that significant fibrosis in patients with CTD-related ILD was associated with a rapid decrease in 6MWT distance. According to these results, lung function tests should be performed in patients with CTD-related ILD to evaluate the severity of the disease and to help predict the prognosis.

The importance of evaluating the decrease in PFT parameters in predicting disease progression or mortality is indisputable but because our study coincided with the COVID-19 pandemic period, follow-up measurements of only a small number of patients could be made. Therefore, the interpretation was made based on the basal measurement values.

In the current study, it was determined that the fibrosis rate on HRCT was >10%, and the presence of calcific nodules, pleural effusion, bronchial wall thickening, and fibrotic changes were associated with mortality. In a recent study, it was found that the presence of a usual interstitial pneumonia (UIP) radiologic pattern was associated with the worst prognosis.[17] The UIP pattern has also been found to be associated with both disease progression and mortality in patients with SSc-ILD and PM/DM.[18,19] In a recent retrospective cohort study mortality risk was independently associated with extent of fibrosis on HRCT at baseline (adjusted HR 1.05).[2] Additionally, in another retrospective study, a fibrotic HRCT pattern at baseline was associated with a 3.11-fold higher risk of progression.[20] According to these findings, the presence and severity of fibrosis on HRCT can be utilized to predict prognosis in patients with CTD-related ILD.

Limitations

It was performed in a single center, the number of patients was small, PFT and DLCO measurements could not be performed at certain intervals during the follow-up period, and the number of patients who died was low.

CONCLUSION

Patients with CTD-related ILD with comorbidities, low basal respiratory function parameters, fibrosis rates of >10%, calcific nodules, pleural effusion, bronchial wall thickening, and fibrotic changes should be followed more closely in terms of progression and mortality. Longitudinal studies involving a larger number of patients will contribute to the creation of clinical models that can predict prognosis in CTD-related ILD.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Fırat University Ethics Committee (Date: 17.10.2019, Decision No: 15/01).

Informed Consent

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

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All authors declare that they participated in the design, execution and analysis of the article and approved the final version.

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Coping strategies in bariatric surgery candidates: a case-control study

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ABSTRACT

Aims: The aim of this study was to examine the relationship between coping strategies and some clinical and sociodemographic characteristics of people applied for metabolic bariatric surgery.

Methods: Forty people who applied to Balıkesir University Health Training and Research Hospital, Department of General Surgery to undergo bariatric surgery between August 2023 and November 2023 and 40 healthy volunteers with normal weight were included in the study. Sociodemographic data form and Coping Attitudes Assessment Scale (COPE) were applied to all participants.

Results: COPE positive reinterpretation and development, active coping, and planning subscale scores were statistically significantly higher in individuals with obesity, whereas focusing on the problem and venting of emotions, mental disengagement, and substance use subscale scores were lower in obese individuals compared to non-obese individuals ($p<0.05$). When the sociodemographic characteristics of the participants and the COPE subscale dimension scores were compared, emotion-focused coping subscale scores werefound to be higher in non-alcoholic persons than alcohol users.

Conclusion: Although obesity itself as well as the treatment methods are quite challenging, the fact that individuals who apply for bariatric surgery frequently use coping attitudes that are oriented towards adaptation, supportsthe fact that they are actively trying to cope with obesity.

Keywords: Obesity, coping styles, metabolic bariatric surgery

INTRODUCTION

Obesity is a health problem characterized by abnormal and excessive fat accumulation in the body.[1] The main causes of obesity include increased energy intake through overeating, decreased physical activity and decreased energy expenditure caused by sedentary lifestyle.[2] The World Health Organization (WHO) considers a body-mass index (BMI) of ≥30 kg/m^2 as obesity. According to the Turkey Health Survey 2022 data, 20.2% of individuals aged 15 years and older in Turkey are struggling with the problem of obesity. In addition, it has been reported that 23.6% of women and 16.8% of men are obese, while 30.9% of women, and 40.4% of men are pre-obese.[3] Genetic, metabolic, environmental, diet-related and psychological factors are responsible for the development of obesity. Mental causes of obesity are explained according to different psychological theories. According to the psychodynamic view, inappropriate experiences in the oral period or problems in later psychosexual stages cause the individual to be stuck in the oral period and may lead the individual to try to relieve the sadness or pain in later life by eating excessively. According to learning theory, the repetition of using food as a means of comfort or reward may lead to the conditioning of the child and the development of the perception that he/she can only be comforted by eating food. For example, if a child is rewarded for eating, he/she may repeat this behavior in order to receive a reward or not to postpone the reward.[4] According to the cognitive behavioral view, it is argued that obese individuals have dysfunctional thoughts and behaviors that cause weight gain.[5]

Eating behavior associated with negative emotions such as anger, depression, distress, anxiety and loneliness is defined as emotional eating.[6] According to the psychosomatic theory associated with emotional eating, individuals do not understand internal stimuli correctly and eat in response to their emotions rather than in response to physiological hunger needs and satiety[7,8] It is also thought that emotional eating occurs due to inadequate coping skills, especially with stress, and is used as a mood regulation strategy.[4,9] The relationship between stress and obesity is considered to be bidirectional. Stress may cause overeating and consumption of foods high in

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calories, fat or sugar, and reduces physical activity. Stress can also stimulate the production of biochemical hormones and peptides such as leptin, ghrelin and neuropeptide Y.[10] People encounter stress in various phases of life (adolescence, job change, divorce, loss of relatives, etc.). At this point, coping responses to stress are considered to be very important to eliminate these negative effects of stress. The resistance of the person against the events or factors that create stress for him/her and all of the cognitive, emotional and behavioral reactions to these events are defined as coping[11] According to Lazarus and Folkman's stress and coping model, any event or situation in the environment leads the person to evaluate the meaning and importance of this event. After evaluation of the meaning and consequences of the stressors by the individual, he/she starts to apply coping strategies.[12] Coping strategies are survival mechanisms that the individual activates in order to minimize the emotional, psychological and physical damage that he/she will suffer in the face of a stressful situation. Coping attitudes can generally be divided into two categories as problem-solving-oriented and emotion-driven attitudes.[11,13] Problem-solving -oriented coping attitudes include coping attitudes towards the source of the problem, while emotion-driven oriented coping attitudes include coping attitudes towards the emotional state caused by the source of the problem. Folkman et al.[14] state that problem-focused behaviors involve active, logical, cool-headed and conscious efforts to change the situation. In contrast to problem-focused coping, emotion-focused coping involves passive methods such as distancing, self-control, accepting the situation if there is nothing to be done, seeking social support and reevaluating the situation. Coping attitudes can also be divided into active and passive attitudes. Active ones include behavioral or psychological responses that aim to intervene or eliminate the stressor (s), while passive ones include behaviors that provide distancing from the stressor(s). It is also possible to define coping attitudes as adaptive and maladaptive. Maladaptive coping attitudes are important in revealing the relationship between stressors and psychiatric disorders such as binge eating disorder, which is frequently encountered in obese patients. An individual's confidence in coping mechanisms and a sense of control over the situation leads to the activation of strategies aimed at eliminating the causes of the problem. Conversely, inadequately perceived coping resources and feelings of desperation will lead to the activation of avoidance strategies.[15] Understanding the coping attitudes used by an individual in the face of a stressful event is thought to be helpful in determining treatment goals and monitoring treatment efficacy. For this purpose, our study aimed to determine the coping strategies of metabolic bariatric surgery candidates. Our hypothesis is that coping attitudes differ in obese individuals who are candidates for bariatric surgery compared to non-obese individuals and will be related to various sociodemographic and clinical variables.

METHODS

Ethics

Before starting the study, the necessary ethics committee approval for the conduction of this research was obtained from Balıkesir University Health Sciences Non-interventional Researches Ethics Committee (Date: 15.08.2023, Decision No: 2023/81). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The Place, Time, Type and Purpose of the Study

This cross-sectional study was planned in Balıkesir University Health Practice and Research Hospital, Department of Mental Health and Diseases between August 2023 and November 2023.

Research Population and Sample

The population of the study consisted of people who applied to Balıkesir University Health Practice and Research Hospital for metabolic bariatric surgery. The sample was selected by simple random sampling method among the applicants aged between 18-65 years. Illiterate patients, patients with active psychotic episodes, dementia, alcohol and substance use disorders were not included in the study. As the control group, age-matched healthy individuals with a BMI <30 kg/m^2 who did not have any psychiatric illness and met the inclusion criteria were included in the study.

Data Collection Tools

Sociodemographic Data Form: Sociodemographic data form inquiring the age, gender, education level, height, weight, marital status, household people, history of psychiatric illness, family history of psychiatric illness, chronic diseases, alcohol use and smoking status of the participants was prepared by the researchers.

Coping Attitudes Assessment Scale (COPE): The scale developed by Carver et al. in 1989 was translated into Turkish by Ağargün et al. in 2005 and a reliability study was conducted. Cronbach's α value was found to be 0.79 and a positive, and statistically significant correlation existed between the subscale scores with the COPE total score of 51. The scale consisted of 60 questions and 15 subscales in which different coping attitudes were evaluated. Each subscale consists of four questions. The higher scores of the subscales give the possibility to comment on the coping attitude which is used more frequently by the study participant.[16,17]

Statistical Analysis

The statistical analyzes were performed using SPSS 26.0 (The Statistical Package for the Social Sciences) package program. The conformity of the numerical variables to normal distribution was evaluated according to p>0.05 in the Kolmogorov-Smirnov test and the conformity of the histogram graph to the bell curve. In descriptive analyses, number and percentage values were given for categorical data; mean and standard deviation, median, minimum and maximum values were given for continuous data. The Mann-Whitney U test was used in the analysis of independent variables with two groups that did not meet the parametric conditions, and the Kruskal Walli' test was used in the analysis of independent variables with three or more groups.

RESULTS

The mean age of the bariatric surgeryl candidates (38.60±13.66 years), and the control subjects (41.67±10.55 years) included in the study population were as indicated female, and married individuals constituted the majority of both groups. Hypertension was found to be the most common comorbid chronic disease in study participants of both groups. Sociodemographic data of the participants are presented in Table 1.

Respective percentages of obese (47.5%), and non-obese (32.5%) individuals were smokers. The 25% of the obese and 30% of non-obese participants were alcohol users. There was no statistically significant difference between the groups in terms of alcohol and cigarette use (p>0.05) (Table 2).

When the COPE subscale scores of the individuals participating in the study were compared between the groups, it was found that the sub-dimension scores of positive reinterpretation and development, active coping, and making plans among coping attitudes were higher in obese individuals

Table 1. Distribution of sociodemographic characteristics of the participants

			Bariatric surgery candidates		Control group			
			n	%	n	%	X^2	p
Gender	Female		25	62.5	23	57.5	0.21	0.64
	Male		15	37.5	17	42.5		
Marital status	Single		14	35.0	12	30.0	0.99	0.61
	Married		22	55.0	21	52.5		
	Divorced/widower		4	10.0	7	17.5		
The individual(s) living together with the study participant	Alone		5	12.5	12	30.0	3.71	0.15
	Family		33	82.5	26	65.0		
	Dormitory/roommate		2	5.0	2	5.0		
Education status	Primary school		10	25.0	5	12.5	2.38	0.30
	High school		15	37.5	20	50.0		
	University		15	37.5	15	37.5		
Psychiatric diseases	Yes	Panic disorder	2	5.0	1	2.5	1.40	0.23
		Depression	2	5.0	1	2.5		
		Anxiety disorder	1	2.5	0	0.0		
	No		35	87.5	38	95.0		
Family history of psychiatric disease	Yes	Panic disorder	2	5.0	1	2.5	0.83	0.36
		Depression	2	5.0	2	5.0		
		Bipolar disorder	1	2.5	2	5.0		
		Anxiety	0	0.0	3	7.5		
	No		35	87.5	32	80.0		
Family members with psychiatric disease (n=13)	Mother		1	2.5	3	7.5	0.74	0.65
	Father		0	0.0	2	5.0		
	Sibling		3	7.5	2	5.0		
	Son		0	0.0	1	2.5		
Comorbidity (ies)	Yes		15	37.5	12	30.0	0.50	0.48
	No		25	6..5	28	70.0		

Table 2. Characteristics of Alcohol and Cigarette Use of the Participants

		Bariatric surgery candidates		Control group			
		n	%	n	%	X^2	p
Alcohol use	Yes	10	25.0	12	30.0	0.25	0.61
	No	30	75.0	28	70.0		
Frequency of alcohol use (n=22)	Less than once a month	3	30.0	2	16.7	0.70	0.87
	2-4 times a month	5	50.0	7	58.3		
	2-3 times a week	1	10.0	1	8.3		
	≥4 times a week	1	10.0	2	16.7		
Smoking status	Smoker	19	47.5	13	32.5	1.87	0.17
	Nonsmoker	21	52.5	27	6.5		

compared to non-obese individuals, but the sub-dimension scores of focusing on the problem and venting of emotions, mental disengagement and substance use were lower in obese individuals compared to non-obese individuals (Table 3).

When the sociodemographic characteristics of the participants were compared with the COPE subscale dimension scores, it was found that the emotion-focused coping subscale score was higher in non-alcohol users than in users (Table 4).

Table 3. Intergroup comparisons of COPE subscale dimension scores

	Control group median (min-max)	Bariatric surgery candidates median (min-max)	Test value	p
Emotion-focused coping	53 (35-71)	54.5 (20-74)	-0.84	0.39
1. Seeking emotional/social support	12 (5-16)	11 (4-16)	-1.19	0.23
2. Positive reinterpretation and growth	12 (6-16)	14 (4-16)	-2.74	0.006*
3. Acceptance	10 (5-14)	10 (4-15)	-1.08	0.28
4. Humor (Hitting the joke)	8 (4-16)	9 (4-15)	-0.30	0.76
5. Turning to religion	12 (4-16)	13 (4-16)	-1.42	0.15
Problem-focused coping	55 (32-74)	57 (22-74)	-1.47	0.14
6. Active coping	11 (4-16)	13 (5-16)	-2.59	0.009*
7. Planning	12 (6-16)	13 (4-16)	-2.64	0.008*
8. Suppression of competing activities	10 (7-16)	10 (4-16)	-0.30	0.76
9. Restraint coping	9.5 (5-13)	9 (4-15)	-0.21	0.83
10. Seeking useful social support	12.5 (4-16)	12 (4-16)	-1.49	0.21
Nonfunctional coping	45 (30-66)	36.5 (26-57)	-4.34	0.001*
11. Focusing on problem and venting of emotions	12 (7-16)	10.5 (4-16)	-3.18	0.01*
12. Denial	6 (4-16)	6 (4-11)	-0.73	0.46
13. Mental disengagement	11 (6-15)	9 (4-16)	-2.73	0.006*
14. Behavioral disengagement	6.5 (4-13)	5 (4-11)	-2.30	0.02
15. Substance use	8 (4-16)	4 (4-13)	-3.19	0.001*

Table 4. Comparison of the participants' sociodemographic characteristics and COPE subscale dimension scores

		Emotion-focused coping median (min-max)	Problem- focused coping median (min-max)	Non-functional coping median (min-max)
Gender	Female	53.5 (20-73)	56 (22-72)	40 (28-62)
	Male	54.5 (27-74)	56.5 (24.74)	40 (26-66)
	Test Z value/p	Z:-0.60 p:0.55	Z:-0.26 p:0.79	Z:-0.16 p:0.87
Education status	Primary education	53 (20-71)	57 (22-74)	37 (26-56)
	High school	53 (36-74)	56 (32-74)	40 (26-66)
	University	54.5 (35-69)	55.5 (36-74)	40.5 (31-56)
	Test value/p	KW:0.81 p:0.66	KW:0.31 p:0.85	KW:2.31 p: 0.32
Marital status	Single	53 (36-74)	55 (32-74)	38 (27-66)
	Married	54 (20-73)	56 (22-74)	41 (26-57)
	Divorced/widower	56 (45-66)	56 (50-70)	38 (32-51)
	Test value/p	KW:0.60 p:0.74	KW:0.84 p:0.65	KW:1.19 p:0.55
The individual(s) living together with the study participant	Alone	55 (36-71)	53(32-70)	37(27-66)
	Family	54 (20-74)	56(22-74)	40(26-62)
	Dormitory/roommate	49 (43-67)	57(50-71)	39(37-47)
	Test value/p	KW:0.54 p:0.76	KW:2.04 p:0.36	KW:54 p:0.76
Psychiatric disease	Yes	50 (45-73)	56 (47-72)	38 (36-46)
	No	54 (20-74)	56 (22-74)	40 (26-66)
	Test value/p	Z:-1.09 p:0.27	Z:-0.13 p:0.89	Z:-0.58 p:0.55
Comorbidity	Yes	55 (27-69)	58 (24-74)	38 (26-56)
	No	53 (20-74)	55 (22-74)	40 (28-66)
	Test value/p	Z:-0.21 p:0.83	Z:-1.09 p:0.27	Z:-0.93 p:0.35
Family history of psychiatric disease	Yes	48 (36-61)	56 (44-60)	41 (26-56)
	No	55 (20-74)	56 (22-74)	40 (26-66)
	Test value/p	Z:-2.67 p:0.008	Z:-0.75 p:0.45	Z:-0.07 p:0.94
Smoking status	Smoker	54.5 (27-74)	56 (24-74)	39.5 (26-56)
	Nonsmoker	53 (20-71)	55.5 (22-74)	40 (28-66)
	Test value/p	Z:-0.67 p:0.49	Z:-0.42 p:0.67	Z:-0.39 p:0.69
Alcohol use	Yes	51 (35-67)	56 (32-71)	42 (26-66)
	No	55 (20-74)	56 (22-74)	39.5 (26-62)
	Test value/p	Z:-2.16 p:0.03*	Z:-0.52 p:0.60	Z:-1.37 p:0.17

DISCUSSION

This study examined the characteristics of obese individuals, the coping strategies they use to cope with obesity, and the relationship between coping strategies and some sociodemographic characteristics. Our main results showed that individuals applied for bariatric surgery used more frequently emotion-focused and problem-focused functional coping strategies.

Considering our sociodemographic and clinical data; our study participants are in the middle age group consisting mainly of female candidates similar to what is reported in the literature.[18,19] Compared to men, women are more likely to be diagnosed with obesity and to seek and receive all types of obesity treatment, including behavioral, pharmacological interventions and bariatric surgery.[20] In addition, in many studies, the proportion of women applying for bariatric surgery was found to be higher than men.[21] In terms of education level, primary school graduates are more common among bariatric surgery candidates. Most studies in developed countries have reported that education level is negatively correlated with risk of obesity in both men and women.[22,23]

Hypertension was found to be the most common comorbidity observed in both male and female study participants. Several studies have shown a clear relationship between increased blood pressure and weight gain.[24] It has been shown that obese people are 3.5 times more likely to develop hypertension and 60% of cases of hypertension can be attributed to an increase in fat stores in the body.[25] In this study, 47.5% of obese and 32.5% of non-obese individuals were smokers. Smoking has been shown to induce the distribution of body fat and may be associated with central obesity.[26,27] It has also been reported that the impact of obesity is not evenly distributed in the society and that smokers constituted the group that may be prone to obesity-related problems.[28]

According to our results, the sub-dimension scores of positive reinterpretation and development, active coping, and making plans from coping attitudes were higher in obese individuals compared to non-obese individuals, but the sub-dimension scores of focusing on the problem and venting emotions, mental disengagement, and substance use were lower in obese individuals. In summary; in our study, it was found that individuals who applied for bariatric surgery used emotion-focused and problem-focused functional coping strategies more frequently. In another study, it was found that patients who volunteered for bariatric surgery used problem-solving style to manage their stress.[29] Similarly, a study showed that the most common coping strategies of morbidly obese individuals were planning, active coping and positive reinterpretation.[30] In our study, focusing on the problem and venting emotions, mental distraction and substance use, which are among the sub-headings of dysfunctional coping strategies, were observed less frequently in bariatric surgery candidates. When the coping strategies relative to obesity are evaluated, it is expected that the frequency of using dysfunctional attitudes increases in parallel with the level of obesity. However, the authors associated this situation with the fact that the participants were morbidly obese but were able to make the decision of undergoing surgery during the treatment process and were actively seeking a solution to the problem. However, longer-term studies evaluating levels and duration of obesity, and treatment interventions are needed to determine this relationship. It was also stated that using active coping strategies may be a determinant for better weight loss outcomes after bariatric surgery.[31] Therefore, establishment of a multidisciplinary approach, requring interactive cooperation among bariatric surgeon, dietician, mental healthcare workers, and other healthcare professionals is recommended.

Our study has some limitations including its single center design, relatively small sample size, and the use of self-report scales, where participants having approval anxiety attempt to be healthy which may cause bias in the preoperative psychiatric evaluation.

CONCLUSION

In conclusion, obesity is not only a metabolic disorder but also a multisystem disorder with psychological components. Considering mental components of obesity should be regarded as an important step in facilitating patient compliance with treatment and preventing recurrences. It is thought that determining the general characteristics of bariatric surgery candidates, evaluating their mental status and revealing the differences between genders, determining coping skills and applying therapeutic techniques to improve their health status will help to predict the success and possible outcomes of surgery when supported by postoperative follow-up studies in the future. For this purpose; setting specific and achievable goals in the preoperative and postoperative period, diet and exercise plans, developing solutions by identifying the obstacles encountered, and including social supports in the process may increase the motivation of the patienta and reduce their stress in the postoperative period.

ETHICAL DECLARATIONS

Ethics Committee Approval
The study was carried out with the permission of Balıkesir University Health Sciences Non-interventional Researches Ethics Committee (Date: 15/08/2023, Decision No: 2023/81).

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

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
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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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Urinary stone disease in pediatric patients: a mixed-methods study

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ABSTRACT

Aims: Childhood urinary stone disease (USSD) varies in frequency based on several factors such as, gender, age, body mass index, geography, diet, genetic disorders, and kidney anatomy. This study aims to retrospectively evaluate the demographic and clinical characteristics, symptoms, diagnostic methods, predisposing factors, associated urinary system anomalies, treatments, and prognosis of patients diagnosed with USSD in our clinic over the past three years.

Methods: This mixed-methods study retrospectively examined the records of 175 patients diagnosed with USSD between April 2020 and May 2023. Demographic data, symptoms, laboratory results, imaging findings, and treatment outcomes were analyzed. Additionally, qualitative data were gathered from semi-structured interviews with 10 volunteer participants to understand the impact of symptoms on their lives.

Results: Among the 175 pediatric patients diagnosed with urolithiasis, 120 (68.5%) were symptomatic, with common complaints such as irritability (29.1%), pain (18.2%), vomiting (23.4%), and macroscopic hematuria (20%). Significant differences were observed in symptoms based on age and stone size, with older children more likely to experience pain and hematuria, while younger children showed more irritability ($p<0.01$). Metabolic disorders were present in 78.8% of cases, with hypercalciuria being the most frequent. Qualitative data revealed significant emotional and social challenges. Children expressed fear, anxiety, and embarrassment due to symptoms like pain and bedwetting. These experiences impacted their daily lives, disrupting sleep, play, and social interactions. Family support played a crucial role in managing these emotional burdens, though peer interactions often exacerbated feelings of isolation and discomfort.

Conclusion: The study highlights the critical importance of early diagnosis and individualized treatment strategies in managing pediatric urolithiasis to prevent long-term complications like end-stage renal failure. Presenting symptoms and treatment outcomes are significantly influenced by factors such as age, stone size, and metabolic risk factors. Medical treatment remains the primary approach, while surgical interventions are reserved for complex cases. The findings emphasize the need for personalized management plans, particularly for high-risk children with family history or consanguineous marriages, and underscore the emotional and social challenges these children face.

Keywords: Childhood urinary stone disease, USSD, demographics and clinical characteristics, symptoms, metabolic risk factors

INTRODUCTION

The prevalence of urinary system stone disease (USSD) varies in studies depending on several factors such as race, gender, age, body mass index, geography, diet, genetic diseases, and the anatomical structure of the kidney.[1,2] The earliest historical records of this disease date back to 4400 BC. A significant increase in the frequency of the disease has been observed from the Industrial Revolution to the present day.[3]

Metabolic risk factors play a crucial role in the development of kidney stone disease and its recurrence. These factors include metabolic disorders such as hypercalciuria, hyperoxaluria, hypocitraturia, and hyperuricosuria. Hypercalciuria, characterized by excessive calcium excretion in the urine, is one of the most common metabolic causes of kidney stones, particularly leading to the formation of calcium oxalate stones.[4] Metabolic syndrome has also been identified as an important contributor to kidney stone formation, with conditions like hypercalciuria further reinforcing this link. Additionally, hypercalciuria has been shown to significantly increase the risk of stone recurrence, particularly in pediatric patients.[5] Hyperoxaluria, which involves the excessive excretion of oxalate in the urine, is another major metabolic disorder contributing to kidney stone development, known for increasing both the hardness of the stones and the likelihood of recurrence.[6]

Hypocitraturia, a deficiency of citrate-a natural inhibitor of stone formation-facilitates the development of calcium stones

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and has been observed more frequently in obese children, raising their risk of stone formation.[7] Hyperuricosuria, characterized by excessive uric acid excretion, leads to the formation of uric acid stones and requires special consideration in treatment and follow-up.[8] These metabolic disorders not only accelerate stone formation but also complicate the treatment process and increase the risk of recurrence. Therefore, early diagnosis and effective management of these metabolic risk factors are essential for improving the prognosis of individuals prone to kidney stone disease.[4-8]

In studies conducted in the United States, Soucie and colleagues determined the lifetime prevalence of urinary system stones to be 4% in women and 10% in men, while Curhan and colleagues found this rate to be 8.7% regardless of gender.[9,10] In childhood, most stones consist of calcium oxalate (45-65%) and calcium phosphate (14-30%), whereas uric acid, cystine, and struvite (magnesium-ammonium-phosphate) stones are seen at lower rates (5-10%).[11] Symptoms can vary with age. In a young child, symptoms like irritability, non-specific abdominal pain, and nausea can present, while in older children or adolescents, these symptoms are replaced by classic symptoms specific to stone disease such as renal colic pain, flank pain, nausea, and vomiting. Hematuria can be present in 30-90% of children with stones, although significant macroscopic hematuria is rare. The diagnosis of urolithiasis in young children is often made during the follow-up of urinary tract infections (UTIs) or incidentally.[12]

The classic symptoms and findings of urolithiasis are less clear in children compared to adults, leading to delayed diagnosis, which can result in chronic pyelonephritis and end-stage renal failure. The risk of chronic renal failure is 1.7% in idiopathic calcium oxalate stones but can rise to 70% in patients with cystinuria.[13] The Turkish Society of Nephrology reported that urolithiasis accounted for 3.3% of the etiology in children who started renal replacement therapy in 2008 due to chronic renal failure.[14]

The primary aim of this study is to retrospectively evaluate the demographic characteristics, clinical findings, diagnostic and treatment processes, metabolic factors contributing to stone formation, and prognoses of pediatric patients diagnosed with urolithiasis who have been followed up in our clinic over the past three years. In the study, the retrospective data of 175 patients were analyzed, and qualitative data were also collected from 10 patients to gain in-depth insights into their experiences with the disease. The study focuses on identifying the factors contributing to stone formation in pediatric urolithiasis cases and assessing the risk of stone recurrence. The quantitative aspect of the study involves analyzing patient data such as age, gender, family history, and laboratory and imaging results to gather critical information about the clinical course of the disease. On the other hand, the qualitative aspect aims to evaluate the individual experiences of patients and their families, focusing on how urolithiasis impacts the quality of life in children. The combination of both methods offers a comprehensive view of the disease's clinical, biological, social, and psychological effects.

In line with the research objective, the study seeks to answer the following sub-questions:

- What are the demographic characteristics and clinical findings of urolithiasis patients at the time of presentation?
- What metabolic risk factors are identified in urolithiasis patients, and how do these factors affect stone formation and recurrence risk?
- What laboratory and imaging methods are used in the diagnosis of urolithiasis, and how effective are these methods?
- What are the prognoses of urolithiasis patients, and what are the recurrence rates of the stones?
- How does urolithiasis affect the lives of children diagnosed with the disease, and how do the children and their families experience the disease process?

The significance of this study stems from the fact that pediatric urolithiasis has typically been studied in the context of adult populations in the literature. Children with kidney stones often present with fewer or different symptoms compared to adults, complicating the diagnostic and treatment processes. Moreover, the impact of metabolic risk factors in pediatric patients has not been thoroughly investigated, and this study aims to fill that gap by providing important contributions to this area. Additionally, the qualitative exploration of patients' personal experiences allows for a better understanding of the social and psychological aspects of the disease. Thus, a holistic evaluation that encompasses both clinical and patient perspectives will reveal the multidimensional impacts of pediatric urolithiasis. This study is expected to serve as a foundation for future research and offer insights to improve the management of the disease in clinical practice.

METHODS

In this study, the records of 175 patients who had been followed for at least 12 months with a diagnosis of urolithiasis at the Pediatric Nephrology Clinic of the Samsun Training and Research Hospital between April 2020 and May 2023 were retrospectively reviewed. The research was approved by the Ethics Committee of Samsun University (Date: 14.08.2024, Decision No: 2024/14/2). The ethics committee approval is included in the supplementary file. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patients' age, gender, family history and presenting complaints were obtained from patient records. Urine culture, spot urine calcium/creatinine ratio, oxalate/creatinine, citrate/creatinine ratio, uric acidxGFR or 24-hour metabolic stone analyses and routine ultrasonography findings were identified from the records. The distribution of the demographic characteristics of the cases is shown in Table 1. Retrospective data collection was acknowledged as having potential limitations such as missing or inaccurate records; however, efforts were made to minimize these limitations by using well-documented and consistent clinical records.

Table 1. Distribution of demographic characteristics			
		n	%
Diagnosis age	0-1 year	100	57.1
	1-3 years old	24	13.7
	3-5 years old	12	6.8
	5-10 years old	25	14.2
	≥10 years old	14	8
Gender	Male	90	51.4
	Female	85	48.6
Family history	Yes	105	61.04
	No	70	38.9
Consanguineous marriage	Yes	25	14.2
	No	150	85.7

The study was designed as a mixed-methods research. Mixed-methods research is an approach that combines qualitative and quantitative research methods. In this method, the processes of collecting, analyzing, and interpreting qualitative and quantitative data are integrated.[15] The aim of mixed-methods research is to comprehensively and in-depth examine the research question by leveraging the strengths of both methods.[16] In this study, quantitative and qualitative data were not only collected separately but also carefully integrated to provide a more comprehensive understanding of the research findings. The integration of both data types was essential to address the complexity of urolithiasis in pediatric patients, offering both statistical trends and personal experiences.

Urolithiasis patients with urinary system infection were evaluated as those who had a history of urinary tract infection and those in whom a significant number of bacteria grew in urine culture at the time of presentation. In ultrasonographic imaging, stones 3 mm and smaller were considered microcalculi, while stones larger than 3 mm were considered macrocalculi. Urinary incontinence was evaluated in patients over the age of 3 who were out of diapers, had completed toilet training, and had gained daytime bladder control.

Calcium excretion in spot urine was defined as hypercalciuria if it was >0.8 mg/mg creatinine for 0-6 months, >0.6 mg/mg creatinine for 7-12 months, and >0.21 mg/mg creatinine for those older than 2 years. For 24-hour urine, calcium excretion over 4 mg/kg/day was also considered hypercalciuria. Oxalate excretion in spot urine was considered hyperoxaluria if it was >0.15-0.26 mmol/mmol creatinine for those under 1 year, >0.11-0.12 mmol/mmol creatinine for those aged 1-5 years, >0.006-0.15 mmol/mmol creatinine for those aged 5-12 years, and >0.002-0.083 mmol/mmol creatinine for those older than 12 years. For all age groups, oxalate excretion over 0.5 mmol/1.73 m^2/day in 24-hour urine was also considered hyperoxaluria. Uric acid excretion in spot urine was defined as hyperuricosuria if it was 3.3 mg/dL GFR in term infants and >0.53 mg/dl GFR in patients older than 3 years. In 24-hour urine, uric acid excretion over 815 mg/1.73 m^2/day was also considered hyperuricosuria. Citrate excretion was defined as hypocitraturia if it was below 400 mg/g creatinine in spot urine and below 180 mg/g in 24-hour urine.

During follow-ups, the absence of stones in at least two consecutive ultrasound examinations was considered recovery. Recurrence was defined as the detection of stones by ultrasound again or stone passage in patients who had no stones in at least two consecutive ultrasound examinations.

In the qualitative part of the study, data were collected through semi-structured interviews with 10 volunteer participants out of the 175 patients. The 10 volunteer participants were selected based on typical case sampling. Participants were chosen from those who took part in the quantitative part of the study and were considered representative of the 175-person quantitative sample according to the findings of the disease. The use of typical case sampling was justified by its ability to capture the most representative characteristics of the overall population, ensuring that the insights gained from these cases could be generalized to similar populations. Typical cases are situations that, among many similar ones in the population, provide enough information to generally explain the phenomenon or case being examined.[17] At this point, a typical case refers to situations that have the ability to represent the population and do not differ from the population in terms of fundamental characteristics.[18] The questions and answers in the semi-structured interview form were kept short due to the limited responses and age groups of the children. Although data saturation was reached with the 8th participant, the research was limited to 10 participants.

The semi-structured interview form was developed considering the literature on the disease. The questions were designed to ensure effective communication with the children. The qualitative part of the study aimed to allow patients to describe in their own words how their presenting complaints affected their lives. This approach aimed to provide a new dimension to the literature and offer insights into how patients describe their complaints.Parents accompanied the patients during the interviews. The presence of parents was carefully managed to ensure it did not influence the children's responses. Steps were taken to minimize parental interference during interviews, though their presence was necessary due to the young age of the participants.

Although data saturation was reached with the 8th participant, the decision was made to continue with 10 participants to ensure comprehensive data collection. The decision to limit the interviews to 10 participants was based on the practical considerations of the sample and the ability to gather sufficient data for analysis, balancing the need for depth against the constraints of time and participant availability. The interviews were short, planned to last between 7-10 minutes due to the young age of the children, resulting in a total of 86 minutes of data collected from participants aged 3 years and older. Although the interviews were short, every effort was made to ensure that the questions were concise yet sufficiently detailed to elicit meaningful responses from the participants.

Statistical Analysis

In line with best practices in mixed-methods research, quantitative and qualitative data were analyzed separately and then integrated in the interpretation phase to provide a comprehensive understanding of the study outcomes.

The statistical analyses of the findings obtained in this study were performed using SPSS (Statistical Package for Social Sciences) Windows 15.0 software. When evaluating the study data, descriptive statistical methods such as mean, standard deviation, and frequency values were calculated. To compare qualitative data, the Chi-Square test was applied, and Fisher's Exact test was preferred for smaller sample groups to obtain more reliable results. A significance level of $p<0.05$ was accepted for statistical analyses, indicating a 95% confidence level for the findings to be considered statistically significant. This approach ensured the robust statistical interpretation of the quantitative data, providing scientifically valid conclusions.

In the qualitative part, data were transcribed and analyzed using content analysis with the help of the NVIVO program. The aim was to allow patients to describe in their own words how their presenting complaints affected their lives, thereby offering a new dimension to the understanding of pediatric urolithiasis. In particular, care was taken to ensure that the themes identified from the qualitative data were aligned with the clinical trends observed in the quantitative data, thus strengthening the mixed-methods approach by linking patient narratives to clinical outcomes.

RESULTS

Among the presenting complaints, it was found that 120 cases (68.5%) were symptomatic, while 55 cases (31.5%) were asymptomatic. Among the symptomatic cases, the presenting complaints were as follows: 36 cases (20.5%) had nausea, 41 cases (23.4%) had vomiting, 13 cases (7.4%) had stone passage, 35 cases (20%) had macroscopic hematuria, 24 cases (13.7%) had dysuria, 19 cases (10.8%) had urinary incontinence, 51 cases (29.1%) had irritability, and 32 cases (18.2%) had pain.

According to the data in Table 2, there were significant differences in the distribution of presenting complaints by age at diagnosis. Nausea (61% vs. 19.4%, 2.7%, 11.1%, and 5.5%; p=0.168), vomiting (73.1% vs. 14.6%, 2.4%, 9.75%, and 3%; p=0.192), stone passage (30.7% vs. 23%, 0%, 15.3%, and 30.7%; p=0.404), and asymptomatic findings (65% vs. 12%, 3%, 15%, and 5%; p=0.341) did not show statistically significant differences among age groups. However, there were significant differences in some complaints depending on the age at diagnosis.

Macroscopic hematuria (60% vs. 8.5%, 2.8%, 22.8%, and 5.7%; p=0.002), dysuria (45.8% vs. 16.6%, 4.1%, 12.5%, and 20.8%; p=0.001), urinary incontinence (0% vs. 0%, 31,5%, 63%, and 5,5%; p=0.001), irritability (88.2% vs. 7.8%, 3.9%, 0%, and 0%; p=0.001), and pain (0% vs. 9.3%, 6.2%, 28.1%, and 56.2%; p=0.001) showed significant variations by age at diagnosis. The rate of macroscopic hematuria was significantly higher in children aged 5 years and older compared to those under 5 years ($p<0.01$). Dysuria was more frequent in children aged 10 years and older compared to those under 10 years ($p<0.01$). The rate of urinary incontinence was notably higher in the 5-10 year age group compared to other age groups ($p<0.01$). Incontinence complaints in the 0-1 and 1-3 age groups were not taken into consideration. Irritability was significantly more common in the 0-1 year age group compared to other age groups ($p<0.01$). Lastly, pain was significantly more prevalent in children aged 5 years and older compared to those under 5 years ($p<0.01$).

These findings demonstrate a significant relationship between the age at diagnosis and the frequency of certain presenting complaints. Specific complaints are more commonly observed in certain age groups, highlighting the importance of considering the age at diagnosis in clinical evaluations.

According to the table data, there are significant differences in the distribution of presenting complaints based on stone size. For the stone sizes, the rates of nausea (30.5% vs. 69.4%; p=0.475), vomiting (43.9% vs. 56.1%; p=0.744), stone passage (38.4% vs. 61.6%; p=1.000), and asymptomatic findings (43.6% vs. 56.3%; p=0.395) did not show statistically significant differences. However, some complaints showed significant differences depending on stone size.

Macroscopic hematuria (22.8% vs. 77.2%; p=0.079), dysuria (25% vs. 75%; p=0.076), urinary incontinence (21% vs. 79%; p=0.014), irritability (39.2% vs. 60.7%; p=0.019), and pain (25% vs. 75%; p=0.001) showed significant variations based on stone size. The occurrence of pain was significantly higher in cases with stone sizes over 3 mm ($p<0.01$), while the occurrence of irritability was significantly higher in cases with stone sizes under 3 mm ($p<0.05$).

Table 2. Evaluation of presenting complaints by age at diagnosis

	Diagnosis age					
	0-1 year	1-3 years old	3-5 years old	5-10 years old	≥10 years old	
Presenting complaints	n (%)	n (%)	n (%)	n (%)	n (%)	p
Nausea	22 (61%)	7 (19.4%)	1 (2.7%)	4 (11.1%)	2 (5.5%)	0.168
Vomiting	30 (73.1%)	6 (14.6%)	1 (2.4%)	4 (9.75%)	0 (3%)	0.192
Passage of stone	4 (30.7%)	3 (23.0%)	0 (0%)	2 (15.3%)	4 (30.7%)	0.404
Asymptomatic	45 (65%)	3 (12%)	1 (3%)	4 (15%)	2 (5%)	0.341
Macroscopic hematuria	21 (60%)	3 (8.5%)	1 (2.8%)	8 (22.8%)	2 (5.7%)	0.002**
Dysuria	11 (45.8%)	4 (16.6%)	1 (4.1%)	3 (12.5%)	5 (20.8%)	0.001**
Urinary incontinence	0 (0%)*	0 (0%)*	6 (31.5%)	12 (63%)	1 (5.5%)	0.001**
Restlessness	45 (88.2%)	4 (7.8%)	2 (3.9%)	0 (0%)	0 (0%)	0.001**
Pain	0 (0%)	3 (9.3%)	2 (6.2%)	9 (28.1%)	18 (56.2%)	0.001**

[1]Chi-square test, *Incontinence complaints in the 0-1 and 1-3 age groups were not taken into consideration, **p<0.05

These findings demonstrate a significant relationship between stone size and the frequency of certain presenting complaints. Pain complaints are more common in patients with larger stones, while irritability is more frequent in patients with smaller stones (Table 3).

Table 3. Evaluation of presenting complaints by stone size

	Stone size		
	Less than 3 mm	3 mm and above	
Presenting complaints	n (%)	n (%)	p
Nausea	11 (30.5%)	25 (69.4%)	[2]0.475
Vomiting	18 (43.9%)	23 (56.1%)	[1]0.744
Passage of stone	5 (38.4%)	8 (61.6%)	[2]1.000
Asymptomatic	24 (43.6%)	31 (56.3%)	[1]0.395
Macroscopic hematuria	8 (22.8%)	27 (77.2%)	[1]0.079
Dysuria	6 (25%)	18 (75%)	[1]0.076
Urinary incontinence	4 (21%)	15 (79%)	[1]0.014*
Restlessness	20 (39.2%)	31 (60.7%)	[1]0.019*
Pain	8 (25%)	24 (75%)	[1]0.001**

[1]Chi-square test, [2]Fisher's Exact test, *p<0.05, **p<0.01

According to the table data, there are significant differences in the distribution of presenting complaints based on whether the stone is single or multiple. The rates of nausea (63.8% vs. 36.1%; p=0.518), vomiting (53.6% vs. 46.3%; p=0.308), stone passage (46.1% vs. 53.9%; p=0.581), asymptomatic findings (60% vs. 40%; p=0.779), macroscopic hematuria (65.7% vs. 34.3%; p=1.000), dysuria (58.3% vs. 41.7%; p=0.496), urinary incontinence (78.9% vs. 21.1%; p=0.108), and irritability (52.9% vs. 47.1%; p=0.341) did not show statistically significant differences based on whether the stone is single or multiple. However, there was a significant difference in pain complaints depending on whether the stone was single or multiple (56.2% vs. 43.7%; p=0.004).

These findings indicate that the presence of single or multiple stones does not significantly affect the frequency of other presenting complaints except for pain. The pain complaint significantly varies based on whether the stone is single or multiple; pain is more common in cases where the stone is single (p<0.01). This emphasizes that the number of stones is an important factor in clinical evaluation, particularly regarding pain complaints (Table 4).

When evaluating metabolic risk factors, a total of 173 cases underwent metabolic assessment. Metabolic disorders were present in 138 patients, while no metabolic disorders were found in 35 patients. Among these cases, 50 (36.2%) had hypercalciuria, 29 (21.01%) had hyperoxaluria, 25 (18.11%) had hypocitraturia, 5 (3.6%) had hyperuricosuria, 12 (8.69 %) had both hypercalciuria and hyperoxaluria, 6 (4.34%) had both hypercalciuria and hypocitraturia, 3 (2.17%) had both hypocitraturia and hyperoxaluria, 2 (1.44%) had both hypercalciuria and hyperuricosuria, 2 (1.44%) had both hypocitraturia and hyperuricosuria, 2 (1.44%) had hypercalciuria, hypocitraturia, and hyperoxaluria, 1 (0.72%) had hypercalciuria, hypocitraturia, and hyperuricosuria,

Table 4. Distribution of presenting complaints by stone count

		Stone count		
		Single	Multiple	
Presenting complaints		n (%)	n (%)	p
Nausea	Yes	23 (63.8%)	13 (36.1%)	0.518
Vomiting	Yes	22 (53.6%)	19 (46.3%)	0.308
Passage of stone	Yes	6 (46.1%)	7 (53.9%)	0.581
Asymptomatic	Yes	33 (60%)	22 (40%)	0.779
Macroscopic hematuria	Yes	23 (65.7%)	12 (34.3%)	1.000
Dysuria	Yes	14 (58.3%)	10 (41.7%)	0.496
Urinary incontinence	Yes	15 (78.9%)	4 (21.1%)	0.108
Restlessness	Yes	27 (52.9%)	24 (47.1%)	0.341
Pain	Yes	18 (56.2%)	14 (43.7%)	0.004**

Chi-square test, **p<0.01

and 1 (0.72%) had hypocitraturia, hyperuricosuria, and hyperoxaluria. Hypercalciuria was the most common metabolic disorder observed. The most frequently co-occurring metabolic disorders were hypercalciuria and hyperoxaluria. Cystinuria was not detected in any cases. There were no statistically significant differences in the occurrence rates of hypercalciuria, hypocitraturia, and hyperuricosuria according to the age at diagnosis (p>0.05). Cystine was measured in the urine of 35 patients, and cystinuria was not detected in any of them. The prevalence of metabolic disorders by age at diagnosis is summarized in Figure.

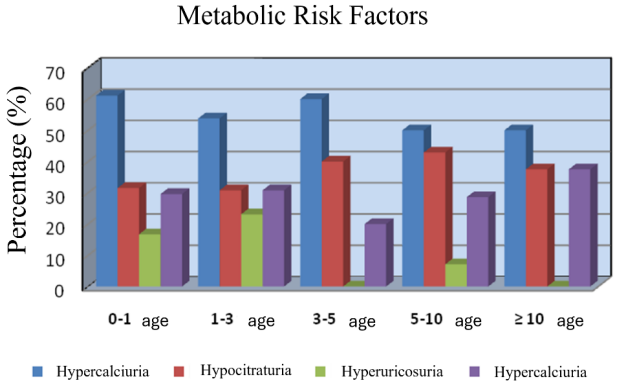

Figure. Metabolic assessment by age at diagnosis

When examining the distribution of treatment and prognosis, 156 cases (89.1%) received medical treatment, 14 cases (8%) underwent surgical treatment, and 5 of these (2.8%) were treated with ESWL (Table 5). Outcome information was available for 173 patients. Among these, 150 cases (85.7%) achieved complete recovery, 18 cases (10.2%) did not achieve complete recovery, and 5 cases (2.8%) experienced stone recurrence. There were no statistically significant differences in age at diagnosis, gender, stone size, incidence of urinary infections, and presence of metabolic disorders based on prognosis (p>0.05) (Table 6).

In the research, qualitative data obtained were analyzed with codes and anecdotes under the theme 'Chief Complaints of Kidney Stones'. Codes and anecdotes related to the chief complaints of 10 participants are presented in Table 7.

Table 5. Distribution of treatment and prognosis			
		n	%
Treatment	Medical	156	89.1
	Surgical	14	8
	ESWL	5	2.8
Prognosis	Total	175	85.7
	Complete recovery	150	
	No complete recovery	18	10.2
	Stone recurrence	5	2.8
	Total	173	

The qualitative data obtained from the study provides codes that support the presenting complaints, showing complete alignment between the obtained codes and the chief complaints. Additionally, the anecdotes provided reveal the problems patients experience during the course of kidney stone disease. The data highlights that anecdotes depict a challenging process for children in the relevant age groups.

The data from the qualitative analysis, especially from the codes and anecdotes, paints a vivid picture of the daily struggles experienced by children suffering from kidney

Table 6. Evaluations according to prognosis					
		Prognosis			
		Complete recovery	No complete recovery	Stone recurrence	
		n (%)	n (%)	n (%)	p
Diagnosis age	0-1 year	85 (85%)	12 (12%)	3 (%3)	0.251
	1-3 years old	22 (91.6%)	2 (8.4%)	0 (%0)	
	3-5 years old	11 (91.6%)	1 (8.4%)	0 (%0)	
	5-10 years old	20 (80%)	3 (12%)	2 (%8)	
	≥10 years old	12 (85.7%)	2 (14.3%)	0 (%0)	
Gender	Male	77 (85.5%)	10 (11.1%)	3 (3.3%)	0.186
	Female	65 (76.4%)	18 (21.1%)	2 (2.3%)	
Stone size	Less than 3 mm	60 (85.7%)	9 (12.8%)	1 (1.4%)	0.934
	3 mm and above	87 (84.4%)	15 (14.5%)	1 (1.1%)	
UTI	Yes	69 (81.1%)	15 (17.6%)	1 (1.1%)	0.657
	No	74 (89.1%)	13 (15.6%)	1 (1.2%)	
Metabolic disorder	No	30 (85.7%)	5 (14.7%)	0 (0%)	0.572
	Single	84 (77.06%)	21 (19.2%)	4 (3.66%)	
	2 or 3	25 (86.2%)	3 (10.3%)	1 (3.44%)	
Metabolic disorder	Hypercalciuria	52 (71.2%)	18 (24.6%)	3 (4.10%)	0.314
	Hyperoxaluria	37 (78.7%)	8 (17.2%)	2 (4.25%)	0.835
	Hypocitraturia	31 (77.5%)	9 (22.5%)	0 (0%)	0.347
	Hyperuricosuria	8 (72.7%)	3 (27.2%)	0 (0%)	0.883

Chi-square test, UTI: Urinary tract infection

Table 7. Problem, code, f and anecdote			
Problem	Code	f	Anecdote
How do you generally feel during the day?	Generally I feel good	3	-Some days I feel very good, some days I feel bad -I usually feel good when I play
	I'm scared	7	-Sometimes I get excited, I'm scare -I'm scared my stomach will hurt -I'm afraid to move
	I'm in pain	5	-My waist hurts like someone hit it -My back hurts, I always want to lie down
	I feel weak	9	-I don't go play games with my friend -I get tired quickly when I go out
Can you describe the complaints you told your family about?	It burns when I go to the toilet	8	-Lately, it always burns when I pee -It burns when I pee at school
	I feel nauseous	6	-My stomach felt nauseous once in class -I always feel nauseous in the car
	My stomach hurts	8	-I told my mom my stomach hurts -I told my teacher my stomach hurts
	I can't sleep	4	-I can't sleep at night
Have you ever experienced a problem that you couldn't forget or bothered you a lot?	My friends laughed at me	3	-Once my pants got wet with pee, my friend laughed at me -My bed got wet with pee at night, my mom didn't get mad
	I was scared	6	-I was scared I wouldn't get better -I was scared the first time I came to the hospital
	It hurt badly	5	-Once when I was playing soccer, my stomach, legs, and back hurt a lot, my friends brought me home -My back hurt a lot at school, the principal called my dad
	I threw up	8	-Once I threw up at the playground, but I couldn't hold it in -I accidentally threw up in my brother's stroller

stone disease. It highlights the social and emotional toll the condition takes on young patients. Below is an interpretation based on the presented information.

Emotional and Physical Struggles

Fear and anxiety: The high frequency of the code "I'm scared" (7 occurrences) and the supporting anecdotes demonstrate that many children experience fear and anxiety related to their condition. Whether it is the fear of pain, or the fear of movement leading to more discomfort, the emotional weight is significant. This emotional burden, combined with the anecdotal evidence of their reactions ("I'm scared my stomach will hurt"), suggests that children feel vulnerable and anxious about unpredictable pain.

Physical pain: The recurring themes of pain, particularly the code "I'm in pain" (5 occurrences) and "It hurt badly" (5 occurrences), make it clear that the physical symptoms are overwhelming. Descriptions like "My waist hurts like someone hit it" and "Once my stomach, legs, and back hurt a lot" point toward the pervasive and multi-faceted nature of the pain these children experience. This also hints at the possible interruption of their daily activities, such as playing or attending school.

Nausea and weakness: Nausea and weakness appear in 6 and 9 cases, respectively, showing how this illness drains children's physical strength and well-being. The frequent mention of nausea during school or in cars indicates how the disease affects their daily routines, making even ordinary tasks challenging.

Social Impact

Isolation and embarrassment: Several children express feelings of embarrassment or humiliation. The code "My friends laughed at me" (3 occurrences) and associated anecdotes about bedwetting or accidents during school time illustrate how their condition can create social isolation. Being laughed at for something they cannot control (e.g., wetting themselves) not only reinforces their fear but also causes social discomfort, potentially affecting their self-esteem and peer relationships.

Support and understanding: Interestingly, some anecdotes reveal moments of emotional support, such as "My mom didn't get mad" when a child wet the bed. These moments, though few, suggest that family members or caregivers may play a role in buffering the emotional strain caused by these experiences. However, they also highlight the lack of broader social understanding from peers.

Cognitive Understanding of Their Condition

Incomprehension of severity: Some of the children's fears, such as "I was scared I wouldn't get better" and "I was scared the first time I came to the hospital," reveal a lack of understanding about their illness. This points to a gap in communication between healthcare providers, parents, and the child. Explaining the condition more thoroughly and in age-appropriate ways might alleviate some of this fear and anxiety.

Disruption of Daily Activities

Impact on sleep and play: The data shows that these children experience disrupted sleep, with 4 instances of "I can't sleep" and 9 instances of "I feel weak," revealing how the disease not only affects their physical activity but also compromises their rest. Given that play and sleep are essential for the cognitive and emotional development of children, the disruption of these activities may lead to further complications in their overall well-being.

DISCUSSION

Urolithiasis, though not life-threatening, can lead to long-term end-stage renal failure due to delays in diagnosis and treatment that impair kidney function.[19] According to the Turkish Society of Nephrology's 2008 data, urolithiasis was found in 3.3% of children starting renal replacement therapy.[3] Therefore, it is a condition with significant morbidity and recurrence effects, emphasizing the vital importance of early diagnosis and treatment. While research in this field has increased, studies on treatment and prognosis remain limited globally and in our country. This study provides essential information on treatment outcomes and the impact of age, stone size, and number on presenting complaints.[20]

This study revealed significant variations in presenting complaints based on age and stone size, with complaints such as macroscopic hematuria, dysuria, urinary incontinence, irritability, and pain showing notable associations with age at diagnosis. Pain was more prevalent with larger stones, while restlessness was more common with smaller stones. These findings are supported by qualitative data, where children frequently described pain as the most distressing symptom, particularly in older age groups, while younger children exhibited more emotional distress and irritability. The presence of single versus multiple stones significantly affected pain complaints but showed less variation in other symptoms.

Significant differences were found in the distribution of symptoms by age. Specifically, macroscopic hematuria, dysuria, urinary incontinence, irritability, and pain were more common in certain age groups. Macroscopic hematuria and dysuria were more frequently observed in older children (aged 5 and above), while irritability was more common in younger children (0-1 years). Pain was more frequently reported in children aged 5 years and above. The qualitative data further confirmed these age-specific patterns, as younger children expressed fear and anxiety, while older children were more focused on physical symptoms such as pain.In Chen et al.'s[21] study, it was noted that kidney stones caused age-related symptoms. Similarly, Matlaga et al.[22] highlighted that age played an important role in the severity and distribution of symptoms in pediatric patients. Sas et al.[23] further emphasized that the variety of symptoms increased with age, and metabolic factors varied based on age. However, Schaeffer et al.[24] reported that symptoms did not significantly differ between pediatric age groups, arguing that symptoms were similar across all ages.

A significant relationship between stone size and certain symptoms was observed. Larger stones (>3 mm) were

associated with more frequent complaints of pain, while smaller stones (<3 mm) were more commonly linked to irritability. Urinary incontinence was also more frequently observed in cases with larger stones. Qualitative findings supported these results, with children describing larger stones as a source of severe pain. Xu et al.[6] reported that stone size was related to metabolic changes, with larger stones causing more severe symptoms. Demirtas et al.[5] emphasized that larger stones directly affected the treatment process and the severity of symptoms. Klib et al.[25] also noted that stone size played a key role in determining the severity of symptoms. In contrast, Kirkali et al.[26] found no significant relationship between stone size and symptom severity, suggesting that the patient's overall condition and metabolic characteristics were more critical than the stone size in determining symptoms.

Pain complaints were more common in cases with a single stone compared to multiple stones. No significant differences were found in other symptoms (nausea, vomiting, stone passage, macroscopic hematuria, dysuria) between cases with single or multiple stones. This was consistent with children's narratives in the qualitative portion, where they frequently mentioned pain as their primary concern, especially in single stone cases. Demirtas et al.[5] also studied the effect of stone count on clinical symptoms and reached similar conclusions. However, Schaeffer et al.[24] suggested that multiple stones, especially in cases with metabolic risk factors, could lead to different clinical presentations.

Among the metabolic disorders, hypercalciuria was the most common, observed in 36.2 % of cases. Hypercalciuria and hyperoxaluria were the most frequently co-occurring metabolic disorders. No cases of cystinuria were detected. In Spivacow et al.'s[27] study, hypercalciuria and hyperoxaluria were also reported as the most common risk factors in children. Sarica's[28] study highlighted the critical role of genetic and metabolic factors in pediatric stone formation. However, Rizvi et al.[29] reported that cystinuria, a rare metabolic disorder, was observed at a higher rate than expected in pediatric urolithiasis cases. While our study found no cystinuria cases, Rizvi's[29] findings indicate that rare metabolic disorders may be more prevalent in broader populations.

The majority of cases (89.1%) were managed with medical treatment, and 85.7% of patients achieved complete recovery. Surgical treatment and ESWL were reserved for more complex cases. The recurrence rate was found to be 2.8%, indicating a low rate of recurrence. This low recurrence rate emphasizes the effectiveness of medical management in most pediatric urolithiasis cases. Öner et al.'s[8] study similarly reported that medical management is the primary approach for pediatric stone disease, with surgical interventions reserved for more complicated cases. Kirkali et al.'s[26] study also supported the preference for minimally invasive surgical procedures in more complex stone cases. Chen et al.[21] compared the effectiveness of surgical and medical treatment methods for kidney stones and concluded that medical management is preferred in most cases.

The emotional and social impacts of the disease on children were evident, with symptoms such as fear, isolation, shame, and disruption of daily activities being observed. Qualitative data enriched our understanding of these psychosocial effects, revealing that children with urolithiasis not only experience physical discomfort but also significant emotional stress. Ayyad et al.[30] also reported that the quality of life for children with kidney stones was negatively affected by such social and emotional factors. Culhane-Pera and Lee's[31] study, which explored kidney stone patients within the Hmong community, emphasized the social and emotional consequences of the disease on children. Klib et al.[25] also highlighted similar social and emotional effects, stressing the importance of emotional support during this process.

The patient's age and stone size are important factors in clinical evaluation and treatment planning. The higher frequency of certain symptoms in specific age groups suggests that age-specific treatment strategies are needed. The alignment of qualitative and quantitative findings in this study reinforces the importance of a holistic approach to patient care, considering both physical and emotional factors in managing pediatric urolithiasis. Sarica[28] found similar results, noting that age-specific pathophysiological differences should be considered in treatment strategies. Issler et al.[32] also emphasized the importance of age in clinical management, noting that symptoms and treatment approaches vary by age group. Similarly, Coward et al.[33] reported that the distribution of symptoms and treatment approaches varied significantly depending on the age of the child.

All children with urinary stone disease deserve a meticulous risk factor assessment that forms the basis of personalized and targeted treatment. Early diagnosis and appropriate treatment selection are crucial in managing stone disease. Regular urological examinations are necessary for high-risk groups, such as those with a family history, to enhance awareness and effectiveness of early diagnosis and treatment. Further comprehensive genetic research on stone disease will enhance understanding and support the development of personalized treatment approaches. The findings of this study can serve as an important reference for clinicians and health policymakers, aiding in the development of strategies for the management and prevention of stone disease.

CONCLUSION

This study highlights the significant impact of urolithiasis on children, emphasizing the importance of early diagnosis and tailored treatment strategies to prevent long-term complications, including end-stage renal failure. The findings demonstrate that presenting symptoms such as hematuria, dysuria, urinary incontinence, irritability, and pain vary with age, stone size, and the presence of single or multiple stones. Metabolic risk factors, particularly hypercalciuria and hyperoxaluria, were identified as the most common contributors to stone formation, with no cases of cystinuria detected in this study.

Medical management remains the primary treatment approach, with surgical interventions, including minimally invasive endoscopic surgeries and extracorporeal shock wave lithotripsy (ESWL), being reserved for more complex cases. The study also underscores the importance of genetic and

metabolic assessments to provide personalized treatment plans, especially for children with a family history of stone disease or consanguineous marriages, who are at higher risk.

The analysis of the chief complaints and experiences shared by children suffering from kidney stones shows that they endure not only physical discomfort but also significant emotional and social challenges. These experiences, including feelings of fear, embarrassment, and isolation, are compounded by the condition's disruption of their normal activities like playing, sleeping, and attending school. Support systems, both within the family and socially, can play a crucial role in mitigating these challenges, but there appears to be room for improvement in educating children about their condition and fostering a more supportive environment both at home and among peers.

Given the rising prevalence of urolithiasis in Turkiye and neighboring regions, future research should focus on genetic predispositions and more advanced diagnostic and treatment options. Regular follow-ups, metabolic evaluations, and preventive measures in high-risk groups are essential for improving clinical outcomes and reducing recurrence rates. The insights from this study can serve as a valuable reference for clinicians and policymakers, helping to refine strategies for managing and preventing pediatric urolithiasis effectively.

ETHICAL DECLARATIONS

Ethics Committee Approval
The study was conducted with the permission of the Samsun University Non-interventional Clinical Researches Ethics Committee (Date: 14.08.2024, Decision No: 2024/14/2).

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 received no financial support.

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

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Original Article

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Investigation of the chemical composition, antioxidant and anticholinesterase activities of *Consolida orientalis*

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ABSTRACT

Aims: It is known that a decrease in the amount of acetylcholine in the body, which is known to be responsible for learning and cholinergic activity in the nervous system, causes Alzheimer's disease. Acetylcholine is destroyed by acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE) enzymes in the nervous system. *Consolida orientalis (C. orientalis)* is a species that belongs to the Ranunculaceae family and grows naturally in many parts of the world. It is known that it plays a role in many biological activities thanks to its content of important phytochemical components such as phenolics and alkaloids. In this study; It was aimed to investigate the antioxidant activity, AChE and BChE enzyme inhibition activities of *C. orientalis* flower extracts.

Methods: The chemical content of ethanol extracts obtained from the flowers of *C. orientalis* plant, which was collected and identified from Sivas İmaret village between June and July 2023, was examined with 6 different reference substances (gallic acid, rosmarinic acid, myrcetin, quercetin, apigenin and camphorol). Antioxidant activity was determined by 2,2-Diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) tests. Ascorbic acid and trolox were used as positive controls. The inhibition capacity of the samples on AChE and BChE enzymes was determined by the Ellman method.

Results: Chemical content analysis of the extract was performed by high pressure liquid chromatography (HPLC) and only gallic acid was detected among the standard compounds. When C. orientalis ethanol extracts were examined with DPPH and ABTS tests, they showed low-moderate antioxidant activity (IC50 (µg/ml) DPPH=4.8, IC50 (µg/ml) ABTS=4.4) compared to standard substances. *C. orientalis* ethanol extract was studied at a concentration of 20 µg/ml. The extract inhibited the AChE enzyme at 66.5% and the BChE enzyme at 53.2%. It was observed that the extract inhibited both enzymes at moderate to good levels, although not higher than galantamine used as positive control.

Conclusion: This study shows us that *C. orientalis* flowers have therapeutic potential for the effective management of neurological disorders due to their antioxidant and anticholinesterase activity. It is thought that our data will contribute to the literature as a preliminary study for the development of a new phytotherapeutic agent in the treatment of Alzheimer's disease.

Keywords: Acetylcholinesterase, Alzheimer's disease, antioxidant, butyrylcholinesterase, *Consolida orientalis*

INTRODUCTION

When the activity of free radicals in the body exceeds the body's own defense mechanism, a condition called oxidative stress occurs. Oxidative stress caused by the imbalance between the neutralization and production of free radicals by the antioxidant mechanism leads to irreversible cell damage, cardiovascular disease, cancer, accelerated aging, and many diseases, including neurodegenerative disorders such as Alzheimer's and Parkinson's.[1,2]

Efforts are being made to elucidate why and how the disease occurs with different hypotheses such as cholinergic, amyloid and oxidative stress. Among these, the cholinergic hypothesis; It is the only hypothesis that clarifies the cause of Alzheimer's disease and is currently accepted in the scientific world. According to this hypothesis, a decrease in the amount of acetylcholine, an important neurotransmitter that increases learning and cholinergic activity in the nervous system, causes Alzheimer's. Acetylcholine is destroyed by AChE and BChE enzymes in the nervous system.[3] For this reason, recently the phytochemicals contained in plants; Its inhibitory effects on acetyl and butyrylcholinesterase enzymes, which play a major role in the treatment of neurodegenerative diseases such as Alzheimer's and dementia, are being investigated.

Traditionally used herbal medicines are of great interest as pharmacological targets in the prevention and treatment of various diseases. Although compounds isolated from plants

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play a very important role in the pharmaceutical industry; it is known that many plants are still not sufficiently researched in terms of their phytochemical components and biological activities.

Consolida is a genus belonging to the *Ranunculaceae* family, consisting of approximately 52 species that grow naturally in many parts of the world, such as Western Europe, the Mediterranean and Asia. Many members of the genus *Consolida* contain important phytochemicals such as phenolics and alkaloids.[1,4] In 1960, the chemical structure of 11 alkaloids obtained from the *Consolida* plant was determined and it was reported that these alkaloids could affect the neuromuscular pathway.[5] Turkiye's flora is very rich in species belonging to the *Consolida* genus from the *Ranunculaceae* family. It is known that there are 29 different species, 14 of which are endemic. *Consolida*; it is a breed that can easily grow in dry climatic conditions and is frequently seen in steppes, deserts and dry stony slopes.[6,7] *C. orientalis* is a medium-tall, sticky-hairy annual plant with simple or branched stems 20-74 cm long and numerous ribbon-like sword leaves. The flowers are purple in color and in the form of dense clusters. It is frequently preferred in the cut flower trade and dry plant designs as dried and fresh cut flower plants.[8]

Phenolic acids, tyrosol derivatives, diterpene alkaloids, lignans and stilbenes, mainly flavonoids, are responsible for the biological activity of *C. orientalis*.[1,4] Previous *in vivo* and *in vitro* studies have shown that; It has antioxidant, antibacterial, anti-tyrosinase, anticancer effects as well as polyphenols and phytosterols (β-sitosterol).[1,9,10]

The purpose of this study; Determination of phytochemical content of *C. orientalis* flower extracts by HPLC, investigation of antioxidant activity, AChE and BChE enzyme inhibition activities.

METHODS

Ethics

No human or animal biological material was used in the study. This is a laboratory study with *Consolida orientalis* plants. Therefore, ethics committee decision is not required. All procedures were carried out in accordance with the ethical rules and the principles.

Plant Material

The *C. orientalis* plant used in the study was collected in June-July 2023 from the area with an altitude of 1400 m, at the coordinates of 39°41'40"N, 37°02'25"E, in Sivas İmaret village. The taxonomic description of the collected samples was made by Anadolu University Faculty of Pharmacy Faculty Member Professor Yavuz Bülent KÖSE. A sample of the collected plant was labeled with the herbarium number (16195) and was recorded and stored in the Herbarium of Anadolu University Faculty of Pharmacy.

Preparation of Plant Extract

Plant extracts prepared from the flower parts of *C. orientalis* were used in our study. After the samples were washed first with tap water and then with pure water, they were dried on blotting papers, ground in a grinder and 100 grams were taken and 1000 ml of ethanol was added. It was kept at room temperature in a shaker at 150 rpm for 24 hours. At the end of the extraction process, the extract was filtered through filter paper, and then the solvent was removed in a rotary evaporator at 40°C. The obtained extract was placed in a dark glass bottle and stored at -20 °C to be used in experimental procedures.[11]

High Pressure Liquid Chromatography (HPLC)

C. orientalis ethanol extract was studied at a concentration of 10 mg/ml and analyzed by filtering through a 0.22 µm membrane filter after dissolving in ethanol. Solutions of the standard substances used (gallic acid, rosmarinic acid, myrcetin, quercetin, apigenin and camphorol) were prepared with methanol. HPLC analyzes were carried out with a UV-DAD detector connected to the Agilent 1100 HPLC system. While C18 column (250 x 4.6mm, 5μm) was used as the stationary phase, A [acetonitrile: distilled water: formic acid (10:89:1, v/v)] and B (acetonitrile: distilled water: formic acid [89:10:1, v/v)] were used as the mobile phase. The flow rate was set to 1.0 ml/min and gradient flow was provided. For the gradient flow B mobile phase, a range of 15-100% was studied in the 40-minute method. Each sample was injected in triplicate. Peaks were analyzed at 330 nm. Injection volume was set as 20 µL, column temperature was set at 40°C.[12]

Antioxidant Capacity

2.2-Diphenyl-1-picrylhydrazyl (DPPH) antioxidant activity test: The total antioxidant capacity of *C. orientalis* ethanol extract was determined using the DPPH method described by Blois et al.[13] The reaction mixture contained 100 µM DPPH• and formulations in methanol. After 30 min, absorbance was read at 517 nm using a UV spectrophotometer (UV-1800, Shimadzu, Japan) at 25±2 °C.[14] Ascorbic acid was used as a positive control. Results are calculated as IC50 (µg/ml).

2.2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) antioxidant activity test: The antioxidant capacity of the samples was determined by Re et al.[15] ABTS was measured using the radical cation decolorization protocol described by. ABTS and 2.45 mm potassium persulfate dissolved in 7 mm water; mixed to form ABTS. The mixture was kept in a dark room at 25°C for 16 hours before use. Ethanol was added to the mixture and absorbance was measured at 734 nm at 25°C. The process was carried out in three repetitions. Ethanol was used as a negative control and trolox as a positive control.[14] Results are calculated as IC50 (µg/ml).

Acetylcholinesterase and Butyrylcholinesterase Inhibition

Cholinesterase inhibition was determined spectrophotometrically by the modified Ellman method. Standard galantamine was applied as a positive control, and the solvent ethanol was used as a negative control. Sodium phosphate buffer (pH:8.0), AChE enzyme stock solution and *C. orientalis* ethanol extract at a concentration of 20 µg/ml were mixed and incubated for 30 minutes. Following the incubation, the reaction was started after adding Ellman's reagent 5.5-dithio-bis-(2-nitrobenzoic acid) (DTNB) and acetylthiocholine. Butyrylthiocholine chloride was used as a

substrate to test the BChE enzyme under the same conditions. The reaction was observed by monitoring the formation of the yellow 5-thio-2-nitrobenzoate anion, which forms as a result of the reaction between DTNB and thiocholine, at a wavelength of 412 nm. All experiments were repeated three times and results are reported as % inhibition value.[16]

RESULTS

High Pressure Liquid Chromatography (HPLC)

The column leaving times (*t*R) of the standard compounds used for HPLC analyzes (gallic acid, rosmarinic acid, myrcetin, quercetin, apigenin and camphorol) and the presence of these standards in *C. orientalis* flower extract are given in Table 1.

Table 1. Retention times of standard compounds and their presence in the extract

Standard compound	t_R	Status on statement
Gallic acid	3.752	Detected
Rosmarinic acid	9.595	None
Myrcetin	10.437	None
Quercetin	14.334	None
Apigenin	17.060	None
Camphorol	18.354	None

t_R: Retention time

The HPLC chromatogram of *C. orientalis* flower extract is shown in Figure. When compared to the chromatogram of standard compounds, only gallic acid with the same *t*R value was detected in the extract.

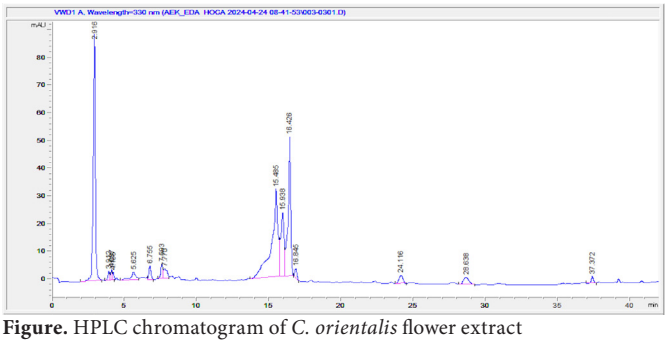

Figure. HPLC chromatogram of *C. orientalis* flower extract

Antioxidant Capacity

The antioxidant capacity of *C. orientalis* ethanol extract measured using DPPH and ABTS methods (ascorbic acid and trolox were used as positive control, respectively) is shown in Table 2. When the antioxidant capacity of the extract was evaluated according to the results of the DPPH test, the IC50 value was calculated as 4.8 µg/ml, and when evaluated according to the results of the ABTS test, it was calculated as 4.4 µg/ml.

Table 2. DPPH and ABTS activities of *C. orientalis* ethanol extract

	C. orientalis ethanol extract	Positive control
	IC50 (µg/ml)	
DPPH•	4.8	0.002 (Ascorbic acid)
ABTS•	4.4	0.01 (Trolox)

DPPH: 2,2-Diphenyl-1-picrylhydrazyl, ABTS: 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)

In the study on the antioxidant activity of *C. orientalis* methanolic extract,[17] the antioxidant capacity was calculated in % and it was determined that different results were obtained at different concentrations. Considering the concentration closest to that used in this study (0.2 mg/ml), the antioxidant capacity of the methanol extract in the study was determined to be 8.97%. This result is compatible with the results obtained in our study.

Acetylcholinesterase and Butyrylcholinesterase Inhibition

C. orientalis ethanol extract was studied at a concentration of 20 µg/ml. The results of the AChE and BChE activity tests of the extract are given in Table 3. The extract inhibited the AChE enzyme at 66.5% and the BChE enzyme at 53.2%. It was observed that the extract inhibited both enzymes at moderate to good levels, although not higher than galantamine used as positive control.

Table 3. Cholinesterase enzyme inhibition of *C. orientalis* ethanol extract (20 µg/ml)

Tested samples	AChE inhibition	BChE inhibition
C. orientalis ethanol extract	%66.5	%53.2
Galantamine (Positive control)	%99.2	%86.9

Studies show that medicinal plants have a wide range of therapeutic effects and have therapeutic potential for the effective management of neurological disorders associated with AChE dysregulation.[18] For this reason, this study was designed about AChE and BChE inhibition of *C. orientalis* plant.

DISCUSSION

There are not enough studies in the literature regarding the medical effects of *C. orientalis*. In particular, no anticholinesterase activity study has been found for this species. Our study is the first in this sense. When the studies were examined, it was determined by researchers that it has antioxidant, antibacterial, anti-tyrosinase and anticancer effects.

The *Consolida* genus contains important bioactive components such as phenolic compounds and alkaloids. In the study conducted with methanol extracts of 6 different species (*C. glandulosa, C. hellospontica, C. raveyi, C. regalis, C. staminosa* and *C. stenocarpa*); 236 flavonoids, 93 phenolic acids, 78 tyrosol derivatives, 49 diterpene alkaloids, 29 lignans and 7 stilbenes were found in the content of the plants. It is known that other phytochemicals, especially polyphenolic compounds (gallic acid, quercetin) and diterpene alkaloids, are responsible for many biological activities such as antimicrobial, antiparasitic, antioxidant and antitumor in the plant.[4,19,20]

In the studies conducted, norditerpenoid, diterpenoid and norditerpene (18-demethylpubeskenine) alkaloids were found in the content of *C. orientalis*.[19,21,22]

DPPH and ABTS radical scavenging tests of ethanol extracts of different organs of the *Consolida regalis* plant belonging to the *Consolida* genus were examined in terms of antioxidant activity. It was concluded that all extracts showed cleaning

activity depending on concentration, thus the plant has antioxidant activity.[23]

The antioxidant activity of methanol, ethyl acetate and water extracts of *C. orientalis* was investigated, the extract with the best antioxidant capacity was found to be methanol, and the extract with the lowest antioxidant capacity was ethyl acetate.[17]

In the study where the antibacterial and antioxidant activities of different extracts of *C. orientalis* were evaluated against selected bacteria; The extracts have high antimicrobial activity against *Proteus mirabilis*, *Enterobacter cloacae*, *Klebsiella pneumonia* and *Staphylococcus aureus*; It has also been reported to display weak nitric oxide scavenging activity and Fe^{2} chelating ability.[9]

In a study conducted to determine the cytotoxic effect of *C. orientalis* flower extract; It was determined that plant extracts did not show any cytotoxic effect on the WI-38 human fibroblast cell line even at a concentration of 5 mg/100 µL.[24]

In another study; It was aimed to evaluate the *in vitro* cytotoxic activity of the ethanol extract of *C. orientalis* collected from Mazandaran in the north of Iran using the human cervical carcinoma cell line HeLa. In the results of working; The anticancer potential of the ethanolic extract of the plant in the HeLa cell line has been proven. And this result showed us the presence of cytotoxic compounds in ethanolic extracts of *C. orientalis.*[10]

In the study conducted with different species of the *Consolida* genus (*C. glandulosa, C. hellospontica, C. raveyi*); As a result of cholinesterase inhibition analyses, it was observed that extracts of *C. hellospontica* and *C. glandulosa* exhibited high inhibitory effects.[4]

Ghanbarpour et al.[25] reported that *Consolida* extract could be used as a strategy to control tick resistance to synthetic acaricides.[26]

Limitqations

The most important limitation of the study is that only 6 of the phytochemical components in the plant extract (gallic acid, rosmarinic acid, myrcetin, quercetin, apigenin and camphorol) could be investigated. In addition, the absence of similar studies in the literature limits our study in terms of references.

CONCLUSION

Acetylcholinesterase inhibitors used in current treatment reduce the symptoms of Alzheimer's disease and slow the progression of the disease, but do not provide a complete cure. Therefore, recently in the prevention and treatment of Alzheimer's disease; studies on the detection of acetylcholinesterase and butyrylcholinesterase inhibitors obtained from new and natural sources and without toxicity have gained great importance.

In our study, the chemical content of the ethanol extracts of the flowers of the *C. orientalis* plant was examined by HPLC; Flavonoid-derived compounds (gallic acid, rosmarinic acid, myrcetin, quercetin, apigenin and camphorol), which are common in plants, were investigated and only gallic acid was detected in the extract. The reason for this is; It is known that the phytochemical profiles of plants vary depending on the time the plant was collected, the characteristics of the soil in which it grows, and other characteristics of the geographical region where it is located. Its antioxidant capacity and effects on acetylcholinesterase and butyrylcholinesterase enzymes were investigated, and a moderate to good effect of the plant was determined, especially on AChE and BChE enzymes. It is thought that our data will contribute to the literature as a preliminary study for the development of a new phytotherapeutic agent in the treatment of Alzheimer's disease. For further research, it is recommended to be supported by *in vitro* and *in vivo* studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

No human or animal biological material was used in the study. This is a laboratory study with *Consolida orientalis* plants. Therefore, ethics committee decision is not required.

Informed Consent

No human or animal biological material was used in the study. This is a laboratory study with *Consolida orientalis* plants. Therefore, informed consent is 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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Effects of repeated anti-VEGF injections on macular vessel density in Turkish proliferative diabetic retinopathy cases

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ABSTRACT

Aims: Although a dramatic increase has been observed in Turkish diabetic retinopathy (DR) patients due to the rising cases of diabetes mellitus (DM), ophthalmological advancements facilitate treatment for DM and its ophthalmic complications, such as proliferative diabetic retinopathy (PDR). To determine the effectiveness of the repeated anti-vascular endothelial growth factor (anti-VEGF) intra-vitreal injections (IVI or IVIs) on the macular vascular density (VD) in PDR.

Methods: This theme includes methodological research, retrospective validation studies, and multivariate meta-analysis. The data were obtained from the PubMed, Google Scholar, SCOPUS, WoS, and Google Academic Papers between 2004 and 2023. The injections which completed within 6 months, consecutively administered monthly for three times. This editorial involves diabetic cases that were previously injected with any of Anti-VEGF agent, particularly aflibercept, ranibizumab, and bevacizumab in PDR populace. They were selected over eighteen years who owned high-quality images of "optical coherence tomography angiography" (OCTA). The retinas of thirty-five sufferers from DR were bilaterally analyzed by utilizing keywords.

Results: The analysis of VD relevant to PDR did not identify notable alterations of TCP, DCP and SCP, central retinal vascular layers, both before and after the first anti-VEGF IVI cure. Similar events were detected by the consecutive second and third phases. Besides, central retinal thickness (CRT) decreased at least 10 % from the associated with control cases. Twenty eyes were cure-resistant, whereas fifteen eyes were medical care-responsive. Thirty-five humans with PDR were selected. The gender distribution in the study was sixty percent men and forty percent women, and their average age ranged between forty and eighty.

Conclusion: The article revealed that VD measures did not illustrate any expressive difference in TCP, DCP and SCP before and after three injections. In other words, the baseline VD measurements did not suggestively conclude while CRT was reducing slightly.

Keywords: Anti-VEGF and PDR vessel density, intra-vitreal anti-VEGF and VD in PDR, anti-VEGF and macular VD in PDR, proliferative diabetic retinopathy and anti-VEGF, vascular macular modifications with anti-VEGF in PDR

INTRODUCTION

An expeditious advancement in health-related problems has been announced in the past few years. This raise has urged eye care professionals to find remedies that might help to cope with the proliferative diabetic retinopathy (PDR)-affected issues.[1,2] As in other countries, diabetic cases have seen an increment in Turkiye for the past few decades. According to the International Diabetes Federation, in 2000, there were almost 1.8 million sufferers from diabetes mellitus (DM) between 20 and 79 years. Then, their numbers reached to nearly nine million in 2021. Figure 1. demonstrates the unusual increase peak of DM population in Turkiye. It similarly reveals the future statistics of the Turkish populace as regards DM might be increased to 13.5 million.[3]

As the image established the prediction speed of diabetic cases in Turkiye, the DR occurrences have been simultaneously rising. This is why the document was focused on considering the repeated anti-vascular endothelial growth factor (anti-VEGF) intra-vitreal injection (IVI) effects in PDR.

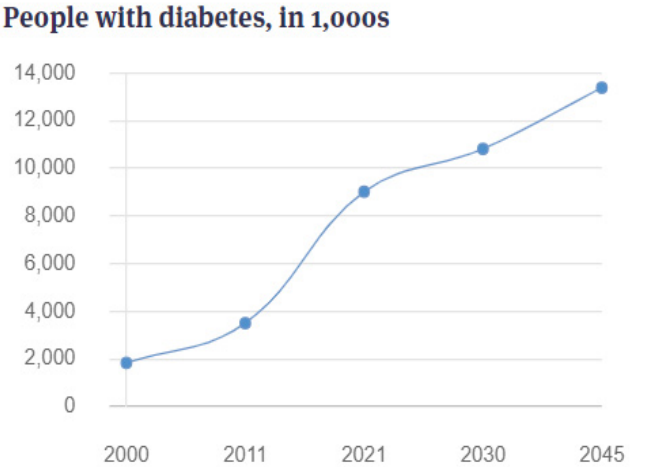

Figure 1. Diabetes statistics of Turkiye between 2000 and 2045. It is predicted that DM cases will increase by 700 percent in Turkiye between 2000 and 2045.[3]

DM: Diabetes mellitus

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The percentage of men with diabetes is 9.12% and in women is 13.10%. The studies declared that Turkish women own a more significant predisposition to DM than men, for instance, this gender affinity is also valid for PDR.[4] If DM is not treated in time; it will seriously predispose heart, kidney, and ocular destructions, such as PDR pattern.[5] It has been remarked that diabetic patients are more likely to develop ophthalmic complications. The commonplace diabetic pathologies based on detractive visual acuity consist of cataracts, macular edema, DR, and glaucoma.[6] Conforming to recent statistics, the percentage of sick people was 13.5%, out of which 6.2% of them were complicated by DR in Turkiye.[3,7]

DR is one of the most frequent reasons for decreased visual acuity belonging to DM, which is accompanied by the high blood glucose level. Retinal signals communicated with brain were blocked that often result in vision loss due to the retinal vascular obstruction in the presence of PDR.[8,9] Different methods and medical techniques are employed to provide PDR remediation. These therapies involve therapeutical solutions, such as corticosteroids, anti-VEGF IVI agents and different sub-units of laser procedure can prevent the leakage in the retinal blood vessels,[10] and one of the extremely effective remedies of DR is the utilization of them.[11] In addition, the injection, which contained anti-bodies, is applied into vitreous and helps to terminate the leakage, and growth of blood vessels by suppressing the VEGF.[12] They chemically named bevacizumab, ranibizumab, and aflibercept, are well-known and commonplace therapeutics in Turkiye.

DR is the most common microvascular complication of Diabetes Mellitus.[13] Nearly one-third of rehabilitants with diabetes develop DR cases worldwide, with a higher risk occurring in the moderate-severe period of the disease.[14] The World Health Organization (WHO) has estimated that DR causes 15-17% of total sight loss in Europe and the USA.[15] The severity condition of vascular lesions has been employed to define and evaluate DR progression, since the detection of retinal inner vascularization became easier. DR is divided into two phases: non-proliferative DR (NPDR), and more destructive form proliferative DR (PDR). These stages are based on the stage of microvascular degradation and concerned with ischemic damage. The development of DR is accompanied by the permeability of the blood-retinal barrier (BRB), growing microvascular complications with vascular endothelial cell. Then, capillary blockage, swelling of the vascular basement membrane (BM), and destructive retinal neuronal and glial irregularities pursue.[16]

Anti-VEGF treatment is the best ophthalmic medication for PDR. The Diabetic Retinopathy Clinical Research Network, known as the DRCR Retina Network, has significantly managed the clinical handling of diabetic eye conditions over the last 2 decades. The network studies guided how to conduct them as an efficient alternative to pan-retinal photocoagulation in eyes suffering from PDR.[17] Medication blocks VEGF when it is intra-vitreally administered to the eye. In general, the procedure is implemented in a treating room or operating theater. After mydriatic eye drop and local anesthetic agent, the peri-orbital skin is cleaned, the ocular surface is sterilized, the orbit is draped, and a clean lid speculum is inserted before the IVI technique. The solution should be safely injected through the lateral spot, where is 3.5-4 mm far from the limbus, and into the pars plana infero-temporally applied.[18]

The injection process has been performed once-a-month as long as a quarter of year is sufficient period for the loading dosage, more subsequently has followed by regular monthly evaluations for two years in PDR. Each visit consists of a normal retinal examination assessment. The administered cure depends on how severe the condition is and its revision if necessary.[19] The advancement of Anti-VEGF remedy might be an effective tool in the battle against DR-affected visual impairment.[20] The cost of these repetitions-required drugs and the need for a couple of medical visits are an enormity in the ophthalmological sector and induce tremendous concerns regarding the disadvantaged individuals. Nevertheless, this medical procedure provided a clearly superior to the other courses in terms of effectiveness and safety by illustrating a decline in the prevalence of blindness related to PDR.[21]

Anti-VEGF therapy has been illustrated in investigations to contribute to DR decrease in both NPDR and PDR. They can ameliorate the severity of PDR.[22] Therapies for DR with Anti-VEGF involve few limitations; individuals complain by overpriced medicine, the rehabilitation ought not to be discontinued in just a few ophthalmological monitoring and the cure does not own permanently beneficial effects.[23] The medication is not able to be safely discontinued after any known management periods. In agreement with the studies, DR will recur or decline, if the medicine is discontinued,[24] the requirement for regular evaluations and the unpredictability of long-term consequences with them become more complicated and worrisome issues in young PDR individuals.

Anti-VEGF medication, which reduces the mass of DR, is linked to a decrease in the incidence of PDR development. It should be utilized in rehabilitants only who can be regularly monitored if there is retinal edema. On the contrary, it could be implemented to treat the deeper reason of retinopathy connected with PDR and may postpone but does not eliminate a requirement for surgery. Additionally, it is able to occur the tractional retinal detachment, which impairs vision in the presence of progressive vitreoretinal membranes condition.[25]

METHODS

This report involves methodological research, retrospective validation studies, and multivariate meta-analysis. The data were provided with the PubMed (The National Center for Biotechnology Information, the U.S.), Google Scholar (The Google Co., the U.S.), SCOPUS (The ELSEVIER Co., The Netherlands), WoS (The Clarivate analytics Co., UK & USA), and Google Academic Papers (The Google Co., the U.S.) in between 2004 and 2023. It was prepared in accordance with the principles of the Declaration of Helsinki. The academic work was approved and obtained on 14th September 2023 with 774 protocol number by the Medipol University Non-interventional Clinical Researches Ethics Committeee (Date: 21.09.2023, Decision No: 5985). All procedures were carried out in accordance with the ethical rules and the principles

of the Declaration of Helsinki. Among PDR events over 18 years receiving anti-VEGF IVI, those with optical coherence tomography angiography (OCTA) images were preferred. The medical records were reviewed to compile baseline demographic data, including gender, diabetes duration, systemic and ocular history, such as IVI procedure. The best-corrected visual acuity (BCVA) of the most recent ophthalmic examination, slit-lamp bio-microscopy, and fundus examination outcomes were noted. The retinas of thirty-five patients with PDR were bilaterally evaluated to deal with this dissertation.

SPSS software (version 25; SPSS, Inc., Chicago, IL, USA) was utilized for statistical analysis. Multivariate analysis aimed at examining the type of prior Anti-VEGF therapy and its effect on variation in VD measurements. The "t" test was applied to evaluate baseline VD in the responsive and treatment-resistant PDR population. Repeated measures and paired "t" quantitative data were managed with ANOVA analytic test. Before and after the first injection, PDR response and VD mass values were compared applying binomial logistic regression and linear regression analysis, respectively, and a "p value" of 0.05 or less was considered graphical.

Exclusion Criteria

- Exclusion criteria consisted of myopia higher than four diopters, complicated ocular conditions, uncontrolled glaucoma, a history of endophthalmitis, vitreomacular traction, pan-retinal photocoagulation (PRP) laser procedure applied within the last three months, steroidal IVI, and any ocular surgery in the previous six months.
- OCTA images quality-degrading with media opacity were excluded.

Inclusion Criteria

- Rehabilitants who had priorly received anti-VEGF IVI were comprised in the paper.
- The RT-Vue XR 100 Avanti device of the Optovue brand (Inc., Fremont, California, USA) was preferred to perform OCTA imaging in eyes with PDR. The best 3 mm and 6 mm photographs were selected because they had a qualified signal-to-noise ratio and were successfully centered on the fovea. images rated 6/10 and above were included.

The automated segmentation of Angio-Vue module was applied to analyze superficial and deep capillary retinal plexus projections. If segmentation troubles were found, Angio-Vue's proprietary software would be practiced for manual repairing. Due to the deep retinal capillary plexus limits in six eyes and the outside boundary of the superficial capillary plexus in three eyes being incorrectly determined, manual correction was required in nine eyes. The internal limiting membrane (ILM) served as the inner border for the superficial retinal capillary plexus (SCP), and the inner plexiform layer (IPL) functioned as the outer boundary. The inner verge of the deep retinal capillary plexus (DCP) was ten micrometers (μm) inside the IPL, whereas the outside borderline was ten μm below the outer plexiform. This work has informed that segmentation could be difficulty supervised during the presentation of diabetic macular edema (DME) (Figure 2).

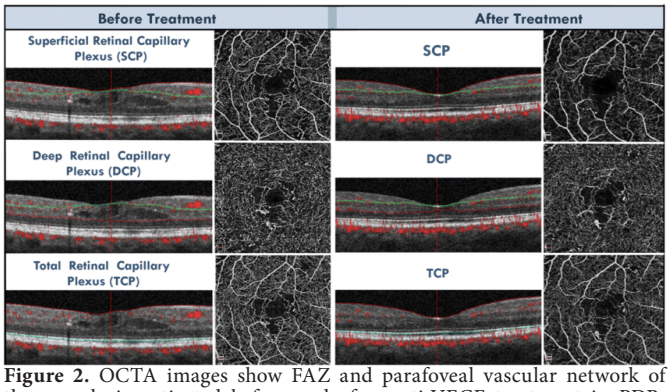

Figure 2. OCTA images show FAZ and parafoveal vascular network of the macula investigated before and after anti-VEGF treatment in PDR. Following the three intermittent IVIs, micro-decreases were observed in VD belonging to the SCP, DCP, and TCP.[26, 27]

OCTA: Optical coherence tomography angiography, FAZ: Foveal avascular zone, anti-VEGF: Anti-vascular endothelial growth factor, PDR: Proliferative diabetic retinopathy, VD: Vessel density, SCP: Superficial retinal capillary, DCP: Deep retinal capillary, TCP: Total retinal capillary plexuses

A quantitative investigation of VD was executed in the OCTA images by virtue of the Angio-Vue program. The software automatically calculated the proportion of the vascular area with flow. It was defined as pixels that possess decorrelation values above the threshold level for the entire ETDRS grid, composed of concentric rings at 1-3-6 mm from the foveal center, and its subunits.[26,27] VD was calculated by applying the entire ETDRS grid, that corresponds to a 3 mm circle in a 3-9-3 mm OCTA and a 6 mm circle in a 6-9-6 mm OCTA scan before and after processing.

RESULTS

In the OCTA images, recorded 9 days before and 51 days after the injection, a decrease in macular vessel density was observed due to the effect of two intravitreal anti-VEGF injection cures and was evaluated as significant. Additionally, CRT reduced at least 10.0% from the associated baseline (BL), despite the twenty eyes becoming resistant and fifteen eyes responding to remedy. (126.07±38.02 μm) ($p<0.001$) were not considered notable following the completion of three Anti-VEGF IVIs (Table 1).

Table 1. VD analysis after first Anti-VEGF injection.[25-27]

	MD	SD	p
SCP			
Scan=3 9 3 mm			
PDR pt	- 1.37	4.81	0.43
Scan=6 9 6 mm			
PDR pt	- 2.42	5.61	0.25
DCP			
Scan=3 9 3 mm			
PDR pt.	- 42.24	120.67	0.34
Scan=6 9 6 mm			
PDR pt	- 2.35	3.76	0.13
TCP			
Scan=3 9 3 mm			
PDR pt.	0.031	3.02	0.96
Scan=6 9 6 mm			
PDR pt	-3.23	4.96	0.11

MD: Mean difference, pt: Patient, SD: Standard deviation, Table 1 showed the VD volumes had never scientifically changed in TCP, DCP and SCP, before and after the first injection

The scan of 3-9-3 mm within DCP statistically showed an unimportant increase in the VD after the first injection of Anti-VEGF reagent. Likewise, Table 2 demonstrated non-meaningful changes between subgroups of the PDR patients who were injected with second and third anti-VEGF consecutively.

Table 2. VD analysis after 2nd and 3rd anti-VEGF injection (inj).[25-27]

	MD	SD	p
SCP			
Scan=3 9 3 mm			
2nd inj	1.15	4.68	0.18
3rd inj	1.42	4.03	0.07
Scan=6 9 6 mm			
2nd inj	0.44	4.16	0.61
3rd inj	1.03	4.02	0.23
DCP			
Scan=3 9 3 mm			
2nd inj	- 0.03	7.21	0.97
3rd inj	- 0.34	7.06	0.82
Scan=6 9 6 mm			
2nd inj	0.22	5.27	0.82
3rd inj	1.11	4.84	0.26
TCP			
Scan=3 9 3 mm			
2nd inj	0.021	3.48	0.95
3rd inj	- 0.32	4.83	0.73
Scan=6 9 6 mm			
2nd inj	2.17	9.04	0.22
3rd inj	0.71	3.66	0.34

anti-VEGF: Anti-vascular endothelial growth factor, SD: Standard deviation, SCP: Superficial retinal capillary, DCP: Deep retinal capillary, TCP: Total retinal capillary plexuses

Finally, no impressive decrease or increase in VD measurements could be demonstrated with the effect of three consecutive anti-VEGF IVIs. These results are compatible with the outcomes of similar studies in the literature with much larger data.

Figure 3 displays that the VD capacities mathematically remained unchanged via administration of the anti-VEGF IVI. The obtained results were constant in all scans. These outcomes were acquired by three IVI with the associated anti-VEGF for the current theme.

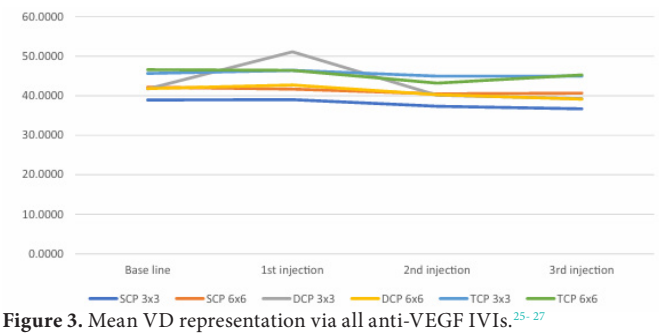

Figure 3. Mean VD representation via all anti-VEGF IVIs.[25-27]

VD: Vessel density, anti-VEGF: Anti-vascular endothelial growth factor, IVIs: Intra-vitreal injections

The impact on previous anti-VEGF procedure was observed on the "VD mass changes" after the administration of initial its injection. For this purpose, multivariate analysis was utilized. Table 3 displayed that both previous medication and the third anti-VEGF IVI did not affect the VD pattern. In addition, it did not act the consequences for DCP, TECP and SCP in both scans.

Table 3. Multivariate analysis.[25-27]

	f	p
Effect on treatment of anti-VEGF in VD measurements		
PT	1.106b	0.368
Btw-sub effects of anti-VEGF		
SCP		
Scan=3 9 3 mm	0.575	0.565
Scan=6 9 6 mm	2.358	0.106
DCP		
Scan=3 9 3 mm	0.905	0.413
Scan=6 9 6 mm	0.284	0.756
TCP		
Scan=3 9 3 mm	0.002	0.998
Scan=6 9 6 mm	0.184	0.833
Effect on previous treatment of anti-VEGF in VD measurements		
PT	1.333b	0.265
Btw-sub effects of anti-VEGF's previous treatment		
SCP		
Scan=3 9 3 mm	0.085	0.918
Scan=6 9 6 mm	0.603	0.553
DCP		
Scan=3 9 3 mm	1.716	0.193
Scan=6 9 6 mm	0.008	0.992
TCP		
Scan=3 9 3 mm	0.083	0.921
Scan=6 9 6 mm	0.577	0.566

anti-VEGF: Anti-vascular endothelial growth factor, Btw: Between, sub: Subjects, PT: Pillai's trace, VD: Vessel density, SCP: Superficial retinal capillary, DCP: Deep retinal capillary, TCP: Total retinal capillary plexuses

Table 4. T-test- difference in VD measurement of treatment-resistant versus responsive groups.[25-27]

	MD	p
SCP		
Scan=3 9 3 mm	- 0.00378	0.997
Scan=6 9 6 mm	1.22158	0.412
DCP		
Scan=3 9 3 mm	0.14736	0.932
Scan=6 9 6 mm	- 1.70605	0.403
TCP		
Scan=3 9 3 mm	1.02575	0.542
Scan=6 9 6 mm	0.65226	0.728
CRT	- 60.37878	0.014*

SCP: Superficial retinal capillary, DCP: Deep retinal capillary, TCP: Total retinal capillary plexuses

The relationship between the response of PDR to Anti-VEGF and the dimensions of VD was shown in Table 4. According to t test, no remarkable changes were observed in CRT and TCP thicknesses following the injections.

Even though the "binominal logistic regression model" was applied for determining the VD quantifications, the "linear regression model" was considered for the testing of the correlation with the associated PDR therapy. Similar endings were noticed in the t-tests (Table 5).

Table 5. Correlation between macular edema (ME) response to treatment incorporating Anti-VEGF and VD measurement.[25-27]

		B	p
VD measurement baseline as predictor to PDR resistant	**SCP**		
	Scan=3 9 3 mm	0.198	0.172
	Scan=6 9 6 mm	- 0.282	0.062
	DCP		
	Scan=3 9 3 mm	0.045	0.506
	Scan=6 9 6 mm	0.093	0.126
	TCP		
	Scan=3 9 3 mm	- 0.317	0.066
	Scan=6 9 6 mm	0.185	0.102
PDR response to 1st Anti-VEGF injection	**SCP**		
	Scan=3 9 3 mm	- 2.503	0.212
	Scan=6 9 6 mm	- 2.321	0.195
	DCP		
	Scan=3 9 3 mm	- 0.605	0.802
	Scan=6 9 6 mm	- 2.395	0.295
	TCP		
	Scan=3 9 3 mm	- 1.373	0.401
	Scan=6 9 6 mm	- 1.658	0.406

Table 5 explained that an insignificant VD reduction was formed in PDR-related patients with DME after a single dose of anti-VEGF injection, SCP: Superficial retinal capillary, DCP: Deep retinal capillary, TCP: Total retinal capillary plexuses

DISCUSSION

The result confirmed the absence of major effect of three consecutive anti-VEGF IVIs on macular VD referred to PDR. It was also clear from the study that VD was not linked to previously performed procedures.

Results that confirm our study or do not support our hypothesis are discussed with a few examples below.

The article of Sorour et al.,[27] Anti-VEGF IVI effect in macular VD variations and PDR-associated DME" paralleled our outcomes.

Another example is the review by Zhao et al.,[28] they confirmed how VD differs after improvement of PDR with pan-retinal photocoagulation (PRP) or intravitreal conbercept (IVC). Their research compared retinal VD and modifications to OCTA, and they revealed that the method did not improve the PDR-VD process.

Chatziralli et al.[29] detailed their research to evaluate the relationship between retinal nonperfusion and Anti-VEGF IVI in PDR subjects and they searched the literature to determine whether IVI had effects on the density of the macula and retinal vessels. The results of the paper did not provide any convincing evidence for effective amelioration of the PDR-VD process with Anti-VEGF.

Mirshahi et al.[30] Announced their article regarding macular microvascular changes after intravitreal bevacizumab injection in diabetic macular edema.

Our scientific study, to reduce VD with repeated Anti-VEGF IVIs in PDR, revealed details much the same to those discovered by the researchers above.

While most similar studies are based on the general vascular density of the whole retina, a more specific area, the macula, was preferred for this study. As is known, the normal macula consists of FAZ and perifovea. FAZ is an avascular region responsible for detailed, daytime and color vision. In cases of PDR, pathologies that threaten central vision such as bleeding, DME, abnormal vascular proliferation, and macular hole because of its location in the macula rather than the peripheral retina are observed. The effects of three repeated injections were "much less" than the VD reducing effects stated in the literature might be considered a remarkable difference. Therefore, more careful planning in the application of Anti-VEGF IVI in Turkish PDR patients would provide advantages. In summary, except for selected cases, discontinuation of more than 1 (one) course of anti-VEGF IVI could be considered and discussed in a Turkish ophthalmology council.

Theoretical Implications

It similarly described the increasing rate of diabetes in Turkiye, which needs to be contemplated. DR approaches and VD responses in the duration of repeated anti-VEGF IVI were discussed. The article aimed at reaching its optimal number of repetition cycle.

Practical Implications

This composition, which provides an insight into the conduct, will be beneficial for the ophthalmologists to discuss and comment the ideal number of repeated pharmaceuticals, and to inspect the relationship between anti-VEGF IVI and VD modifications in PDR for Turkiye.

Limitations

Although this article has interesting implications, there are several corresponding shortcomings in the resulting analysis. Anti-VEGF IVI associated with DR was specifically addressed in the review; other parameters that may affect the reliability, results, hypotheses and recommendations of the study should not be forgotten. Some of these are the number of cases, the age of the patient, additional ocular and systemic diseases, and the duration of the study. For example, in this article, the Turkish diabetic population aged Eighteen and over was selected, although the disease was seen at the age of Fourteen. Because local data do not contain sufficient figures regarding the early adolescence period of DM. This article was conducted in the Turkish context only, thus the findings may differ in the other countries. In this thesis, the effects of repeated

doses were checked; The situation may change depending on long-term use. Moreover, the same Anti-VEGF agent was not regularly injected. Any of the Ranibizumab, Bevacizumab or Aflibercept agents, available in Turkish medicine market, was injected. This was also considered as a limiting parameter.

CONCLUSION

This theme addressed how to consider and accredit the ideal number of repeated anti-VEGF IVIs for the PDR rehabilitation plan. The PDR-VD study indicated that the required improvement in SCP, TCP and DCP and reduction in VD before and after the first Anti-VEGF IVI administration were not achieved. Similar actions were seen in the second and third repeated processes. The findings subsequently confirmed that CRT was almost never lowered in relevant cases, with many eyes not responding to treatment, whereas a few eyes were care-responsive Literature studies recommend monthly anti-VEGF injections for three times depending on the loading dosage in PDR, and then regular 6-monthly follow-up for the first two years, and eye examinations to determine whether anti-VEGF injections are necessary or not. In this study, mathematically, much lower variations were observed under the influence of the agent in basic VD dimensions than the other studies. Therefore, instead of three-monthly repeated loading doses, a single dose of IVI and then 6-monthly checks in the first 2 years and annual checks after 2 years could be recommended.

For impact and cost planning, anti-VEGF agents that are not available in Turkiye might be produced and/or imported. Efforts to discover new drugs that eliminate macular abnormal VD, such as anti-VEGF and other agents, could be accelerated.

Future Additional Recommendations

This work is also composed of the recommendations because of further research. Researchers can examine other approaches of DR such as corticosteroids medicines, and several types of laser cure to see whether they are effective to treat the illness or not. Since exposure to DM cases have developed as early as the age 14, the baseline of screening should involve with age for Turkiye, and much more research shall be assisted to see the difference in Turkish reports. Furthermore, the long-term effects of Anti-VEGF IVI need to be conceived.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Medipol University Non-interventional Clinical Researches Ethics Committeee (Date: 21.09.2023, Decision No: 5985).

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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Case Report

HEALTH SCIENCES
MEDICINE

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A rare form of tuberculosis: a case of tuberculosis verrucosa cutis

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ABSTRACT

Cutaneous involvement is a relatively uncommon manifestation of tuberculosis. Cutaneous lesions account for less than 2 percent of all extrapulmonary manifestations. Due to the paucibacillary nature of the lesions, there is a potential for misdiagnosis, which could result in the chronicity of the skin infection. This article presents the case of a 34-year-old male butcher who presented with plaques exhibiting characteristics of verrucosa, acanthosis, and hyperkeratosis on both fingers for a period of 10 years. The diagnosis of *Mycobacterium tuberculosis* was confirmed by histopathologic examination. The patient was subsequently treated with a standard anti-tuberculosis regimen, which resulted in notable improvement in the skin lesions.

Keywords: Tuberculosis verrucosa cutis, *Mycobacterium tuberculosis*, extrapulmonary tuberculosis, cutaneous lesions

INTRODUCTION

Tuberculosis is a public health problem due to its high prevalence, severe morbidity and high mortality. In 2020, 9.9 million people were diagnosed with tuberculosis worldwide.[1] Cutaneous tuberculosis is a rare manifestation of the disease, accounting for only 1-1.5% of all extrapulmonary tuberculosis cases and 8.4-13.7% of all tuberculosis cases.[2] Cutaneous tuberculosis was first documented in 1826, when Laennec reported his own "prosector's wart," a lesion that likely represented tuberculosis verrucosa cutis, a variant of tuberculosis that results from direct entry of the organism into the skin.[3] *Mycobacterium tuberculosis*, a slow-growing, acid-fast bacillus, is the predominant causative organism of cutaneous tuberculosis. Additionally, both *Mycobacterium bovis (M. bovis)* and the Bacille Calmette-Guérin (BCG) vaccine, which is composed of attenuated *M. bovis*, have been linked to the emergence of cutaneous lesions.[4] Classification systems for cutaneous tuberculosis vary. Commonly, cutaneous tuberculosis is divided into two major groups: true cutaneous tuberculosis and tuberculids. The skin diseases covered by true cutaneous tuberculosis include: scrofuloderma, tuberculosis cutis orificialis, lupus vulgaris, acute miliary tuberculosis, metastatic tuberculous abscess, tuberculosis verrucosa cutis.[2] Those at greatest risk for infection with this pathogen are children who play in contaminated areas and adults with occupational exposure to mycobacteria, including pathologists, laboratory technicians, undertakers, butchers, and farmers.[5] Tuberculosis verrucosa cutis lesions are typically solitary, painless, and most prevalent in anatomical locations susceptible to trauma, such as the fingers and toes. The lesions initially manifest as erythematous papules with a purplish inflammatory halo. Over time, they evolve into asymptomatic verrucous plaques, which can reach a diameter of 5 cm.[6] The primary method for diagnosing tuberculosis verrucosa cutis is the correlation of the physical findings with a skin biopsy and other evidence of tuberculosis infection, such as a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA).[7] The histopathologic findings of tuberculosis verrucosa cutis include the following: pseudoepitheliomatous hyperplasia, marked hyperkeratosis, and a frequent presence of an inflammatory infiltrate composed of epithelioid cells and giant cells in the upper and middle dermis.[8] If left untreated, skin lesions may persist for years; however, spontane ous resolution is also a possibility.[8] Patients typically improve with anti- tuberculosis therapy.[2] We present a case of 34-year-old male patient with tuberculosis verrucosa cutis of the fingers.

CASE

A 34-year-old male butcher presented with a wound on his fingers. The patient exhibited verrucous plaque-like lesions on the fingers (Figure 1). The patient has been afflicted with lesions for approximately a decade, with the lesions increasing in size over time. In other medical services, he was treated with topical and oral drugs, including corticosteroids, antimycotics, and antiallergics, with no improvement in his condition. Moreover, no similar lesions were observed in his family members. The patient is not afflicted with any chronic disease. Upon physical examination, the patient exhibited pale erythematous plaques with squamous plaques on the first and fifth fingers of the left hand. The complete blood count and biochemistry tests yielded normal results. Furthermore, the tests for HIV, hepatitis B and C, and syphilis were negative. The patient was subjected to a TST, which exhibited a positive result 48 hours following inoculation, displaying a diameter exceeding 15 mm. The patient was not found to have active pulmonary tuberculosis. Additionally, it was ascertained that there was no familial history of pulmonary tuberculosis. A

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biopsy was performed on the patient's finger, and histologic sections were stained with hematoxylin-eosin (HE) and the Ziehl-Neelsen technique. The skin fragments were cultured in Lowenstein-Jensen medium, and a polymerase chain reaction (PCR) was employed to identify the etiological agent. The histologic section of the skin stained with HE revealed the presence of hyperkeratosis, acanthosis, and papillomatosis in the epidermis, as well as a notable degree of inflammation comprising a multitude of polymorphic leukocytes in the upper dermis. Additionally, the immunohistochemical study identified the presence of giant cells and granuloma-like structures (Figure 2). No bacilli were observed to be present in the culture of the skin fragments, nor were any bacilli seen in sections stained with the Ziehl-Neelsen technique. The samples did not yield any acid-resistant bacilli (ARB), and the tuberculosis PCR was negative. However, given the compatibility of the pathology result with a granulomatous infection, the appearance of the lesions was consistent with that of tuberculosis, and the patient exhibited a positive reaction to the skin tuberculin test, the diagnosis was rendered as tuberculosis verrucosa cutis. The patient was initiated on quadruple antituberculosis treatment, comprising isoniazid (INH) 300 mg, rifampicin (RIF) 600 mg, ethambutol (ETM) 1500 mg, and pyrazinamide (PZA) 2000 mg. The patient's lesions demonstrated regression with the initiation of treatment. Following a four-month course of treatment, the lesions had completely resolved. The patient's treatment was terminated after a six-month period.

Figure 1. Pale erythematous plaques with squamous plaques on the first and fifth fingers of the left hand

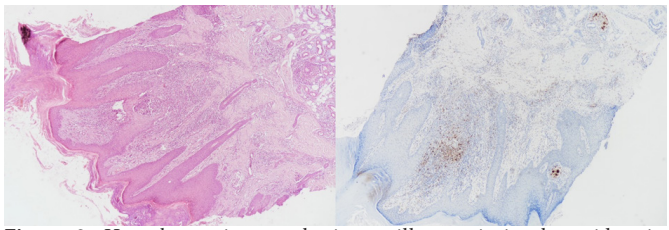

Figure 2. Hyperkeratosis, acanthosis, papillomatosis in the epidermis; intense inflammation and giant cells rich in polymorphonuclear leukocytes in the dermis

DISCUSSION

Cutaneous tuberculosis represents a rare form of tuberculosis that is challenging to diagnose due to the non-specific clinical characteristics exhibited by the lesions. The clinical manifestations of cutaneous tuberculosis can be mistaken for those of other diseases due to their resemblance and the low bacillary load. Nevertheless, it is a skin infection that should be considered in the differential diagnosis of cases presenting with long-lasting, non-healing skin lesions that fail to respond to basic antibacterial treatments.[2,9] The differential diagnosis of cutaneous tuberculosis includes leishmaniasis, leprosy, chromomycosis, sporotrichosis, mycetoma and granulomatous and verrucous lesions of different origin.[9] The histopathologic evaluation of tuberculoid granulomas, lymphocytes, Langhans-type giant cells, and caseous necrosis is a characteristic presentation of tuberculosis.[9] The diagnosis was made on the basis of a histopathologic examination. The diagnosis of cutaneous tuberculosis is frequently complicated by the absence of ARB positivity, which is often attributed to the low bacillary load present in such cases.[10] The results of the ARB test were negative in this case. This has been linked to a low bacillary load in cutaneous tuberculosis.[10] In this instance, there was no observable growth in the culture. The low rate of growth observed in the culture was attributed to the low bacillary load present in the case of cutaneous tuberculosis. In general, the treatment of cutaneous tuberculosis is six months in duration, comprising a quadruple regimen (isoniazid, rifampicin, pyrazinamide, and ethambutol) for a period of two months, followed by four months of a dual regimen (isoniazid and rifampicin).[9] The standard antituberculosis treatment was administered. The patient was monitored meticulously, and the course of treatment was completed.

CONCLUSION

In conclusion, cutaneous tuberculosis presents with a range of clinical features that can be mistaken for those of other diseases. In patients presenting with atypical skin lesions, a diagnosis of cutaneous tuberculosis should be considered and appropriate diagnostic procedures should be initiated. The treatment of cutaneous tuberculosis is a lengthy and arduous process. It is imperative that patients be monitored closely.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and 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

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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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