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Does intranasal *Demodex* infestation play a role in allergic rhinitis?

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ABSTRACT

Aims: The aim of this study is to evaluate the prevalence of *Demodex* mites in the intranasal follicles of patients with allergic rhinitis and investigate their potential role in the etiology of allergic rhinitis.

Methods: The study involved 50 patients diagnosed with allergic rhinitis and 50 healthy controls matched for age and gender. The severity of the disease was evaluated using the Score for Allergic Rhinitis and the Total Nasal Symptom Score (TNSS). To evaluate the presence of *Demodex* in nasal follicles, a total of 8 terminal follicles, 4 from each of the right and left nasal vestibules, were epilated using sterile forceps. The samples were examined under a light microscope at 10x, 40x, and 100x magnification by two dermatologists.

Results: *Demodex* mites were found in the intranasal follicles of 3 (6%) individuals from the healthy control group. Intranasal *Demodex* mites were found in 3 (6%) patients with allergic rhinitis, showing no statistically significant difference between the two groups (p=1). The mean total nasal symptom score was 7.66±1.52 in the 3 allergic rhinitis patients with *Demodex* positivity, and 7.61±1.13 in the 47 patients without *Demodex* infestation, with no statistically significant difference between the two groups (p>0.05). No significant correlation was observed between *Demodex* positivity, disease severity, and TNSS in patients with allergic rhinitis (p>0.05).

Conclusion: Based on our study results, we think that intranasal antiparasitic treatments may be unnecessary in patients with allergic rhinitis.

Keywords: Demodex, allergic rhinitis, TNSS

INTRODUCTION

Allergic rhinitis (AR) is the most prevalent form of non-infectious rhinitis, impacting approximately 40% of adults d 25% of children worldwide. AR is characterized by symptoms such as sneezing, nasal itching, congestion, excessive nasal discharge, and watery eyes. These symptoms arise from IgE-mediated responses to airborne allergens, including pollen, dust mites, and pet dander.[1-3] The diagnosis of AR relies on a thorough patient history, the presence of characteristic clinical symptoms, and a favorable response to empirical treatment with antihistamines or nasal glucocorticoids.[2] *Demodex* mites are among the most frequently encountered ectoparasites in humans. They inhabit the normal skin of adults, predominantly within the pilosebaceous units of the face. *Demodex* mites can cause mechanical obstruction of follicles, and their antigens, secretions, and excretions may trigger delayed-type hypersensitivity and inflammatory reactions in the host. In recent years, only a few researchers have explored the role of *Demodex* infestation in the pathogenesis of AR.[4,5] To the best of our knowledge, this is the first study to evaluate the frequency of detecting *Demodex* mites in intranasal follicles in patients with AR. This study aims to explore the potential relationship between AR and *Demodex* mites and to assess the necessity of antiparasitic treatment in managing AR.

METHODS

This study was conducted between January and July 2022 in the Dermatology and Otolaryngology Clinics of Elazığ Fethi Sekin City Hospital. The study involved 50 patients diagnosed with AR and 50 healthy controls matched by age and gender. The diagnosis of AR was made by an ear, nose, and throat (ENT) specialist based on patient history and clinical presentation in patients with symptoms of nasal discharge, congestion, itching, and sneezing, with a good response to empirical treatment using an antihistamine or nasal glucocorticoid. Healthy controls were selected based on the absence of a history of atopy or AR symptoms, and no dermatological conditions such as rosacea, seborrheic dermatitis, acne vulgaris, atopic dermatitis, or perioral dermatitis, particularly in the facial area. Additionally, all controls had normal results

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on other systemic examinations. The study adhered to the ethical principles outlined in the World Medical Association's Declaration of Helsinki and received approval from the Ethics Committee of Fırat University Faculty of Medicine (Date: 10.02.2022, Decision No: 2022/02-23). Informed about the study's details, all participants provided written consent before participation. Patients and healthy volunteers who had not used any systemic or local antibiotics, topical steroids or drops, or received local or systemic radiotherapy and chemotherapy, acaricidal or immunosuppressive therapy within past month were included in the study. The AR score and Total Nasal Symptom Score (TNSS) system were used to assess disease severity. AR severity was classified as mild or moderate-to-severe based on the intensity of symptoms and their impact on sleep, as well as social, work, and school life. The TNSS is one of the most important subjective tests used to diagnose rhinitis. In this scoring, 4 symptoms including sneezing, nasal itching, nasal congestion and runny nose were questioned. Patients rated their symptoms as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). The TNSS was calculated by summing the scores corresponding to the severity of these four symptoms.

Demodex Diagnosis

The presence of *Demodex* mites was examined in both nasal vestibules of all volunteers who agreed to participate in the study. To assess *Demodex* infestation in the nasal follicles, a total of 8 terminal follicles, 4 from each of the right and left nasal vestibules, were epilated using sterile forceps. Two drops of immersion oil were placed on the slide, covered with coverslips, and examined under a light microscope at 10x, 40x, and 100x magnification by two dermatologists. The number of *Demodex* mites detected was recorded. The presence of at least one *Demodex* mite was considered evidence of *Demodex* infestation.

Statistical Analysis

Study results were presented as numbers, and percentages. Fisher's exact test was used to compare the rates of intranasal *Demodex* infestation between the groups. SPSS (SPSS Inc., Chicago, IL) statistical analysis was performed for statistical analysis. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The age range of the 50 patients included in the study was 18 to 60 years, with a mean age of 21.4±2.92 years. The 50 healthy control subjects had an age range of 19 to 58 years, with a mean age of 22.4±2.86 years. The patient group consisted of 38 (76%) females and 12 (24%) males, while the control group included 35 (70%) females and 15 (30%) males. There was no significant difference between the groups in terms of age or gender (p>0.05 In this study, *Demodex* positivity in intranasal follicles was detected in 3 (6%) individuals from the healthy control group. Similarly, 3 (6%) patients with AR were found to have *Demodex* mites intranasally, with no statistically significant difference compared to the healthy controls (p=1). The mean TNSS score in the 3 AR patients with *Demodex* positivity was 7.66±1.52, compared to 7.61±1.13 in the 47 AR patients with *Demodex* negativity, with no statistically significant difference between the two groups (p>0.05). Additionally, no significant correlation was found between *Demodex* positivity, disease severity, and TNSS scores in AR patients (p>0.05).

DISCUSSION

AR has been reported to negatively impact quality of life.[9] In adult patients, sleep disorders affect up to 66%, and both work and school performance deteriorate. The diagnosis of AR relies on a thorough medical history, the presence of characteristic symptoms, and the patient's response to empirical treatment with antihistamines or nasal glucocorticoids.[1-3]

Demodex mites are typically present in the pilosebaceous units of the skin, with a preference for areas such as the face, forehead, cheeks, nose, nasolabial folds, and eyelashes.[5] It is believed that the penetration of *Demodex* mites into the dermis, or more commonly, a proliferation of mites in the pilosebaceous unit exceeding >5/cm², triggers inflammation by promoting the release of inflammatory cytokines.[10] The proteins within *Demodex* mites, along with their remnants or waste products, can trigger inflammatory responses in the host through delayed hypersensitivity or an innate immune reaction.[11-14]

In recent years, research has emphasized uncovering the involvement of *Demodex* mites in the etiology of AR. According to research conducted by Yengil et al.[8] involving 63 patients with allergic rhinitis (AR) and 65 healthy individuals, the prevalence of *Demodex* on the eyelashes and cheeks was examined in relation to AR. Four eyelashes were collected from each participant to assess the density of *Demodex*. They found that the frequency of *Demodex* on the eyelashes was 50.8% in the AR group compared to 38.1% in the control group. On the face, the frequency was 38.1% in the AR group and 12.3% in the control group. As a result, the prevalence of *Demodex* on the face and eyelashes was markedly higher in the AR group compared to the control group (p=0.001 and p=0.0001, in that order). The authors observed a significant association between ocular symptoms and *Demodex* positivity on the eyelashes in AR patients. However, no significant relationship was found between nasal symptoms and *Demodex* positivity on the eyelashes or cheeks in AR patients.[8]

In another study investigating the coexistence of AR and diabetes mellitus (DM) and the role of *Demodex* mites, the researchers included 92 patients and 30 healthy individuals as the control group. They identified *Demodex* positivity in 44 out of 92 patients (47.8%) and in 1 out of 30 individuals in the control group (3.3%). *Demodex* positivity was observed in 14 patients with DM (43.7%), 12 patients with AR (40%), and 18 patients with coexisting AR and DM (60%). The researchers observed a statistically significant prevalence of *Demodex* across all three patient groups relative to the control group. They concluded that *Demodex* mites ought to be considered in cases of AR unresponsive to conventional treatments. Furthermore, the same study suggested that the elevated prevalence of *Demodex* infestation might worsen existing AR

symptoms and that antiparasitic treatment could positively impact the quality of life in this patient group.[7,13]

No studies were identified in the literature investigating the frequency of intranasal *Demodex* infestation. In our study, we detected *Demodex* positivity in the intranasal follicles of 3 (6%) individuals in the healthy control group. *Demodex* positivity was detected in our 3 (6%) patients with AR without any statistically significant difference compared to healthy controls (p=1). We found no significant correlation between *Demodex* positivity and disease severity or TNSS scores in the AR patient group. The reason why *Demodex* was found less frequently in the nasal cavity of our healthy control group compared to other parts of the face may be related to the the continuous airflow in the nasal passage and regular expulsion of nasal secretions. Likewise, we think that the reason for the lower than the expected *Demodex* positivity rates in our group of patients with AR may be increased nasal discharge and continuous mechanical cleaning of the nasal follicles and its surroundings.

CONCLUSION

We could not establish a link between nasal anatomy and intranasal *Demodex* infestation in AR patients. Although the study by Aril et al.[7] reported that antiparasitic treatment could potentially alleviate symptoms in patients with a high *Demodex* infestation, our findings did not reveal a significant association between *Demodex* and AR. In conclusion, we suggest that intranasal antiparasitic treatments may be unnecessary in the management of patients with AR.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethical Committee of the Fırat University Faculty of Medicine (Date: 10.02.2022, Decision No: 2022/02-23).

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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Original Article

HEALTH SCIENCES
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Evaluation of the relationship between body fat distribution and abdominal aorta calcified plaques with computed tomography

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ABSTRACT

Aims: In this study, we aimed to investigate the relationship between the development of calcified plaques in the abdominal aorta and the amount and distribution of abdominal fat tissue.

Methods: Between September 2021 and April 2024, we selected 69 patients with calcified plaques in the abdominal aorta and 165 control patients who underwent non-contrast abdominal computed tomography for suspected ureterorenal stones. Demographic characteristics, clinical features, subcutaneous, visceral, and total fat tissue areas, their ratios, and the diameter of the abdominal aorta lumen were recorded.

Results: Patients with abdominal aortic calcified plaques showed significantly higher visceral fat area, visceral fat ratio, hypertension, diabetes, and hepatosteatosis. In contrast, no significant differences were found between the two groups regarding height, weight, body-mass index, and total fat tissue area. Additionally, patients with aortic wall calcification had significantly larger aortic lumen diameters compared to those without.

Conclusion: Calcified atherosclerotic plaques in the abdominal aorta are particularly associated with visceral fat area.

Keywords: Atherosclerosis, computed tomography, body fat distribution

INTRODUCTION

Obesity is defined as the accumulation of an excessive amount of fat in the body. Clinically, it is usually assessed by an increase in body weight, and the most commonly used parameter is the body-mass index (BMI), which is calculated by dividing weight in kilograms by the square of height in meters.[1] BMI is the preferred tool for reporting the prevalence of obesity in the community; however, obesity is a highly heterogeneous condition.[1] Furthermore, different fat depots carry different metabolic risks.[2-5] Particularly, visceral adipose tissue is considered a unique pathogenic fat depot.[2,3,6] It is also linked to various pathological conditions such as increased insulin resistance, susceptibility to cancers, and higher mortality rates in hospitals.[3,7] The accumulation of visceral fat tissue also increases the risk of arterial hypertension and cardiovascular diseases.[3,8] Both visceral and subcutaneous adipose tissues can be measured using a specialized software through abdominal computed tomography (CT).

Although the underlying mechanisms of vascular calcification are not fully understood, known factors include diabetes, hypertension, smoking, aging, dialysis, and osteoporosis.[9] Abdominal aortic calcification correlates with an increased incidence of myocardial infarction, stroke, and peripheral artery disease.[10-15] Abdominal aortic calcification may be an indicator of more advanced atherosclerosis. CT and lateral abdominal X-Rays are used to assess aortic wall calcification.[2] Recent studies have increasingly focused on the impact of ectopic fat depots, particularly visceral fat tissue, on arterial calcification. Findings from these studies provide valuable insights into how abdominal fat distribution affects vascular health, enhancing our understanding of the pathophysiology of atherosclerosis.[15]

In this study, we evaluated the relationship between the amount and distribution of abdominal adipose tissue and the development of calcified atherosclerotic plaques in the abdominal aorta.

METHODS

The study was initiated with the approval of the Kastamonu University Faculty of Medicine Clinical Researches Ethics Committee (Date: 26.09.2024, Decision No: 2024/59). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Between

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September 2021 and April 2024, we recorded 69 patients with calcified atherosclerotic plaques in the abdominal aorta who had undergone non-contrast abdominopelvic CT for suspected urolithiasis. The control group included 165 patients who also underwent non-contrast abdominopelvic CT for suspected urolithiasis without evidence of calcified atherosclerotic plaques in the abdominal aorta in the clinical database. Age, sex, body weight (kg), and height (cm) were recorded for both patient and control groups. Additionally, BMI was calculated by dividing weight (kg) by height squared (m^2).

All CT examinations were conducted using a 64-detector CT scanner (Revolution EVO; GE Medical Systems, JAPAN) with axial images reconstructed at 1.25 mm thickness from the diaphragm to the pubic symphysis. Patients were scanned using a standard protocol without intravenous or oral contrast material. The CT protocol parameters were as follows: 120 kVp, 150-165 mAs tube current, maximum 2.5 mm collimation, 1.25 mm slice thickness, and 0.5 s rotation time. Images were reconstructed with multiplanar reformations.

Two radiologists re-evaluated the CT images to reach consensus. The presence of calcified atherosclerotic plaques in the abdominal aorta was identified from the aortic hiatus to the iliac bifurcation, and the abdominal aortic diameter was measured (Figure 1).

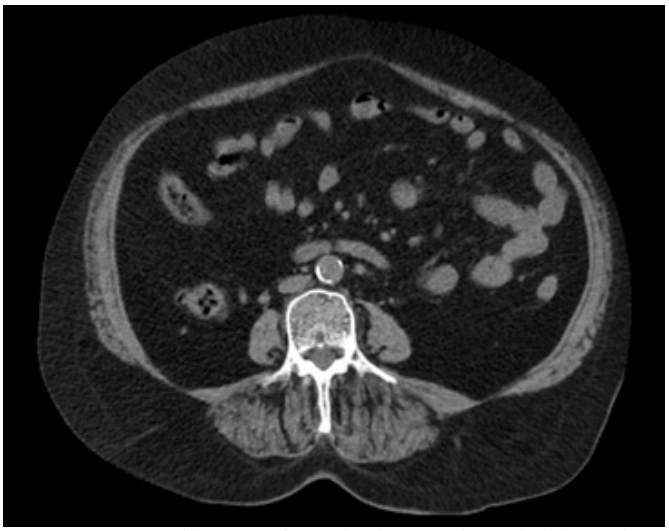

Figure 1. 46 year-old man with renal colic. Unenhanced abdominal CT image shows calcified atherosclerotic plaques in the abdominal aorta

CT: Computed tomography

Axial CT images at the level of the umbilicus were used to measure both visceral and subcutaneous fat areas. Measurements were performed using the workstation software (ADW 4.7, GE), applying regions of interest (ROI) (Figure 2). Total fat area (TFA=SFA+VFA), visceral fat percentage (VF%=VFA/TFA×100), and subcutaneous fat percentage (SF%=SFA/TFA×100) were calculated and recorded.

The liver attenuation of the right lobe was measured using a standard ROI of approximately 200 mm^2, and hepatosteatosis was defined as a liver attenuation value of 40 HU or less.[16-18] Additionally, the presence of hypertension and diabetes mellitus was recorded for both patient and control groups.

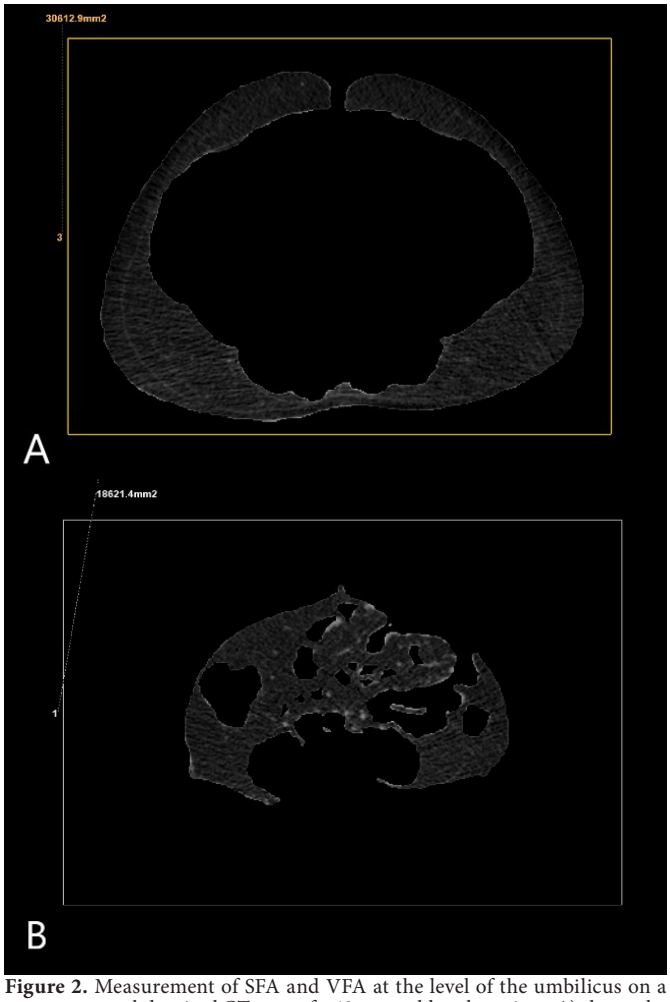

Figure 2. Measurement of SFA and VFA at the level of the umbilicus on a non-contrast abdominal CT scan of a 49-year-old male patient. A) shows the SFA measurement, recorded as 306.12 cm^2. B) shows the VFA measurement, recorded as 186.21 cm^2

SFA: Subcutaneous fat area, VFA: Visceral fat area, CT: Computed tomography

All data were analyzed using the Statistical Package for the Social Sciences (SPSS 20.0, SPSS Inc., Chicago, IL, USA) and MedCalc Statistical Software version 16.8 (MedCalc Software bvba, Ostend, Belgium). Means and ranges for age, abdominal aortic diameter, BMI, SFA, VFA, TFA, SF%, and VF% values were calculated for both groups. The Kolmogorov-Smirnov test was used to assess deviation from normal distribution. The Mann-Whitney U test and Student's t-test were used to compare the CT findings of the patient and control groups. The Mann-Whitney U test was used to analyze BMI. The student's t-test was used for the analysis of age, abdominal aortic diameter, VFA, SFA, TFA, SF%, and VF%. Additionally, chi-square tests were used to examine the differences in the frequencies of hepatosteatosis, hypertension, and diabetes mellitus between the two groups. Finally, univariate analysis was used to obtain odds ratios (ORs). Results with a p-value of less than 0.05 were considered statistically significant.

RESULTS

In this study, 69 patients (38 men, 31 women) with calcified atherosclerotic plaques in the abdominal aorta and 165 control patients (87 men, 78 women) were evaluated. The average ages of the patient and control groups were 63.96 (±11.95) and 61.61

(±7.36) years, respectively. The average heights (cm) and body weights (kg) of the patient and control groups were 168.77 (±10.05) cm and 164.92 (±7.09) cm, 83.57 (±14.01) kg and 84.51 (±14.87) kg, respectively. The average BMI (kg/m²) values for the patient and control groups were 29.63 (±6.00) and 31.17 (±5.53), respectively. No statistically significant difference was observed between the two groups in terms of average height, body weight, or BMI (p=0.06).

The average values of SFA, VFA, TFA, VF%, and SF% in the patient and control groups were as follows: SFA: 241.51 cm² and 325.23 cm²; VFA: 246.62 cm² and 162.41 cm²; TFA: 488.13 cm² and 487.64 cm²; VF%: 47.26 and 33.58; SF%: 52.72 and 66.42. No significant difference was observed in TFA (p=0.98). However, significant differences were detected between the two groups in terms of VFA, SF%, and VF% (p < 0.001) (Figure 3, 4) (Table 1). The average abdominal aortic diameters in the patient and control groups were 19.03 cm and 17.41 cm, respectively, with a significant difference between the two groups (p<0.001).

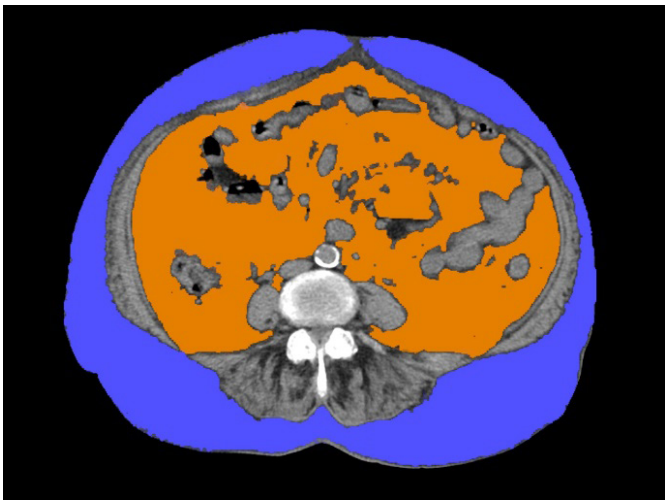

Figure 3. 46 year-old man with the calcified atherosclerotic plaques in the abdominal aorta shows increased VFA/TFA

VFA: Visceral fat area, TFA: Total fat area

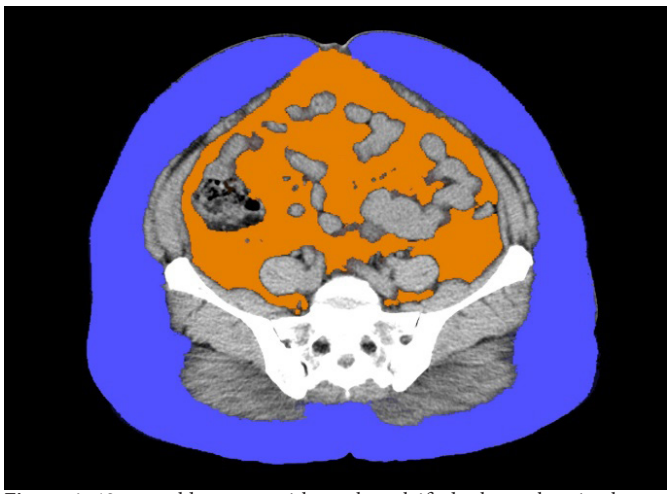

Figure 4. 48 year-old woman without the calcified atherosclerotic plaques in the abdominal aorta shows decreased VFA/TFA

VFA: Visceral fat area, TFA: Total fat area

Data on the presence of hepatosteatosis (HS), hypertension (HT), and diabetes mellitus (DM) are provided in Table 1. The rate of HS in patients with calcified atherosclerotic plaques in the abdominal aorta was statistically significantly higher compared to the control group (p<0.05), and the rates of HT and DM were observed to be significantly higher (p<0.001). OR analyses indicated that the presence of DM (OR=4.11), the presence of HT (OR=3.31), an increase in aortic diameter (OR=2.25), VFA greater than 160cm² (OR=4.04) and VF% (OR=4.47) were associated with the presence of calcified atherosclerotic plaques in the abdominal aorta (Table 2).

DISCUSSION

In this retrospective study, we found a strong association between calcified atherosclerotic plaques in the abdominal aorta and visceral obesity. Additionally, an increase in aortic diameter was identified as a factor associated with the presence of calcified atherosclerotic plaques in the abdominal aorta.

Obesity, defined as abnormal or excessive fat accumulation in the body, is typically assessed using BMI, which is the preferred tool for evaluating obesity prevalence within communities. However, obesity is a highly heterogeneous condition.[1] There is also a J-shaped relationship between BMI and the risk of morbidity and mortality, which is linked to hypertension, dyslipidemia, diabetes mellitus, cardiovascular diseases, and cancer.[19-21] Many studies in the literature have investigated abdominal fat distribution by using VFA and SFA, both evaluated by CT. VFA has been shown to correlate more strongly with cardiometabolic risk than SFA.[3,22] For example, Rosenquist et al.[23] demonstrated that an increase in VFA may elevate cardiometabolic risks.

Major clinical risk factors for calcified atherosclerotic plaques in the abdominal aorta include genetic predisposition, male gender, smoking, a sedentary lifestyle, metabolic syndrome, hypertension, and, notably, visceral obesity.[24-28] The mechanisms underlying aortic calcification are complex and often interconnected, with one factor potentially triggering multiple others in a cycle of adverse outcomes. Efe et al.[29] reported that a high levels of VFA increase the risk of aortic atherosclerosis. In our study, we selected a control group with no significant differences in height, weight, or BMI compared to the patient group. We observed that patients with calcified atherosclerotic plaques in the abdominal aorta had higher VFA and VF% than controls, while lower SFA and SF% values were noted in the patient group compared to the control group.

We also found that patients with calcified aortic plaques experienced hepatosteatosis, hypertension, and diabetes mellitus more frequently than those without, consistent with findings by Efe et al.[29] Our study identified DM, HT, VF% greater than 34%, and VFA over 160 cm² as the strongest factors associated with calcified aortic plaques.

The prevalence of calcified plaques in the abdominal aorta ranges from 2.1% to 14.7% depending on the age and characteristics of the selected population.[30-33] This condition becomes more common with age, and one study found it to be more prevalent among older patients with ischemic heart disease.[32] Calcified plaques in the abdominal aorta can be evaluated using lateral abdominal X-Rays, electron-

Table 1. Demographic and clinical characteristics of patients with and without calcified atherosclerotic plaques

	Total	Calcified atherosclerotic plaques in the abdominal aorta		p value
		Present±SD (Min- Max)	Absent±SD (Min- Max)	
Number	234	69	165	
Age (year)	62.30±9.00 (44-89)	63.96±11.95 (44-89)	61.61±7.36 (45-72)	0.132
Gender				
Male	125	38	87	0.85
Famele	109	31	78	
Height (cm)	166.06±8.24 (149-191)	168.77±10.05 (150-191)	164.92±7.09 (149-182)	0.16
Weight (kg)	84.23±14.60 (58-140)	83.57±14.01 (62-129)	84.51±14.87 (58.00-140.00)	0.64
BMI	30.72±5.70 (19.38-48.44)	29.63±6.00 (22.23-46.09)	31.17±5.53 (19.38-48.44)	0.06
Hepatosteatosis				
Present	92	36	56	0.014
Absent	142	33	109	
Diabetes mellitus				
Present	56	30	26	<0.001
Absent	178	39	139	
Hypertension				
Present	98	43	55	<0.001
Absent	136	26	110	
VFA (cm^2)	187.24±105.47 (37-610)	246.62±158.00 (56-610)	162.41±57.88 (37-373)	<0.001
VF%	37.61±13.43 (11-80)	47.26±15.81 (21-80)	33.58±9.84 (11-69)	<0.001
SFA (cm^2)	300.54±103.44 (85-601)	241.51±93.11 (85-464)	325.23±97.60 (140-601)	0.005
SF%	62.38±13.42 (20-89)	52.72±15.79 (20-79)	66.42±9.84 (31-89)	<0.001
TFA (cm^2)	487.79±148.19 (154-936)	488.13±200.54 (154-936)	487.64±120.52 (228-846)	0.98
Aortic diameter (mm)	17.89±2.19 (14.30-26.59)	19.03±2.83 (15.41-26.59)	17.41±1.65 (14.30-22.68)	<0.001

SD: Standard deviation, Min: Minimum, Max: Maximum, BMI: Body-mass index, VFA: Visceral fat area, VF%: Percentage of visceral fat, SFA: Subcutaneous fat area, SF%: Percentage of subcutaneous fat, TFA: Total fat area

Table 2. Odds ratio of the presence of calcified atherosclerotic plaques in the abdominal aorta

Variable	Odds ratio	95% CI
Male gender	1.41	0.81-2.63
Age >63 y	0.95	0.54-1.66
BMI (>30.4)	0.52	0.29-0.92
Hepatosteatosis	2.12	1.20-3.76
Hypertension	3.31	1.84-5.94
Diabetes mellitus	4.11	2.18-7.75
VFA (>160 cm^2)	4.04	2.19-7.48
VF% (>34)	4.47	2.40-8.32
SFA (<296 cm^2)	2.08	1.17-3.71
TFA (>476 cm^2)	0.98	0.56-1.72
Aort diameter (>17.5 mm)	2.25	1.26-4.03

BMI: Body-mass index, VFA: Visceral fat area, VF%: Percentage of visceral fat, SFA: Subcutaneous fat area, SF%: Percentage of subcutaneous fat, TFA: Total fat area

beam computed tomography, or plain CT, with each method having its own advantages and limitations. Plain CT, the most commonly used method, was also preferred in our study.

Our findings show that patients with calcified plaques in the abdominal aorta have significantly larger aortic diameters than those without. Visceral obesity may contribute to a larger aortic diameter, thicker aortic walls, and increased vascular thickness. This phenomenon can be attributed to several factors, including adaptation to elevated blood pressure due to hypertension, increased blood volume, and structural or functional abnormalities in the aorta specific to obesity.[24] Furthermore, visceral obesity accelerates vascular aging and raises the risk of future cardiovascular events.[34]

Visceral obesity is associated with various pathological conditions, such as abnormal glucose and lipid metabolism, insulin resistance, and increased risk of cardiovascular diseases. It also predisposes individuals to certain cancers and surgical complications.[7] As an active endocrine tissue, visceral fat releases atherogenic factors that promote atherosclerosis. Consequently, visceral obesity accelerates vascular aging and increases the risk of cardiovascular diseases, hypertension, and calcified plaques.[7] Additionally, increased visceral fat may contribute to dysfunctional subcutaneous fat tissue, resulting in excessive fat accumulation in ectopic locations like the heart, liver, skeletal muscle, pancreas, and gastrointestinal tract. This ectopic fat may be a cause of hepatosteatosis.[35] Despite the strong relationship between metabolic syndrome and visceral adiposity and hepatosteatosis, visceral adiposity and hepatosteatosis are not currently considered diagnostic criteria for metabolic syndrome.

Limitations

This study has several limitations. First, we evaluated the CT images based on consensus and did not assess inter-observer and intra-observer variability. Second, the sample size was relatively small. Third, we had no access to laboratory parameters such as lipid panels. Fourth, measurements of adipose tissue areas were obtained from a single CT slice at the level of the abdomen instead of volume calculations. Fifth, the single-center design, absence of long-term follow-up data, and lack of control for potential confounding factors such as lifestyle variables may limit the generalizability of our findings. Conducting larger, multicenter studies could enhance the generalizability of the findings and help validate the results across diverse population groups

CONCLUSION

Calcified atherosclerotic plaques in the abdominal aorta are associated with obesity, particularly visceral obesity. Patients with calcified atherosclerotic plaques in the abdominal aorta may have higher rates of hypertension, diabetes mellitus, increased VFA, VF%, and aortic diameter compared to those without. However, further studies are needed to better understand the relationship between calcified aortic plaques, diabetes mellitus, cardiovascular diseases, and metabolic syndrome.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kastamonu University Faculty of Medicine Clinical Researches Ethics Committee (Date: 26.09.2024, Decision No: 2024/59)

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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Food neophobia in the elderly: evaluation of constipation, malnutrition, and nutrition

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ABSTRACT

Aims: This study aimed to evaluate food neophobia, constipation, malnutrition, and nutritional status in elderly individuals.

Methods: The study was conducted on individuals aged ≥65 years selected by random sampling method and 406 individuals were reached. A questionnaire was used to collect demographic parameters (age, gender) of the participants. Anthropometric measurements were taken by researchers and then body-mass index (BMI) and waist-to-height ratio (WHR) were determined by standard methods, and a validated Food Neophobia Scale (FNS) was used to determine the food neophobia levels of individuals. One-day food consumption of individuals was determined by the 24-hour retrospective reminder method. Constipation was defined according to the modified Rome IV criteria.

Results: There was a statistically significant relationship between food neophobia levels and BMI classifications of women, men, and all elderly individuals ($p<0.001$). There was a statistically significant relationship between the level of food neophobia and waist/height ratio in women, men, and all elderly individuals ($p<0.001$). There was a statistically significant relationship between food neophobia levels and the constipation status of women and all elderly individuals ($p<0.05$). There was a statistically significant relationship between food neophobia levels and mini nutritional assessment (MNA) classifications of women, men, and all elderly individuals ($p<0.001$). While there was no statistically significant difference between malnutrition groups according to energy, carbohydrate, fat, protein, and pulp levels (median) ($p>0.05$), there was a statistically significant difference between malnutrition groups of neutral and non-constipated elderly individuals only according to water consumption levels (median) ($p<0.05$). The water consumption level (median) of the elderly in the malnourished group was significantly lower than the water consumption level of the elderly in the risk of malnutrition and normal nutritional status groups.

Conclusion: Treatments for age-related conditions such as constipation, malnutrition, and undernutrition that focus on novel foods need to be carefully designed. The elderly should be a market segment that promotes healthy products, where new products can be introduced and purchased without concern.

Keywords: Food neophobia, elderly, constipation, malnutrition, nutrition

INTRODUCTION

The dictionary definition of "old age" is defined as the state of being old and showing the effects of increased age. The World Health Organization (WHO) defines people aged 65 and over as "elderly". The elderly population is also divided into subgroups, with the 65-74 age group labeled as "young elderly", the 75-84 age group as "old elderly" and the 85 and over age group as "very old".[1] As a physiological process, old age is a period that reduces or limits people's activity level and functionality, making them socially, physically, and emotionally dependent to varying degrees. With the advancement of age, changes may occur in physiological, psychological, cognitive, and social areas, while the cognitive and functional capacity of the individual decreases and the number of chronic diseases increases. The increase in risk factors associated with chronic diseases and the development of lifestyle-related diseases may lead to a fear of new foods.[2-4]

Fear of trying new foods, i.e. food neophobia (FN), is a behavioral definition that explains individuals' avoidance of experiencing and tasting unfamiliar/never-tried foods.[5] Age is an important determinant of FN.[6] It is known that elderly individuals who are satisfied with their lives are also satisfied with the food they consume and have low levels of food neophobia. Food Neophobia in the elderly is thought to change as senses such as taste, smell, and vision decline over time. As a result of all these effects, decreased canine consumption may cause various disorders such as constipation in the elderly.[7]

Constipation is generally defined as a decrease in the frequency of defecation, increased stool hardness, lower than normal number of stools, the need for intensive straining, incomplete emptying of stool, and dry stools.[8] Although the exact cause of constipation is not known, it is reported that the incidence increases with age, and 40% of elderly individuals

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aged 65 years and over experience constipation problems.[9] It is a common complaint, especially among geriatric patients, and may result in malnutrition among the elderly in nursing homes.[10]

Malnutrition refers to a persistent imbalance between the intake of nutrients (protein, energy, and other nutrients) consumed and meeting changing metabolic needs. Malnutrition affects approximately 28% of community-dwelling older adults in developed countries.[11] This results in loss of body mass and organ-system dysfunction. Malnutrition is an important and often neglected public health problem in the elderly. Malnutrition in the elderly is closely associated with pathological conditions leading to loss of autonomy, decreased quality of life, increased hospital admissions, prolonged hospital stays, infections, delayed wound healing, gait disturbances, falls and fractures, and untimely deaths.[12] Malnutrition has been defined as an imbalance between intake and requirements that causes changes in human metabolism, compromising the body's function and leading to loss of body mass. Malnutrition is a nutritional condition in which a deficiency, excess, or imbalance of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form (body shape, size, composition) and function and clinical outcome.[13] The causes of malnutrition in the elderly are factors such as reduced food consumption, gastrointestinal diseases, and digestive and absorption disorders. Ensuring adequate and balanced nutrition in old age is important in preventing diseases, protecting, improving, and developing health, organizing lifestyle habits, and increasing life span and quality of life.[14]

This study aimed to evaluate food neophobia, constipation, malnutrition, and nutritional status in elderly individuals.

METHODS

Subjects and Survey Method

The study was performed following the Declaration of Helsinki. Approval for the study was obtained from the Süleyman Demirel University Ethics Committee (Date: 07.11.2023, Decision No: 69/11).

This study was conducted as a descriptive study with elderly individuals living in Isparta province between 18.11.2023 and 27.06.2024. The study was conducted on individuals aged ≥65 years selected by snowball sampling method. There are 620.019 elderly individuals living in Isparta province. As a result of the statistical power analysis, it was determined that at least 384 individuals should be included in the study with a 95% confidence interval. In this study, 406 individuals were reached. Elderly individuals from the researcher's close circle and acquaintances who volunteered to participate in the study were included in the study. Elderly individuals with chronic gastrointestinal diseases, psychiatric disorders, and oral nutrition deficiencies were not included in the study. The questions in the questionnaire and measurements were obtained by the researcher by applying the face-to-face interview technique.

Demographic Questionnaires

A questionnaire was used to collect demographic parameters (age, gender) of the participants.

Assessment of Anthropometric Measurements

Height was measured (cm) with feet close together and the head in the Frankfort plane, using a portable stadiometer. Weight (kg) was measured using the Tanita Bc 601 brand electronic scale. Waist circumference was measured at the midpoint between the last rib and the iliac crest using an anthropometric tape measure. Participants' weight and height were measured following the method and body-mass index (BMI) was calculated based on the following formula. Body weight (kg) / height (kg/m^2). The WHO classification was used to evaluate BMI. Individuals with a BMI of <18.5 kg/m^2 are underweight, 18.5-24.9 kg/m^2 are normal weight, 25.0-29.9 kg/m^2 are overweight, and >30.0 kg/m^2 are obese (WHO, 2000). Waist-to-height ratio (WHR) was calculated by the circumference of the waist (cm) divided by the height (cm). According to the Ashwell classification, a waist circumference/height ratio of <0.4 is at risk, 0.4-<0.5 is normal, 0.5-<0.6 is at risk, and >0.6 need treatment.[15]

Assessment of Food Neophobia

The Food Neophobia Scale (FNS) was used to determine the Food Neophobia levels of individuals. This scale was adapted to Turkish by Duman et al.[16] in 2020. The FNS is evaluated with a single-factor and 10-item 5-point Likert scale ("I totally agree" 5 points, "I Agree" 4 points, "I neither agree nor disagree" 3 points, "I disagree" 2 points, and "I totally disagree" 1 point). Items 2, 3, 5, 7, 8, and 9 are evaluated as "trust in new foods", and items 1, 4, 6, and 10 are reverse-scored and evaluated as "willingness to try new foods".[17] Since a 5-point Likert scale is used, total scores can vary between 10 and 50. Participants were divided into two separate groups as neophilic and neophobic individuals. High scores between 33-50 obtained from FNS indicate Food Neophobia and low scores between 10-25 indicate food neophilia (liking food).[18]

Assessment of Nutrition

One-day food consumption of individuals was determined by the 24-hour retrospective reminder method.[19] Individuals' meal distribution and food consumption according to meal times were determined. Individuals' food consumption was obtained from the "food and nutrition photo catalog".[20] This information was entered into the "nutrition information system (BEBIS)" 8.1 full version program and the amounts of energy and nutrients taken by individuals in a day were determined.[21]

Assessment of Constipation

The presence of constipation in elderly individuals was assessed according to the "Rome IV criteria" developed by Palsson et al.[22] in 2016. The Rome IV criteria consist of a series of yes/no questions about gastrointestinal conditions. According to Rome IV Criteria, symptoms must have started at least 6 months before the diagnosis and have persisted for the last 3 months. A diagnosis of constipation was made if at least two of the three findings were accompanied by abdominal pain or discomfort at least one day a week. Participants with two

or more positive items were classified into the constipation group and the remaining participants were classified into the non-constipation group.

Assessment of Malnutrition

The mini nutritional assessment short form (MNA-SF) tool was used as a marker of malnutrition in the elderly. The MNA-SF was developed and validated by Rubenstein et al.[23] in 2001 and revised in 2009. This form consists of six items and is scored according to factors such as change in appetite, weight loss in the last 3 months, mobility in the last 3 months, psychological distress or acute illness, neuropsychological problems, and body-mass index. According to the MNA-SF score, individuals with a score of 11-14 are categorized as normally fed, individuals with a score of 7-10 are categorized as at risk and individuals with a score of <7 are categorized as severely malnourished.

Statistical Analysis

The study data were transferred to IBM SPSS Statistics 26 (IBM, Armonk, NY, USA), and the analysis was completed. When evaluating the data, frequency distributions were given for categorical variables, and descriptive statistics (mean, standard deviation, median, minimum, maximum) were given for numerical variables. To decide on the analyses to be applied, firstly, the Kolmogorov Smirnov test (n>30) was applied for the assumption of normal distribution of nutrient variables. As a result of the test, it was seen that the measurements did not meet the assumption of normal distribution. Therefore, nonparametric tests were used in comparisons. The Kruskal-Wallis Test was used to determine whether there was a difference between more than two independent groups according to the scores, and the Bonferroni Test was used to determine which groups were different. The relationship between two independent categorical variables was examined with the Chi-square test, and if the Chi-square test did not meet the assumption, Freeman Halton Fisher's Exact Chi-square test (Fisher's exact test) was used in nxm tables.

RESULTS

Table 1 shows the results examining whether there is a relationship between the gender of elderly individuals and food neophobia status. Accordingly, there was no statistically significant relationship between the gender of the elderly and food neophobia (p>0.05).

Table 1. Comparison of food neophobia status prevalence according to gender

Food neophobia status	Women (n=203)	Men (n=203)	Total (n=406)	Chi-square, p-value
	n (%)	n (%)	n (%)	
Neophilic	57 (28.1)	58 (28.6)	115 (28.3)	0.090, 0.965
Neutral	139 (68.5)	137 (67.5)	276 (68.0)	
Neophobic	7 (3.4)	8 (3.9)	15 (3.7)	

x^2: Chi-square test, p: Significance level

Table 2 also shows the results of the examination of the relationship between neophobia levels and age, BMI, waist/height ratio, constipation status, and MNA assessment of elderly individuals according to their gender.

The mean age of women in the neophilic group was 75.91 (±6.666), the mean age of women in the neutral group was 75.9 (±6.579), and the mean age of women in the neophobic group was 74.88 (±8.114). The mean age of men in the neophilic group was 75.77 (±6.614), the mean age of neutral men was 76.03 (±6.616), and the mean age of neophobic men was 72.71 (±6.626). The mean age of the elderly individuals in the neophilic group was 75.84 (±6.612), the mean age of the neutral males was 75.96 (±6.586), and the mean age of the neophobic males was 73.87 (±7.279).

There was a statistically significant relationship between food neophobia levels and BMI classifications of women, men, and all elderly individuals (p<0.001). Accordingly, neophilic women were significantly more likely to be obese (87.9%), neutral women were significantly more likely to be overweight (65.0%) and neophobic women were significantly more likely to be underweight (37.5%). Neophilic men were significantly more likely to be obese (89.5%), neutral men were significantly more likely to be overweight (66.2%) and neophobic men were significantly more likely to be underweight (28.6%). Neophilic older adults were significantly more likely to be obese (88.7%), neutral older adults were significantly more likely to be overweight (65.5%) and neophobic older adults were significantly more likely to be underweight (33.3%).

There was a statistically significant relationship between the level of food neophobia and waist/height ratio in women, men, and all elderly individuals (p<0.001). Accordingly, the proportion of neophilic women in the treatment group (86.2%), neutral women in the risk group (59.9%), and neophobic women in the normal group (62.5%) were significantly higher. The proportion of neophilic men in the treatment group (82.5%), neutral men in the risk group (64.0%), and neophobic men in the normal group (57.1%) were significantly higher. The proportion of neophilic older adults in the treatment group (84.3%), neutral older adults in the risk group (62.0%), and neophobic older adults in the normal group (60.0%) were significantly higher.

There was a statistically significant relationship between food neophobia levels and the constipation status of women and all elderly individuals (p<0.05). Accordingly, the rate of constipation was significantly higher in neophilic and neutral women (98.3%, 94.9%) and in neophobic women (25.0%). The rate of no constipation was significantly higher in neophilic and neutral older adults (93.0%, 94.2%), while the rate of constipation was significantly higher in neophobic older adults (26.7%).

There was a statistically significant relationship between food neophobia levels and MNA classifications of women, men, and all elderly individuals (p<0.001). Accordingly, neophilic women were significantly more likely to be in the risk of malnutrition group (67.2%), neutral women were significantly more likely to be in the normal nutritional status group (50.4%) and neophobic women were significantly more likely to be in the malnourished group (62.5%). Neophilic men were significantly more likely to be in the risk of malnutrition group (71.9%), neutral men were significantly more likely to be in the normal nutritional status group (51.1%) and neophobic men were significantly more likely to be in the malnourished

Table 2. Investigation of the relationship between neophobia levels according to gender and age, BMI, waist/height ratio, constipation status, and MNA assessment

	Women (n=203)			Men (n=203)			Total (n=406)		
	Neophilic	Neutral	Neophobic	Neophilic	Neutral	Neophobic	Neophilic	Neutral	Neophobic
Food neophobia status	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**
Age	75.91±6.666	75.9±6.579	74.88±8.114	75.77±6.614	76.03±6.616	72.71±6.626	75.84±6.612	75.96±6.586	73.87±7.279
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
BMI classification									
Underweight	0_a (0.0)	0_a (0.0)	3_b (37.5)	0_a (0.0)	0_a (0.0)	2_b (28.6)	0_a (0.0)	0_a (0.0)	5_b (33.3)
Normal	0_a (0.0)	48_b (35.0)	2_b (25.0)	0_a (0.0)	47_b (33.8)	3_b (42.9)	0_a (0.0)	95_b (34.4)	5_b (33.3)
Overweight	7_a (12.1)	89_b (65.0)	$3_{a,b}$ (37.5)	6_a (10.5)	92_b (66.2)	$2_{a,b}$ (28.6)	13_a (11.3)	181_b (65.5)	5_a (33.3)
Obese	51_a (87.9)	0_b (0.0)	0_b (0.0)	51_a (89.5)	0_b (0.0)	0_b (0.0)	102_a (88.7)	0_b (0.0)	0_b (0.0)
Chi-square; p-value		197.971; 0.000***			197.948; 0.000***			404.354; 0.000***	
Waist/height ratio									
Normal	0_a (0.0)	25_b (18.2)	5_c (62.5)	0_a (0.0)	25_b (18.0)	4_c (57.1)	0_a (0.0)	50_b (18.1)	9_c (60.0)
Risk	8_a (13.8)	82_b (59.9)	$3_{a,b}$ (37.5)	10_a (17.5)	89_b (64.0)	$3_{a,b}$ (42.9)	18_a (15.7)	171_b (62.0)	$6_{a,b}$ (40.0)
Treatment	50_a (86.2)	30_b (21.9)	0_b (0.0)	47_a (82.5)	25_b (18.0)	0_b (0.0)	97_a (84.3)	55_b (19.9)	0_b (0.0)
Chi-square; p-value		85.258; 0.000***			83.328; 0.000***			172.899; 0.000***	
Constipation status									
Constipation	1_a (1.7)	$7_{a,b}$ (5.1)	2_b (25.0)	7 (12.3)	9 (6.5)	2 (28.6)	8_a (7.0)	16_a (5.8)	4_b (26.7)
Non-constipation	57_a (98.3)	$130_{a,b}$ (94.9)	6_b (75.0)	50 (87.7)	130 (93.5)	5 (71.4)	107_a (93.0)	260_a (94.2)	11_b (73.3)
Chi-square; p-value		6.002; 0.037*			[d]5.114; 0.066			[d]9.651; 0.016*	
MNA classification									
Malnourished	4_a (6.9)	12_a (8.8)	5_b (62.5)	3_a (5.3)	13_a (9.4)	4_b (57.1)	7_a (6.1)	25_a (9.1)	9_b (60.0)
Risk of malnutrition	39_a (67.2)	56_b (40.9)	1_b (12.5)	41_a (71.9)	55_b (39.6)	1_b (14.3)	80_a (69.6)	111_b (40.2)	2_b (13.3)
Normal nutritional status	15_a (25.9)	69_b (50.4)	$2_{a,b}$ (25.0)	13_a (22.8)	71_b (51.1)	$2_{a,b}$ (28.6)	28_a (24.3)	140_b (50.7)	$4_{a,b}$ (26.7)
Chi-square; p-value		25.745; 0.000***			27.812; 0.000***			[d]71,895; 0.000***	

*p<0.05, **p<0.001; a-a, b-b, c-c: No difference between the groups; a-b, a-c, b-c: There is a difference between the groups, x^2: Chi-square test, dx^2: Freeman Halton Fisher's exact Chi-square test, p: Significance level, SD: Standard deviation, BMI: Body-mass index

group (57.1%). The proportion of neophilic older adults in the risk of malnutrition group (69.6%), neutral older adults in the normal nutritional status group (50.7%), and neophobic older adults in the malnourished group (60.0%) were significantly higher.

Table 3 shows the results of the examination of whether there is a difference between the malnutrition status of elderly individuals in terms of their neophobia levels and constipation status according to their nutrient levels (median). While there was no statistically significant difference between malnutrition groups according to energy, carbohydrate, fat, protein, and pulp levels (median) (p>0.05), there was a statistically significant difference between malnutrition groups of neutral and non-constipated elderly individuals only according to water consumption levels (median) (p<0.05). Accordingly, the water consumption level (median) of the elderly in the malnourished group was significantly lower than the water consumption level of the elderly in the risk of malnutrition and normal nutritional status groups.

DISCUSSION

Scientific studies evaluating the health and nutritional status of the elderly in improving the quality of life of the elderly are important today when the elderly population is increasing rapidly. Changes in individuals' opinions about new foods and various diseases that occur with aging affect nutrition and health status.[24]

Elderly individuals exhibit mostly neutral and neophobic attitudes towards unfamiliar foods.[25] The percentages of neophilic, neutral, and neophobic attitudes of all elderly individuals participating in our study were 28.3%, 68.0%, and 3.7%, respectively. In a study, one-third of older adults were neophobic, more than half were neutral and very few were neophilic towards novel foods.[26] Communication messages to older adults about the benefits of consuming novel foods (e.g., exposure to new cultures and flavors, dietary diversity, health benefits, etc.) should also be targeted at neophobic older consumers, thus increasing their numbers by making their attitudes more positive.

Food neophobia is generally thought to differ by age and increases with age. Considering demographic characteristics, higher age is associated with food neophobia.[27] The mean ages of all elderly individuals who participated in our study were 75.84, 75.96, and 73.87, respectively, according to their neophilic, neutral, and neophobic status. In another study, neophilic attitudes towards new foods were mostly observed in people aged 61-70 years, while neophobic attitudes were mostly observed in people older than 70 years. Neutral

Table 3. Investigation of the relationships between malnutrition status and dietary intake levels according to food neophobia levels and constipation status

Food neophobia		Neophilic		Neutral		Neophobic	
Constipation status		Constipation	Non-constipation	Constipation	Non-constipation	Constipation	Non-constipation
Dietary intake	MNA classification	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)
Energy (kcal)	Malnourished	2182.67	1292.88 (766.18-2421.73)	1565.09 (1085.21-1817.14)	1661.96 (893.72-3067.44)	936.30 (903.43-96.11)	968.09 (786.12-2029.72)
	Risk of malnutrition	1624.42 (1207.65-3112.11)	1740.81 (725.14-3068.44)	1417.23 (1287.68-1785.12)	1552.05 (818.94-2713.02)	-	1659.68 (1518.91-1800.46)
	Normal nutritional status	2112.36 (1541.51-2683.20)	1631.76 (1017.92-3632.41)	1416.81 (874.73-2696.9)	1646.33 (606.91-3038.22)	-	1766.19 (1206.68-2035.71)
KW; p		0.450; 0.799	3.678; 0.159	0.240; 0.887	1.646; 0.439	-	3.455; 0.178
Carbohydrate (g)	Malnourished	269.71 (269.71-269.71)	157.65 (82.15-326.22)	143.73 (113.04-226.67)	183.59 (88.87-389.83)	107.34 (80.51-124.94)	124.94 (94.56-195.84)
	Risk of malnutrition	224.00 (141.34-344.46)	209.32 (96.07-389.83)	180.62 (149.63-205.22)	170.22 (62.52-354.07)	-	184.64 (146.43-222.86)
	Normal nutritional status	281.21 (219.67-342.75)	193.04 (72.38-411.28)	130.39 (94.56-245.56)	189.84 (29.09-483.69)	-	209.9 (118.17-229.30)
KW; p		0.450; 0.799	1.954; 0.376	0.722; 0.697	3.810; 0.149	-	4.041; 0.133
Fat (g)	Malnourished	92.60	46.08 (18.97-79.08)	63.07 (33.91-79.07)	57.14 (27.16-127.40)	37.85 (27.16-45.06)	28.83 (18.97-96.17)
	Risk of malnutrition	53.54 (37.57-113.90)	67.56 (8.20-147.67)	58.11 (34.99-70.35)	61.29 (24.96-122.54)	-	68.37 (62.52-74.22)
	Normal nutritional status	79.755 (44.37-115.14)	63.36 (22.00-153.80)	51.59 (29.56-147.67)	61.18 (26.82-127.67)	-	64.22 (59.89-96.30)
KW; p		0.667; 0.717	3.925; 0.141	0.045; 0.978	0.655; 0.821	-	3.364; 0.186
Protein (g)	Malnourished	60.86 (60.86-60.86)	53.56 (35.97-92.12)	81.83 (47.07-98.27)	68.85 (34.28-116.71)	35.86 (33.78-65.80)	35.97 (33.71-88.41)
	Risk of malnutrition	59.46 (35.84-147.21)	65.50 (24.36-137.21)	61.8 (31.64-85.41)	60.55 (26.76-185.53)	-	69.79 (51.52-88.06)
	Normal nutritional status	58.13 (53.64-62.63)	56.295 (25.71-140.34)	64.87 (21.49-113.30)	63.41 (24.01-147.21)	-	68.18 (47.80-82.73)
KW; p		0.450; 0.799	1.421; 0.491	0.765; 0.682	0.645; 0.724	-	0.723; 0.697
Fiber (g)	Malnourished	25.08	24.43 (9.78-36.33)	12.91 (10.81-20.35)	21.17 (10.32-54.73)	16.77 (7.52-25.07)	14.26 (10.80-27.27)
	Risk of malnutrition	23.30 (18.27-32.01)	23.29 (10.04-54.73)	20.69 (8.16-48.77)	19.46 (6.14-179.17)	-	31.64 (27.99-35.29)
	Normal nutritional status	26.80 (24.99-28.61)	28.06 (11.2-62.03)	17.93 (8.02-27.47)	20.60 (3.30-102.70)	-	27.155 (15.36-33.00)
KW; p		0.583; 0.747	0.883; 0.643	0.467; 0.792	0.556; 0.757	-	4.791; 0.091
Water (ml)	Malnourished	1250	1600 (1000-1600)	1200 (1100-1650)	1100 (650-1750)	715 (500-860)	950 (720-1800)
	Risk of malnutrition	1200 (1200-1600)	1300 (900-1800)	1375 (1200-1600)	1350 (650-2100)	-	1050 (1000-1100)
	Normal nutritional status	1300 (1200-1400)	1250 (900-1800)	1100 (900-1800)	1300 (0-2300)	-	1500 (1300-1800)
KW; p		0.058; 0.972	0.915; 0.633	1.409; 0.494	7.667; 0.022*	-	4.118; 0.128
Difference		-	-	-	1-2.3	-	-

*p<0.05; 1: Malnourished, 2: Risk of malnutrition, 3: Normal nutritional status, MNA: Mini nutritional assessment, Min: Minimum, Max: Maximum, KW: Kruskal Wallis test, Difference: Bonferroni test, p: Significance level

attitudes were found mostly in individuals aged 51-60 years.[28] In another study, an increase in the level of Food Neophobia was observed with increasing age.[4] It is thought that the fact that older individuals have not grown up exposed to various food sources and are less familiar with different foods may be associated with higher levels of food neophobia.

Food neophobia is considered a behavioral trait that affects BMI by being associated with inadequate eating habits and poor diet quality.[4] In our study, 88.7% of elderly obese individuals were neophilic, 65.5% of overweight individuals were neutral, and 33.3% of underweight individuals were neophobic. In a study, it was determined that obese individuals showed higher levels of food neophobia than normal-weight individuals and obese men had lower taste sensitivity.[30] However, in another study, neophobic individuals had lower BMI values than neophilic individuals.[31] In another study, when individuals were divided into neophilic, neutral, and neophobic groups according to their new food neophobia levels, the mean BMIs were found to be 24.62, 25.47, and 25.35 kg/m^2, respectively. However, the group with the lowest number of obese individuals was determined as neophobic.[27] It can be suggested that neophobia tendency may increase if BMI levels go beyond the normal range in old age. In addition, the disease anxiety brought about by weight gain in elderly individuals increases the likelihood of fear of trying new foods.

Anthropometric measurements are of critical importance in determining nutritional status, and measurement of height and waist circumference are among the most commonly used methods. The waist/height ratio helps to evaluate the risk of chronic diseases that may occur in individuals.[32] In the waist/height ratios of the elderly individuals in our study, it was found that 60% of neophobic individuals were normal, 62% of neutral individuals were risky, and 84.3% of neophilic individuals needed treatment. In a study, the mean waist/height ratio was calculated as 0.50±0.08 for neophilic individuals, 0.51±0.09 for neutral individuals, and 0.52±0.09 for neophobic individuals.[27] To optimize the waist/height ratios of elderly individuals and reduce their neophobia levels, it would be beneficial to develop comprehensive nutrition education programs and support services to increase physical mobility.

Constipation is not a disease but a symptom. Constipation may develop due to idiopathic causes or may occur due to various factors including diet, sports habits, medications, and disease processes.[33] Most of the elderly neophilic (93%), neutral (94%) and neophobic (73.3%) individuals in our study did not have constipation. Adherence to the adaptation of healthy and sustainable diets is low among food neophobics, increasing their risk of diet-related chronic diseases.[34] In a study, elderly individuals stated that they did not like the food given in the nursing home, that it did not contain much fiber, and that such a diet caused irregular bowel habits.[35] If neophobia is present in elderly individuals, constipation is likely to be seen with inadequate fiber intake and inactivity that may occur due to inadequate food intake.

In elderly individuals, inadequate nutrient intake causes malnutrition, especially with losses in lean body mass. In the early diagnosis of malnutrition, screening tests such as Mini Nutritional Assessment and anthropometric measurements such as calf circumference and upper mid-arm circumference are important to determine nutritional status.[16] Most of the elderly neophobic individuals in our study were malnourished (60%). In one study, Food Neophobia in older adults was found to be significantly associated with the risk of malnutrition and has been reported to significantly reduce the intake of 20 nutrients.[36] In another study, the food consumption habits of 139 individuals aged 18 years and over were examined and it was found that the consumption of fruit, protein drinks, and water consumption decreased with increasing neophobia levels, while the consumption of starch, snacks, sweets, milk, and soda increased. This revealed that neophobic individuals tended to turn to less nutritious foods and dietary diversity was limited.[37] It is possible to say that neophobia negatively affects the healthy eating habits of elderly individuals, decreasing the quality of their diet and creating a risk of malnutrition.

It has also been reported that energy intake decreases by 25% from the age of 40 to 70 years old.[38] In a healthy diet, it is of great importance that protein, carbohydrate, and fat ratios are balanced. It is recommended that 55-60% of the daily energy requirement should come from carbohydrates, 10-15% from proteins, and a maximum of 30% from fats. These ratios play a fundamental role in meeting the body's energy balance and nutritional requirements.[34] Inadequate fiber and fluid intake and a sedentary lifestyle increase the risk of constipation, and low energy intake, low meal consumption, and depression also support this risk. Constipation can generally be alleviated by increasing fiber and fluid intake and physical activity.[9] In a study, the rates of meeting the energy requirements of the participants were calculated as 69.82% for neophilic individuals, 71.90% for neutral individuals, and 83.20% for neophobic individuals and it was found that there was a difference between the groups.[17] In another study, it was stated that increased food neophobia may lead to a decrease in fruit and vegetable consumption in individuals. It was observed that increasing neophobia level decreased vegetable consumption, but did not affect fruit consumption. A decrease in fiber intake was also observed in parallel with increased fear levels. Therefore, it was recommended to support individuals with high Food Neophobia to increase their vegetable consumption and diversity.[16] A study conducted in Poland showed that neophobic individuals consumed meat products more frequently and desserts less frequently. In addition, the limited consumption of vegetables and fruits by neophobics was associated with food preferences acquired in childhood, and it was stated that these preferences may change with health problems in old age. The importance that neophobes attach to health in their food choices may affect their dietary compliance. It has been stated that being neophobic should be taken seriously in terms of nutritional counseling and it has been thought that this situation may lead to nutritional deficiencies and chronic disease risk.[31] In our study, the mean energy, carbohydrate, fat, protein, fiber, and water consumption of neophobic and constipated malnourished individuals were 936.30 kcal, 107.34 g, 37.85 g, 35.86 g, 16.77 g, and 715 ml, respectively. Inadequate energy intake affects the quality of life of the individual as seen in general studies. Fear of food at a level that affects the health of individuals may cause malnutrition and increase the likelihood of constipation. Therefore, attention should be paid to energy intake, adequate macro and micronutrients, and fiber and fluid intake in elderly individuals with food neophobia.

Limitations
Due to the difficulties encountered by elderly individuals in the recall process, 24-hour retrospective food consumption records could not be obtained for three days. The cultural and geographical characteristics of the place where the study was conducted may influence the dietary habits and health status of individuals. This may limit the generalizability of the results.

CONCLUSION
Physiological changes and diseases seen in the increasing elderly population both in the world and in our country affect the nutrition and health status of elderly individuals. While appetite and sensory abilities are known to decrease with age, physical barriers that may affect eating, food preparation, and food supply may increase with age. The FNS is a valid and reliable measurement tool used to determine food neophobia, adapted to Turkish for individuals aged 19-64 years, and can be used in Turkey. Confirmatory Factor Analysis was used to evaluate the usability of the FNS in individuals aged 65 years and over, and it was shown that the instrument is a valid and reliable measurement tool for the elderly population. In conclusion, treatments for age-related conditions such as constipation, malnutrition, and undernutrition that focus on novel foods need to be carefully designed. Novel food products with balanced nutrient content and high digestibility should be carefully designed to meet the specific nutritional needs of older people. The elderly should be a market segment that promotes healthy products, where new products can be introduced and purchased without concern. In addition, a multidisciplinary approach should be adopted for the success of treatment approaches and effective cooperation between nutritionists, dietitians, clinicians, and food technologists should be ensured.

ETHICAL DECLARATIONS

Ethics Committee Approval
The study was carried out with the permission of the Süleyman Demirel University Ethics Committee (Date: 07.11.2023, Decision No: 69/11).

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

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The author has no conflicts of interest to declare.

Financial Disclosure
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Author Contributions
Author declares that participated in the design, execution, and analysis of the paper, and that have approved the final version.

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Evaluation of family physicians' knowledge, attitudes and awareness on orthodontic treatments and oral health

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ABSTRACT

Aims: This study aims to evaluate the knowledge, attitudes, and awareness of family physicians regarding orthodontic treatments and oral health, which are primary aspects of general healthcare services.

Methods: This descriptive study was conducted in 2023 with the participation of 309 family physicians from Diyarbakır and surrounding provinces. A total of 20 questions, including 16 questions to assess knowledge of orthodontic treatments and oral health, and 4 sociodemographic questions, were administered online to the participating physicians.

Results: Among the physicians who participated in the study, 69.58% had over six years of professional experience, and 65.05% examined more than 51 patients per day. It was observed that 33.01% of the physicians had knowledge about orthodontic treatments. Of the physicians in our study, 24.92% recommended an annual oral and dental examination, while 32.36% reported that they referred patients with observed dental crowding during clinical examinations to an orthodontist/specialist. A statistically significant relationship was found between professional experience and both orthodontic awareness and the likelihood of providing oral hygiene care recommendations to patients ($p<0.05$).

Conclusion: Regular in-service training sessions should be provided to family physicians to enhance their knowledge and awareness of oral and dental health, orthodontic malocclusions, and preventive and interceptive treatments.

Keywords: Family physician, public health, orthodontics, oral health

INTRODUCTION

Oral and dental health is widely recognized as an essential component of overall health. Oral and dental diseases can adversely affect general health by causing pain, nutritional deficiencies, and disrupted sleep quality. Furthermore, the high costs associated with dental disease treatment impose a significant burden on healthcare systems, impacting the health economy negatively.[1]

In recent years, significant advancements have been made in both medical and dental treatment methods. However, regardless of how advanced these methods become, prevention remains the most critical tool in the fight against disease.[2]

The aim of preventive dentistry is to identify potential dental issues at an early stage and implement precautionary measures. Despite being largely preventable, dental caries remains a prevalent issue due to insufficient tooth brushing and is still considered a major public health concern in some societies. Tooth decay can lead to pain and nutritional challenges during the deciduous tooth period and can predispose individuals to further caries in permanent teeth. In this context, preventive dentistry practices serve as an effective approach to reducing the incidence of caries.[3] Another consequence of inadequate tooth brushing is the development of gum diseases, which can ultimately result in tooth loss. Early diagnosis of these diseases is crucial for both the effectiveness and cost-efficiency of treatment.[4]

The preventive orthodontic approach is a crucial component of preventive dentistry, aiming to prevent potential disorders in the teeth and jaw. These practices include placeholder applications following the early loss of deciduous teeth in children aged 0-15, extraction of molars and deciduous teeth to facilitate the eruption of permanent teeth, correction of simple crossbites with inclined plane aligners, and intervention to prevent harmful oral habits.[5]

A family physician is a primary care provider who delivers comprehensive and continuous healthcare services regardless of patients' age, gender, or specific health conditions.[6] Oral and dental health assessments should not be overlooked during routine examinations in family medicine. It is

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essential for family physicians to take a holistic approach by assessing patients' oral and dental health, offering appropriate recommendations, and referring patients to a dentist when necessary. Research indicates that primary healthcare providers play a pivotal role in promoting oral and dental health.[7]

This study aims to increase family physicians' awareness of oral health, dental health, and orthodontic issues, while also informing health policies focused on enhancing the population's overall oral and dental health. Additionally, it seeks to support the development of preventive and interceptive orthodontic treatments.

METHODS

This study received approval from the Batman University Clinical Researches Ethics Committee (Date: 31.01.2024, Decision No: 2024/01-22). The research was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Through a review of previous studies and publications on family medicine, oral health, and dental health, key topics essential for family physicians' knowledge of oral health and orthodontics were identified. Survey questions were then developed based on these topics.[8-11]

This is a cross-sectional study involving 309 family physicians (88 women, 221 men) aged between 27 and 62 years from Diyarbakir and its neighboring provinces, all of whom voluntarily completed our online questionnaire. The questionnaire was created using Google Forms and shared with doctors who volunteered to participate in the study through a link, ensuring the confidentiality of their responses.

In the first part of the questionnaire, sociodemographic information such as gender, age, weekly working hours, number of patients examined per day, and years of experience in the profession were recorded. The second part included questions assessing the attitudes and behaviors of family physicians regarding oral examinations and recommendations for oral care. Finally, the third part consisted of questions aimed at evaluating the level of knowledge of family physicians concerning the diagnosis, management, and prevention of orthodontic problems in patients. The survey questions are shown in Table 1.

Statistical Analysis

The data obtained in this study were analyzed using IBM SPSS Statistics Version 21 package program. Frequency analysis of the study variables was conducted, with results presented as frequencies and percentages.

Chi-square analysis was used to examine the relationships between groups of nominal variables. For 2x2 tables, Fisher's Exact Test was applied when the expected cell frequencies were insufficient, while for RxC tables, Pearson's Chi-square analysis was conducted using Monte Carlo simulation.

A significance level of 0.05 was set for the interpretation of the results.

Table 1. Survey questions

Do you recommend annual oral and dental examinations for adults?	None	Very little	Little	Middle	Good	Very good
Do you advise your patients on oral hygiene care?	None	Very little	Little	Middle	Good	Very good
Do you give advice to parents about their children's oral hygiene care?	None	Very little	Little	Middle	Good	Very good
Do you perform the first intraoral examination on babies immediately after birth?	None	Very little	Little	Middle	Good	Very good
Do you refer children to the dentist after their first baby teeth erupt?	None	Very little	Little	Middle	Good	Very good
Do you recommend night feeding with a bottle for babies?	None	Very little	Little	Middle	Good	Very good
Do you recommend fluoride toothpaste for families?	None	Very little	Little	Middle	Good	Very good
Can you give advice on oral hygiene care during pregnancy?	None	Very little	Little	Middle	Good	Very good
Do you know the specialties of dentistry?	None	Very little	Little	Middle	Good	Very good
Do you know about orthodontic treatments?	None	Very little	Little	Middle	Good	Very good
In your clinical examinations, do you refer your patients with a history of 'joint pain, noise coming from the joint area' to orthodontists?	None	Very little	Little	Middle	Good	Very good
Do you evaluate your patients with a history of 'mouth breathing' in your clinical examinations in terms of dental and gingival health?	None	Very little	Little	Middle	Good	Very good
Do you refer your patients with a history of 'thumb sucking' in your clinical examinations to orthodontists?	None	Very little	Little	Middle	Good	Very good
Do you refer your patients with a history of 'sleep apnea' in your clinical examinations to orthodontists?	None	Very little	Little	Middle	Good	Very good
Do you refer your patients who have a history of 'wrong swallowing' in your clinical examinations to orthodontists?	None	Very little	Little	Middle	Good	Very good
Do you refer your child/adult patients to orthodontists when you notice crowding in their teeth during your clinical examinations?	None	Very little	Little	Middle	Good	Very good

RESULTS

In our study, 10.03% of the participants were between 24 and 30 years of age, 48.87% were between 31 and 40 years of age, and 41.1% were over 41 years of age. Additionally, 28.48% of the participants were women, and 71.52% were men.

Of the physicians who completed our questionnaire, 69.58% had more than 6 years of professional experience, and 65.05% examined more than 51 patients per day (Figure 1, 2).

While 24.92% of the study participants recommend annual oral and dental examinations for adults, 27.18% recommend oral hygiene care for their patients (Table 2).

A total of 30.42% of the physicians provide recommendations to parents regarding the oral hygiene care of their children. However, only 21.86% of the physicians referred children to a dentist after the eruption of the first deciduous teeth (Table 2).

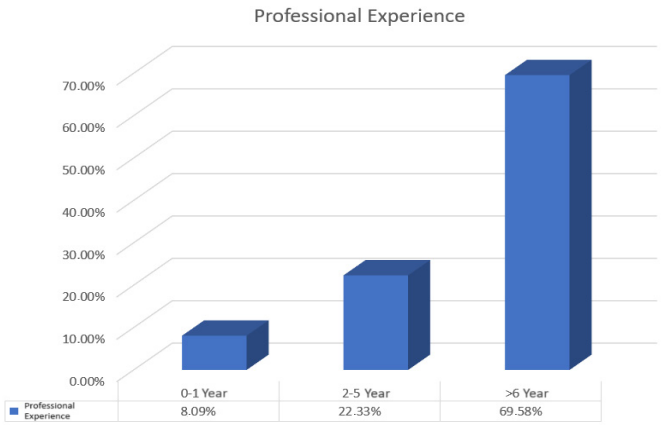

Figure 1. Scatter graph for professional experience

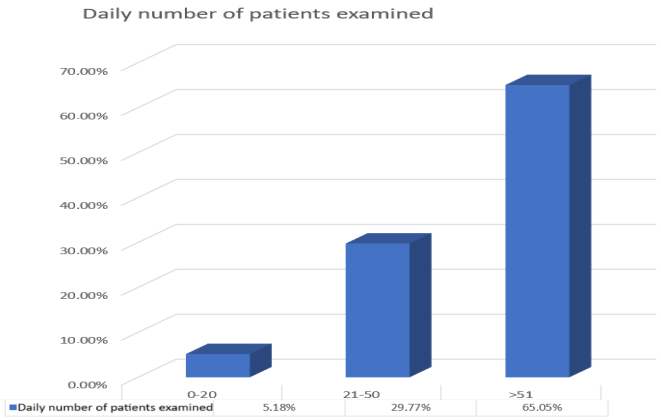

Figure 2. Scatter plot of number of patients

Approximately half of the physicians did not recommend bottle-feeding at night (Table 2).

Overall, 26.21% of the physicians did not recommend fluoride toothpaste to families (Table 3).

Overall, 23.95% of the physicians make recommendations regarding oral hygiene care during pregnancy (Table 3). Additionally, 21.36% of the participating physicians conduct the first oral examination of infants immediately after birth, at a moderate level (Table 4).

Among the physicians participating in the study, 30.01% were aware of the specialty branches of dentistry. The percentage of physicians with knowledge of orthodontic treatments was moderate, at 33.01% (Table 5).

Overall, 27.83% of the physicians did not refer patients with a history of 'joint pain or noise coming from the joint area' to an orthodontist during clinical examinations (Table 5).

Of the physicians who participated in the study, 23.3% evaluated their patients with a history of 'mouth breathing' for dental and gingival health during clinical examinations (Table 6).

The percentage of physicians who referred their patients with a history of 'finger sucking' to an orthodontist during clinical examinations was found to be low, at 26.54% (Table 6).

Overall, 31.39% of the physicians referred their patients with a history of 'sleep apnea' to an orthodontist during clinical examinations. (Table 6).

Table 2. Distribution of evaluations regarding orthodontic treatments and oral health

	None		Very little		Little		Middle		Good		Very good		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Do you recommend annual oral and dental examinations for adults?	17	5.5	58	18.77	57	18.45	77	24.92	53	17.15	47	15.21	309	100
Do you advise your patients on oral hygiene care?	13	4.21	44	14.24	53	17.15	84	27.18	72	23.3	43	13.92	309	100
Do you give recommendations to parents about their children's oral hygiene care?	7	2.27	28	9.06	43	13.92	79	25.57	94	30.42	58	18.77	309	100
Do you perform the first intraoral examination on babies immediately after birth?	40	12.94	64	20.71	41	13.27	66	21.36	62	20.06	36	11.65	309	100
Do you refer children to the dentist after their first milk teeth erupt?	62	20.06	83	26.86	68	22.01	45	14.56	29	9.39	22	7.12	309	100
Do you recommend bottle feeding at night?	170	55.02	82	26.54	32	10.36	22	7.12	2	0.65	1	0.32	309	100

Table 3. Distribution of evaluations regarding orthodontic treatments and oral health

	None		Very little		Little		Middle		Good		Very good		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Do you recommend fluoride toothpaste for families?	81	26.21	47	15.21	40	12.94	64	20.71	56	18.12	21	6.8	309	100
Do you make recommendations about oral hygiene care during pregnancy?	36	11.65	41	13.27	43	13.92	74	23.95	65	21.04	50	16.18	309	100
Do you know the specialties of dentistry?	6	1.94	33	10.68	38	12.3	93	30.1	81	26.21	58	18.77	309	100
Do you know about orthodontic treatments?	12	3.88	52	16.83	52	16.83	102	33.01	60	19.42	31	10.03	309	100
Do you refer your patients with a history of 'joint pain. sound coming from the joint area' to orthodontist/orthodontic specialist in your clinical examinations?	86	27.83	61	19.74	43	13.92	49	15.86	47	15.21	23	7.44	309	100
Do you evaluate your patients with a history of 'mouth breathing' in your clinical examinations in terms of dental and gingival health?	46	14.89	55	17.8	65	21.04	72	23.3	47	15.21	24	7.77	309	100
Do you refer your patients with a history of 'finger sucking' in your clinical examinations to an orthodontist/orthodontic specialist?	69	22.33	82	26.54	50	16.18	43	13.92	41	13.27	24	7.77	309	100
Do you refer your patients with a history of 'sleep apnea' in your clinical examinations to an orthodontist/orthodontic specialist?	94	30.42	97	31.39	50	16.18	32	10.36	24	7.77	12	3.88	309	100
Do you refer your patients with a history of 'wrong swallowing' in your clinical examinations to an orthodontist/orthodontic specialist?	100	32.36	89	28.8	48	15.53	38	12.3	25	8.09	9	2.91	309	100
Do you refer your child/adult patients to orthodontist/orthodontics specialist when you notice crowding in their teeth during your clinical examinations?	16	5.18	25	8.09	22	7.12	50	16.18	100	32.36	96	31.07	309	100

Table 4. Relationships between age group and orthodontic treatments and oral health assessments

		Age									
		24-30		31-40		>41		Total		Chi-square test	
		n	%	n	%	n	%	n	%	Chi-square	p
Do you recommend annual oral and dental examinations for adults?	None	1	3.23	7	4.64	9	7.09	17	5.5	16.417	0.088
	Very little	11	35.48	31	20.53	16	12.6	58	18.77		
	Little	3	9.68	32	21.19	22	17.32	57	18.45		
	Middle	11	35.48	31	20.53	35	27.56	77	24.92		
	Good	3	9.68	26	17.22	24	18.9	53	17.15		
	Very good	2	6.45	24	15.89	21	16.54	47	15.21		
	Total	31	100	151	100	127	100	309	100		
Do you advise your patients on oral hygiene care?	None	0	0	7	4.64	6	4.72	13	4.21	24.569	0.006
	Very little	9	29.03	23	15.23	12	9.45	44	14.24		
	Little	8	25.81	25	16.56	20	15.75	53	17.15		
	Middle	10	32.26	46	30.46	28	22.05	84	27.18		
	Good	4	12.9	27	17.88	41	32.28	72	23.3		
	Very good	0	0	23	15.23	20	15.75	43	13.92		
	Total	31	100	151	100	127	100	309	100		
Do you give recommendations to parents about their children's oral hygiene care?	None	0	0	4	2.65	3	2.36	7	2.27	*	0.027
	Very little	4	12.9	13	8.61	11	8.66	28	9.06		
	Little	6	19.35	25	16.56	12	9.45	43	13.92		
	Middle	14	45.16	39	25.83	26	20.47	79	25.57		
	Good	6	19.35	39	25.83	49	38.58	94	30.42		
	Very good	1	3.23	31	20.53	26	20.47	58	18.77		
	Total	31	100	151	100	127	100	309	100		
Do you perform the first intraoral examination on babies immediately after birth?	None	2	6.45	22	14.57	16	12.6	40	12.94	11.877	0.293
	Very little	12	38.71	26	17.22	26	20.47	64	20.71		
	Little	4	12.9	21	13.91	16	12.6	41	13.27		
	Middle	6	19.35	33	21.85	27	21.26	66	21.36		
	Good	7	22.58	28	18.54	27	21.26	62	20.06		
	Very good	0	0	21	13.91	15	11.81	36	11.65		
	Total	31	100	151	100	127	100	309	100		
Do you refer children to the dentist after their first milk teeth erupt?	None	6	19.35	29	19.21	27	21.26	62	20.06	11.328	0.333
	Very little	6	19.35	42	27.81	35	27.56	83	26.86		
	Little	4	12.9	34	22.52	30	23.62	68	22.01		
	Middle	10	32.26	21	13.91	14	11.02	45	14.56		
	Good	4	12.9	13	8.61	12	9.45	29	9.39		
	Very good	1	3.23	12	7.95	9	7.09	22	7.12		
	Total	31	100	151	100	127	100	309	100		

Overall, 32.36% of the physicians referred their patients with a history of 'improper swallowing' to an orthodontist (Table 6).

A total of 32.36% of the physicians refer their pediatric and adult patients to an orthodontist when they notice crowding in the teeth during clinical examinations, at a good level (Table 6).

A statistically significant relationship was found between age group and all evaluations ($p<0.05$) (Table 4-6).

A statistically significant relationship was found between professional experience and the recommendation of annual oral and dental examinations for adults ($p<0.05$). There was also a statistically significant difference between 44% of the new family physicians and the other groups regarding the recommendation of annual oral and dental examinations for adults (Table 7).

A statistically significant correlation was found between professional experience and making recommendations to patients about oral hygiene care ($p<0.05$). Among family physicians, 28% of those with 0-1 years of experience, 24.64% of those with 2-5 years of experience, and 27.91% of those with more than 6 years of experience make moderate recommendations to their patients about oral hygiene care (Table 7).

Table 5. Relationships between age group and orthodontic treatments and oral health assessments

		Age								Chi-square test	
		24-30		31-40		>41		Total			
		n	%	n	%	n	%	n	%	Chi-square	p
Do you recommend bottle feeding at night?	None	10	32.26	78	51.66	82	64.57	170	55.02	*	0.071
	Very little	12	38.71	44	29.14	26	20.47	82	26.54		
	Little	5	16.13	13	8.61	14	11.02	32	10.36		
	Middle	4	12.9	13	8.61	5	3.94	22	7.12		
	Good	0	0	2	1.32	0	0	2	0.65		
	Very good	0	0	1	0.66	0	0	1	0.32		
	Total	31	100	151	100	127	100	309	100		
Do you recommend fluoride toothpaste for families?	None	6	19.35	39	25.83	36	28.35	81	26.21	9.485	0.487
	Very little	8	25.81	18	11.92	21	16.54	47	15.21		
	Little	4	12.9	23	15.23	13	10.24	40	12.94		
	Middle	4	12.9	33	21.85	27	21.26	64	20.71		
	Good	8	25.81	25	16.56	23	18.11	56	18.12		
	Very good	1	3.23	13	8.61	7	5.51	21	6.8		
	Total	31	100	151	100	127	100	309	100		
Do you make recommendations about oral hygiene care during pregnancy?	None	1	3.23	20	13.25	15	11.81	36	11.65	28.239	0.002
	Very little	11	35.48	20	13.25	10	7.87	41	13.27		
	Little	6	19.35	22	14.57	15	11.81	43	13.92		
	Middle	5	16.13	42	27.81	27	21.26	74	23.95		
	Good	4	12.9	23	15.23	38	29.92	65	21.04		
	Very good	4	12.9	24	15.89	22	17.32	50	16.18		
	Total	31	100	151	100	127	100	309	100		
Do you know the specialties of dentistry?	None	0	0	3	1.99	3	2.36	6	1.94	*	0.33
	Very little	4	12.9	18	11.92	11	8.66	33	10.68		
	Little	6	19.35	22	14.57	10	7.87	38	12.3		
	Middle	10	32.26	40	26.49	43	33.86	93	30.1		
	Good	8	25.81	34	22.52	39	30.71	81	26.21		
	Very good	3	9.68	34	22.52	21	16.54	58	18.77		
	Total	31	100	151	100	127	100	309	100		
Do you know about orthodontic treatments?	None	0	0	7	4.64	5	3.94	12	3.88	12.866	0.231
	Very little	6	19.35	22	14.57	24	18.9	52	16.83		
	Little	9	29.03	30	19.87	13	10.24	52	16.83		
	Middle	8	25.81	52	34.44	42	33.07	102	33.01		
	Good	7	22.58	26	17.22	27	21.26	60	19.42		
	Very good	1	3.23	14	9.27	16	12.6	31	10.03		
	Total	31	100	151	100	127	100	309	100		
Do you refer your patients with a history of 'joint pain, sound coming from the joint area' to orthodontist/ orthodontic specialist in your clinical examinations?	None	7	22.58	47	31.13	32	25.2	86	27.83	9.117	0.521
	Very little	7	22.58	33	21.85	21	16.54	61	19.74		
	Little	5	16.13	17	11.26	21	16.54	43	13.92		
	Middle	7	22.58	25	16.56	17	13.39	49	15.86		
	Good	4	12.9	18	11.92	25	19.69	47	15.21		
	Very good	1	3.23	11	7.28	11	8.66	23	7.44		
	Total	31	100	151	100	127	100	309	100		

It was observed that physicians who made recommendations to parents regarding the oral hygiene care of their children had more than 6 years of professional experience, with a statistically significant difference ($p<0.05$) (Table 7).

Although a significant proportion of physicians do not refer children to a dentist after the eruption of the first deciduous teeth, it was found that this rate decreases with increasing professional experience, with a statistically significant difference ($p<0.05$) (Table 7).

A statistically significant correlation was found between professional experience and making recommendations regarding oral hygiene care during pregnancy ($p<0.05$).

Table 6. Relationships between age group and orthodontic treatments and oral health assessments

		Age									
		24-30		31-40		>41		Total		Chi-square test	
		n	%	n	%	n	%	n	%	Chi-square	p
Do you evaluate your patients with a history of 'mouth breathing' in your clinical examinations in terms of dental and gingival health?	None	2	6.45	27	17.88	17	13.39	46	14.89	16.687	0.082
	Very little	9	29.03	30	19.87	16	12.6	55	17.8		
	Little	8	25.81	34	22.52	23	18.11	65	21.04		
	Middle	7	22.58	25	16.56	40	31.5	72	23.3		
	Good	4	12.9	21	13.91	22	17.32	47	15.21		
	Very good	1	3.23	14	9.27	9	7.09	24	7.77		
	Total	31	100	151	100	127	100	309	100		
Do you refer your patients with a history of 'finger sucking' in your clinical examinations to an orthodontist/orthodontic specialist?	None	4	12.9	37	24.5	28	22.05	69	22.33	5.171	0.879
	Very little	11	35.48	41	27.15	30	23.62	82	26.54		
	Little	6	19.35	24	15.89	20	15.75	50	16.18		
	Middle	3	9.68	20	13.25	20	15.75	43	13.92		
	Good	4	12.9	17	11.26	20	15.75	41	13.27		
	Very good	3	9.68	12	7.95	9	7.09	24	7.77		
	Total	31	100	151	100	127	100	309	100		
Do you refer your patients with a history of 'sleep apnea' in your clinical examinations to an orthodontist/orthodontic specialist?	None	7	22.58	45	29.8	42	33.07	94	30.42	10.536	0.395
	Very little	13	41.94	47	31.13	37	29.13	97	31.39		
	Little	2	6.45	27	17.88	21	16.54	50	16.18		
	Middle	4	12.9	17	11.26	11	8.66	32	10.36		
	Good	5	16.13	8	5.3	11	8.66	24	7.77		
	Very good	0	0	7	4.64	5	3.94	12	3.88		
	Total	31	100	151	100	127	100	309	100		
Do you refer your patients with a history of 'wrong swallowing' in your clinical examinations to an orthodontist/orthodontic specialist?	None	7	22.58	52	34.44	41	32.28	100	32.36	*	0.617
	Very little	11	35.48	44	29.14	34	26.77	89	28.8		
	Little	6	19.35	17	11.26	25	19.69	48	15.53		
	Middle	2	6.45	22	14.57	14	11.02	38	12.3		
	Good	4	12.9	11	7.28	10	7.87	25	8.09		
	Very good	1	3.23	5	3.31	3	2.36	9	2.91		
	Total	31	100	151	100	127	100	309	100		
Do you refer your child/adult patients to orthodontist/orthodontics specialist when you notice crowding in their teeth during your clinical examinations?	None	2	6.45	9	5.96	5	3.94	16	5.18	21.564	0.017
	Very little	2	6.45	16	10.6	7	5.51	25	8.09		
	Little	5	16.13	11	7.28	6	4.72	22	7.12		
	Middle	9	29.03	27	17.88	14	11.02	50	16.18		
	Good	9	29.03	48	31.79	43	33.86	100	32.36		
	Very good	4	12.9	40	26.49	52	40.94	96	31.07		
	Total	31	100	151	100	127	100	309	100		

None of the family physicians with 2-5 years of experience (15.94%) or those with over 6 years of experience (11.63%) made recommendations regarding oral hygiene care during pregnancy (Table 8).

A statistically significant correlation was found between professional experience and referring pediatric/adult patients to an orthodontist when crowding in their teeth was noticed during clinical examinations ($p<0.05$). While 36% of family physicians with 0-1 years of experience, 30.43% with 2-5 years of experience, and 32.56% with more than 6 years of experience referred their pediatric/adult patients to an orthodontist for crowding, 8.7% of those with 2-5 years of experience and 4.65% of those with more than 6 years of experience did not refer their patients in such cases (Table 9).

There was no statistically significant relationship between professional experience and the other evaluations ($p>0.05$).

DISCUSSION

Oral and dental health is recognized as an integral part of general health services by the World Health Organization (WHO), aiming to protect overall health and promote a healthy life. The family medicine system, recognized as primary health care, encompasses both preventive and treatment services.[12]

Table 7. The relationship between professional experience and orthodontic treatments and oral health assessments

		How many years have you been working as a family physician?									
		0-1 year		2-5 year		>6 year		Total		Chi-square test	
		n	%	n	%	n	%	n	%	Chi-square	p
Do you recommend annual oral and dental examinations for adults?	None	0	0	3	4.35	14	6.51	17	5.5	*	0.023
	Very little	7	28	21	30.43	30	13.95	58	18.77		
	Little	4	16	12	17.39	41	19.07	57	18.45		
	Middle	11	44	13	18.84	53	24.65	77	24.92		
	Good	3	12	10	14.49	40	18.6	53	17.15		
	Very good	0	0	10	14.49	37	17.21	47	15.21		
	Total	25	100	69	100	215	100	309	100		
Do you advise your patients on oral hygiene care?	None	1	4	2	2.9	10	4.65	13	4.21	*	0.022
	Very little	5	20	17	24.64	22	10.23	44	14.24		
	Little	8	32	14	20.29	31	14.42	53	17.15		
	Middle	7	28	17	24.64	60	27.91	84	27.18		
	Good	4	16	11	15.94	57	26.51	72	23.3		
	Very good	0	0	8	11.59	35	16.28	43	13.92		
	Total	25	100	69	100	215	100	309	100		
Do you give recommendations to parents about their children's oral hygiene care?	None	0	0	1	1.45	6	2.79	7	2.27	*	0.038
	Very little	5	20	8	11.59	15	6.98	28	9.06		
	Little	6	24	12	17.39	25	11.63	43	13.92		
	Middle	9	36	21	30.43	49	22.79	79	25.57		
	Good	4	16	16	23.19	74	34.42	94	30.42		
	Very good	1	4	11	15.94	46	21.4	58	18.77		
	Total	25	100	69	100	215	100	309	100		
Do you perform the first intraoral examination on babies immediately after birth?	None	2	8	12	17.39	26	12.09	40	12.94	10.111	0.431
	Very little	9	36	13	18.84	42	19.53	64	20.71		
	Little	4	16	9	13.04	28	13.02	41	13.27		
	Middle	4	16	17	24.64	45	20.93	66	21.36		
	Good	6	24	11	15.94	45	20.93	62	20.06		
	Very good	0	0	7	10.14	29	13.49	36	11.65		
	Total	25	100	69	100	215	100	309	100		
Do you refer children to the dentist after their first milk teeth erupt?	None	4	16	15	21.74	43	20	62	20.06	20.85	0.022
	Very little	4	16	19	27.54	60	27.91	83	26.86		
	Little	4	16	16	23.19	48	22.33	68	22.01		
	Middle	11	44	8	11.59	26	12.09	45	14.56		
	Good	1	4	8	11.59	20	9.3	29	9.39		
	Very good	1	4	3	4.35	18	8.37	22	7.12		
	Total	25	100	69	100	215	100	309	100		

Guidance from family physicians and patient education can help prevent potential problems, provide treatment opportunities, and increase patient awareness. In this regard, primary health care institutions play a crucial role.[13,14]

In a study conducted on the knowledge, attitudes, and practices of orthodontic patients regarding their treatment, it was observed that although the majority of patients had good knowledge, their attitudes toward orthodontic treatment and their related practices were not as favorable.[15]

In another study, it was found that patients who were informed about oral health issues had significantly more positive attitudes toward fixed orthodontic treatment and oral hygiene. The study also suggested that information-provision strategies could be effective in promoting positive attitudes and increasing awareness within the community".[16]

The literature has reported what family physicians should know about oral and dental health.[8,9,17] The aim of this study was to investigate family physicians' knowledge not only about oral and dental health but also about orthodontic awareness, the presence of orthodontic problems, the necessity of treatment, their awareness of parafunctional habits that may lead to orthodontic issues, and whether they refer their patients for orthodontic treatment.

Within the scope of our study, many family physicians participated via an online survey. There are several survey-based studies aimed at evaluating the awareness and

Tablo 8. The relationship between professional experience and orthodontic treatments and oral health assessments

		How many years have you been working as a family physician?									
		0-1 year		2-5 year		>6 year		Total		Chi-square test	
		n	%	n	%	n	%	n	%	Chi-square	p
Do you recommend bottle feeding at night?	None	10	40	28	40.58	132	61.4	170	55.02	*	0.094
	Very little	7	28	24	34.78	51	23.72	82	26.54		
	Little	4	16	9	13.04	19	8.84	32	10.36		
	Middle	4	16	6	8.7	12	5.58	22	7.12		
	Good	0	0	1	1.45	1	0.47	2	0.65		
	Very good	0	0	1	1.45	0	0	1	0.32		
	Total	25	100	69	100	215	100	309	100		
Do you recommend fluoride toothpaste for families?	None	6	24	15	21.74	60	27.91	81	26.21	*	0.911
	Very little	4	16	14	20.29	29	13.49	47	15.21		
	Little	4	16	11	15.94	25	11.63	40	12.94		
	Middle	5	20	14	20.29	45	20.93	64	20.71		
	Good	5	20	12	17.39	39	18.14	56	18.12		
	Very good	1	4	3	4.35	17	7.91	21	6.8		
	Total	25	100	69	100	215	100	309	100		
Do you make recommendations about oral hygiene care during pregnancy?	None	0	0	11	15.94	25	11.63	36	11.65	22.902	0.011
	Very little	6	24	16	23.19	19	8.84	41	13.27		
	Little	5	20	10	14.49	28	13.02	43	13.92		
	Middle	9	36	13	18.84	52	24.19	74	23.95		
	Good	3	12	10	14.49	52	24.19	65	21.04		
	Very good	2	8	9	13.04	39	18.14	50	16.18		
	Total	25	100	69	100	215	100	309	100		
Do you know the specialties of denitistry?	None	0	0	2	2.9	4	1.86	6	1.94	*	0.295
	Very little	2	8	11	15.94	20	9.3	33	10.68		
	Little	7	28	7	10.14	24	11.16	38	12.3		
	Middle	8	32	16	23.19	69	32.09	93	30.1		
	Good	5	20	21	30.43	55	25.58	81	26.21		
	Very good	3	12	12	17.39	43	20	58	18.77		
	Total	25	100	69	100	215	100	309	100		
Do you know about orthodontic treatments?	None	0	0	3	4.35	9	4.19	12	3.88	*	0.313
	Very little	3	12	15	21.74	34	15.81	52	16.83		
	Little	8	32	8	11.59	36	16.74	52	16.83		
	Middle	8	32	21	30.43	73	33.95	102	33.01		
	Good	6	24	16	23.19	38	17.67	60	19.42		
	Very good	0	0	6	8.7	25	11.63	31	10.03		
	Total	25	100	69	100	215	100	309	100		
Do you refer your patients with a history of 'joint pain, sound coming from the joint area' to orthodontist/orthodontic specialist in your clinical examinations?	None	4	16	24	34.78	58	26.98	86	27.83	*	0.454
	Very little	6	24	16	23.19	39	18.14	61	19.74		
	Little	4	16	9	13.04	30	13.95	43	13.92		
	Middle	7	28	10	14.49	32	14.88	49	15.86		
	Good	3	12	6	8.7	38	17.67	47	15.21		
	Very good	1	4	4	5.8	18	8.37	23	7.44		
	Total	25	100	69	100	215	100	309	100		

knowledge levels of family physicians regarding oral and dental health.[10,11,18]

It was observed that only a small proportion of the physicians participating in our study recommended annual dental examinations (24.92%), while the majority did not recommend oral hygiene care (35.6%).

Rabiei et al.[11] reported that the majority of non-dentist physicians lack sufficient knowledge about oral and dental health, emphasizing the need for training in this field.

According to the treatment protocol published by the American Academy of Pediatric Dentistry (AAPD) in 2018, the first dental visit should occur between the 6th and 12th

Tablo 9. The relationship between professional experience and orthodontic treatments and oral health assessments

		How many years have you been working as a family physician?									
		0-1 year		2-5 year		>6 year		Total		Chi-square test	
		n	%	n	%	n	%	n	%	Chi-square	p
Do you evaluate your patients with a history of 'mouth breathing' in your clinical examinations in terms of dental and gingival health?	None	1	4	15	21.74	30	13.95	46	14.89	15.702	0.108
	Very little	7	28	17	24.64	31	14.42	55	17.8		
	Little	7	28	14	20.29	44	20.47	65	21.04		
	Middle	6	24	12	17.39	54	25.12	72	23.3		
	Good	4	16	6	8.7	37	17.21	47	15.21		
	Very good	0	0	5	7.25	19	8.84	24	7.77		
	Total	25	100	69	100	215	100	309	100		
Do you refer your patients with a history of 'finger sucking' in your clinical examinations to an orthodontist/orthodontic specialist?	None	3	12	15	21.74	51	23.72	69	22.33	5.828	0.83
	Very little	8	32	18	26.09	56	26.05	82	26.54		
	Little	6	24	12	17.39	32	14.88	50	16.18		
	Middle	4	16	7	10.14	32	14.88	43	13.92		
	Good	3	12	9	13.04	29	13.49	41	13.27		
	Very good	1	4	8	11.59	15	6.98	24	7.77		
	Total	25	100	69	100	215	100	309	100		
Do you refer your patients with a history of 'sleep apnea' in your clinical examinations to an orthodontist/orthodontic specialist?	None	5	20	20	28.99	69	32.09	94	30.42	*	0.245
	Very little	8	32	26	37.68	63	29.3	97	31.39		
	Little	3	12	6	8.7	41	19.07	50	16.18		
	Middle	5	20	8	11.59	19	8.84	32	10.36		
	Good	4	16	6	8.7	14	6.51	24	7.77		
	Very good	0	0	3	4.35	9	4.19	12	3.88		
	Total	25	100	69	100	215	100	309	100		
Do you refer your patients with a history of 'wrong swallowing' in your clinical examinations to an orthodontist/orthodontic specialist?	None	4	16	23	33.33	73	33.95	100	32.36	*	0.362
	Very little	8	32	25	36.23	56	26.05	89	28.8		
	Little	4	16	5	7.25	39	18.14	48	15.53		
	Middle	5	20	8	11.59	25	11.63	38	12.3		
	Good	3	12	5	7.25	17	7.91	25	8.09		
	Very good	1	4	3	4.35	5	2.33	9	2.91		
	Total	25	100	69	100	215	100	309	100		
Do you refer your child/adult patients to orthodontist/ orthodontics specialist when you notice crowding in their teeth during your clinical examinations?	None	0	0	6	8.7	10	4.65	16	5.18	*	0.038
	Very little	2	8	8	11.59	15	6.98	25	8.09		
	Little	5	20	4	5.8	13	6.05	22	7.12		
	Middle	6	24	14	20.29	30	13.95	50	16.18		
	Good	9	36	21	30.43	70	32.56	100	32.36		
	Very good	3	12	16	23.19	77	35.81	96	31.07		
	Total	25	100	69	100	215	100	309	100		

month of life, following the eruption of the first deciduous tooth.[19] In our study, 26.86% of the participating physicians believed that the first dental examination should occur immediately after the eruption of a child's first teeth, which aligns with the findings of other studies.[20-22]

Cleft palate and pediatric syndromes can lead to sleep apnea by restricting mouth opening and neck movements, enlarging the tongue, and obstructing the airway. Therefore, it is crucial to perform an oral cavity examination in newborns to identify and address potential life-threatening risks.[23] Among the physicians who participated in our study, 21.36% reported performing an oral cavity examination after delivery, which was considered a moderate rate.

The use of fluoride toothpaste is recommended by the AAPD.[24] In our study, the proportion of physicians who did not recommend fluoride toothpaste to families was lower than those who did recommend it. Additionally, a significant relationship was found between years of professional experience and the likelihood of recommending fluoride toothpaste. This finding is consistent with previous studies.[22,25]

During pregnancy, oral and dental health is as important as the health of other tissues and organs. Numerous studies have shown that oral and dental health issues during the prenatal period, particularly periodontal diseases and dental caries, may be associated with certain pregnancy complications.[26,27] Therefore, in primary care family medicine practices, it is

essential to assess the oral and dental health of all pregnant women, educate them on proper oral hygiene, and refer them to a dentist when necessary.[28] However, in our study, only 23.95% of the physicians provided recommendations to pregnant women regarding oral and dental health.

In our study, 30.01% of family physicians had a moderate level of knowledge about the specialty branches of dentistry, while the proportion of physicians who were knowledgeable about orthodontic treatments was lower than those who lacked such knowledge. Studies have reported that physicians often acquire insufficient knowledge and skills in oral health during their education and training.[29,30]

Early diagnosis of parafunctional habits, such as thumb sucking, abnormal swallowing, and mouth breathing, and referral to the appropriate specialist is crucial for ensuring optimal oral hygiene, preventing the costs of orthodontic treatment, and avoiding potential complications.[31-33] A study conducted with pediatricians found that physicians with more than 21 years of professional experience increased the rate of referring patients with dental and jaw problems to orthodontists by 12.75%.[34]

A study on dentists reported that physicians with more than 6 years of professional experience had a higher rate of diagnosing and being aware of orthodontic problems.[35]

In our study, the increase in awareness of orthodontic problems and the rate of patient referral to orthodontists with increasing professional experience among family physicians was statistically significant ($p<0.05$). This finding aligns with the results of the study by Büyük et al.,[36] in which the orthodontic awareness of family physicians was examined.

Similar to our study, other studies have found that the number of medical practitioners performing oral, dental, and maxillofacial examinations during routine check-ups is low.[34-36]

CONCLUSION

As a result of our study, we observed that family physicians have below-average knowledge and awareness of general oral and dental health, as well as orthodontic problems and their early treatment. To improve the public's oral health on a broader scale, cooperation between dentists and physicians from all medical specialties is essential.

Family medicine, as a primary health care institution, plays a critical role in preventive dentistry, early detection, and treatment of orthodontic problems and parafunctional habits. To enhance knowledge and improve practices, training seminars, online courses, webinars, and informational brochures or books on basic oral and dental health, as well as orthodontic treatments, should be organized by orthodontists.

Undergraduate and/or specialty training curricula for medical doctors can be enriched with oral and dental health education. Joint clinical studies or rotation programs with orthodontists, as well as multidisciplinary meetings and case discussions, can also be organized. A combination of these approaches may be effective in enhancing the orthodontic knowledge and awareness of family physicians. Expanding training and practical opportunities is crucial for physicians to more effectively identify orthodontic problems and guide patients appropriately.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Batman University Clinical Researches Ethics Committee (Date: 31.01.2024, Decision No: 2024/01-22).

Informed Consent

Written informed consent forms were obtained from physicians in the study.

Peer Review Process

External peer review.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Financial Disclosure

The authors declared that this study did not receive any 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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The effect of intrapartum labor induction with oxytocin on maternal depression scoring in early postpartum period: a retrospective cohort study

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ABSTRACT

Aims: Studies showing that synthetic oxytocin (SO) used for induction during labor increases the risk of postpartum maternal depression are increasing day by day in literature. Objective was to investigate the effect of SO administered for induction during labor on the tendency to maternal depression in early postpartum period.

Methods: The study encompassed nulliparous women, all of whom delivered at gestational weeks 37 to 41 between 2020 and 2022 and underwent standard postpartum assessments on the 10th day following delivery. Exclusion criteria comprised pregnant individuals with predisposing factors for depression before conception, during gestation, or in the postpartum period. Pregnants who were admitted to delivery room due to labor and gave birth without any induction method were classified as group C (n=137), and who were induced with SO were classified as group O (n=122). Edinburgh Postnatal Depression Scale (EPDS) scores on 0th day and 10th day postpartum of two groups were compared. Additionally, relationship between duration of induction and EPDS scores was analyzed.

Results: No statistically significant difference was detected between two groups in terms of age, gestational week, or educational status (p>0.05). No statistically significant difference was detected between the groups in EPDS scores on 0th or 10th day postpartum (p>0.05). There was no significant difference between induction time and EPDS scores on 0th or 10th day postpartum (p>0.05).

Conclusion: SO used for labor induction may not primary affect the tendency to postpartum depression in the early period. Further studies in populations without risk factors for depression are needed.

Keywords: Delivery, EPDS, labor induction, postpartum depression, synthetic oxytocin

INTRODUCTION

Oxytocin is a hormone necessary for various maternal abilities such as labor pains, breastfeeding, and the mother's bonding with the baby. As a neurotransmitter in the central nervous system, it affects various parts of the brain (hippocampus, amygdala and nucleus accumbens), such as the limbic system, which is related to emotions and social relationships. In the periphery, it helps with labor by causing the uterus to contract. It helps breastfeeding by stimulating the breast to release milk.[1] In the clinic, synthetic oxytocin is used to induce labor, augment labor pain and prevent postpartum hemorrhage.

In a study conducted, in the study group consisting of mothers with high psychosocial stress levels after birth, those with high endogenous oxytocin levels were less depressed.[2] Likewise, blood oxytocin levels of women with depressive features were found to be lower in the 2nd-month postpartum.[3] Researches indicate that physiological oxytocin levels have an impact on maternal mood during the postpartum period. Also, there are researches indicating that synthetic oxytocin used for labor induction increases the risk of postpartum depression.[4-6] Induction of labor with synthetic oxytocin is a common method applied by many physicians around the world. And can synthetic oxytocin have such a negative effect on maternal mood? In the studies mentioned and, in the literature, the Edinburgh Postnatal Depression Scale (EPDS) was used to understand mood assessment/tendency to depression. Although it varies from country to country, according to this 30-point scale, a score of 10 or higher suggests a mild to elevated risk of experiencing postpartum depression.[7,8]

Considering the studies showing that physiological and synthetic oxytocin may affect maternal mood, a question arises: Can synthetic oxytocin given for labor induction really be effective on maternal mood? Does the administered oxytocin

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protect from depressive tendencies in the early period, or does synthetic oxytocin taken from external sources cause a tendency to depression by increasing in maternal blood and decreasing rapidly after treatment?

Given this background, the aim was to analyze the influence of synthetic oxytocin administered for induction during labor on the tendency to maternal depression in the early postpartum period.

METHODS

Ethics

The study was planned and completed as a retrospective cohort study. The study was executed adhering to the ethical guidelines outlined in the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Başakşehir Çam and Sakura City Hospital (Date: 26.10.2022, Decision No: KAEK/2022.10.340).

Design of the Study

Pregnant women who delivered at city hospital from September 2020 to September 2022 and received standard postpartum assessments on the 10th day after delivery childbirth were retrospectively screened via hospital records. It was evaluated whether there were risk factors that could predispose to depression before, during and after pregnancy. Women identified with such risk factors were excluded from the study. Whether participants received induction with synthetic oxytocin during the labor process were determined. EPDS scores were determined by the Edinburgh Postpartum Depression Scale, which was filled in right after birth. The records of puerperants who were routinely called for puerperium control on the 10th postpartum day and routine psychologist evaluation on the same day were examined. And on the 10th day EPDS scores were determined. Both the EPDS applied right after birth and the EPDS applied on the 10th postpartum day are routine practices of our hospital. Participants who did not attend psychologist appointments or had incomplete information regarding their EPDS scores were not included in the study (**Figure**).

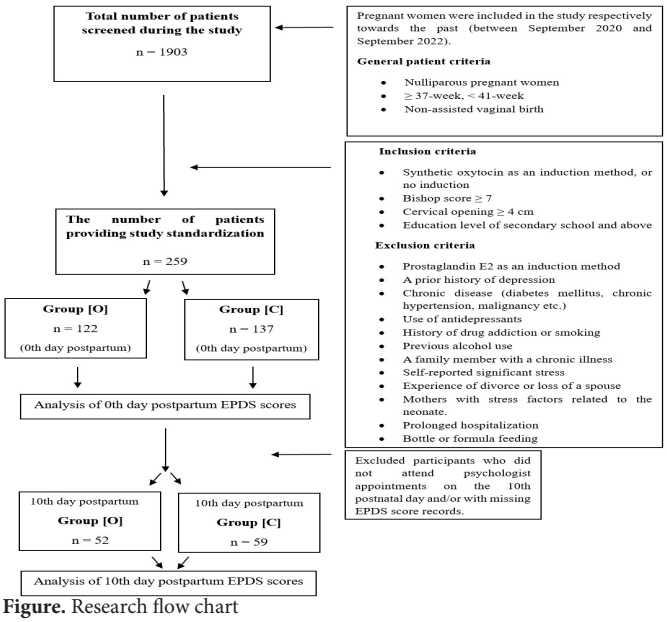

Figure. Research flow chart

2 groups were formed from the pregnant participants without depression risk factors.

Group oxytocin, (O): The group consisted of patients who were admitted to the delivery room due to labor and who were induced with synthetic oxytocin because of insufficient labor pain. As a routine practice in our hospital, an induction solution is prepared by adding 5 I.U. synthetic oxytocin (Synpitan forte, Deva, İstanbul, Turkiye) into 500 cc isotonic. Induction is started with a dose of 4 drops/hour and increased until an effective contraction (>200 montevideos/10 minutes) occurs. Afterwards, it is continued at a constant dose until labor is completed.

Group control, (C): Patients who were admitted to the delivery room due to labor and gave birth without any induction method because their labor pain was sufficient.

- EPDS scores on the 0th day postpartum of patients who received oxytocin induction and who did not receive any induction were compared.
- EPDS scores on the 10th day postpartum of two groups were compared.
- In the group receiving synthetic oxytocin induction, the relationship between the duration of induction and EPDS scores (day 0 or day 10 separately) was analyzed.

Inclusion and Exclusion Criteria

In order to mitigate the influence of various factors on EPDS scores, the study included nulliparous pregnant women aged between 20 and 38 years who were at or beyond 37 weeks of gestation. Pregnant women classified as post-term (41 weeks and beyond) were excluded from the study. The study included only patients who had a normal vaginal birth without assistance and who received only synthetic oxytocin as an induction method, or no induction method. Among the pregnant women who were induced with synthetic oxytocin, patients with a Bishop score at or above 7 and a cervical opening at or above 4 cm were included. Patients with an education level of secondary school and above who discharged with recovery 24 hours after birth were included.[9-16]

The study excluded patients who induced with Prostaglandin E2 or gave birth by cesarean section. Additionally, individuals with any of the following conditions were considered ineligible and excluded: a prior history of depression, presence of any chronic illness, use of antidepressants, history of drug addiction or smoking, previous alcohol use, a family member with a chronic illness potentially affecting domestic harmony, a first-degree relative who passed away within the last 5 years, self-reported significant stress, experience of divorce or loss of a spouse, and those who underwent a complicated delivery.[9-16] "Patients experiencing stress factors related to the neonate, such as admission to the neonatal intensive care unit, jaundice, or any condition necessitating additional follow-up, were also excluded from the study. Patients with prolonged hospitalization for any reason, mothers with feeding methods other than breastfeeding (eg, bottle or formula feeding) were excluded from the study".[16] In order to ensure patient standardization; the patient population was determined

with the depression risk criteria that have been applied in the literature.[9-16] Also, these criteria had been applied in our (Sivas et al.)[16] study where we investigated the importance of "number of breastfeeding sessions per day on postpartum depression".

Statistical Analysis

A power value of 0.80, a margin of error of 0.05 and an effect size of 0.6 was taken for determining the sample size. Calculations were performed in accordance with the protocol with gpower3.1 software (https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower). It was determined that there should be at least 36 patients in each group for statistical significance. Due to the possibility of patient loss between day 0 and day 10 analyses, an attempt was made to increase the number of patients as much as possible. To evaluate the distribution of the data, the Shapiro-Wilk test was used. Mann-Whitney U test was used for comparisons between two independent groups. Pearson's chi-square test and Fisher's exact test were used for comparisons. The relationships between variables were analyzed with Spearman's correlation coefficient. A p-value of <0.05 was considered as statistically significant.

RESULTS

In the process of study, records of 1903 patients were initially reviewed. Following the application of inclusion and exclusion parameters, the study proceeded with 259 appropriate participants. Day 0 analyzes were conducted with 259 participants in total (group O 122 patients, group C 137 patients). After excluding the participants who did not attend psychologist appointments on the 10th postnatal day and/or with missing EPDS score records, the 10th day analyzes were conducted with 111 participants in total (group O 52 patients, group C 59 patients) (**Figure**).

Evaluation of Descriptive Statistics

No statistically significant difference was found between the two groups in terms of age, gestational week, or educational status on the 0th day postpartum (p>0.05) (**Table 1, 2**).

Table 1. Comparison of age, week of gestation and 0th-day EPDS scores between the groups

	Group	n	Median	Min	Max	p value
Age	Group C	137	24.00	20.00	38.00	0.583
	Group O	122	24.00	20.00	36.00	
Week of gestation	Group C	137	39.00	37.00	40.00	0.591
	Group O	122	39.00	37.00	40.00	
EPDS score (day 0)	Group C	137	5.00	0.00	21.00	0.748
	Group O	122	5.00	0.00	21.00	

p<0.05, Mann-Whitney U test, EPDS: Edinburgh Postnatal Depression Scale, Min: Minimum, Max: Maximum

No statistically significant difference was found between the two groups in terms of age, gestational week, or educational status on the 10th day postpartum (p>0.05) (**Table 3, 4**).

Table 2. Comparison of education status between the groups (based on postpartum 0th-day data)

			Group C	Group O	p value
Education status	Secondary school	n	67	52	0.192
		%	48.9%	42.6%	
	High school	n	38	34	
		%	27.7%	27.9%	
	Associate degree	n	9	9	
		%	6.6%	7.4%	
	University	n	23	25	
		%	16.8%	20.5%	
	Post graduate	n	0	2	
		%	0.0%	1.6%	

p<0.05, Fisher's exact test

Table 3. Comparison of age, gestation week, 10th-day EPDS scores between groups (postpartum 10th-day data)

	Group	n	Median	Min	Max	p value
Age	Group C	59	26.00	20.00	37.00	0.352
	Group O	52	24.00	20.00	32.00	
Week of gestation	Group C	59	39.00	37.00	40.00	0.703
	Group O	52	39.00	37.00	40.00	
EPDS score (day 10)	Group C	59	6.00	0.00	17.00	0.416
	Group O	52	7.00	0.00	20.00	

p<0.05, Mann-Whitney U test, EPDS: Edinburgh Postnatal Depression Scale, Min: Minimum, Max: Maximum

Table 4. Comparison of education status between the groups (based on postpartum 10th day data)

			Group C	Group O	p value
Education status	Secondary school	n	17	14	0.654
		%	28.8%	26.9%	
	High school	n	22	20	
		%	37.3%	38.5%	
	Associate degree	n	7	8	
		%	11.9%	15.4%	
	University	n	13	10	
		%	22%	19.2%	

p<0.05, Pearson's Chi-square test

Comparison of EPDS Scores Between Groups

There was no statistically significant difference between EPDS scores following labor (day 0) (p>0.05) (**Table 1**). When group O was evaluated within itself, no significant difference was found between induction time and the EPDS scores on the 0th day postpartum (p>0.05) (**Table 5**).

No statistically significant difference was found in the EPDS scores on the 10th day postpartum between the groups (p>0.05) (**Table 3**). When group O was evaluated within itself,

no significant difference was found between induction time and the EPDS scores on the 10th day postpartum (p>0.05) (Table 5).

Table 5. The relationship between induction time and 0th/10th day EPDS scores of group oxytocin

		Induction time (min)
EPDS score (day 0)	r	-0.072
	p	0.417
EPDS score (day 10)	r	-0.019
	p	0.898

p<0.05, Spearman's correlation analysis, EPDS: Edinburgh Postnatal Depression Scale, Min: Minute

DISCUSSION

When the results of the study were evaluated, the postpartum EPDS scores (day 0 or day 10) of pregnant women who received induction with synthetic oxytocin were not significantly different from those who did not receive induction. No significant relationship was found between the duration of synthetic oxytocin exposure during the labor and EPDS scores. There was no relationship between synthetic oxytocin and early postpartum depression.

Studies examining the relationship between physiological oxytocin in the postpartum period and postpartum depression are available in the literature. In a study examining maternal endogenous oxytocin levels during the puerperal period; in the study group consisting of mothers with high psychosocial stress levels, endogenous oxytocin levels were found to be higher in mothers who were found to be less depressed.[2] In the 8th week after delivery, blood oxytocin levels of puerperant with postpartum depression were found to be lower than those who were not depressed.[3] These studies suggest that endogenous oxytocin may have a protective effect against the tendency for depression. In another study conducted by measuring oxytocin levels in maternal saliva, oxytocin levels were not found to be lower in women with postpartum depressive or anxious behaviors.[17] While the current study reaches a different conclusion from the aforementioned studies, it suggests that there may be differences in oxytocin receptor and post-receptor molecular pathways in patients with the same oxytocin levels. In a systematic review based on related studies, it is emphasized that more studies should be conducted on this subject.[18] Furthermore, genetic analyses show that oxytocin receptor expression may vary depending on external factors.[19,20]

While there are studies on how endogenous oxytocin affects maternal mood, there are only a few studies in the literature on how synthetic oxytocin affects maternal mood. A study presenting results on the relationship of synthetic oxytocin with depression in the long term found that pregnant women who were administered synthetic oxytocin during the labor process had a higher risk of being diagnosed with maternal anxiety disorder/depression in the 1-year postpartum period. The study investigating the late-stage effects of synthetic oxytocin was completed based on patients who were diagnosed with depression after childbirth or prescribed psychotropic drug.[4] In another study, the EPDS scores in the first 48 hours postpartum were analyzed in patients who were exposed to synthetic oxytocin for a longer or less period during labor. Those who scored 12 and above in the EPDS score were proportionately higher in patients who received synthetic oxytocin for a longer period.[5] In the study indicating that mothers who received less synthetic oxytocin at birth had higher breastfeeding rates and less formula administration feeding, a positive correlation was reported between the amount of synthetic oxytocin administered and postpartum 2nd-month depressive symptoms.[6]

The above studies did not investigate whether patients included in the study had a history of depression and/or risk factors for depression in the prenatal period. A depressive background present before or during labor may have completely affected the study results. EPDS scores may have been detected higher in women who were prone to depressive tendencies due to depression risk factors. Women who were prone to depressive tendencies due to low endogenous oxytocin levels may have needed more synthetic oxytocin to accelerate the labor process. Therefore, EPDS scores may have been detected higher in those who received more synthetic oxytocin. Similarly, a pre-existing depressive disorder may have caused a high score in the EPDS scores administered at 48th- hour or 2th-month after birth.

Unlike the results of the mentioned studies, when we analyzed the results of the standardized patient population that we formed by excluding depression risk factors, we determined that synthetic oxytocin did not make a significant change in EPDS scores both on postnatal day 0 and day 10. The fact that there was no significant difference in postnatal day 0 results indicates that synthetic oxytocin did not have a major positive or negative effect on patient EPDS scores at the time of use. In addition, the low EPDS scores observed in both groups on day 0 indicate the homogeneity and success of standardized groups created by excluding pregnant women with depression risk factors. Similarly, when the patients in the synthetic oxytocin group consisting of standardized patients were evaluated within the group, there was no significant difference between the duration of synthetic oxytocin exposure and EPDS scores.

One notable strength of the current study lies in its utilization of a standardized population. The assessment of depression risk factors both before and after childbirth was conducted, thereby mitigating the potential effects and variables mentioned earlier. Furthermore, the study analyzed the EPDS scores of women postpartum, adding to its comprehensiveness. Through the establishment of a standardized patient group, the study exclusively investigated the impact of synthetic oxytocin on EPDS scores. This characteristic makes our study the first in the literature to explore the effects of synthetic oxytocin on maternal mood independently of depression. Our study contributes to the literature as it obtained different results from the existing studies.

Limitations

The first limitation is the low number of participants fitting the standardized profile. Although this study included a 2-year patient archive, the number of participants to be included in the study was severely reduced when patients with

depression risk factors were excluded. Other limitation is that this study does not have the criteria to exclude the effect of receptor and downstream pathways when investigating the effect of synthetic oxytocin infusion. Likewise, epigenetic factors affecting receptor expression were not investigated. Simultaneous measurement of blood oxytocin levels while examining EPDS scores will increase the sensitivity of the study. Additionally, the labor duration of the groups should be taken into account.

CONCLUSION

Synthetic oxytocin used for labor induction may not primary affect the tendency to postpartum depression in the early period. Further studies with large populations consisting of participants with depression risk factors excluded, examining the effects of synthetic oxytocin on postpartum depression in early/late period are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of Başakşehir Çam and Sakura City Hospital Ethics Committee (Date: 26.10.2022, Decision No: KAEK/2022.10.340).

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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Comparison of mechanical properties of polyethylene and polyurethane blocks as model materials for in vitro cortical bone modelling

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ABSTRACT

Aims: The aim of this study was to compare polyethylene (PE) and polyurethane (PU) blocks at a density of 60 pcf in terms of flexural strength (FS), elastic modulus (EM), elongation, and hardness in vitro for use in cortical bone modelling.

Methods: This in vitro study was conducted at Van Yüzüncü Yıl University Faculty of Dentistry Department of Orthodontics and the testing and laboratory phases of the study were conducted at Van Yüzüncü Yıl University Faculty of Dentistry Research Laboratory. PE (group 1) and PU (group 2) blocks with a density of 60 pcf (0.96 g/cm^3) were used in the study. The 3-point bending test was performed on a universal testing machine and FS, EM, elongation, and hardness were measured. A total of 30 samples, 15 in the PU group and 15 in the PE group, were included in the study.

Results: The FS and hardness values of PE and PU did not show statistically significant differences ($p>0.05$). Statistically significant differences were found between the PE and PU groups for EM and elongation values ($p<0.05$).

Conclusion: This study showed that PE blocks can be used in orthodontics for in vitro cortical bone modelling.

Keywords: Polyethylene block, polyurethane block, cortical bone, orthodontics, flexural strength, elastic modulus

INTRODUCTION

In recent years, it has been observed that many materials and devices used in the oral and maxillofacial region are polymer-based. The reasons for the preference of polymers are their biocompatibility and the fact that their mechanical properties meet the requirements of the region in which they will be used. Polyethylene (PE) is a versatile and adaptable biomaterial that is widely used in in vitro and in vivo studies.[1] PE is preferred because of its low cost, chemical inertness, good electrical properties, and relative ease of processing.[2] In the medical sector, it is used in the manufacture of disposable or reusable medical devices and in the production of various implants.[3]

Polyurethane (PU) is another synthetic polymer with a wide variety of chemical compositions and properties that are used in many areas of our daily lives.[4] Again, due to the rapid developments in biomaterials used in prostheses and medical devices in recent years, PU has started to be widely used in the medical field due to its mechanical properties and excellent biocompatibility.[5] The PU bone model, which can be prepared in different densities and microstructures, can mimic human bone and the mechanical and physical properties of the cortical and cancellous bone components.[6]

PU bone models allow standardization of biomechanical evaluation in in vitro studies due to their homogeneous structure. PU sheets with different densities are available to simulate different bone types and these sheets are often used as bone models in in vitro studies of orthodontic mini-implants. In the literature, PU sheets with densities of between 40 and 50 pcf have been used to simulate cortical bone.[7,8] Although PE is widely used in the medical field due to its structural properties, there is no study in the literature using it as a bone model material. Presenting data to support what type of bone PE can be used for modelling in vitro studies will pave the way for the use of PE for this purpose. PE sheets with a density of 60 pcf are currently available on the market. With regard to the use of PU sheets with a density of 60 pcf for modelling cortical bone, we believe that it would be more accurate and valuable to compare the mechanical properties of PE sheets of the same density with the mechanical properties of a polymer such as PU, which is accepted in the literature as a reference for its mechanical properties in in vitro modelling of cortical bone. The aim of this study was to compare PE and PU blocks at a density of 60 pcf in terms of flexural strength (FS), elastic

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modulus (EM), elongation and hardness in vitro for use in cortical bone modelling. The null hypothesis of the study was that there would be no difference in flexural strength, modulus, strain and hardness between 60 pcf PE blocks and 60 pcf PU blocks.

METHODS

Ethics committee approval is not required since this study was conducted on polyethylene and polyurethane blocks in the laboratory. All procedures were carried out in accordance with the ethical rules and principles.

This in vitro study was conducted at Van Yüzüncü Yıl University Faculty of Dentistry and the testing and laboratory phases of the study were conducted at Van Yüzüncü Yıl University Faculty of Dentistry Research Laboratory. PE (group 1) (Simitçioğlu Metal Stainless Construction Industry and Trade Limited Company, İstanbul, Turkiye) and PU (group 2) (Quantum Polyurethane Machine Material Industry Trade Limited Company, Bursa, Turkiye) sheets with a density of 60 pcf (0.96 g/cm^3) were used in the study. The literature indicates that the flexural strength of the material is generally measured when evaluating the mechanical properties of polymeric materials. Therefore, it was decided to measure the flexural strength of PE and PU to evaluate their mechanical properties in this study. The three-point flexure test, which is one of the uniaxial tests used for the flexural strength of polymers and plastics, was preferred for the evaluation of mechanical properties.[9] The materials to be tested with the 3-point flexure test have to be prepared to a certain standard size for standardization. For this reason, the PE and PU blocks used in the study were prepared according to the ISO 178 standard with a length of 80 mm, a width of 10 mm, and a thickness of 4 mm (**Figure 1, 2**).[10]

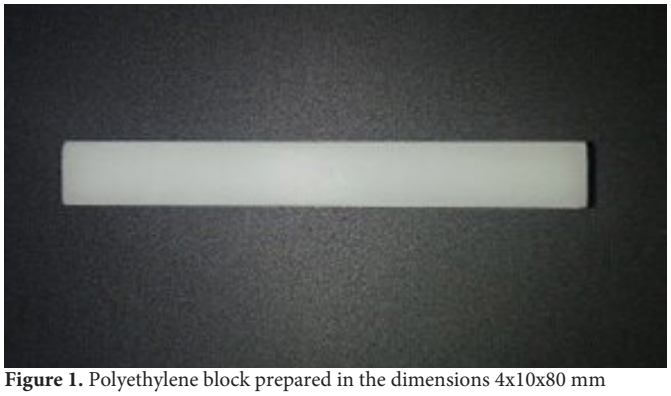

Figure 1. Polyethylene block prepared in the dimensions 4x10x80 mm

Figure 2. Polyurethane block prepared in the dimensions 4x10x80 mm

The 3-point bending test was performed on a universal testing machine (Shimadzu AGS-X, Shimadzu Corporation, Kyoto, Japan) (**Figure 3**).

Figure 3. Universal test device used in the study

The length, width, and thickness data of the PE and PU blocks were recorded on the Trapezium X materials testing software (Shimadzu Corporation, Kyoto, Japan) integrated with the universal testing machine (**Figure 4**).

Figure 4. Trapezium X materials testing software compatible with Universal testing machine

The distance between two supports in the universal testing machine was set at 40 mm. The force was applied from the center of the blocks at a rate of 1 mm/min. Using these parameters, a 3-point flexural test was performed on the universal testing machine (Figure 5, 6). The blocks in both groups were tested under the same humidity and temperature conditions.

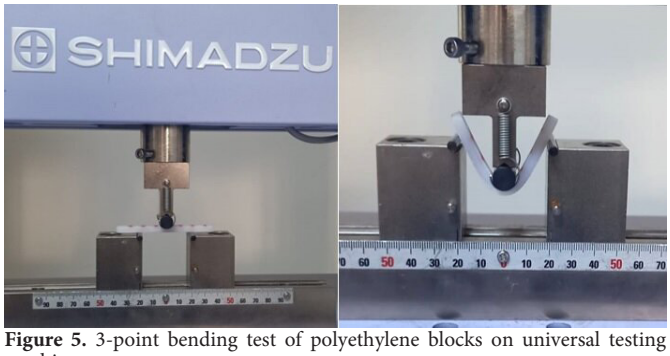

Figure 5. 3-point bending test of polyethylene blocks on universal testing machine

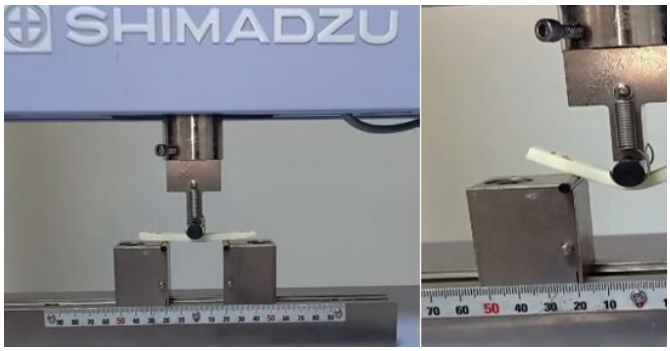

Figure 6. 3-point bending test of polyurethane blocks on universal testing machine

The flexural strength values obtained as a result of the test were recorded in Newtons and the elongation values were recorded in mm. The values obtained were converted to MPa in accordance with ISO standards. The elastic modulus, stress, and strain values were calculated using the following formulae.

The stress-strain formula was used to calculate the elastic modulus.

- Stress (MPa) = 3LF/2WT2
- L (mm) = Distance between two supports
- F (n) = Force
- W (mm) = Width of the block
- T (mm) = Thickness of the block
- Strain L0 (amount of elongation) / L (original length).[11]

A digital durometer (Shore D Durometer, Digital ShoreMeter DJD, Loyka Instruments, Turkiye) with an accuracy of 0.5 HD in the range of 0-100 HD was used to measure the surface hardness. Three different points from the surface of each block were measured and the average value obtained was used for the hardness measurement.

In one study in the literature evaluating flexural strength, the effect size was calculated to be 1.57. In accordance with the reference parameters, the sample size for this study was calculated using G*power (version 3.1.9.6) as d=1.57, power=0.95, α=0.05 with a 95% confidence interval, and a minimum of 13 samples for each group.[12]

Statistical Analysis

Data analyses were performed using SPSS 24.0. To determine the suitability of the quantitative values for normal distribution, the normal distribution condition was examined and kurtosis and skewness coefficients were calculated. Kurtosis and skewness values between +3 and -3 are considered sufficient for normal distribution.[13] Quantitative variables in this range are normally distributed (skewness /kurtosis coefficients are within limits) and therefore parametric methods were used in the analyses of strain, FS, EM, and hardness values in this study (Table 1). Independent groups t-test was used to compare groups and the significance level was p<0.05.

Table 1. Coefficients of skewness and kurtosis of the elongation, FS, EM, and hardness values of the blocks

	Skewness	Kurtosis
Elongation (mm)	-0.427	-0.187
Flexural strength (MPa)	0.763	1.912
Elastic modulus (MPa)	1.097	0.731
Hardness	-0.373	-0.557

FS: Flexural strength, EM: Elastic modulus, mm: Milimeter, MPa: Megapascal

RESULTS

A total of 30 samples, 15 in the PU group and 15 in the PE group were included in the study. During the tests, all the blocks in the PU group broke, while all the blocks in the PE group bent without breaking.

When the amount of elongation was analysed, it was found that the PU group elongated an average of 6.30±1.13 mm and the PE group elongated an average of 8.48±0.96 mm. When the elongation amounts of the PU and PE groups were compared, the difference between the elongation amounts was statistically significant and the elongation amount of PE was higher (p=0.000, p<0.001) (Table 2).

Table 2. Comparison of elongation, FS, EM, and hardness values between groups

	Polyurethane				Polyethylene				
	Min	Max	Mean	SD	Min	Max	Mean	SD	p
Elongation (mm)	3.571	8.514	6.3	1.13	5.82	9.977	8.48	0.96	0.000*
Flexural strength (MPa)	48.375	100.125	74.8	16.53	60	124.5	77.85	15.16	0.603
Elastic modulus (MPa)	383.2	1239	822.55	240.42	465.63	1426.25	631.2	228.02	0.033*
Hardness	74	79	76.7	1.64	74	78	76.4	1.17	0.643

p<0.05, *Independent groups T test, FS: Flexural strength, EM: Elastic modulus, Min: Minimum, Max: Maximum, SD: Standard deviation, MPa: Megapascal

When the FS was analysed, the FS of the PU group was calculated to be 74.80±16.53 MPa, while the FS of the PE group was calculated to be 77.85±15.16 MPa. When the FS values of the PU and PE groups were compared, it was found that there was no statistical difference between the two groups in terms of FS values (p=0.603, p>0.05) (**Table 2**).

When the EM was analysed, it was found that the EM of the PU group was 822.55±240.42 MPa, while the EM of the PE group was 631.20±228.02 MPa. When the EM values of the PU and PE groups were compared, the difference between the two groups was statistically significant and the EM of the PU was higher (p=0.033, p<0.05) (**Table 2**).

When hardness was analysed, the mean hardness of the PU group was 76.7±1.64 and the mean hardness of the PE group was 76.4±1.17. When the hardness values of the PU and PE groups were compared, it was found that there was no statistical difference between the two groups in terms of hardness values (p=0.603, p>0.05) (**Table 2**).

DISCUSSION

This study investigated the mechanical properties of PE and PU blocks and found that there was a difference between PE and PU blocks in terms of elongation and elastic modulus. Therefore, the null hypothesis of the study was accepted for flexural strength and hardness but rejected for elongation and elastic modulus. Misch et al.[14] showed that the mean elastic modulus of mandibular bone including cortical bone was 96.2 MPa, whereas the mean elastic modulus of mandibular bone excluding cortical bone was 56 MPa. Shash et al.[15] showed that the mean elastic modulus of cortical bone was 13.7 GPa. Arendts and Sigololto found the elastic modulus of mandibular bone to be 17.3 GPa[16] and Dechow et al.[17] 19.4 GPa. Stoppie et al.[18] found an elastic modulus of 374.51 MPa in both maxillary and mandibular specimens containing both cortical and trabecular bone. In the samples where only trabecular bone was evaluated, this value was 342.26 MPa. It can be seen that the reason for the difference in modulus between studies is due to the cortical and trabecular content of the region from which the sample was taken. It is understood that where there is more cortical bone, the elastic modulus will be higher. Misch et al.[14] found that the mean elastic modulus of mandibular trabecular bone was 56 MPa. In this study, the mean elastic modulus of PU was 822.55 and that of PE was 631.2 MPa. These values show that the elastic modulus of the 60 pcf density PE and PU used in this study is higher than the elastic modulus of trabecular bone. Therefore, when the elastic moduli obtained from the 60 pcf density PE and PU blocks used in this study are compared with the results of the aforementioned studies, it can be seen that both blocks are close to cortical bone in terms of EM. In the present study, it was observed that the amount of elongation of the PE blocks was higher than the amount of elongation of the PU blocks. The higher amount of elongation indicates that PE has a more flexible structure. The reason for the lower modulus of the PE blocks is that the amount of elongation of PE is higher. Young's modulus values of 60 pcf density PE blocks support the use of these blocks for in vitro modelling of cortical bone.

In mini-implant studies, PU blocks are used instead of bone.[19] It is generally not possible to perform studies to evaluate the characteristics of orthodontic mini-implants such as length, diameter, head-neck-body design, surface structure, and implant material in the clinical setting.[20,21] In addition to the difficulty of clinical evaluation of these bone-related studies, there are many standardization and ethical issues. In particular, PU blocks are preferred due to their homogeneous structure, bone-like mechanical properties, availability of different densities, and ease of use.[7] ASTM (American Society for Testing and Materials) has confirmed that rigid PU blocks are an ideal material to use as a bone substitute in in vitro studies of mini-implants.[22] Therefore, we selected PU blocks as one of our study groups in this study.

In some studies, PU blocks of different densities are used to model different bone types. Researchers prefer to use the PU block with a density that matches the structural properties of the bone being modelled.[23] It can be seen that PU blocks used to model cortical bone are preferred at densities of 30 pcf and above. Marchi et al.[8] compared the insertion torques of self-drilling mini-implants in different types of bone created in vitro. The authors preferred PU blocks of 40 and 50 pcf density for modelling cortical bone. Elibol et al.[24] evaluated the effect of cortical bone thickness and density on the stability of mini-implants and used 40, 45, and 50 pcf density PU blocks to model cortical bone. They preferred 25 pcf density PU blocks for modelling trabecular bone. Möhlhenrich et al.[19] investigated the effect of bone density on the stability of mini-implants. The authors preferred PU blocks with a density of 40 pcf for D1 bone, 30 pcf for D2 bone, 20 pcf for D3 bone, and 10 pcf for D4 bone. The authors also used PU with a density of 40 pcf in the simulation of the cortical part of the PU blocks. Jin et al.[25] evaluated the effect of cortical bone density on the primary stability of orthodontic mini-implants and used PU blocks consisting of cannellated and cortical parts. They preferred PU foam with densities of 30, 40, and 50 pcf for modelling cortical bone. The authors showed that orthodontic mini-implant stability was associated with increasing cortical bone density. Marchi et al., Elibol et al., Möhlhenrich et al. and Jin et al. used PU foams of different densities to model cortical bone. These studies used PU blocks consisting of trabecular and cortical portions. In contrast to these studies, this study preferred to use PU blocks with a density of 60 pcf to model cortical bone. In the literature, Orhan and Ciğerim[26] preferred a single-layer 60 pcf PU sheet for modelling cortical bone as in this study. The reason for choosing a 60 pcf density PU block was mainly to standardize it with PE. Another reason for our preference was the thought that 60 pcf density would have higher mechanical properties. In support of this idea, Jin et al. showed that the stability of orthodontic mini-implants increased with increasing density of PU foams, and according to this result, increasing the density of PU blocks indicates that the mechanical properties of the blocks also increase.

There is no consensus on the density of PU for modelling cortical bone. No study has evaluated the mechanical properties of the 60 pcf PU blocks used in this study. No study was found using PE blocks for bone modelling in dentistry.

In this study, the flexural strength and hardness values of PE and PU blocks were found to be similar. Since PE blocks have similar properties to PU blocks, which have been accepted for use in mini-implant studies, it shows that PE blocks can be used for bone modelling. The flexural stiffness of cannellous bone was found to be 10-25 MPa and the flexural stiffness of cortical bone was found to be 135-193 MPa.[27] Singh et al.[28] found the average FS of human humerus, ulna and radius to be 128.43, 135.16 and 80.31 respectively and tested corticocancellous bone in their study. The flexural strength of the PE blocks used in this study was found to be 77.85 MPa, which is higher than that of cancellous bone. The flexural strength of the PE blocks used in this study was found to be 77.85 MPa, which is higher than that of cancellous bone. The flexural strength values obtained from the 60 pcf density PE blocks used in this study provide further data to support the use of PE blocks in the modelling of cortical bone. The results of the present study support the use of PE blocks in the in vitro simulation of bone in dentistry. We used PE blocks with a density of 60 pcf to model cortical bone in this study. With their current mechanical properties, we believe that they can be used to model not only cortical bone but also cancellous and corticocancellous bone. As with PU blocks, we recommend that PE blocks are prepared in different densities and used for in vitro modelling of different bone types in orthodontics, oral and maxillofacial surgery and other areas of dentistry.

Limitations

The PE and PU blocks used in the study may have been exposed to different temperature and humidity conditions during manufacture and shipping, which may have affected the test results. In addition, the heat generated during the manufacture of the PE and PU blocks used in the study may have affected the mechanical properties of the blocks to some extent, which may have affected the test results.

The PE and PU blocks used in the study were 60 pcf blocks. In the study, blocks with a single density were preferred and if PU and PE blocks with different densities had been preferred, it is likely that different results would have been obtained in terms of the evaluated mechanical properties of the blocks in terms of FS, EM, and hardness. Therefore, the results obtained are more suitable for interpreting blocks with a density of 60 pcf without generalization.

CONCLUSION

In conclusion, this is the first study to investigate the use of PE blocks for in vitro modelling of jaw cortical bone. It was found that a 60 pcf density PE block had similar properties to a PU block of the same density in terms of flexural strength and stiffness. In addition, the elastic modulus values of the PE block were found to be higher than those of cannellous bone and close to those of cortical bone. These results support the use of 60 pcf density PE in the in vitro modelling of jaw cortical bone. Further studies are needed to investigate the use of different density PE blocks for in vitro modelling of different bone types.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethics committee approval is not required since this study was conducted on polyethylene and polyurethane blocks in the laboratory.

Informed Consent

Since this study was performed in the laboratory on polyethylene and polyurethane blocks, written consent forms were not obtained.

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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Perinatal outcomes of patients who underwent cervical cerclage and their relationship to systemic inflammatory indices

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ABSTRACT

Aims: This study aimed to evaluate the perinatal outcomes of patients who underwent cervical cerclage and to investigate the relationship between these outcomes and systemic inflammatory indices.

Methods: A retrospective study was conducted at Ankara Etlik City Hospital between November 2022 and November 2023. Patients were divided into three groups based on the indication for cerclage: history-indicated cerclage (H-IC), ultrasound-indicated cerclage (U-IC) and physical examination-indicated cerclage (PE-IC). The systemic inflammatory markers neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), Systemic Immune-Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI), pan-immune inflammation value (PIV) and multi-inflammation indices (MII), were measured. The perinatal outcomes, including gestational age at delivery, birth weight and APGAR Scores, were compared among the groups.

Results: Seventy patients were included in the study. The rate of preterm birth was highest in the PE-IC group (61.1%), followed by the U-IC group (40.9%) and the H-IC group (36.7%). Birth weight, 1- and 5-minute APGAR Scores were significantly lower in the PE-IC group, and neonatal intensive care unit admission rates were significantly higher in the PE-IC group. Inflammatory markers NLR, SII and PIV were significantly higher in the U-IC group compared to the H-IC group. However, no significant differences were observed between the U-IC and PE-IC groups in terms of these markers.

Conclusion: Patients who underwent PE-IC had poorer perinatal outcomes compared to those who underwent H-IC or U-IC. The systemic inflammatory indices NLR, SII and PIV may serve as useful markers for predicting pregnancy outcomes and guiding early interventions in patients at risk of preterm birth. Further large-scale prospective studies are needed to validate these findings.

Keywords: Cervical cerclage, cervical insufficiency, perinatal outcomes

INTRODUCTION

Preterm births, which include 5 to 15% of all pregnancies, are defined as births that occur before the 37th week of pregnancy.[1,2] Increased newborn mortality and morbidity are linked to this disease.[3] Cervical insufficiency affects about 1% of pregnant women and is a major risk factor for preterm birth.[4-6] The incapacity of the cervix to sustain a pregnancy prior to the commencement of labour is known as cervical insufficiency and the therapy as well as the management of this condition are complicated by our incomplete understanding of its pathogenesis.[4] Mechanical injuries to the cervix (e.g. conization, dilatation of the cervix during curettage), congenital anomalies of Muller's system, collagen disorders of the cervix and infections, are among the causes that are held responsible for the ethology of cervical insufficiency.[4,6,7]

The cervix has a mechanical function as well as serving as a barrier to keep ascending pathogens out of the uterus and the best way to treat cervical insufficiency is with a cervical cerclage, which strengthens the cervix by offering mechanical support.[5] Studies to determine how the systemic inflammatory response affects the outcome of pregnancy have been bolstered by the observation that 80% of patients with cervical insufficiency, also have an intrauterine infection.[8,9] Research has demonstrated a negative correlation between a patient's prognosis and elevated proinflammatory cytokines and chemokines in the amniotic fluid, during cerclage surgery.[10,11] Neutrophils, lymphopenia, thrombocytosis and elevated C-reactive protein (CRP) are laboratory indicators that are readily tested in mother blood and

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are related with systemic inflammation.[12] These novel and comprehensive inflammatory markers, which can appropriately influence local immune status and systemic inflammation throughout the human body, include the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), systemic immune inflammation index (SII), systemic inflammatory response index (SIRI), pan-immune inflammation value (PIV) and multi-inflammation index (MII)1-2-3.[11,13-16]

Considering the relationship between inflammation and cervical insufficiency, evaluation of systemic inflammation markers in patients undergoing cervical cerclage is of great importance. For the purpose of managing preterm labour, birth planning and postpartum care, it is critical to evaluate the prognosis of both the mother and the fetus in patients receiving cervical cerclage. The purpose of this research is to examine the perinatal outcomes of cervical cerclage patients and how they relate to systemic inflammatory indices.

METHODS

Between November 2022 and November 2023, a retrospective study was carried out in the Perinatology Clinic of Ankara Etlik City Hospital. Three groups of patients were assigned to the study group: those who received physical examination-indicated cerclage (PE-IC), ultrasound-indicated cerclage (U-IC) and history-indicated cerclage (H-IC). The Ankara Etlik City Hospital No. 1 Clinical Researches Ethics Committee gave its permission to the study protocol (Date: 16.08.2023, Decision No: AEŞH-EK1-2023-473). The Declaration of Helsinki's guidelines were followed in the conduct of this study.

Regardless of the status of the current pregnancy, patients with a history of two or more preterm deliveries or mid-trimester pregnancy losses were included in the H-IC group. In the mid-trimester, U-IC is recommended for asymptomatic patients with a small cervical length (<25 mm), particularly for those who have a history of preterm births.[17] Patients with an asymptomatic cervical dilatation of at least 2 cm, a cervical effacement of at least 60% or an amniotic membrane prolapse in the middle trimester, were included in the PE-IC group.[5,7,18] The decision on cerclage was made after the first trimester screening test in the group in which the medical history was decisive, as well as at the time of diagnosis in the group in which the ultrasound scan and physical examination were decisive. Patients were checked for uterine contractions, fever, membrane rupture, hemorrhage, chorioamnionitis, placental abruption and fetal distress prior to cerclage. Vaginal and urine cultures were requested from all patients for whom a cerclage was planned and patients with positive culture results received appropriate antibiotic therapy. Cerclage procedures were not performed on pregnant women beyond twenty-four weeks of pregnancy and all cerclage procedures in patients were performed by experienced physicians in our perinatology department using the McDonald technique, under anesthesia. In the lithotomy posture, a 5 mm long braided polyester fiber (Mersilene®-40 cm) was positioned in a circular motion around the cervix. All patients received 1 g of cefazolin intravenously prophylactically during the operation. After discharge, all pregnant women received intravaginal progesterone treatment. Cerclage is removed in individuals who are at or beyond the 37th week of pregnancy.

The first day of the last menstrual cycle and/or the fetal crown-rump length, which was assessed in the first trimester and verified by ultrasound examinations, were used to compute the gestational age of the study participants. Exclusion criteria included chronic maternal conditions such as heart disease and thyroid dysfunction, smoking, alcohol consumption, the presence of congenital anomalies, multiple pregnancies and patients for whom no information could be obtained. Our hospital's data network was investigated for the patients past medical records and demographic information was noted. Hemoglobin, leukocytes, monocytes, lymphocytes, platelets, thyroid-stimulating hormone, alanine aminotransferase, aspartate aminotransferase, albumin, CRP and fibrinogen were all analyzed from maternal venous blood drawn before cerclage. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), platelet count×neutrophil count/lymphocyte count (SII), monocyte count×neutrophil count/lymphocyte count (SIRI), NLR×CRP (MII-1) and PLR×CRP (MII-2) and SII×CRP (MII-3) and neutrophil count×platelet count×monocyte count/lymphocyte count (PIV).[9,14]

The patients' birth information, birth weight, gender, APGAR 1/APGAR 5 Scores and any neonatal morbidities, if any, were recorded.

Statistical Analysis

The G-Power 3.1.9.7 application was used to calculate the sample size for the investigation. The sample size was calculated using the Student's Paired Test with a power of 80%, a probability of error of α=0.05 and a Cohen effect size of 'medium'. Accordingly, it was considered appropriate to complete the study with at least forty-six patients. The IBM Corporation SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) was used to conduct the statistical analysis. The normal distribution conformance was examined using the Kolmogorov-Smirnov test. Descriptive statistics of continuous variables are shown as "mean±standard deviation" for those with normal distribution and as "median (min-max value)" for those that did not. The Analysis of variance (ANOVA) test was used to compare more than two groups. The statistical significance of the ANOVA test was determined according to the number of groups. The Fisher's exact test or the chi-squared test were used to compare categorical variables. The independent sample t-test and the Mann-Whitney U test were used to compare continuous variables that were and were not regularly distributed. All tests were considered statistically significant if the P-value was less than 0.05.

RESULTS

This study includes seventy patients who had cervical cerclage. Three groups of patients were created: H-IC, U-IC, and PE-IC. Thirty H-IC patients (42.9%), twenty U-IC patients (31.4%) and eighteen PE-IC patients (25.7%) were identified. The demographic details and test results of the individuals who had cerclage are displayed in Table 1. Age, body-mass index (BMI), weight gain during pregnancy, and

progesterone use prior to application did not significantly differ across the three groups (p=0.499, p=0.578, p=0.385, and p=0.443, respectively). Regarding gravidity, there was no significant difference (p=0.940) between groups 2 and 3, whereas there was a significant difference (p<0.001, p=0.005) between groups 1 and 2. In terms of parity, there was a significant difference (p=0.001 and p=0.005, respectively) between groups 1 and 2. Between groups 2 and 3, there was no discernible change (p=0.1). Hemoglobin, white blood cell count, lymphocytes, neutrophils, monocytes, platelets, thyroid-stimulating hormone, C-reactive protein, aspartate aminotransferase, alanine aminotransferase, albumin, fibrinogen and leukocytes in urinalysis, did not significantly differ between the three groups when the laboratory values were compared (p=0.076, p=0.023, p=0.024, p=0.018, p=0.096, p=0.908, p=0.766, p=0.581, p=0.529, p=0.954, p=0.310, p=0.744, respectively). In all three groups, there was a significant difference in the length of the cervix (p<0.001). The cervical length varied across the H-IC group (35.3±4.2 mm), U-IC group (15.6±5.1 mm) and PE-IC group (8.0±6.2 mm). There were no patients with funnelling in the H-IC group and the presence of funnelling varied considerably (p<0.001) across the three groups. Group 1 and groups 2 and 3 differed statistically significantly from one another when the weeks of cerclage were assessed for each of the three groups (p<0.001). Between groups 2 and 3, there was no discernible change (p=0.996). The H-IC group had a median cervical insertion week of 14+2 (12+1-20+5) weeks, the U-IC group had a median week of 21+6 (12-24+6) weeks, and the PE-IC group had a median week of 21 (14+1-24). Following cerclage, there was a significant difference in cervical length (p<0.001) between groups 1 and 2. Between groups 2 and 3, there was no discernible change (p=0.055). Following cerclage, the cervix length was measured in the H-IC group as 38.3±8.2 mm, the U-IC group as 22.7±6.4 mm, and the PE-IC group as 16.3±9.9 mm. Regarding the duration of hospital stay following cerclage, there was a statistically significant difference (p=0.012 and p=0.016, respectively) between groups 1 and 2. Between groups 1 and 2, there was no discernible difference (p=0.885). The H-IC group had a mean hospital stay of 2 (2-5)

Table 1. Descriptive and comparative analysis of demographic and laboratory data between patients with history-indicated cerclage, ultrasound-indicated cerclage and physical examination- indicated cerclage groups

Parameter	History-indicated cerclage n=30 (42.9%)	Ultrasound-indicated cerclage n=22 (31.4%)	Physical examination-indicated cerclage n=18 (25.7%)	p-value
Age[a] (y)	28.7±5.2	28.9±5.9	30.1±5.5	0.499[c]
Body-mass index[a] (kg/m^2)	31.2±6.3	29.8±6.5	30.8±5.2	0.578[c]
Weight gain during pregnancy[b] (kg)	10 (2-25)	10 (3-20)	9 (3-20)	0.385[d]
Gravida[b]	3 (2-12)	2 (1-4)	2 (1-7)	<0.001[d]
Parity[b]	1.5 (0-3)	0 (0-2)	0 (0-2)	<0.001[d]
Progesterone usage	22 (73.3%)	15 (68.2%	10 (55.6%)	0.443[e]
Hemoglobin (g/dl)	12.3±1.1	11.5±1.0	11.8±1.3	0.076[c]
White blood cell count[a] (10^9/L)	9.5±2.1	11.3±3.4	11.6±3.2	0.023[c]
Lymphocyte count[a] (10^9/L)	2.0±0.5	1.7±0.5	2.7±2.2	0.024[c]
Neutrophil count[a] (10^9/L)	6.8±1.7	8.9±3.3	8.1±3.2	0.018[c]
Monocyte count[a] (10^9/L)	0.55±0.1	0.78±0.9	0.70±0.2	0.096[c]
Platelet count[a] (10^9/L)	263.3±65.4	252.7±63.6	260.3±83.5	0.908[c]
Thyroid stimulating hormone[a] (mU/ml)	2.04±2.3	2.42±1.9	2.64±0.9	0.766[c]
C-reactive protein[a] (mg/L)	6.32±6.96	12.2±15.1	15.8±19.3	0.084[c]
Aspartate aminotransferase[a] (IU/L)	21.5±21.5	16.6±4.7	19.4±6.4	0.581[c]
Alanine aminotransferase[a] (U/L)	17.8±22.6	12.2±4.1	14.8±6.8	0.529[c]
Albumin[a] (g/L)	37.9±3.4	37.7±2.9	38.1±2.6	0.954[c]
Fibrinogen[a] (mg/dl)	439±81	475±103	453±63	0.310[c]
Leukocytes in the urine analysis	0 (0-3)	0 (0-3)	0 (0-3)	0.744[d]
Cervical Length[a] (mm)	35.3±4.2	15.6±5.1	8.0±6.2	<0.001[c]
Funneling	0 (0%)	19 (86.4%)	17 (94.4%)	<0.001[e]
Cerclage week[b]	14+2 (12+1-20+5)	21+6 (12-24+6)	21 (14+1-24)	<0.001[d]
Cervical length after cerclage[a] (mm)	38.3±8.2	22.7±6.4	16.3±9.9	<0.001[c]
Hospitalization day after cerclag[b]	2 (2-5)	2 (1-7)	5 (1-19)	<0.001[d]
Duration of antibiotic use[b] (days)	0 (0-22)	0 (0-21)	3 (0-14)	0.265[d]
Gestational weeks at deliver[b]	37+1 (20+1-40)	37 (22+3-41)	25 (19+4-40+4)	<0.001[d]
Duration from cerclage to delivery[b] (days)	158 (45-185)	104 (13-179)	35 (4-167)	<0.001[d]
Hospitalization day after the deliver[b]	3 (1-14)	2 (2-5)	4 (1-8)	0.193[d]

SD: Standard deviation, NA: Not applicable [a]: Mean±SD, [b]: Median (min-max), [c]: One-way anova with bonferoni, [d]: One way anova with tamhane, [e]: Pearson Chi-square, [f]: Fisher's exact test

days, the U-IC group of 2 (1-7) days, and the PE-IC group of 5 (1-19) days. Group 1 and Group 3 had significantly different weeks of birth (p=0.013). Between groups 2 and 3 (p=0.046) and 1 and 2 (p=0.831), there was no significant difference. For the H-IC group, it was 37+1 (20+1-40) weeks; for the U-IC group, it was 37 (22+3-41) weeks; and for the PE-IC group, it was 25 (19+4-40+4) weeks (Figure). There was a significant difference (p<0.001) in the duration between cerclage and delivery between groups 1 and 2. Between groups 2 and 3, there was no discernible change (p=0.052). The H-IC group experienced 158 (45-185) days, the U-IC group 104 (13-179) days, and the PE-IC group 35 (4-167) days. All three groups had comparable antibiotic use durations and hospitalization days following delivery (p=0.265, p=0.193).

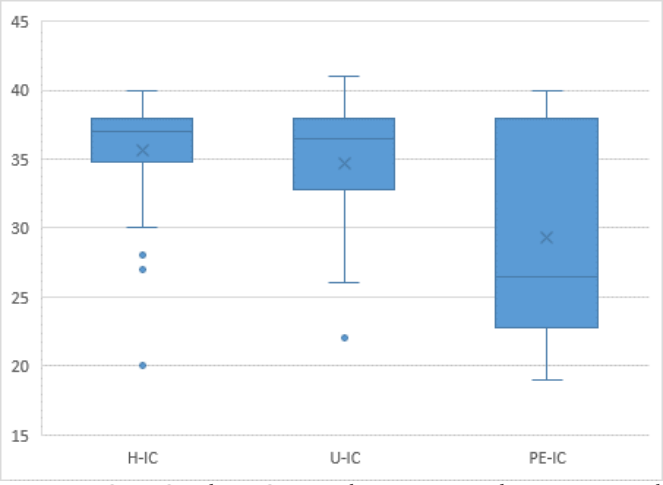

Figure. H-IC, U-IC and PE-IC groups histogram according to gestational weeks at delivery

H-IC: History-indicated cerclage, U-IC: Ultrasound-indicated cerclage, PE-IC: Physical examination-indicated cerclage

Pregnancy problems that arose during the follow-up of the study participants are displayed in Table 2. Gestational diabetes mellitus occurred in seven patients (23.3%) in the H-IC group, three patients (13.6%) in the U-IC group, and three patients (16.6%) in the PE-IC group during the pregnancy follow-up. Between the three groups, there was no discernible difference (p=0.438). Within the H-IC group, three patients (10%) had fetal growth restriction (FGR). In the other two groups, there were no patients suffering from FGR. Three patients (10%) in the H-IC group had gestational hypertension, one patient (4.5%) in the U-IC group pre-eclampsia, and one patient (5.6%) in the PE-IC group pre-eclampsia. In all three groups, there was no discernible variation in the onset of hypertensive pregnancy problems (p=0.312). One patient (3.3%) experienced postpartum hemorrhage, one patient (3.3%) experienced cholestasis of pregnancy, and one patient (3.3%) experienced chorioamnionitis in the PE-IC group.

Table 3 shows the birth-related information and the characteristics of the newborns of the patients included in the study. The study found that there were similarities in the three groups for pregnancy termination method, newborn gender, preterm delivery, and antenatal corticosteroid use (p=0.102, p=0.136, p=0.238, and p=0.443, respectively). Group 3's birth weight differed significantly from groups 1 and 2's birth weight (p=0.004 and 0.013, respectively). Between groups 1 and 2, there was no change (p=1). There was a statistically significant difference between group 3 and groups 1 and 2 in 1st minute APGAR Score (p=0.006 and p=0.007 respectively). There was no significant difference between group 1 and group 2 (p=1). There was a significant difference between group 3 and groups 1 and 2 at the 5th minute APGAR Score (p=0.007 and p=0.010, respectively). Between groups 1 and 2, there was not a significant difference (p=0.983). One patient (3.3%) in the H-IC group, four patients (18.2%) in the U-IC group, and six patients (33.3%) in the PE-IC group experienced preterm premature rupture of membranes (PPROM). Between the groups, there was a significant difference (p=0.014). There was no statistically significant difference observed between the three groups when it came to the length of hospital stay in the neonatal intensive care unit, neonatal hypoglycemia, respiratory distress syndrome, need for phototherapy, intraventricular hemorrhage, need for surfactant, and necrotizing enterocolitis (NEC) (p=0.886, p=0.215, p=0.052, p=0.403, p=0.175, p=0.035, p=0.308, p=0.144, respectively). Ten (45.5%) patients from the U-IC group, ten (55.5%) patients from the PE-IC group, and eight (27.6%) patients from the H-IC group were admitted to the neonatal critical care unit. Group 1 had a considerably lower value (p=0.043). Out of the patients in the H-IC group, five (16.6%) needed mechanical breathing and one (3.4%) needed continuous positive airway pressure (CPAP). Three patients (13.6%) and six patients (27.3%) in the U-IC group needed MV. One patient (5.5%) and seven patients (38.8%) in the PE-

Table 2. Pregnancy complications of history-indicated cerclage, ultrasound-indicated cerclage and physical examination- indicated cerclage groups

Parameter	History-indicated cerclage n=30 (42.9%)	Ultrasound-indicated cerclage n=21 (31.4%)	Physical examination-indicated cerclage n=17 (25.7%)	p-value
Gestational diabetes mellitus	7 (23.3%)	3 (13.6%)	3 (16.6%)	0.438[a]
Fetal growth restriction	3 (10%)	0 (0%)	0 (0%)	0.179[a]
Hypertension				**0.312[a]**
Absent	26 (86.7%)	21 (95.5%)	16 (88.9%)	
Gestational hypertension	3 (10%)	0 (0%)	0 (0%)	
Preeclampsia	0 (0%)	1 (4.5%)	1 (5.6%)	
Cholestasis of pregnancy	1 (3.3%)	1 (4.5%)	0 (0%)	1[a]
Chorioamnionitis	0 (0%)	0 (0%)	1 (5.6%)	0.257[a]
Postpartum hemorrhage	1 (3.3%)	0 (0%)	0 (0%)	1[a]

[a]: Pearson Chi-square

Table 3. Comparison of findings regarding newborn characteristics and labor

Parameter	History-indicated cerclage n=30 (42.9%)	Ultrasound-indicated cerclage n=22 (31.4%)	Physical examination-indicated cerclage n=18 (25.7%)	p-value
Pregnancy termination way				0.102[b]
Cesarean section	19 (63.3%)	17 (77.3%)	8 (44.4%)	
Normal spontaneous vaginal birth	11 (36.7%)	5 (22.7%)	10 (55.6%)	
Gender				0.136[b]
Female	11 (36.7%)	14 (63.6%)	10 (55.6%)	
Male	19 (63.3%)	8 (36.4%)	8 (44.4%)	
Fetal weight (gr)	2679±794	2628±956	1683±1333	<0.003[a]
1st min APGAR Score	9 (0-9)	8 (1-9)	3 (0-9)	<0.001[c]
5th min APGAR Score	9 (0-10)	9 (3-10)	6 (0-10)	<0.001[c]
Preterm birth	11 (36.7%)	9 (40.9%)	11 (61.1%)	0.238[b]
Preterm premature rupture of membranes	1 (3.3%)	4 (18.2%)	6 (33.3%)	0.014[a]
Antenatal corticosteroid	15 (50%)	14 (63.6%)	12 (66.7%)	0.443[b]
Admission to neonatal intensive care unit	8 (27.6%)	10 (45.5%)	10 (55.5%)	0.043[b]
Hospitalization duration in neonatal intensive care unit (days)	0 (0-46)	0 (0-71)	1 (0-46)	0.886[a]
Neonatal hypoglycemia	0 (0%)	0 (0%)	1 (5.5%)	0.215[b]
TTN	1 (3.4%)	5 (22.7%)	0 (0%)	0.052[b]
Respiratory distress syndrome	5 (16.6%)	5 (22.7%)	5 (27.7%)	0.403[b]
Need for CPAP	1 (3.4%)	6 (27.3%)	1 (5.5%)	0.037[b]
Need for mechanical ventilator	5 (16.6%)	3 (13.6%)	7 (38.8%)	0.001[d]
Need for phototherapy	1 (3.4%)	1 (4.5%)	0 (0%)	0.175[b]
IVH	1 (3.4%)	1 (4.5%)	4 (22.2%)	0.035[b]
Neonatal sepsis	0 (0%)	0 (0%)	0 (0%)	NA
Need for surfactant	0 (0%)	2 (9.1%)	1 (5.5%)	0.308[d]
Neonatal Seizures	0 (0%)	0 (0%)	0 (0%)	NA
NEC	1 (3.4%)	2 (9.1%)	3 (16.6%)	0.144[d]
Blood culture of newborn	5 (16.6%)	9 (40.9%)	8 (44.4%)	0.024[b]

APGAR: Appearance, Pulse, Grimace, Activity and Respiration, TTN: Transient tachypnea of the newborn, CPAP: Continuous positive airway pressure, IVH: Intraventricular hemorrhage, NEC: Necrotizing enterocolitis, [a]: One-way anova with tamhane, [b]: Pearson chi-square, [c]: One way anova with bonferoni, [d]: Fisher's exact test

IC group needed MV. Between the three groups, there was a significant difference (p=0.037 and p=0.001, respectively). After birth, blood cultures were obtained in five (16.6%) of the newborns in the H-IC group, nine (40.9%) in the U-IC group and eight (44.4%) in the PE-IC group. In the 1st group there was one abortion (less than 500 grams) and four abortions in the 3rd group.

Table 4 shows the inflammation parameters examined in the three groups. Between the groups, the PLR, SIRI, MII-1, MII-2 and MII-3 values were comparable (p=0.069, p=0.037, p=0.080, p=0.152, and p=0.071, to be exact). In terms of NLR, group 1 and group 2 differed significantly (p=0.004). Between groups 1 and 3, as well as between groups 2 and 3, there was no significant difference (p=1 and p=0.025, respectively). Groups 1 and 2 differed significantly from one another in SII (p=0.006). Neither group 1 nor group 2 nor group 3 differed significantly from the other (p=1 and p=0.026, respectively). Groups 1 and 2 differed significantly from one another on PIV (p=0.013). Between groups 1 and 3, as well as between groups 2 and 3, there was no discernible difference (p=1 and p=0.185, respectively).

Table 4. Comparison of inflammatory indices between history-indicated cerclage, ultrasound-indicated cerclage and physical examination- indicated cerclage groups

Parameter	History-indicated cerclage n=30 (42.9%)	Ultrasound-indicated cerclage n=22 (31.4%)	Physical examination- indicated cerclage n=18 (25.7%)	p-value
NLR	3.7±1.5	6.19±4.07	3.8±2.35	0.004[a]
PLR	140.8±61.7	171.2±114.6	112.7±38	0.069[a]
SII	953±434	1572±1117	946±472	0.006[a]
SIRI	2.05±1.02	4.99±6.66	2.88±2.61	0.037[a]
PIV	525±254	1210±1365	713±509	0.015[a]
MII-1	25.1±35.3	75.5±115.3	52.8±77.4	0.080[a]
MII-2	890±1046	2016±2565	1897±3197	0.152[a]
MII-3	6553±8910	19723 ±26374	15067±25859	0.071[a]

NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index, PIV: Pan-immune-inflammation value, MII-1 (multiinflammatory index): NLR*C-reactive protein, MII-2: PLR*C-reactive protein, MII-3: SII* C-reactive protein, [a]: One-way anova with bonferoni

DISCUSSION

This study examined the maternal and fetal outcomes of patients who had undergone cervical cerclage for various indications and evaluated the association between these outcomes and systemic indices of inflammation. The results show that preterm birth remains a major problem in patients who have undergone cervical cerclage. The preterm birth rate was 36.7% in the H-IC group, 40.9% in the U-IC group and 61.1% in the PE-IC group. In particular, it was found that the weeks of gestation at delivery, birth weight, APGAR Score at the first minute and APGAR Score at the fifth minute were significantly lower and the need for neonatal intensive care was higher, in patients who underwent PE-IC. In PE-IC, patients typically present with significant cervical dilation, effacement or prolapsed membranes, which indicate a more severe pathological state. This advanced stage is associated with higher maternal and neonatal complication rates due to factors such as increased infection risk, preterm labour and reduced efficacy of intervention at this late stage. In addition, it was found that the systemic inflammatory markers NLR, SII and PIV were statistically significantly different between the H-IC and U-IC groups and were higher in the U-IC group.

In our study, a significantly greater cervical length and a lower rate of funnelling were observed in the H-IC group compared to the other groups. In addition, the time to delivery was longer in the H-IC group than in the other groups. The cervical length before cerclage was 38.3±8.2 mm in the H-IC group, 22.7±6.4 mm in the U-IC group and 16.3±9.9 mm in the PE-IC group. Although a significant difference in cervical length was found between all three groups, no significant difference was found between the H-IC and U-IC groups in terms of delivery weeks, preterm births and perinatal outcomes. The longer interval between the cerclage procedure and the week of delivery in the H-IC group is explained by the fact that the cerclage procedure was performed in the earlier week in this group. Although the study by Liu et al.[19] showed that cervical length before cerclage is an independent risk factor for pregnancy outcomes and that a long cervix is associated with lower adverse pregnancy outcomes, the study by Incerti et al.[20] found no improvement in preterm birth rate and pregnancy outcomes at <35 weeks in patients who underwent cerclage with cervical length measurement. This situation shows that cervical length alone is not associated with preterm birth and perinatal outcomes.

Cervical insufficiency is one of the most important causes of preterm labour and the etiology is multifactorial. Inflammation is one of the most important factors emphasized. While NLR, PLR and MLR the systemic inflammatory indices assessed in patients with preterm labour were high in patients with preterm labour, SII and SIRI were similar between study groups.[9] The infection parameters are evaluated before the cerclage procedure, as the presence of an infection influences the success of the cerclage.[8,9,21,22] While amniocentesis is recommended for the detection of infection in these patients, there has recently been an increasing trend towards non-invasive methods. Lin et al.[11] investigated SII and SIRI levels, i.e. systemic inflammatory indices that can be easily measured in maternal blood, in patients undergoing cerclage. They showed that SII and SIRI levels could be important biochemical markers for predicting the outcome of cervical cerclage. They later found that SII and SIRI levels were associated with maternal and perinatal outcomes in a dynamic comparison.[13] In our study, in addition to these indices, we also had the opportunity to examine the MII values and the PIV values, which are new indices that use CRP values.[14,16] NLR, SII and PIV differed significantly between the H-IC and U-IC groups, while no difference was found between either group and PE-IC. We explained this change by the fact that the infection was not the only cause in the patients with cervical insufficiency but that the insufficiency process had already started in the PE-IC patients, as the cervix was already shortened due to the infection.

Chan et al.[23] included forty-seven patients who had undergone cerclage in their study and 59.1% of these patients gave birth after 34 weeks. In that study, patients in the H-IC and U-IC groups had a higher gestational age and better pregnancy outcomes than patients in the PE-IC group. The study conducted by Khan et al.[24] showed that 79.4% of patients who underwent cerclage in the H-IC group, 73.3% in the U-IC group and 47.1% in the PE-IC group had a cerclage by 36 weeks' gestation. While more adverse perinatal events occurred in the PE-IC group, 17.6% had a PPROM. This is one of the most common complications after cerclage.[25] In the study by Gölbaşı et al.,[7] the PPROM rate in the PE-IC group in patients undergoing cerclage, which was divided into H-IC, U-IC and PE-IC, was determined to be 40% and was significantly higher than in the other groups. In our study, adverse perinatal outcomes were also significantly higher in the PE-IC group than in the other two groups, while PPROM developed in six (33.3%) patients. The PPROM rate was higher in the U-IC and PE-IC groups. It would therefore be appropriate to inform patients who have undergone cerclage about possible complications.

Limitations

This study has several limitations. First, no multiple pregnancies were studied, as the surgical indications for multiple pregnancies are unclear. Secondly, the retrospective nature and limited sample size limit the generalizability of the results obtained. One strength of the study is that it was a single center study, which allowed homogenization of cerclage indications, surgical technique and patient follow-up.

CONCLUSION

In this study we compared the perinatal outcomes of cerclage procedures according to indication and examined their relationship to systemic indices of inflammation. Cerclage detected by physical examination was associated with increased perinatal morbidity and risk of preterm delivery, compared with cerclage detected by history and ultrasound. The high preterm birth rates and adverse perinatal outcomes observed in the PE-IC group suggest that this patient group should be monitored more closely. An elective cerclage should therefore be considered before the insufficiency process has already begun. Easily accessible inflammatory indices such as NLR, SII and PIV can help predict pregnancy outcome and

allow earlier intervention in patients at risk of preterm birth. The use of these indices can add an additional dimension to the clinical decision-making process and increase the success of cervical cerclage. Future large-scale prospective studies may further define the clinical utility of these indices.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Etlik City Hospital No. 1 Clinical Researches Ethics Committee (Date: 16.08.2023, Decision No: AEŞH-EK1-2023-473).

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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Is there an association between the serum zonulin concentration and the occurrence of PPROM?

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ABSTRACT

Aims: The aim is to evaluate the association between intestinal permeability, as assessed by zonulin levels, and preterm premature rupture of membranes (PPROM).

Methods: A prospective case-control study was conducted involving 44 pregnant women: 22 with PPROM and 22 matched controls. High-risk pregnancies (gestational diabetes, preeclampsia, multiple pregnancies), chronic diseases, and smoking were exclusion criteria. Demographic and clinical data were collected from medical records. Venous and umbilical cord blood samples were obtained post-delivery, centrifuged at 3000 rpm for 10 min, and stored at -80°C.

Results: No significant differences were found between the PPROM and control groups regarding age, body-mass index, gravidity, previous abortions, history of preterm rupture of membrane (PROM), or PPROM. Maternal and cord blood zonulin levels were comparable between groups ($p>0.05$). In the PPROM group, maternal and fetal cord zonulin levels correlated positively with newborn birthweight ($r=0.607$, $p=0.003$; $r=0.617$, $p=0.002$, respectively). A strong positive correlation was observed between maternal serum and fetal cord blood zonulin levels ($r=0.837$, $p<0.001$).

Conclusion: A positive correlation existed between newborn birthweight and both maternal and fetal cord zonulin levels in the PPROM group. Additionally, a strong positive correlation was observed between maternal serum and fetal cord blood zonulin levels in all participants.

Keywords: Zonulin, intestinal permeability, PPROM, premature preterm rupture of membrane, maternal serum, umbilical cord blood

INTRODUCTION

Zonulin is a 47 kDa molecular weight protein encoded by haptoglobin and acts to increase intestinal permeability. Zonulin was discovered identified by Wang et al.[1] through studies examining the pathophysiology of Vibrio cholerae, enabling the identification of zonulin as a secondary enterotoxin named the zonula occludens toxin (Zot) and its characterization as an endogenous homolog.[1] Fasano et al.[2] proposed that zonulin binds to the epidermal growth factor receptor (EGFR) and activates it. Zonulin can bind to protease-activated receptor type 2 (PAR2) and activate this receptor. When these receptors are activated, they initiate cell signaling, causing a reduction in protein interactions at tight junctions. As tight connections break down, antigens can freely move from the intestine to the surrounding tissue, leading to increased intestinal permeability.[2]

Although the exact role of zonulin in many diseases is not completely clear, increased levels of zonulin leading to increased loss of intestinal barrier function could trigger inflammation. This, in turn, may cause an imbalance or improper distribution of the microbiome throughout the gastrointestinal system. zonulin release can induce the crossing of the epithelial barrier, leading to the release of proinflammatory cytokines and causing microbiome imbalance.[3] The presence of cytokines continues to increase intestinal permeability, allowing for the significant transfer of nutrients and microbial antigens. This leads to the activation of T cells, which can migrate to the intestine or various organs, causing systemic chronic inflammatory diseases such as celiac disease, irritable bowel syndrome, asthma, and chronic obstructive pulmonary disease.[3] Zonulin levels have also been evaluated within the context of gynecological and obstetric diseases, and increased zonulin levels of the protein have been reported in previous studies of women with a diminished ovarian reserve, gestational diabetes mellitus, and complicated pregnancies in previous studies.[4,5]

Preterm premature rupture of membranes (PPROM) is defined as an early birth following the rupture of fetal membranes before 37 weeks of gestation. It is strongly associated with

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severe adverse obstetric outcomes.[6-8] In most PPROM cases, the etiopathogenesis cannot be precisely explained, but it is thought that an increase in risk factors, immunological factors such as amniocytes, and connective tissue physiology-related factors such as cervical shortening following procedures such as cervical incompetence or conization; often, but not always, bacterial proliferation are involved. The subject is so complex that it is not surprising that we have not been able to solve the balance of pro- and anti-inflammatory activity in pregnancy that allows pregnancy to continue.[9]

Our hypothesis was that elevated plasma zonulin levels contribute to PPROM. We postulated that weight factors and inflammatory processes might be involved in PPROM's etiopathogenesis due to increased intestinal permeability, leading to heightened local inflammation via the translocation of microbial antigens. Consequently, we investigated the association between zonulin levels and PPROM, followed by an examination of the relationship between zonulin levels and birth weight.

METHODS

This prospective case-control study was conducted in the obstetrics clinic of a tertiary care center between January and March 2024. Ethical approval was obtained from the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 10.01.2024, Decision No: AEŞK-BADEK-2024-023). The study adhered to the ethical principles outlined in the Declaration of Helsinki (Edinburgh 2000), and informed consent was obtained from all participants.

Patients diagnosed with PPROM between 32 and 37 weeks were included in the study group, while pregnant women without PPROM in the same gestational week were included in the control group. A total of 44 pregnant women were evaluated, with 22 participants in each group.

Exclusion criteria encompassed obstetric complications (other than PPROM), chronic systemic diseases, chronic bowel disease, gastrointestinal surgery, gastroenteric infections during pregnancy, and smoking.

We recorded and analyzed demographic, obstetric, and clinical features, such as age, gravida, parity, body-mass index (BMI), gestational weeks at delivery, and laboratory tests (white blood cell (WBC) count and C-reactive protein (CRP) at the time of PPROM and at similar weeks of pregnancy for the control group, as well as maternal plasma and umbilical cord blood zonulin levels.

Preparation of Blood Samples

Maternal blood samples were collected upon hospital admission for PPROM in the study group and at the corresponding gestational age in the control group. Umbilical cord blood samples were obtained from all newborns immediately after delivery. These samples were centrifuged at 3000 rpm for 10 min within 24 h and stored at -80°C until analysis. Zonulin levels were determined using a human zonulin ELISA kit (BT LAB-Bioassay Technology Laboratories, Shanghai, China) specifically designed for serum zonulin measurement. Intra- and inter-assay coefficients of variation were below 10%. Serum zonulin concentrations were quantified in ng/ml.

Statistical Analysis

Sample size calculations were performed using G*Power Version 3.1.9.4 (Franz Faul, Universitat Kiel, Germany). Based on a standard effect size of 1.23, a 5% significance level, and 95% power, a power analysis of newborn birth weight data indicated that a minimum of 17 patients per group was required (10). Statistical analyses were performed using IBM SPSS 26.0 software (IBM Corp., Chicago, IL, USA). Variables are expressed as the mean±SD, median (min-max), or number and percentage (n, %). The normality of continuous variables was evaluated by using the Shapiro-Wilk test. The parametric data were compared using a t-test. The nonparametric data were compared using the Mann-Whitney U test. The chi-square test or Fisher's exact test was used to compare categorical variables. Since the data did not follow a normal distribution, the Spearman correlation test was used for all correlation analyses. A p-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

A total of 44 pregnant women, 22 with PPROM (study group) and 22 with non-risk term pregnancy (control group), were included in the study. The demographic and clinical characteristics of the women are shown in Table 1.

Table 1. Demographic and clinical characteristics of the PPROM and control groups

Characteristics	PPROM group (n=22)	Control group (n=22)	p value
Age, year	27.3±6.4	27.9±4.4	0.723
BMI, kg/m^2	28.8±4.2	30.4±7.3	0.366
Gestational age at delivery, weeks	34 w	39 w	<0.001
Gravidity	2 (1-7)	2 (1-10)	0.209
Parity	1 (0-5)	1 (0-4)	0.036
Nulliparous	10 (45.5%)	3 (13.6%)	0.021
Previous abortion	8 (36.4%)	4 (18.2%)	0.176
Previous cesarean delivery	2 (9.1%)	8 (36.4%)	0.031
Previous PPROM	4 (18.2%)	1 (4.5%)	0.345
WBC count at admission, cells/mm^3	11210.0±4287.4	9450.0±2964.1	0.019
Hb level at admission, g/dl	11.5 (9.3-13.8)	11.1 (8.6-13.9)	0.250
PLT level at admission, x10^3/mm^3	295.0 (145.0-424.0)	262.0 (116.0-391.0)	0.330
Number of cesarean deliveries	9 (40.9%)	12 (54.5%)	0.365
Birthweight of newborns, g	2244.7±671.3	3417.7±386.9	<0.001

PPROM: Premature preterm rupture of membrane, BMI: Body-mass index, WBC: White blood cell, Hb: Hemoglobin, PLT: Platelet, The data are presented as the n (%), median (min-max) or mean±standard deviation

No significant difference was found between the PPROM group and the control group regarding age, BMI, gravidity, previous abortion, or history of PPROM. In the PPROM group, 14 patients had CRP levels above 5 mg/dl. The median CRP value was 13.37 mg/dl (range: 6.58-35). Additionally, 18 patients had WBC values above 10,000/µl. The median WBC value was 11,820/µl (range: 10,880-23,130). The median gestational age at delivery was 34 weeks in the PPROM group and 39 weeks in the control group (p<0.001). The percentage of nulliparous women was greater in the PPROM group than

in the control group (45.5% vs. 13.6%, p<0.001). The labor and delivery outcomes of the two groups are shown in Table 1. The cesarean delivery rates of the groups were similar (40.9% vs. 54.5%, p=0.365).

The median maternal plasma zonulin concentrations [99.1 (67.5-307.5) ng/ml vs. 95.6 (65.7-320.0) ng/ml] and cord blood zonulin concentrations [81.9 (30.9-271.3) ng/ml vs. 76.9 (44.1-314.8) ng/ml] were greater in maternal and cord blood in the PPROM group than in the control group, but the differences were not statistically significant (p=0.925 and p=0.681, respectively; Table 2).

Table 2. Zonulin levels in the PPROM and control groups

Zonulin level	PPROM group (n=22)	Control group (n=22)	p value
Maternal blood ng/ml	99.1 (67.5-307.5)	95.6 (65.7-320.0)	0.925
Cord blood ng/ml	81.9 (30.9-271.3)	76.9 (44.1-314.8)	0.681

The data are presented as the median (min-max), PPROM: Premature preterm rupture of membrane

We further divided the participants in the PPROM group into subgroups, with those with a BMI below 30 kg/m² categorized as subgroup 1 and those with a BMI above 30 kg/m² categorized as subgroup 2. Subsequent analysis revealed no difference in maternal serum or fetal cord zonulin levels between the two subgroups (p=0.974).

Based on the demographic data, pregnancy outcomes, and laboratory results, we observed a positive correlation between maternal and fetal cord zonulin levels and newborn birth weight in the PPROM group (p=0.003 and p=0.002, respectively). Furthermore, a comparison of zonulin levels in maternal serum and fetal cord blood between the groups highlighted a strong positive correlation between high zonulin levels in both maternal serum and fetal cord blood (Table 3).

Table 3. Comparison of the correlation between maternal serum and fetal cord blood zonulin levels and their characteristic features

	PPROM cases (n=22)			
	Maternal blood zonulin		Cord blood zonulin	
	r	p	r	p
Age	-0.016	0.944	-0.029	0.898
BMI	0.047	0.835	0.035	0.879
Gestational age	0.185	0.410	0.220	0.325
Birthweight	0.607	0.003*	0.617	0.002*
WBC	-0.115	0.609	0.047	0.837
Hb	-0.084	0.709	-0.143	0.527
PLT	0.085	0.706	0.125	0.580
CRP	-0.031	0.893	-0.067	0.768
Cord blood zonulin level	0.944	<0.001*	-	-

*p values less than 0.05 were considered significant, PPROM: Preterm premature membrane rupture, BMI: Body-mass index, WBC: White blood cell, Hb: Hemoglobin, PLT: Platelet, CRP: C-reaktif protein

However, it was considered that this situation might also stem from differences in the weeks of the newborns. Regression analysis indicated no significant relationship between maternal zonulin levels and BMI (r=0.138, p=0.372) or between newborn birth weight and fetal cord zonulin levels (r=0.211, p=0.170). However, a significant positive correlation was found between maternal zonulin levels and fetal cord zonulin levels (r=0.922, p<0.001), possibly related to intestinal permeability (**Figure**).

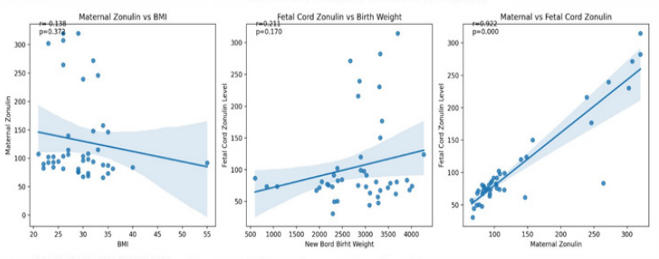

Figure. Distribution of the relationship between zonulin and the factors

A multivariate logistic regression analysis was conducted in a model including statistically significant factors such as parity, previous cesarean, nulliparity, WBC, maternal zonulin levels, and fetal cord zonulin levels. The results are detailed in Table 4. No independent risk factors were identified for PPROM (**Table 4**).

Table 4. Multivariate logistic regression analysis for PPROM

Characteristics	OR (95% CI)
Parity	0.895 (0.429-1.870)
Nulliparous	0.248 (0.029-2.103)
Previous cesarean delivery	2.137 (0.309-14.787)
WBC count at admission	1.000 (1.000-1.000)
Maternal blood zonulin level	1.014 (0.983-1.046)
Cord blood zonulin level	0.989 (0.956-1.024)

PPROM: Preterm premature rupture of membrane, OR: Odds ratio, WBC: White blood cell

DISCUSSION

Previous studies have evaluated the relationship between zonulin and various inflammatory and chronic diseases.[5] However, our study is the first to focus on PPROM patients. We found that zonulin levels did not significantly differ between the PPROM and control groups. However, in the PPROM group, we observed a strong relationship between newborn birth weight and both maternal serum zonulin levels and fetal cord blood zonulin levels. We also found a significant correlation between maternal serum zonulin levels and fetal cord blood zonulin levels in all patients.

Zonulin has been assessed as a new diagnostic marker for intestinal permeability in newborns showing signs of infection and/or inflammation in the gut or at risk of intestinal pathology. Tarko et al.[11] evaluated 81 newborns diagnosed with sepsis, necrotizing enterocolitis, rotavirus infection, or gastroschisis. Zonulin levels did not correlate with CRP or procalcitonin levels in their study. Therefore, the authors suggested that an increase in zonulin might not match the release of inflammatory markers, and that low CRP should not rule out intestinal injury in newborns.[11] In our study, despite the expected development of infection secondary to PPROM, no correlation was found between maternal serum and umbilical cord serum zonulin levels or CRP levels in patients with PPROM. In another study conducted in patients

with preterm rupture of membranes (PROM), zonulin levels were compared between groups with and without PROM. The mean zonulin concentration was greater in the PROM group (155.3±50.2 ng/ml) than in the non-PROM group (128.8±59 ng/ml). However, no statistically significant difference was found between them. Among the inflammatory markers, only C-reactive protein levels were significantly increased in the PROM group.[12] Similarly, in our study, there was no significant difference in zonulin levels between the PPROM group and term pregnant women. However, the level of zonulin, which was high in maternal blood, was also found to be high in cord blood. This finding is significant in terms of intestinal permeability. However, since our study did not routinely measure CRP in term pregnant women, we could not compare its levels between the two groups.

In a study involving 100 healthy newborns and their mothers, zonulin levels in blood samples and calprotectin levels in stool samples were assessed. This study demonstrated that cesarean section delivery and antibiotic use led to an increase in zonulin levels.[13] However, another study reported that long-term cesarean section delivery or antibiotic use did not influence zonulin or other intestinal permeability-related factors.[14] In our study, neither of these two factors resulted in a change in zonulin levels.

For pregnant patients, a weight gain during pregnancy greater than 18 kg or a BMI increase >5.7 during pregnancy is associated with a decrease in zonulin concentrations in the mother's stool and an increase in calprotectin concentrations in the newborn's stool on the seventh day.[13] Changes in maternal BMI during pregnancy can affect intestinal permeability in both the newborn and the mother. The health consequences of increased intestinal permeability in the first days of life are not yet known. Before zonulin and calprotectin tests can be widely used to diagnose increased intestinal permeability, these tests must be validated.[13,15] In our study, analysis of the subjects divided into two groups based on BMI values above and below 30 no significant difference in the comparison of maternal serum and fetal cord blood zonulin levels. This result can be attributed to the lack of a significant difference in BMI values between the study and control groups (28.8±4.2 kg/m^2 vs. 30.4±7.3 kg/m^2) and the presence of only two patients with morbid obesity (BMI=42 kg/m^2 and 55 kg/m^2).

There are numerous studies on the relationship between newborn birth weight and intestinal permeability in various diseases. For instance, in a case-control study involving 368 infants categorized as born below 2500 g and above 2500 g, a notable link was discovered between intestinal permeability and newborn birthweight based on maternal serum zonulin levels.[10] The serum levels of zonulin and zinc in mothers of infants weighing more than 2500 g were found to be significantly greater than those in mothers of low-birth weight infants.[10] In our study, we found a positive correlation between newborn birthweight and maternal serum zonulin levels and fetal cord blood levels in the PPROM group (Table 2). In our study, a positive correlation was found between maternal serum zonulin levels and fetal cord zonulin levels (Table 3). This correlation suggests that changes in zonulin levels may lead to complicated pregnancies with impaired glucose tolerance, insulin resistance, gestational diabetes mellitus, and intrahepatic cholestasis, as indicated in the literature.[16,17]

In complex diseases such as polycystic over syndrome and PROM, which can present with metabolic disorders, gestational diabetes mellitus, or chronic inflammatory bowel diseases, the expected increase in zonulin levels could not be observed in the literature. This is attributed to the unclear relationship between the mechanism of action of zonulin and these diseases.[12,18-20]

Limitations

The major strength of the present study is that it is the first, to our knowledge, to investigate the association between PPROM and zonulin levels. The study is also strengthened by its prospective design. Conversely, the small sample size is a significant limitation. Due to the sample size of obese women, a significant association could not be demonstrated between BMI and zonulin levels.

CONCLUSION

No significant association was found between PPROM and maternal serum/umbilical cord blood zonulin levels in this study. This outcome is attributed to the clinical presentation of PPROM, which is characterized by a localized inflammatory process rather than a systemic process. However, a positive correlation was found between newborn birthweight and maternal serum zonulin levels, as well as fetal umbilical cord levels, in the PPROM group. There was also a positive correlation between maternal serum and fetal umbilical cord zonulin levels in all patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 10.01.2024, Decision No: AEŞK-BADEK-2024-023).

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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Original Article

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Relationship between triglyceride-glucose index and intravenous thrombolysis outcomes for acute ischemic stroke

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ABSTRACT

Aims: The aim of this study was to investigate the effect of triglyceride glucose index, a marker of insulin resistance, on early neurological deterioration (END), development of intracerebral hemorrhage and hemorrhagic transformation and mortality in patients receiving intravenous thrombolytic therapy for acute ischemic stroke.

Methods: This retrospective study included 71 patients with acute ischemic stroke who received intravenous tissue plasminogen activator. Demographic data, clinical and radiological findings, fasting glucose and lipid profile, END, hemorrhage development and mortality rates were analyzed. We also calculated the triglyceride glucose (TyG) index and examined its correlation with early neurological deterioration, hemorrhage development and mortality.

Results: The median age was 74 years (41-88), with a female predominance of 54.9%. The incidence of intracerebral hemorrhage was 9.6%, while END occurred in 39.6% of cases, and the 30-day mortality rate was 28.2%. The mean TyG index was 7.8 (2.8-27.6). The receiver operating characteristic curve analysis indicated that the TyG index predicted mortality with an area under the curve of 84.4%, a sensitivity of 85%, and a specificity of 82.35% in patients with a TyG index above 10.01 ($p<0.01$). According to univariate analyse, the admission NIHSS score was associated with a 1.46-fold increase in the odds of mortality (odds ratio [OR]: 1.459), while a TyG index greater than 10.01 was associated with a 1763.9-fold increase in mortality risk (OR: 1763.9) ($p=0.005$; $p=0.009$, respectively). Patients with higher TyG index also exhibited significantly increased rates of mortality and END ($p<0.001$ for both). There was no association between development of hemorrhage and TyG index ($p>0.05$).

Conclusion: This study supports that a high TyG index is associated with END and mortality but not with the development of hemorrhage. Multicenter studies with larger sample size are needed.

Keywords: Triglyceride glucose index, insulin resistance, intravenous thrombolytic therapy, acute ischemic stroke, hemorrhagic transformation

INTRODUCTION

Stroke is one of the leading causes of mortality and morbidity globally, with ischemic stroke constituting approximately 85% of all stroke cases.[1] In the management of acute ischemic stroke, both mechanical thrombectomy and intravenous thrombolytic therapy can yield favorable outcomes in patients who present within the appropriate time window for intravenous thrombolysis.[2] Intravenous thrombolysis results in an average absolute increase in disability-free survival of approximately 5-10%.[3] Despite encouraging results, the development of hemorrhagic transformation and intracerebral hemorrhage in patients receiving intravenous tissue plasminogen activator (IV tPA) may lead to a significant increase in mortality and morbidity associated with the disease.[3-5]

Insulin resistance (IR) plays a major role in the pathophysiology of diabetes mellitus and metabolic syndrome.[5,6] Also IR is closely associated with obesity and is an independent risk factor for mortality and major disability after stroke.[7] The presence of hyperglycemia (consequence of IR), which can have a negative impact on brain function, has been shown to adversely affect the prognosis of individuals with ischemic stroke, regardless of their diabetic status.[8] IR plays a predisposing role for stroke through the formation of atherosclerosis by promoting thrombosis, but also induces inflammatory response, oxidative stress and neuronal damage, leading to poor prognosis.[8] Although IR has been detected by methods such as hyperinsulinemic-euglycemic clamp, Homeostasis Model Assessment of IR (HOMA-IR), these methods are not practical enough.[5,7] The triglyceride-glucose (TyG) index is a biomarker of IR that is calculated using fasting triglycerides and fasting blood glucose levels, making it easily accessible.[9] The TyG index has been shown to be at least as good as or even superior to the HOMA-IR in detecting IR.[10] Thus, the TyG index has been verified as a simple surrogate marker of IR and is cost-effective and replicable.[6,11]

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Factors that may predict the development of early neurological deterioration and hemorrhage after IV tPA therapy in ischemic stroke have recently become popular areas of research.[3] Studies on the effect of TyG index on early neurological deterioration (END), hemorrhage development and mortality after IV tPA are quite limited and there is no study from our country. The aim of this study is to investigate the effect of TyG index on hemorrhage development and mortality after IV tPA.

METHODS

Study Design

This retrospective study involved patients diagnosed with acute ischemic stroke who received intravenous thrombolysis with alteplase at Kırşehir Training and Research Hospital from 2020 to 2024. The study was approved by the Kırşehir Ahi Evran University Health Sciences Scientific Researches Ethics Committee (Date: 19.03.2024, Decision No: 2024-07/46). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Thrombolytic treatment involves the administration of recombinant tissue plasminogen activator (r-tPA) at a dosage of 0.9 mg/kg up to a maximum of 90 mg, with 10% of the dose given as a bolus and the remaining amount infused over 60 minutes, ideally within 4.5 hours of the onset of a stroke. Patients diagnosed with acute ischemic stroke who did not undergo thrombolytic therapy, patients with transient ischemic attack were excluded from the study. Additionally, patients who underwent interventional procedures, such as thrombectomy, were also excluded. Patients with incomplete data in their medical records were excluded as well. Of the 87 patients who underwent thrombolytic therapy, 5 were referred to an advanced center for thrombectomy and lipid profile was not studied in 11 patients; therefore, 71 patients were included in the study.

Demographic data, comorbidities, medications, and clinical data including admission blood pressures, National Institute of Health Stroke Scale (NIHSS) score, number of hemorrhage developing and mortality, NIHSS score prior to discharge were recorded. Body-mass index (BMI) was calculated as weight (kg) ratio to height squared (m^2). Fasting glucose, fasting triglycerides, fasting cholesterol, fasting low density lipoprotein (LDL) cholesterol and fasting high density lipoprotein (HDL) cholesterol levels were assessed based on laboratory data. Blood samples were examined after 8 hours of fasting after admission to the hospital. TyG index was calculated by the formula: fasting TG (mg/dl) × glucose (mg/dl)/2.[9] END was considered as a decrease of ≥4 points in the total baseline NIHSS score in the first 72 hours, development of intracerebral hemorrhage or resulting in mortality.[12] Hemorrhage detected on computed tomography examination of the brain routinely performed 24 hours after thrombolytic therapy or in case of neurological deterioration. Hemorrhagic transformation and hematoma formation in the infarct area or distant area in the intracranial region until discharge were considered as hemorrhage development. The definitions of hemorrhagic transformation and inracerebral hemorrhage were based on the safe implementation of thrombolysis in stroke-monitoring study study criteria.[13]

Statistical Evaluation

Statistical package for the social sciences (SPSS) version 25.0 was utilized for the statistical analysis of the data. Categorical variables were summarized as counts and percentages, while continuous variables were summarized using the mean, standard deviation, median, minimum-maximum range, and the 25th to 75th percentiles when appropriate. The Chi-square test was employed to compare categorical variables. The Shapiro-Wilk test was conducted to assess whether the study parameters followed a normal distribution. For normally distributed parameters, the independent Student's t-test was applied, whereas the Mann-Whitney U test was used for non-normally distributed parameters. The sensitivity and specificity values of the TyG index were calculated, and the cutoff value was determined by analyzing the area under the receiver operating characteristic (ROC) curve. Spearman's rho correlation coefficient was used to evaluate the relationship between continuous variables. Univariate and multivariate logistic regression models were used to analyze the factors influencing mortality and the development of hemorrhage. A statistical significance level of $p<0.05$ was established for all tests.

RESULTS

In this study involving 71 patients, the median age was 74 years (41-88), with a female predominance of 54.9%. Hypertension was the most prevalent predisposing factor, affecting 69% of the participants. The incidence of intracerebral hemorrhage was recorded at 9.6%, while the occurrence of END was noted in 39.6% of cases. The 30-day mortality rate was found to be 28.2%. The mean TyG index was 7.8 (2.8-27.6). A summary of the demographic, clinical, and laboratory data is presented in Table 1.

The ROC curve demonstrated that the TyG index is a significant predictor of mortality, exhibiting an area under the curve (AUC) of 84.4%, a sensitivity of 85%, and a specificity of 82.35% in patients with a TyG index above 10.01 ($p<0.01$) (Figure).

The comparison of demographic, clinical, and laboratory data between the two groups based on the TyG index is presented in Table 2. The mean values for admission NIHSS, final NIHSS, glucose, triglycerides, LDL, and total cholesterol were significantly elevated in patients exhibiting a high TyG index in comparison to those with a low TyG index ($p=0.002$; $p<0.001$; $p<0.001$; $p<0.001$; $p<0.001$; $p=0.037$; $p=0.006$, respectively). Patients with a higher TyG index demonstrated significantly elevated rates of mortality and END ($p<0.001$ for both). No significant differences were noted for the other parameters ($p>0.05$).

Univariate analysis indicated a significant difference in mortality outcomes among patients based on various factors, including diabetes mellitus, END, admission NIHSS, final NIHSS, glucose levels, triglycerides, LDL and TyG index identified as significant in the univariate analysis, were subsequently incorporated into the multivariate model. According to this model, the admission NIHSS score was associated with a 1.46-fold increase in the odds of mortality

Table 1. Demographic, clinical and laboratory data of patients with acute ischemic stroke who received intravenous thrombolysis (n=71)	
Age	74 (41-88)
Female gender	39 (54.9)
BMI	28.2±4.8
Comorbidities	
Hypertension	49 (69)
Diabetes mellitus	28 (39.4)
Coronary heart disease	26 (36.6)
Atrial fibrillation	9 (12.7)
Chronic obstructive pulmonary disease	8 (11.3)
Congestive heart failure	14 (19.7)
Prior stroke	7 (9.9)
Localization of stroke	
Right middle cerebral artery	33 (46.5)
Left middle cerebral artery	19 (26.8)
Brainstem	2 (2.8)
Cerebellar	5 (7)
Striatocapsular infarct	10 (14.1)
Posterior cerebral artery	2 (2.8)
Carotid and vertebral system examination	
Normal	56 (78.8)
≤49% stenosis	3 (4.2)
50-69% stenosis	6 (8.5)
70%≥ stenosis	6 (8.5)
Clinical data	
Admission SBP (mmHg)	169.9±19.4
Admission DBP (mmHg)	90 (65-130)
Admission NIHSS	14 (4-37)
Final NIHSS	7 (0-42)
Development of hemorrhage	
Hemorrhagic transformation	11 (15.5)
Intracerebral hemorrhage	7 (9.6)
Early neurological deterioration	19 (26.7)
Mortality	20 (28.2)
Symptom/door time	90 (15-180)
Symptom/needle time	180 (45-240)
Laboratory data	
Glucose	133 (71-329)
Triglyceride	122 (53-309)
Low density lipoprotein	110.8±31.1
High density lipoprotein	41 (25-71)
Cholesterol	176.9±38.5
TyGI	7.8 (2.8-27.6)

BMI: Body-mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, NIHSS: National Institute of Health Stroke Scale, TyGI: Triglyceride-glucose index

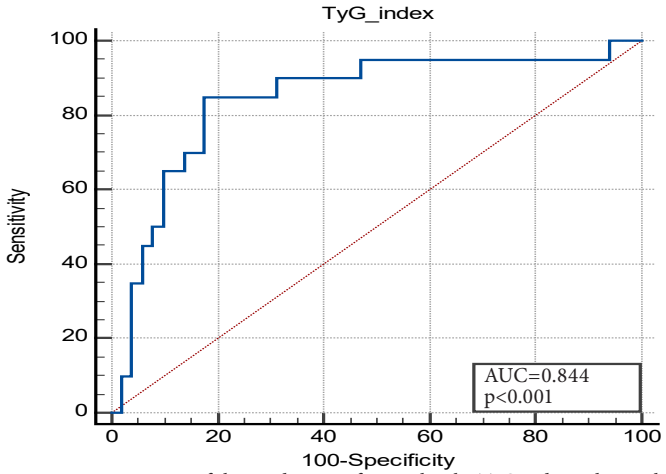

Figure. Investigation of the prediction of mortality by TyG index value with ROC curve test

AUC: Area under the curve, TyG: Triglyceride glucose, ROC: Receiver operating characteristic

Table 2. Comparison of demographic, clinical, and laboratory data of the two groups based on the triglyceride glucose index in patients with intracerebral hemorrhages (n=71)			
	TyGI score <10.01 (n=45)	**TyGI score of >10.01 (n=26)**	**p**
Age	74 (60-78.5)	77 (67-80)	0.364µ
Female gender	23/22	16/10	0.395†
Localization of stroke			
Right middle cerebral artery	22 (48.9)	11 (42.3)	0.343†
Left middle cerebral artery	10 (22.2)	9 (34.6)	
Brainstem	1 (2.2)	1 (3.8)	
Cerebellar	2 (4.4)	3 (11.5)	
Striatocapsular infarct	9 (20)	1 (3.8)	
Posterior cerebral artery	1 (2.2)	1 (3.8)	
Admission NIHSS	11 (8-16)	19 (13.25-23.25)	0.002**µ
Development of hemorrhage	6 (17.7)	10 (38.5)	0.054†
Mortality	3 (6.7)	17 (65.4)	<0.001**†
Final NIHSS	5 (2.5-11)	42 (5.5-42)	<0.001**µ
Early neurological deterioration	5 (17.2)	14 (73.7)	<0.001**†
Carotid and vertebral system examination			
Normal	38 (84.4)	18 (69.2)	0.260†
≤49% stenosis	1 (2.2)	2 (7.7)	
50-69% stenosis	2 (4.4)	4 (15.4)	
70%≥ stenosis	4 (8.9)	2 (7.7)	
Laboratory data			
Glucose	116 (90-138.5)	162 (134-214)	<0.001**µ
Triglyceride	105 (83.5-128)	180.5 (157-207)	<0.001**µ
Low density lipoprotein	104.9±31.2	120.9±28.8	0.037*‡
High density lipoprotein	41 (38-46.5)	41.5 (36.75-47)	0.872µ
Cholesterol	167.3±38.7	193.7±32.7	0.006**‡

TyGI: Triglyceride-glucose index, NIHSS: National Institute of Health Stroke Scale, †: Chi-square, ‡: Independent student t-test, µ: Mann-Whitney U test

[odds ratio (OR): 1.459], while a TyG index greater than 10.01 was linked to a 1763.9-fold increase in mortality risk (OR: 1763.9) (p=0.005; p=0.009, respectively).

Univariate analysis indicated a statistically significant difference in the occurrence of hemorrhage and END, as well as in the final NIHSS, admission systolic blood pressure,

and admission diastolic blood pressure (p=0.004; p=0.028; p<0.001; p<0.001, respectively). The parameters identified as significant in the univariate analysis were included in the multivariate model. According to this model, it was determined that the parameters deemed significant in the univariate analysis had no statistically significant effect on the development of hemorrhage (p>0.05).

DISCUSSION

Several studies have shown that IR is a risk factor for stroke[14] and a poor prognostic marker for stroke.[6,7] It has been proposed that IR may serve as a poor prognostic indicator following thrombolytic therapy in cases of acute ischemic stroke.[4,5,11,15] There are several theories suggesting that IR is linked to a poor prognosis following a stroke. Firstly, IR in adipocytes leads to the production of chemokines, which in turn recruit monocytes and activate pro-inflammatory macrophages.[16] Inflammation, recognized as a negative prognostic indicator in stroke patients undergoing thrombolytic therapy,[17-19] exacerbate worse outcomes in the presence IR. Secondly, it inhibits the membrane translocation of glucose transporter type 4 in insulin receptors, resulting in insufficient glucose uptake and subsequently contributing to neuronal apoptosis.[5] The adverse effects of IR are not only on stroke prognosis but also on thrombolytic therapy. Patients with high IR have elevated blood levels of fibrinolysis inhibitors such as plasminogen activator inhibitors, which may be associated with an impairment in endogenous fibrinolytic capacity and IR may also be associated with a worsened response to intravenous thrombolysis.[4,20] IR can make the structure of the clot denser and more resistant to lysis, making it resistant to IV tPA.[4] Vascular alterations observed in diabetic patients, including cerebral vascular endothelial dysfunction, increased arterial stiffness, and thickening of the capillary basement membrane, as well as hyperglycemia-induced overproduction of reactive oxygen species, significantly contribute to the diminished efficacy of thrombolytic therapy.[12]

TyG index is a biomarker indicative of IR, derived from the values of triglycerides and glucose. It is considered superior to other IR parameters due to its straightforward calculation [9]. Although numerous studies indicate that both hyperglycemia and hypercholesterolemia serve as unfavorable prognostic markers following an acute stroke, research has demonstrated that the TyG index, which is derived from these two parameters, provides a more accurate reflection of prognosis after cardiovascular and cerebrovascular events than either of the individual values alone.[12] A meta-analysis encompassing 18 studies and a total of 592,635 patients revealed that a higher TyG index is correlated with an increased risk of ischemic stroke. Furthermore, a significant association was identified between an increased TyG index and various adverse outcomes related to stroke, particularly with respect to stroke recurrence and heightened mortality rates.[6] Studies on TyG index as a prognostic marker in acute stroke patients receiving thrombolytics are more limited. A study conducted by Zhang et al.,[4] which involved 676 participants, demonstrated that a high TyG index is correlated with END in patients treated with IV tPA. In a study conducted by Toh et al.[12] involving 698 patients who received IV tPA, a high TyG index was found to be associated with increased mortality and poor functional outcomes; however, it was not associated with symptomatic intracerebral hemorrhage. In a study conducted by Calleja et al.,[15] which included 109 patients who underwent thrombolytic therapy, it was found that IR was associated with a poor prognosis; however, it did not have an effect on the development of hemorrhagic transformation. Another study conducted by Bas et al.[21] found that IR had no significant effect on the development of hemorrhage or mortality; however, it was associated with a poor prognosis at the three-month mark. In our study, we similarly observed that the TyG index was correlated with END and mortality; however, it did not demonstrate an association with the occurrence of hemorrhage. In the ROC curve analysis of patients TyG index predicting mortality, it was determined that patients with TyG index above 10.01 predicted mortality with 84.4% AUC, 85% sensitivity, 82.35% specificity.

One of the most important reservations when administering IV tPA to a patient with acute ischemic stroke is the risk of intracerebral hemorrhage.[22] In a meta-analysis of 52,610 patients, the rate of patients who developed only intracerebral hematoma excluding hemorrhagic transformation was 3.2% and more in the female sex and those with higher diastolic blood pressure and higher rates of previous stroke, chronic heart failure and cardioembolism.[3] Our study identified an intracerebral hemorrhage rate of 8.5%. The observed slightly elevated rate of hemorrhage in our research may be due to the relatively higher NIHSS and elevated blood pressure at the time of admission. It is important to note that some studies define intracerebral hematoma as hemorrhage occurring outside the infarct area; however, our methodology included intracerebral hemorrhage within the infarct region. This methodological distinction may have resulted in an increased rate of hemorrhage development in our findings.

Limitations

This study presents several limitations. Firstly, the sample size was limited, and the research design was retrospective and observational in nature. Secondly, the analysis was restricted to the initial 30 days of patient data, thereby lacking long-term follow-up. Thirdly, smoking, a significant risk factor for stroke, was not incorporated into the study due to the unavailability of this information in the patient records. Lastly, the homeostasis model assessment of insulin resistance (HOMA-IR) and the hyperinsulinemic-euglycemic clamp were not included in the study, as these assessments are not routinely conducted for stroke patients at our institution.

CONCLUSION

This study supports that a high TyG index is associated with END and mortality but not with the development of hemorrhage. A high TyG index, which encompasses readily accessible parameters and serves as a biomarker for IR, may provide clinicians with insights into END and mortality risk.

ETHICAL DECLARATIONS

Ethics Committee Approval
The study was carried out with the permission of the Kırşehir Ahi Evran University Health Sciences Scientific Researches Ethics Committee (Date: 19.03.2024, Decision No: 2024-07/46).

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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Does smartphone addiction affect cervical mobility, head posture, body awareness and pain pressure threshold?

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ABSTRACT

Aims: With the rapid development of technology, the increasing use of smartphones has become a subject of concern due to its multifaceted effects on the cervical spine and body awareness. The present study investigates effects of smartphone addiction on general cervical/isolated upper cervical mobility, body awareness, head posture, and cervical pain pressure threshold (PPT).

Methods: This prospective and cross-sectional study was conducted on 108 participants, categorized as heavy users and light users based on daily smartphone use. General cervical / isolated upper cervical mobility (right and left rotation), body awareness, head posture, and PPT (midpoint of the upper trapezius muscle, and 2 cm lateral to the C2 spinous process) were assessed using the Cervical Range of Motion Device (CROM), the Body Awareness Questionnaire, craniovertebral angle, and an algometer, respectively. The comparison of cervical mobility, head posture, body awareness, and pain pressure threshold between the groups was performed using the Independent samples T test.

Results: The results showed that smartphone addiction significantly affects isolated upper cervical mobility in the directions of right and left rotation ($p<0.001$), head posture ($p<0.001$ for both directions), and body awareness ($p=0.035$), but has no significant impact on general cervical mobility in terms of right and left rotation ($p=0.847$, $p=0.848$) or PPT assessed at two different points ($p=0.165$, $p=0.213$), respectively.

Conclusion: This study highlights the clinical implications of smartphone overuse on upper cervical mobility, head posture, and body awareness, independent of pain pressure threshold and general cervical mobility. Clinicians should assess these factors in individuals with smartphone addiction, as early intervention may help prevent long-term dysfunction and sensorimotor disturbances.

Keywords: Smartphone, cervical vertebrae, range of motion, pain, posture

INTRODUCTION

With the rapid development of information and communication technologies, smartphone usage is increasing.[1,2] When using smartphones, users tend to hold their head and neck forward more often.[3-5] Common issues observed in smartphone users include anterior head positioning and rounded shoulders.[6-8] Although the literature has explored the relationship between smartphone usage and cervical posture, few studies have addressed this relationship, and none have specifically examined the lower and upper cervical postures separately. However, considering the cervical region as comprising both lower and upper segments is essential for understanding cervical mobility and compensation mechanisms.[9]

In long-term smartphone users, forward head posture, defined as anterior positioning of the head in the cervical spine, is one of the most common postural deviations in the sagittal plane. The anterior positioning of the head leads to flexion in the lower cervical region while increasing extension in the upper cervical region.[10,11] Consequently, the neck extensors become tight and shortened, whereas the neck flexors become elongated and weakened. These changes in cervical muscles result in abnormal cervical stress.[12] These alterations can affect proprioception by altering the threshold levels of mechanoreceptors responsible for proprioception, thereby impairing proprioceptive awareness.

The cervical region is crucial for postural stability.[13] Due to the abundance of mechanoreceptors in the suboccipital muscles, the cervical region is a major source of proprioceptive information.[14] Additionally, the upper cervical region is closely connected to the central nervous system, vestibular system, and visual system.[15,16] Because of these connections, changes in the cervical spine can impact sensory integration, resulting in proprioceptive deficiencies.[17] In the literature, no previous studies have addressed the effects of smartphone addiction (SPA) on body awareness. In recent years, body awareness

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has emerged as a prominent topic in scientific research within the health field. Body awareness fundamentally refers to an individual's consciousness of their body parts or dimensions. From a neuroscience perspective, body awareness involves the brain's recognition of messages received from other parts of the body and from the external environment. These messages include not only information about the body's own movements (interoceptive or corporeal awareness) but also details about external objects, such as their properties and locations (exteroceptive or extra-corporeal awareness). Over time, this information and experience blend to form the body's perceptual experiences. These experiences are crucial for understanding and interpreting one's own body and surroundings, and for establishing social interactions. Therefore, body awareness involves having knowledge about one's own body and the properties of surrounding objects.[18] Considering the potential impact of SPA on proprioception, it is important to investigate deviations in body awareness. In light of the above information, determining the disruptive impact of SPA on body awareness is of critical importance.

The aim of this study is to investigate the effects of SPA levels on general cervical mobility, isolated upper cervical mobility, head posture, body awareness, and cervical pain pressure threshold.

METHODS

Study Design

The study, planned as a prospective, observational, cross-sectional study, received ethical approval from the Atılım University Non-interventional Clinical Researches Ethics Committee (Date: 24.01.2024, Decision No: 604.01.02-160). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. After providing information about the study to the participants, those who voluntarily agreed to participate were included in the study upon obtaining their written consent. This study was written in accordance with the STROBE checklist.[19]

Participants

The participants were recruited from the staff located on the Atılım University campus. They were invited to participate through a recruitment flyer containing information about the study, which was posted on the announcement page of Atılım University. Individuals who met the inclusion criteria and volunteered, between January/2024 and July/2024, were included in the study. The participants underwent a one-time, face-to-face evaluation by research assistant at the research laboratory of the department of physiotherapy and rehabilitation. The evaluator was unaware of the participants' group assignments during the assessment, thus ensuring blinding from the evaluator's perspective.

The inclusion criteria were being a smartphone user and being between the ages of 18 and 25. The exclusion criteria included neck pain, radicular pain, neurological symptoms, a history of cervical or upper extremity surgery, and cervical trauma. Flow chart is shown in Figure 1.

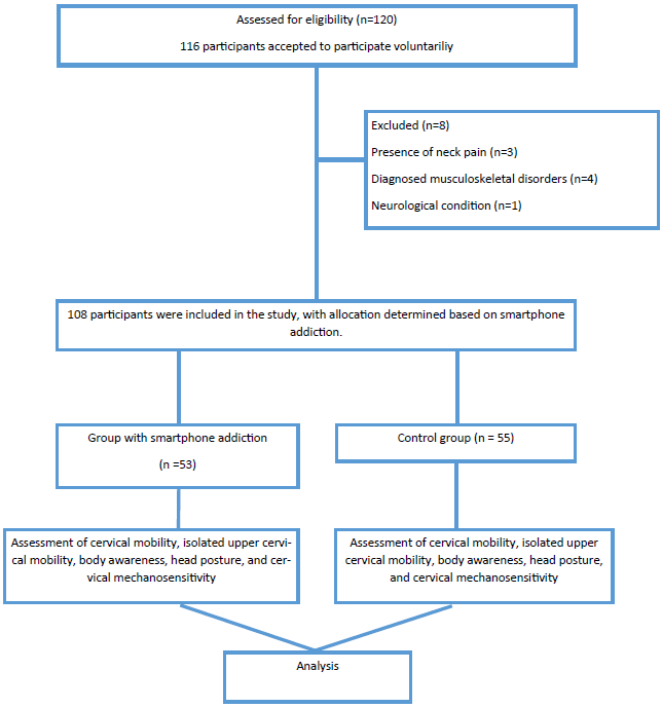

Figure. Study flow chart

In the study, individuals divided into two groups based on their smartphone usage: the experimental group (those using their smartphones for more than 4 hours per day) and the control group (those using their smart phone for less than 4 hours per day). Participants who used their smartphones for more than 4 hours per day were classified as smartphone addicts and included in the experimental group.[8,20]

Data Collection

Assessments were conducted by a researcher who was unaware of the participants' group assignments, ensuring a single-blind design for the study. In the first part of the study, participants were asked to complete a 'body awareness questionnaire', answering all questions face-to-face. In the second part, participants were invited in person for evaluations of general cervical/upper cervical mobility, sagittal head posture, and PPT.

Sociodemographic characteristics assessment: Participants' sociodemographic characteristics, including age, height, weight, body mass index was recorded in the assessment form.

Determining smartphone usage levels: Researchers categorized participants based on their daily smartphone usage into light users (those using the phone for less than 4 hours per day) and heavy users (those using it for more than 4 hours per day).[8,20] To determine smartphone usage times, an application that objectively measures daily phone usage (Screen Time) was used. Participants were instructed to download the application to their smartphones and use it for a period of one month. This application recorded the participants' daily mobile phone usage times. The average daily usage was recorded at the end of one month., and mobile phone addiction was assessed based on this data. Consequently, the classification of participants as light or

heavy users was based on directly observable data, ensuring a scientific foundation rather than relying on subjective reports.

Assessment of body awareness: Body awareness was assessed using the Body Awareness Questionnaire designed to determine normal or abnormal sensitivity levels in body composition.[21] The questionnaire consists of four subgroups: 1) Changes in body processes, 2) Sleep-wake cycle, 3) Prediction of disease onset, and 4) Prediction of body responses, with a total of 18 items. Participants were asked to rate each item using a scale from 1 to 7. It has a minimum score of 18 and a maximum score of 126, with higher scores indicating greater body awareness. The validity and reliability of this questionnaire have been reported to be high.[22]

Assessment of head posture: Head posture was assessed using photographic methods and craniovertebral angle. The craniovertebral angle is calculated as the angle between a horizontal line passing through C7 and a line extending from the tragus of the ear to C7.[23] An angle less than 49 degrees indicates an anterior head position.[4]

A profile photo of the participant in a relaxed standing posture was taken. For the photograph, the camera was placed on a tripod 0.8 meters from the participant, with the camera lens axis perpendicular to the participant's sagittal plane and at a height corresponding to the level of the C7 spinous process.[24] Craniovertebral angles were calculated using the images uploaded to a computer program.

Assessment of cervical pain pressure threshold: The cervical PPTs were assessed using a mechanical pressure algometer (Baseline Force Gauge Model 12-0304; Baseline, NY, USA). A force was applied perpendicularly to a 0.5 cm^2 area at an approximate rate of 3 N/s. While the patient was seated, pressure was applied at the midpoint of the upper trapezius muscle, and 2 cm lateral to the C2 spinous process bilaterally.[25] For each area, two measurements were taken at intervals, and the average of these measurements was calculated to determine the final value.

Assessment of general cervical mobility: Cervical mobility was assessed using the Cervical Range of Motion (CROM) deluxe device, developed by the University of Minnesota. The CROM device is an inclinometer system that utilizes gravity and magnetic effects.[26] It is validated for accuracy and reliability. The device consists of two fixed inclinometers for the sagittal and frontal planes, a horizontal inclinometer with a magnetic needle mounted on the top of the device, a magnetic neck brace, a scale-equipped arm with a ruler mounted on the top, and a vertebra locator arm with a weighing system.

The device is designed in a plastic frame and is positioned over the nose and ears. When properly placed, the device has two fixed vertical inclinometers at the front that measure lateral flexion, and the left side measures flexion-extension. The horizontal inclinometer with a magnetic needle mounted on the top of the device evaluates rotation while the magnetic neck brace eliminates the effects of thoracic movement on rotation.

Assessment of upper cervical mobility: The CROM device was securely attached to the participant's head while they lay supine on a treatment table. The evaluator asked the participant to relax while the neck was brought to its maximum cervical flexion. In the full flexion position, the head and neck were passively rotated as far as possible within the limits of comfortable pain or physiological stiffness. The procedure was repeated twice on each side with a 30-second rest between tests. The sensitivity of the flexion-rotation test was found to be 91%, its specificity 90%, and its overall diagnostic accuracy 91%.[26] The cervical flexion-rotation test is an important tool in identifying movement impairment at the C1/2 segment[26] and can be used accurately and reliably even by inexperienced examiners.[27]

Sample size calculation: In our study, the criterion of upper cervical mobility was taken as the basis in the power analysis evaluation. According to the post-hoc power analysis, at a 5% significance level ($\alpha<0.05$) and with an effect size of 0.5, the power of the study was calculated as 80%.

Statistical Analysis

The analyses were conducted using IBM SPSS Statistics 23 software package (IBM Corporation, Armonk, NY, USA). For the evaluation of the study data, frequencies (count, percentage) were provided for categorical variables, and descriptive statistics (mean, standard deviation) were provided for numerical variables. The normality assumptions of numerical variables across groups were examined using appropriate Shapiro-Wilk or Kolmogorov-Smirnov tests. Since the data met the criteria for normal distribution, an independent samples T test was utilized.

RESULTS

Demographic information of the participants is shown in Table 1. The participants' height, weight, and body mass indices were similar ($p>0.05$). On the other hand, there was a significant difference between groups regarding age and daily smartphone usage time ($p<0.05$).

Table 1. Demographic characteristics of the participants

	Group with smartphone addiction x±SD (min; max) (n=53)	Control group x±SD (min; max) (n=55)	p-value
Age (year)	22.12±1.21 (20; 25)	22.81±2.1 (20; 30)	0.046*
Height (cm)	1.69±0.08 (1.53; 1.84)	1.7±0.09 (1.54; 1.9)	0.595
Weight (kg)	66.89±11.1 (46; 84)	65.86±11.74 (43; 94)	0. 644
BMI (kg/m^2)	23.1±3.08 (17.5; 30.8)	22.45±2.73 (17.2; 27.7)	0.248
Daily smartphone usage time (h/day)	5.62±1.14 (4.1; 8)	2.53±0.92 (1; 3.9)	<0.001*

n: Number of participants, BMI: Body-mass index, SD: Standard deviation, Min: Minimum, Max: Maximum, cm: Centimeter, kg: Kilogram, kg/m^2: Kilogram/$meter^2$, h/day: Hours per day

There were significant differences between the groups in terms of isolated upper cervical mobility, craniovertebral angle, and body awareness ($p<0.05$). However, there were no differences between the groups regarding general cervical mobility or cervical PPT ($p>0.05$), as shown in Table 2.

Table 2. The comparison of cervical mobility, head posture, body awareness, and pain pressure threshold between groups

	Group with smartphone addiction (n=53)	Control group (n=55)	Mean difference	95% Confidence interval of the difference		
	x±SD	x±SD		Lower	Upper	p value[t]
Mobility of upper cervical region (right rotation)	33.41±4.38	43.7±2.87	-6.9	-7.7	-4.87	<0.001*
Mobility of upper cervical region (left rotation)	37.94±4.17	44±2.58	-6.05	-7.39	-4.72	<0.001*
Mobility of general cervical region (right rotation)	46.73±17.76	49.35±18.47	-0.68	-7.66	6.29	0.847
Mobility of general cervical region (left rotation)	49.35±18.47	48.69±17.63	0.66	-6.22	7.55	0.848
Body awareness	78.64±16.52	85.65±17.57	-7.01	-13.52	-0.49	0.035*
Pain pressure threshold (C2)	3.06±1.3	4.83±9.12	-1.76	-4.26	0.73	0.165
Pain pressure threshold (upper part of trapezius)	3.39±1.07	4.11±1.53	-0.31	-0.82	0.18	0.213
Craniovertebral angle	48.16±5.4	52.96±4.69	-4.79	-6.73	-2.85	<0.001*

*p<0.05, n: Number of participants, [t]: Independent Samples T test, SD: Standard deviation

DISCUSSION

The results of this study demonstrate that, particularly among heavy users, long-term smartphone use significantly affects isolated upper cervical mobility, head posture, and body awareness, while it has no significant impact on general cervical mobility or pain threshold. This study is the first to examine the effects of SPA on both general cervical mobility and isolated upper cervical mobility. In previous studies, cervical mobility was evaluated as a whole, whereas this study separately assessed the lower and upper cervical regions. By comprehensively addressing the impact of SPA on musculoskeletal and sensorimotor functions, this study provides valuable insights into the consequences of excessive smartphone use in young adults. This comprehensive approach offers a deeper understanding of how SPA affects the cervical region and awareness processes.

In the present study, the smartphone addiction group and the control group were similar in terms of height, weight, and body mass index. However, when the ages of the participants were statistically compared, individuals in the control group were observed to be older. Age is known to be associated with forward head posture and mobility limitations. Although the control group was at a higher risk for forward head posture, younger individuals in the smartphone addiction group were found to have a greater craniovertebral angle. Similarly, this applies to upper cervical mobility and body awareness. As a result, the age variable did not affect the outcomes for parameters with significant findings. However, it may have obscured the results related to pressure pain threshold and total cervical mobility, where no significant difference was found between the two groups. This should be considered in future studies. In long-term smartphone users, forward head posture, defined as the anterior positioning of the cervical spine, is one of the most common postural deviations in the sagittal plane. According to previous studies, this postural change, characterized by decreased craniovertebral angle, is significantly more pronounced in individuals with SPA.[27-29] The findings of the present study are consistent with previous research, confirming that forward head posture is significantly increased in those with SPA. This result further substantiates the negative impact of prolonged smartphone use on cervical posture. From a clinical perspective, it underscores the need for awareness and the development of ergonomic training programs aimed at preventing head and neck postural issues related to smartphone usage.

The results showed that while isolated upper cervical mobility was significantly affected in individuals with SPA, general cervical mobility did not show a significant change. Specifically, in heavy smartphone users, isolated upper cervical mobility was markedly reduced compared to the control group, independent of general cervical mobility. Upper cervical mobility was assessed using the flexion-rotation test and the CROM device for both right and left rotation. This method of evaluating isolated upper cervical mobility is considered valid and reliable in the literature. While previous studies have focused on the effects of SPA on general cervical mobility, the present study is the first to specifically address the isolated upper cervical region.

This finding suggests that the reduction in upper cervical mobility plays a significant role in limiting upper cervical range of motion due to prolonged smartphone use. Therefore, developing specific therapeutic approaches aimed at preserving and improving upper cervical mobility in individuals with SPA is of great importance in clinical practice.

Another parameter we examined in individuals with SPA in the present study was body awareness. There is only one study investigated effect of SPA on body awareness.[30] According to the results of our study, there is a significant impairment in body awareness among heavy users. This underscores the critical importance of developing awareness training and rehabilitation approaches aimed at improving body awareness in individuals with SPA from a clinical perspective.

Another topic investigated in the present study is the effect of SPA on cervical PPT. Cervical PPTs were measured bilaterally using a mechanical pressure algometer at the lateral sides of the 2nd cervical spinous process and at the midpoint of the upper trapezius muscle. According to the results of the present study, cervical PPTs were similar in individuals with and without SPA. This finding is consistent with previous studies in the literature.[31] One of the factors that may have contributed to the lack of a significant difference in pressure pain threshold between the two groups is the exclusion of individuals with

pain from the study. Individuals with pain and smartphone addiction were not included in the study, as the presence of pain is also associated with forward head posture and could have masked the effects of smartphone addiction. This should be taken into consideration in future studies. Our findings suggest that SPA does not have a significant impact on cervical PPTs, and that cervical dysfunctions related to smartphone use may be more closely associated with posture and upper cervical mobility. Therefore, in clinical practice with individuals who have SPA, focusing on postural and mobility issues rather than PPT may be more beneficial.

Limitations

This study has several important limitations. First, the sample consists only of young individuals. Future studies involving broader age groups and individuals with different health conditions could assess the effects of SPA on cervical mobility, posture, body awareness, and pain threshold. Second, long-term follow-up studies in the future may provide insights into the time-dependent effects of SPA on cervical dysfunctions. Finally, PPTs measurements were taken from only two regions. Future studies could collect data from more regions and use different methods, such as pain tolerance.

This study comprehensively examined the effects of SPA on cervical mobility, head posture, body awareness, and cervical PPTs. It is the first study to specifically investigate the effects of SPA on isolated upper cervical mobility, making a significant contribution to the literature. Additionally, the methodologies used in this study were evaluated with valid and reliable measurement tools, which suggests that the findings are also clinically relevant.

CONCLUSION

This study provides important insights for clinical practices aimed at preventing and treating postural and mobility disorders related to SPA. The findings suggest that long-term smartphone use may lead to a decrease in isolated upper cervical mobility and impairments in body awareness, highlighting the need for rehabilitation programs to focus on these areas. In individuals with SPA, treatment approaches incorporating awareness training and specific mobility exercises could enhance clinical outcomes.

Future studies should include broader age groups and individuals to assess the effects of SPA. Additionally, long-term follow-up studies could provide valuable data on the time-dependent postural and neuromuscular changes related to SPA. Future research could also explore pain threshold more extensively by evaluating additional regions and using different methods, helping to better understand the impact of SPA on this parameter.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Atılım University Non-interventional Clinical Researches Ethics Committee (Date: 24.01.2024, Decision No: 604.01.02-160).

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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Changes in body composition and muscle strength in girls with idiopathic central precocious puberty during gonadotropin-releasing hormone agonist therapy

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ABSTRACT

Aims: Our objective is to explore changes in body fat distribution and muscle strength among a cohort of girls with idiopathic central precocious puberty (ICPP) undergoing the gonadotropin-releasing hormone analogs (GnRHa) therapy.

Methods: A total of 50 patients who were newly diagnosed with ICPP and treated with GnRHa were included in the study. Patients were investigated at baseline, 6th months and 12th months.

Results: Body-mass index (BMI) standard deviation score (SDS) was similar throughout the treatment duration. The percentage of body fat (PBF) increased from 24.2±5.1% at the beginning to 26.3±5.3% at the 6th month and to 27.7±5.43% at the 12th month ($p<0.001$). While lean body mass (LBM) increased during the treatment duration ($p<0.001$), there was a decrease in the LBM percentage in both the 6th month and 12th month ($p=0.001$, $p=0.005$). The change in PBF between 0 and 12 months was significantly higher in the group with PBF<97th percentile (p), with a median of 2.3 (3.3)%, compared to a median of 0.5 (0.5)% in the group with PBF>97th p ($p=0.005$).

Conclusion: Over the one-year duration of GnRHa treatment, no increase was observed in BMI SDS. While PBF increased, a decrease was noted in LBM percentage. Despite the decrease in LBM percentage, since LBM increased over the course of treatment, an increase in muscle strength was observed under GnRHa therapy. Additionally, the alteration in PBF during GnRHa treatment exhibited variations based on the initial PBF status.

Keywords: Central precocious puberty, GnRHa therapy, body composition, lean body mass, muscle strength

INTRODUCTION

Pubertal development involves the chemical maturation of body tissues, leading to changes in the quantity and distribution of adipose tissue, as well as increases in bone mass and fat-free lean tissue mass.[1] Key features of puberty include the appearance of secondary sex characteristics, accelerated skeletal maturation, and alterations in body fat distribution.[2] Central precocious puberty (CPP) results from the premature reactivation of the gonadotropin-releasing hormone (GnRH) pulse generator in the hypothalamus, causing the onset of secondary sexual characteristics before the age of eight in females and nine in males.[3] The idiopathic CPP (ICPP) diagnosis is established once all organic causes have been ruled out.[4] GnRH analogs (GnRHa) are the standard of care for treating CPP. However, despite their established safety and efficacy, significant questions persist, particularly concerning their impact on body-mass index (BMI).[3] The literature presents diverse data concerning the impact of GnRHa on BMI and raises concerns about body fat composition. There is variability in the findings, and particular attention has been drawn to the potential susceptibility of children with CPP to the development of adiposity.

Dual-energy lowercase letter (X-Ray) absorptiometry, bioelectrical impedance analysis (BIA), ultrasonography (USG), computed tomography, and magnetic resonance imaging (MRI) serve as essential tools for evaluating adiposity as well as the quantity and distribution of muscle mass in pediatric and adolescent patients.[1] Particularly, BIA stands out as a widely embraced method for assessing body composition, attributed to its user-friendly application, safety, non-invasiveness, cost-effectiveness, repeatability, and rapid result delivery.

During puberty, changes in hormone levels can lead to an increase in muscle mass and the development of muscle strength. However, the effects on muscle strength during puberty can vary from person to person. These effects may depend on various factors such as genetic factors, level of physical activity, dietary habits, and other environmental factors. The impact of early onset puberty and halting pubertal

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progression through the treatment on muscle strength is also a topic of interest. To measure muscle strength, various methods can be used including manual muscle testing, the Oxford Scale, isotonic, isokinetic, and isometric methods. Isometric methods measure the maximum static strength of the muscle. Evaluating muscle function, especially in children and adolescents, can be challenging. The most commonly used technique, due to its low cost and affordability, is hand dynamometry.[5]

This study aims to investigate alterations in BMI, body fat distribution with BIA and muscle strength with hand dynamometry in a group of girls with ICPP undergoing GnRHa therapy. Additionally, it aims to explore the factors influencing fat distribution during treatment.

METHODS

Study Design

Approval was obtained from the Akdeniz University Faculty of Medicine Clinical Researches Ethics Committee prior to the commencement of the study (Date: 16.03.2022, Decision No: KAEK-195). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This study was designed as a single-center, descriptive, longitudinal investigation. The cohort comprised 50 girls newly diagnosed with ICPP and treated with GnRHa at the pediatric endocrinology clinic of our hospital between September 2020 and January 2022. The research focused on examining these patients' clinical and laboratory findings at the initiation of GnRHa therapy, as well as at the 6th and 12th months of treatment, with subsequent comparisons. Exclusion criteria encompassed patients diagnosed with peripheral precocious puberty, those with concurrent chronic illnesses, and patients using medications that could impact puberty and growth. Additionally, boys diagnosed with ICPP were excluded from the study due to distinct growth and body composition patterns.

Patients were divided into two groups based on whether their percentage of body fat (PBF) was above or below the 97th percentile (p) upon the diagnosis of ICPP, and subgroup analyses were conducted. PBF reference curves for healthy Turkish children and adolescents were utilized for PBF percentiles according to age from the study by Kurtoğlu et al.[6]

Diagnosis and Treatment Procedure of ICPP Patients

The diagnosis of patients with ICPP was established based on the following criteria (3): (I) the presence of breast buds before the age of 8, (II) a basal luteinizing hormone (LH) level exceeding 1.0 IU/L or a peak LH level surpassing 5 IU/L in response to the LH-releasing hormone stimulation test, (III) evidence of accelerated growth and advancement of bone age (BA) by at least one year compared to chronological age (CA), and (IV) the absence of lesions in the hypothalamus-pituitary region as confirmed by MRI scans. Every subject diagnosed with ICPP received subcutaneous injections of 3.75 mg (initial dose) of GnRHa (Leuprolide acetate, Lucrin depot®) every 28 days. However, during follow-up, the treatment interval was adjusted to 21 days if there was an escalation in pubertal symptoms.

Clinical and Laboratory Investigations

Height, weight, and BMI standard deviation scores (SDS) were determined based on the reference values for Turkish children.[7] BMI was computed as the weight ratio to the square of height (kg/m^2). Overweight status was defined as having a BMI above the 85th percentile for age and sex, referencing Turkish children's norms, while cases exceeding the 95th percentile were classified as obese.[7] Pubertal staging followed the criteria established by Marshall and Tanner,[8] and BA was assessed using the Greulich and Pyle method.[9] For subjects with BA exceeding six years, predicted adult height (PAH) was calculated using the Bayley-Pinneau method.[10] Conversely, for subjects with of BA less than six years, the Roche-Wainer-Thissen (RWT) method was employed to estimate PAH.[11] Additionally, mid-parenteral height (MPH) was determined using the formula: (height of mother + height of father - 13)/2.

Luteinizing hormone levels were assessed through chemiluminescence immunoassay, while estradiol (E2) levels were determined using the electrochemiluminescence immunoassay method, both conducted by Roche in Mannheim, Germany. After treatment was initiated, the levels of LH, FSH, and E2 in the cases were measured 90 minutes later the GnRHa injection. Pelvic USG was carried out by a qualified radiologist for all subjects. Ovarian volume was computed using the formula: (D1×D2×D3/1000)×0.523, where D1 represents the longest longitudinal diameter, D2 denotes the largest anteroposterior diameter, and D3 signifies the largest transverse diameter, all measured in centimeters (cm) for each ovary. The total volume was then calculated as the sum of the volumes of both ovaries, expressed in milliliters. Similarly, uterus volume was determined using the same formula.

Evaluation of Body Composition and Muscle Strength

The Bioelectrical Impedance Analysis method was employed to assess total body fat (TBF) and lean body mass (LBM) using a segmental body composition analyzer, specifically the Tanita BC-418MA (Tanita Corporation, Tokyo, Japan), with adjustments made for minimal indoor clothing. Before the measurement, participants were instructed to abstain from consuming food or beverages for at least one hour, empty their bladders, and wear lightweight clothing. The analyzer, accounting for age, sex, height, and weight, provided precise percentage of body fat (PBF) measurements to the nearest 0.1%. During the assessment, children and adolescents stood barefoot on the analyzer while gripping handholds with each hand. Muscle strength measurements of the cases were conducted using a dynamometer tool that measures isometric contraction force (GRIP-D dynamometer). Three measurements were taken for each hand, and the average was calculated. Total muscle strength was determined by dividing the sum of the average forces of the right and left hands by two.

Statistical Analysis

We conducted the statistical analysis using The Statistical Package for the Social Sciences (SPSS for Windows, Version 23.0, Chicago, IL, USA). Continuous measurements were reported as either median [Interquartile range (IQR)] or mean ± standard deviation, while categorical data were presented as counts and percentages. We employed Pearson's chi-square and Fisher's exact tests to compare categorical variables. The Shapiro-Wilk test was used to assess normality, and distribution was also checked when comparing continuous measurements. Normally distributed parameters were compared using the t-test, while non-normally distributed parameters were compared using the Mann-Whitney U test. A mixed-design repeated measures ANOVA test was employed to determine the time-by-group interaction. In cases where measurements taken at more than two-time points violated the assumption of normal distribution, the Friedman test was utilized for comparisons. The Spearman correlation test assessed relationships between ordinal or non-normally distributed continuous variables. In contrast, the Pearson correlation test was employed for continuously distributed variables conforming to normal distribution. A p-value less than 0.05 was considered indicative of statistical significance.

RESULTS

The results of a total of 50 girls diagnosed with ICPP who were included in the study were analyzed. Changes in anthropometric measures and clinical parameters during the GnRHa therapy are given in Table 1. The mean CA of the cases at the beginning of treatment was 7.37±0.68 years, and the median BA was 8.75 (1.0) years. The maturation degree of BA was decreased at the 12th month of treatment compared to the beginning of treatment (p=0.039). After the initiation of treatment, the Tanner stages of the cases generally remained stable, and no progression in pubertal development was observed. Height SDS was similar at the beginning of treatment, at the 6th month, and at the 12th month. Although BMI was higher at the 6th month and 12th month of treatment compared to the beginning (p=0.003, p<0.001), BMI SDS was similar throughout the treatment duration. While the prevalence of overweight was 26% both at the beginning of GnRHa therapy and at the 12th month, the prevalence of overt obesity was 14% at the beginning and 10% at the 12th month. A statistically significant increase in PAH SDS at the 12th month of treatment was observed due to the decrease in BA maturation compared to the CA (p=0.031).

Changes in body composition during GnRHa therapy are presented in Table 2. Compared to the beginning of treatment, a statistically significant increase in TBF was observed at both the 6th month and 12th month (p<0.001). The PBF increased from an average of 24.2±5.1% at the beginning to 26.3±5.3% at the 6th month and 27.7±5.43% at the 12th month (p<0.001). While LBM increased during the treatment duration (p<0.001), there was a decrease in the LBM percentage in both the 6th month and 12th month (p=0.001, p=0.005). Ten cases had a PBF above the 97th p at the beginning of GnRHa treatment. A comparison of those cases with those whose PBF was below 97th p is presented in Table 3. The CA, BA, height SDS, and PAH SDS levels of the two groups were similar at the beginning of treatment and at the 12th month. Similarly, basal and stimulated LH levels, basal E2 level, and ovarian and uterine volumes were similar at the beginning of treatment in the two groups. In the group with PBF>97th p, the mean PBF

Table 1. Changes in antropometric measures and clinical parameters during the GnRHa therapy

Variable	Basal	6th month	12th month	p
CA (year)	7.37±0.68	7.90±0.68	8.41±0.75	
BA (year)	8.39±1.07	-	9.03±1.08	<0.001[b]
BA/CA	1.12±0.11	-	1.08±0.12	0.039[b]
Statural age (years)	8.43 (1.73)	8.98 (1.09)	9.42 (1.43)	<0.001[a,b]
Tanner stage				
2	46 %	50%	55%	
3	52%	48%	43%	
4	2%	2%	2%	
Weight (kg)	28 (7)	30.5 (8.4)	33.4 (7.9)	<0.001[a,b]
Weight SDS	0.73 (1.56)	0.95 (1.37)	0.88 (1.01)	0.153[a] 0.047[b]
Height (cm)	128 (8.30)	132 (6.4)	134.7 (8.2)	<0.001[a,b]
Height SDS	1.01 (1.29)	1.07 (0.17)	1.02 (1.5)	0.131[a] 0.752[b]
BMI (kg/m^2)	17.40±2.78	17.90±2.73	18.3±2.88	0.003[a] <0.001[b]
BMI SDS	0.61 (1.53)	0.71 (1.20)	0.73 (1.34)	0.103[a] 0.053[b]
Overweight prevalance (%)	26	32	26	
Overt obesity prevalance (%)	14	10	10	
MPH (cm)	162.5±4.6	-	-	
MPH SDS	0.07 (0.97)	-	-	
PAH (cm)	162.5±7.11	-	163.9±7.13	0.011[b]
PAH SDS	0.01 (1.6)	-	0.06 (1.24)	0.031[b]
LH (mIU/ml)	0.72 (0.77)	0.99 (1.0)	1.05 (0.85)	0.183[a] 0.271[b]
LH (peak on LHRH test, mIU/ml)	6.87 (5.63)	-	-	
FSH (mIU/ml)	3.57 (2.90)	1.71 (1.69)	2.05 (1.52)	<0.001[a] 0.001[b]
E2 (pg/ml)	14.7 (23.1)	5.0 (6.8)	5.0 (6.6)	0.003[a] 0.002[b]

Data are expressed as mean or mean±standard deviation or median (IQR) or as number (percent), [a]Comparison of 0-6th month, [b]Comparison of 0-12th month, CA: Chronological age, BA: Bone age, SDS: Standard deviation score, BMI: Body-mass index, MPH: Midparenteral height, PAH: Predicted adult height, GnRHa: Gonadotropin-releasing hormone analog

Table 2. Changes in body composition during the GnRHa therapy

Variable	Basal	6th month	12th month	p
TBF (kg)	7.11±2.72	8.3±2.8	9.41±3.51	<0.001[a,b]
PBF (%)	24.2±5.1	26.3±5.3	27.7±5.43	<0.001[a,b]
LBM (kg)	20.5±3.53	21.6±3.9	22.8±3.62	<0.001[a,b]
LBM percentage (%)	72.1±5.73	69.4±5.0	68.5±5.18	0.001[a] 0.005[b]
Muscle strength (Newton)	8.06±2.04	8.36±2.29	10.60±2.56	<0.001[a,b]

Data are expressed as mean±standard deviation, [a]Comparison of 0-6th month, [b]Comparison of 0-12th month, TBF: total body fat, PBF: percentage of body fat, LBM: Lean body mass, GnRHa: Gonadotropin-releasing hormone analog

Table 3. Subgroup analyzes of subjects according to PBF at the beginning of the GnRHa therapy

Variable	PBF >97 p (n=10)	PBF <97 p (n=40)	p
At the beginning of the treatment			
CA (year)	7.30±0.93	7.37±0.62	0.786
BA/CA	1.08±0.10	1.13±0.12	0.214
Height SDS	0.76 (2.05)	1.0 (1.2)	0.874
BMI SDS	2.05 (0.64)	0.38 (1.2)	<0.001
PAH SDS	0.39 (1.49)	-0.17 (1.6)	0.308
PBF (%)	31.9±4.8	22.2±2.8	<0.001
LBM	22.1±4.8	20.3±3.1	<0.001
LBM percentage (%)	64.1±4.6	74.2±3.8	<0.001
Muscle strength (Newton)	8.57±2.2	7.93±2.0	0.371
LH (basal, mIU/ml)	0.34 (1.2)	0.50 (0.86)	0.582
E2 (basal, pg/ml)	14.1 (22.5)	14.9 (20.8)	0.760
LH (peak on LHRH test, mIU/ml)	6.3 (6.9)	7.3 (5.3)	0.325
Uterus volume (ml)	2.64 (3.4)	3.09 (3.5)	0.333
Total ovarian volume (ml)	3.90 (2.5)	4.05 (3.1)	0.787
At the end of the 12th month of the treatment			
BA/CA	1.07±0.07	1.08±0.13	0.842
Height SDS	1.2 (2.1)	1.01 (1.1)	0.871
BMI SDS	1.91 (1.1)	0.57 (1.2)	<0.001
PAH SDS	0.1 (1.7)	0.02 (1.2)	0.890
PBF (%)	32.6±5.5	26.0±4.2	0.002
LBM	24.5±6.83	22.3±2.5	0.157
LBM percentage (%)	64.1±5.3	70.1±4.0	<0.001
Muscle strength (Newton)	10.2±1.9	10.5±2.6	0.677
Change in BFP (0-12th months)	0.5 (0.5)	2.3 (3.3)	0.005

Data are expressed as mean±standard deviation or median (IQR), CA: Chronological age, BA: Bone age, SDS: Standard deviation score, BMI: Body-mass index, PAH: Predicted adult height, PBF: Percentage of body fat, LBM: lean body mass, LH: Luteinizing hormone, E2: Estradiol, LHRH: Luteinizing hormon releasing hormone, GnRHa: Gonadotropin-releasing hormone analog

was 31.9±4.8 % at the beginning of treatment and 32.6±5.5% at the 12th month, whereas in the group with PBF<97th p, the mean PBF was 22.2±2.8% at the beginning of treatment and 26.0±4.2% at the 12th month. The change in PBF between 0 and 12 months was significantly higher in the group with PBF<97th p, with a median of 2.3 (3.3) %, compared to a median of 0.5 (0.5) % in the group with PBF>97th p (p=0.005).

No significant correlation was observed between the age at the initiation of GnRHa treatment and the 12th month PBF in the correlational analysis, as shown in Table 4. A reverse relationship was found between the maturation degree of BA at the beginning of treatment and the 12th month of PBF. It was observed that significant determinants of the 12th month PBF were the BMI and LBM percentage at the beginning of treatment, at the 6th month, and at the 12th month of the GnRHa treatment (p<0.001).

As shown in Table 5, muscle strength exhibited a positive correlation with LBM during all months within the same period (p<0.05).

Table 4. Correlational analysis of 12th month PBF with other clinical parameters

	12th month PBF	
CA at diagnosis (year)	p=0.455	r=0.132
BMI at diagnosis	p<0.001*	r=0.832
BA/CA at diagnosis	p=0.03*	r=-0.373
PBF at diagnosis	p<0.001*	r=0.839
LBM percentage at diagnosis	p<0.001*	r=-0.829
BMI at 6th month	p<0.001*	r=0.800
PBF at 6th month	p<0.001*	r=0.815
LBM percentage at 6th month	p<0.001*	r=-0.818
BMI at 12th month	p<0.001*	r=0.866
LBM percentage at 12th month	p<0.001*	r=-0.937

*Statistically significant correlation, r=correlation coefficient, CA: Chronological age; BA: Bone age; BMI: Body-mass index; PBF: Percentage of body fat; LBM: Lean body mass

Table 5. Correlational analysis of muscle strength with LBM

	Muscle strength at basal		Muscle strength at 6th month		Muscle strength at 12th month	
LBM at basal	p<0.001*	r=0.539	p=0.002*	r=0.473	p=0.003*	r=0.505
LBM at 6th month	p<0.001*	r=0.541	p<0.001*	r=0.565	p<0.001*	r=0.611
LBM at 12th month	p=0.094	r=0.296	p=0.007*	r=0.481	p=0.006*	r=0.465

*Statistically significant correlation, r=correlation coefficient, LBM: Lean body mass

DISCUSSION

Puberty is characterized by significant hormonal fluctuations and rapid growth in body size, accompanied by noticeable alterations in body composition.[12] Both sexes undergo substantial increases in adiposity, although the body fat the proportion growth rate is comparatively slower in boys due to a simultaneous rapid surge in lean mass.[1] While the BMI proves to be a reliable measure of adiposity in adulthood, its applicability is intricate when applied to children and adolescents due to its dependence on factors such as stature, the relative difference between trunk and leg length, fat-free mass, and maturity level. The sensitivity of BMI in identifying children with excess TBF or PBF is only low to moderate. This implies that using BMI to detect overweight children is characterized as poor to fair.[13,14] Therefore, monitoring body composition rather than solely tracking BMI changes during this developmental stage holds significance, as various aspects of body composition during puberty serve as predictors for subsequent measurements of these traits in adulthood.

The changes in body composition in girls experiencing precocious puberty and the effects of GnRHa treatment on this process are also a subject of curiosity. The impact of GnRHa treatment on body composition in girls experiencing early puberty can vary. The suppression of sex hormone production can affect the typical patterns of fat accumulation and muscle development.[15,16] Studying changes in body composition over time -before, during, and after the administration of GnRHa- offers a distinctive lens through which we can unravel the intricate physiological mechanisms governing growth amid the targeted and reversible suppression of gonadal sex steroids. This analysis allows us to delve into the nuanced regulation of

growth and serves as a valuable avenue to address a common clinical concern: the potential inclination of children with CPP towards developing obesity during GnRHa therapy.[17,18]

Data obtained from 297 healthy Caucasian girls in the Fels Longitudinal Study reveals a steady increase in TBF levels, starting at a mean of approximately 5.5 kg at age 8 and reaching around 15 kg at age 16.[19] In our study, it is noteworthy that at the end of the 12th month of GnRHa treatment in cases of ICPP, the mean TBF was found to be considerably higher at 9.4 kg compared to this study when cases were average 8.4 years old. However, interpreting this finding as an increase in adiposity due to GnRHa treatment is challenging, as the patients already had a fat content of a mean of 7.1 kg at the onset of treatment when they were a mean of 7.3 years old. The potential influence of the early onset of pubertal changes on variations in body composition analysis makes it challenging to unequivocally attribute the observed differences to the effects of GnRHa treatment. On the other hand, increased PBF during treatment in the present study is consistent with numerous studies in the literature.[20-22] As reported in a more extended follow-up study, elevated PBF was observed both at the initiation and cessation of GnRHa treatment, and it normalized two years after the discontinuation of therapy. After an initial aggravation of adiposity, no prolonged adverse effects on PBF were found.[20]

In our study, despite an increase in LBM during treatment, a decrease in LBM percentage was demonstrated due to a comparatively higher increase in TBF, consistent with studies.[20,21] The reported decrease in growth hormone (GH) and insulin-like growth factor-I (IGF-I) levels during GnRH-a therapy may contribute to the increase in PBF and decrease in LBM percentage.[22-24] An inverse correlation between GH levels and BMI was also noted in the study by Kamp et al.[23]

The impact of GnRHa treatment on height extends beyond reduced GH and IGF-1 levels. Despite reports of a decrease in height SDS during the treatment period, GnRHa therapy can positively influence final adult height by slowing down the skeletal growth rate and delaying the closure of growth plates.[3] Although there was an observed decrease in linear growth during GnRHa administration, there is an improvement in growth potential owing to a reduction in the rate of bone maturation induced by prior exposure to high estrogen levels. In our study, a decrease in bone maturation and an increase in PAH were observed, aligning with the findings in the existing literature during the first year of GnRHa treatment.[4,15,16]

The impact of early exposure to gonadal sex steroids in children with CPP on the physiological interpretation of BMI remains uncertain. Undoubtedly, these children exhibit greater height and weight compared to their chronologically age-matched counterparts, potentially influencing their BMI SDS.[17] Although an increase in BMI was observed during our study, there was no significant increase in BMI SDS. Some studies do not report a significant increase in BMI during GnRH treatment.[25,26] On the other hand, several studies report increased BMI during the treatment.[27,28] The variability in results across different groups in the literature can be attributed to genetic factors and significant heterogeneity. For instance, in the study conducted by Boot et al.,[18] a notable increase in BMI SDS during GnRHa treatment was reported. However, the subjects in this study differ from those in other studies, as some girls experienced the onset of puberty after the age of 8 years. Investigating whether these older subjects had shorter treatment durations would be intriguing, considering the inverse relationship between therapy duration and BMI SDS observed in Palmert et al.[17] study. Furthermore, some studies emphasize that BMI changes depend on the initial BMI status. As reported in some studies, children with initially overweight/obese patients exhibited a more remarkable change in BMI compared to those with normal BMI.[4,17] Conversely, more studies reported that the change in BMI SDS was significantly greater in normal-weight patients than in overweight patients.[27,29-31] Aiming to assess the impact of the initial PBF on clinical and laboratory parameters in our study with the same logic, we categorized patients based on whether their PBF was above or below the 97th p at the time of diagnosis. Interestingly, we observed a statistically significant increase in PBF the group with PBF below 97th p when comparing to the higher group, over the 12 months. Throughout the pubertal course, an increase in adiposity in cases with lower fat percentages may stem from diverse dynamics in adipokines, presenting one of the plausible mechanisms. This aspect gains significance when considering data suggesting the necessity of adequate leptin levels for initiating puberty.[32] While elevated serum leptin concentrations have not been proven to induce precocious pubertal development in humans, evidence indicates that CPP occurs in the presence of pubertal stage-appropriate, or in other words, sufficient leptin levels.[33] During the treatment of precocious puberty, variations in adipokine secretion and their impact dynamics may occur based on the initial fat percentage status.

Before puberty, muscle mass shows a linear increase with age.[34] During this phase, the anabolic effects of GH and IGF1 drive physical growth.[35] However, muscle strength gains in this developmental stage appear to be more influenced by neural factors than by an increase in muscle mass.[36] In puberty, muscle strength becomes closely associated with muscle quantity. As physiological functions align more with biological age than chronological age, an early-maturing child likely holds an advantage in absolute strength measures compared to a later-maturing peer of the same sex with less muscle mass. In girls, peak strength gains typically occur after peak height velocity, although there is more individual variability in the strength-to-height and body weight relationship for girls compared to boys, owing to the close association between boys' muscle strength and androgens. Female adolescents generally reach a plateau in muscle strength gains around the age of 15 years.[37,38] In our study, we observed that muscle strength gains continued under GnRHa treatment. This phenomenon may be linked to an increase in LBM despite a decrease in LBM percentage, as muscle strength shows a positive correlation with LBM throughout all months.

Limitations

Our study has certain limitations. The follow-up data for the cases are confined to a one-year duration of the GnRHa

treatment. A more extended follow-up of cases, assessing body composition ratios at the end of the GnRHa treatment and in adulthood, could provide a clearer understanding of the long-term effects of initial PBF. Additionally, conducting studies with larger patient cohorts, including a greater number of cases with initial PBF >97th p, could enhance the reliability of subgroup analyses.

CONCLUSION

Over the one-year duration of GnRHa treatment in girls experiencing ICPP, no increase was observed in BMI SDS and overweight-obesity rates in the present study. While PBF increased, a decrease was noted in LBM percentage. Despite the decrease in LBM percentage, since LBM increased over the course of treatment, an increase in muscle strength was observed under GnRHa therapy. Additionally, the alteration in PBF during GnRHa treatment exhibited variations based on the initial PBF status.

Over the one-year duration of GnRHa treatment in girls with ICPP, no increase was observed in BMI SDS or the rates of overweight and obesity. While the PBF increased, a decrease in LBM percentage was noted. However, despite the reduction in LBM percentage, the overall increase in LBM during the treatment period led to an observed improvement in muscle strength under GnRHa therapy. Moreover, the changes in PBF during treatment varied depending on the initial PBF status. The greater increase in PBF observed in cases with PBF >97th percentile at baseline is important due to the lack of similar data in the literature and its potential to provide insights for future studies. Assessing the PBF at the initiation of GnRHa treatment and monitoring changes in PBF during follow-up may benefit patients for future risk of obesity and metabolic complications.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Akdeniz University Faculty of Medicine Clinical Researches Ethics Committee (Date: 16.03.2022, Decision No: KAEK-195).

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

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Author Contributions

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

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Original Article

HEALTH SCIENCES
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Factors affecting sexual dysfunction in hemifacial spasm

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ABSTRACT

Aims: Hemifacial spasm (HFS) is a movement disorder consisting of involuntary and synchronous contractions of facial nerve innervated muscles, usually involving one half of the face. Sexual health is an important aspect of mental health and has been frequently investigated in movement disorders such as Parkinson's disease. The aim of this study was to investigate the relationship between sexual dysfunction and factors such as age, depression, disease duration, and disease severity in patients with HFS.

Methods: This prospective, descriptive study included 50 patients with HFS. Data were collected using the beck depression inventory (BDI), the HFS severity scale, and the Arizona Sexual Experiences Rating Scale (ASLS) for sexual dysfunction.

Results: The mean age of the patients included in the study was 50.05±9.42 years. 58.2% were female and 41.8% were male. It was observed that sexual dysfunction was more common in female HFS patients and patients with low educational level. In addition, the frequency of sexual dysfunction increased with increasing age and depression level. Although there was a statistically significant relationship between the severity of HFS and sexual dysfunction, the duration of the disease had no significant effect on sexual dysfunction.

Conclusion: This study shows that sexual dysfunction is common in HFS patients and associated with gender and age. Sexual dysfunction has been shown to increase with depression and HFS severity.

Keywords: Hemifacial spasm, sexual dysfunction, depression

INTRODUCTION

Hemifacial spasm (HFS) is a movement disorder consisting of involuntary and synchronous contractions in facial nerve innervated muscles, usually involving one half of the face. Its prevalence is approximately 10 per 100.000 people.[1,2] Spasms may be clonic or more rarely tonic. Involuntary contractions start mostly in the lower eyelid and can be seen around the eyes, cheeks and mouth in the later stages. These contractions are known to be triggered by voluntary contraction of facial muscles, external factors such as wind, or personal factors such as anxiety and phatic. Chronic HFS symptoms lead to loss of self-confidence, social isolation and even depression, which significantly impairs quality of life in approximately 90% of patients.[3]

There are several studies evaluating quality of life in patients with HFS.[4,5] Patients may self-describe physical discomfort such as facial pain, discomfort, visual disturbances, photophobia and trismus due to HFS which affect quality of life. However, they usually hesitate to mention their problems in sexual functioning when they are not questioned. Sexual health is an important component that affects the quality of life of patients. Sexual dysfunctions consist of low sexual desire, sexual aversion disorder, arousal and orgasm disorder, vaginismus and painful sexual intercourse problems in women; and low sexual desire, sexual aversion disorder, erectile dysfunction, premature ejaculation and other ejaculation disorders and painful sexual intercourse problems in men.[4,5]

Sexual functioning is considered an important element of mental health.[6] Studies have found that sexual dysfunction is increased in other movement disorders.[7] The relationship between sexual dysfunction and HFS, on the other hand, remains to be elucidated as a symptom with limited information, which negatively affects the psychological and physical health, quality of life and treatment process of patients. The aim of this study was to investigate the relationship between sexual dysfunction and factors such as age, depression, disease duration, and disease severity in patients with HFS.

METHODS

Study Design

This is a prospective, descriptive study conducted with 50 hemifacial spasm patients who were followed up in the *Botulinum* toxin applications and movement disorders unit of the Neurology Clinic of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital. The study was approved by the Sancaktepe Şehit Prof. Dr. İlhan Varank

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Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 12.08.2024, Decision No: 252). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Population

Patients aged 18-65 years, heterosexual, giving informed consent and without concomitant movement disorders, severe chronic diseases and cognitive impairment were included in the study. All assessments were obtained from patient files and scales administered to patients at least 12 weeks after the last *Botulinum* toxin administration during the dose-ending period.

Patients' age, gender, education level, marital status, duration of illness, duration of *Botulinum* toxin treatment, and presence of comorbidities were obtained from their files filled out during regular end-of-dose evaluations at the *Botulinum* toxin administration clinic. Beck depression inventory (BDI) was used for mood assessment, HFS severity scale[8] was used to assess disease severity, and Arizona Sexual Experiences Rating Scale (ASLS) was used for sexual dysfunction.

Statistical Analysis

In this study, in addition to descriptive statistics, the Chi-square test was applied to examine the relationship between categorical variables and sexual dysfunction. The Mann-Whitney U test was used to assess differences between continuous variables. Spearman's correlation analysis was performed to examine the correlation between data that did not show normal distribution. Statistical significance was considered at $p<0.05$, and GraphPad Prism 10 was used for the analyses.

RESULTS

Descriptive statistics included variables such as age, gender, educational status and marital status. The mean age of the patients was 50.05±9.42 years. 58.2% were female and 41.8% were male (Figure 1). 78.2% of the patients were married and 21.8% were single (including widow) (Figure 2). While 63.6% of the patients had high school or higher education, 36.4% had primary or secondary school education (Figure 3, Table 1).

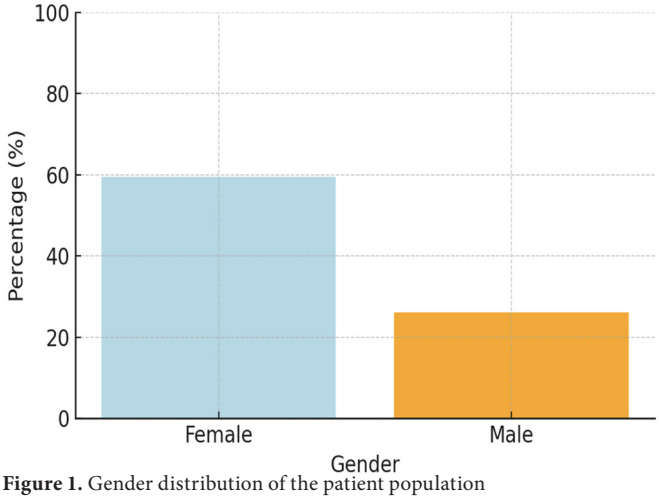

Figure 1. Gender distribution of the patient population

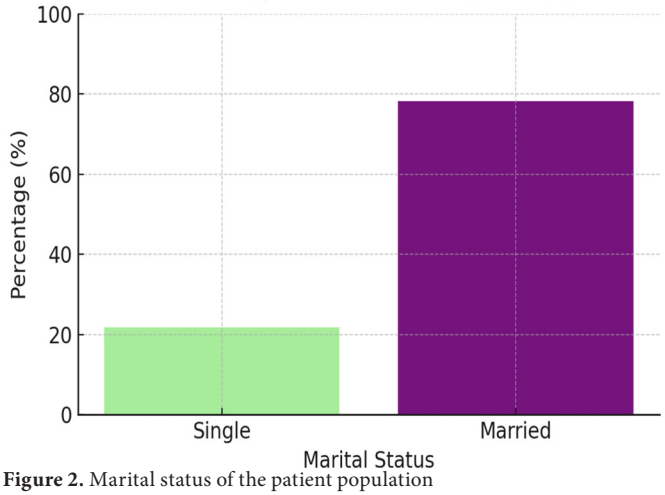

Figure 2. Marital status of the patient population

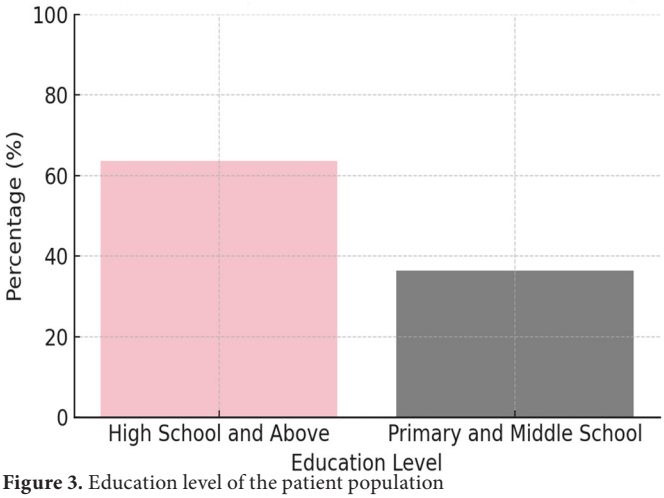

Figure 3. Education level of the patient population

Table 1. Comparison of sexual dysfunction and categorical variables (T test)	
Age (mean±SD)	50.05±9.42
Number of patients	55
Gender	
Female	n=32 (58.2%)
Male	n=23 (41.8%)
Education level	
High school and above	n=35 (63.6%)
Primary school and middle school	n=20 (36.4%)
Marital status	
Married	n=43 (78.2%)
Single (including widowed)	n=12 (21.8%)
Sexual dysfunction	
Present	n=25 (45.5%)
Absent	n=30 (54.5%)
Female patients (n=32)	
Sexual dysfunction present	n=19 (59.4%)
Male patients (n=23)	
Sexual dysfunction present	n=6 (26.1%)

SD: Standard deviation

The relationship between education level and HFS severity was analyzed to identify potential associations. Spearman correlation analysis revealed a significant negative correlation (Spearman p=-0.30, p=0.026), suggesting that individuals with lower levels of education tend to experience higher HFS severity.

When the relationship between sexual dysfunction and categorical variables was analyzed, a statistically significant relationship was found between gender and sexual dysfunction (p=0.030) (Figure 4). Sexual dysfunction was more common in women (Table 2).

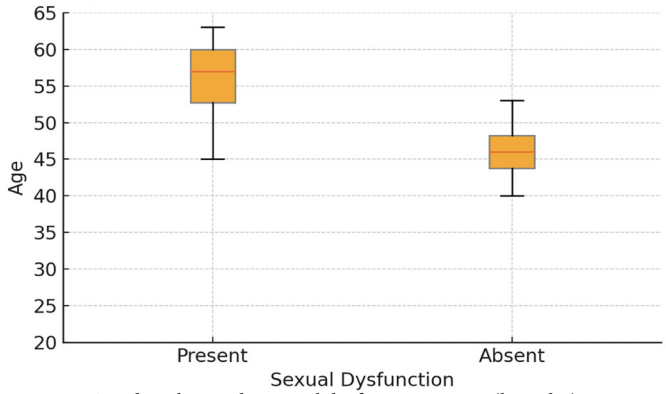

Figure 4. Age distribution by sexual dysfunction status (box plot)

Table 2. Comparison of sexual dysfunction with categorical variables (Chi-square test)

Variable compared with sexual dysfunction	Chi-square value	p-value	Significance
Gender	4.71	0.03	Yes
Marital status	0.47	0.493	No
Education level	13.02	0.00	Yes

No significant relationship was found between marital status and sexual dysfunction (p=0.493) (Table 2). This result indicates that being married or single has no significant effect on the presence of sexual dysfunction. Marital status was not a determining factor for sexual dysfunction in these data.

A strong significant correlation was found between education level and sexual dysfunction (p<0.001) (Table 2). It is understood that sexual dysfunction may be more common in individuals with lower education levels. This finding suggests that education level is an important factor that may affect sexual health.

Mann-Whitney U test was applied to examine the relationship between age data and the presence of sexual dysfunction. Shapiro-Wilk test confirmed that the data were not normally distributed (p=0.033). According to the Mann-Whitney U test results, a statistically significant difference was found between the ages of patients with and without sexual dysfunction (U=656.0, p<0.001). This finding suggests that age may be an important factor affecting the presence of sexual dysfunction. It is observed that sexual dysfunction increases with age.

Spearman correlation analysis was applied to examine the relationship between Beck Depression Inventory (BDI-II) and sexual dysfunction score (ASLS) (Figure 5). Shapiro-Wilk test confirmed that both variables were not normally distributed.

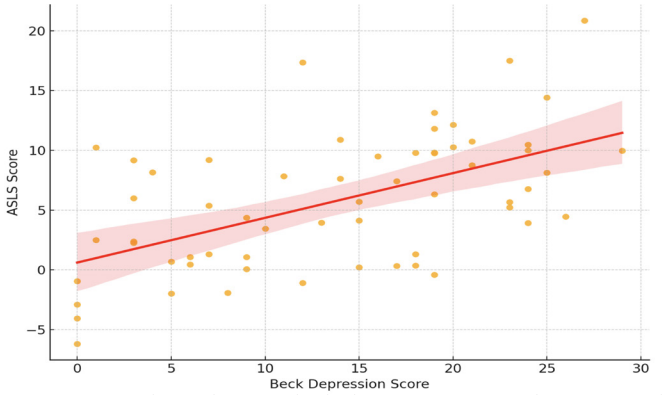

Figure 5. Correlation between beck depression score and ASLS sexual dysfunction score

ASLS: Arizona Sexual Experiences Rating Scale

Spearman's correlation analysis revealed a moderately positive and statistically significant relationship between depression score and sexual dysfunction score (Spearman's p=0.478, p<0.001). This result indicates that sexual dysfunctions increase with increasing levels of depression.

According to the correlation analysis results, a statistically significant and positive correlation was found between HFS severity and sexual dysfunction (r=0.536, p=0.015). This finding suggests that as the severity of HFS increases, sexual dysfunction also increases. Furthermore, a strong and statistically significant negative correlation was observed between the duration of *Botulinum* toxin treatment and sexual dysfunction (r=-0.598, p=0.005), indicating that sexual dysfunction decreases as the duration of treatment increases. On the other hand, no significant correlation was found between disease duration and sexual dysfunction (r=0.023, p=0.924), suggesting that disease duration had no significant effect on sexual dysfunction. Similarly, although there was a negative correlation between HFS severity and duration of *Botulinum* toxin treatment (r=-0.386, p=0.092), this relationship was not statistically significant (Table 3).

To further understand the factors influencing sexual dysfunction, logistic regression analysis expanded to include gender, age, depression score, disease duration, HFS severity, and treatment duration as predictors. The results indicate

Table 3. The relationship between HFS severity and sexual dysfunction, disease duration and botox duration

Variable	HFS severity	Sexual dysfunction (ACYO)	Disease duration (years)	Botox duration (months)
HFS severity	1.0 (p=0.0)	0.536 (p=0.015)	0.003 (p=0.989)	-0.386 (p=0.092)
Sexual dysfunction (ASLS)	0.536 (p=0.015)	1.0 (p=0.0)	0.023 (p=0.924)	-0.598 (p=0.005)
Disease duration (years)	0.003 (p=0.989)	0.023 (p=0.924)	1.0 (p=0.0)	0.081 (p=0.735)
Botox duration (months)	-0.386 (p=0.092)	-0.598 (p=0.005)	0.081 (p=0.735)	1.0 (p=0.0)

ASLS: Arizona Sexual Experiences Rating Scale

that both gender and age remain significant predictors of sexual dysfunction in this more comprehensive model. Specifically, being female (p=0.013) and older age (p=0.001) are both significantly associated with a higher likelihood of sexual dysfunction. Although depression score demonstrated a positive association with sexual dysfunction, this was not statistically significant (p=0.194) in the context of other predictors. Disease duration, HFS severity, and treatment duration similarly showed no significant effects, with p-values of 0.487, 0.496, and 0.868, respectively, indicating that these disease-specific factors may not independently influence sexual dysfunction when controlling for demographic variables (Table 4).

Table 4. Multivariate analysis: factors affecting sexual dysfunction

Predictor	Coefficient	SE	z-value	p-value	Significant (p<0.05)
Constant	-22.24	6.45	-3.45	0.001	Yes
Gender (female)	3.48	1.40	2.48	0.013	Yes
Age	0.35	0.10	3.35	0.001	Yes
Depression score	0.15	0.12	1.30	0.194	No
Disease duration (months)	-0.01	0.01	-0.70	0.487	No
HFS severity	0.47	0.70	0.68	0.496	No
Treatment duration (months)	-0.004	0.03	-0.17	0.868	No

SE: Standard error

DISCUSSION

The aim of our study was to investigate the prevalence of sexual dysfunction in patients with HFS and to examine the relationship between sexual dysfunction and various factors such as age, depression, disease duration and severity. There are no studies on this subject in our country.

Chronic HFS symptoms interfere with social functioning in almost 90% of patients, leading to loss of self-confidence, social isolation and even depression that significantly impairs the quality of life of these patients.[3] Despite the known effect of depression and anxiety on HFS symptoms,[9,10] no study has evaluated the effect of these emotions on sexual dysfunction in HFS patients. Stigma is also one of the important factors causing depression. The effect of stigma on the quality of life of patients with HFS has also been shown.[11] Self-perceived stigmatization may impair factors such as self-confidence and body image, which are very important for sexual health. In our study, a moderate positive and statistically significant correlation was found between depression score and sexual dysfunction score. This result indicates that sexual dysfunctions increase with increasing depression level.

Although there are several studies in the literature indicating that sexual dysfunction is increased in patients with dystonia,[12] sexual dysfunction in HFS patients was compared with dystonia patients (spasmodic torticollis and blepharospasm patients) in only one study.[13] In this study in which well-being in sexual life was evaluated and compared in patients with blepharospasm, cervical dystonia and hemifacial spasm, impaired sexual functioning was observed in all groups. In our study, 25 (45.5%) of HFS patients were found to have sexual dysfunction.

In the same study, dystonia patients (blepharospasm, cervical dystonia) were not satisfied with their sexual life, whereas HFS patients reported the same level of satisfaction as healthy controls.[13] In this study, the fact that all patient groups (BFS, CD, HFS) had normal scores on the sexual avoidance subscale was interpreted by the authors of the study as indicating that the personal and emotional aspects of sexual life were excessively protected, especially in patients whose movement disorders were limited to craniofacial muscles.

In our study, a statistically significant and positive correlation was found between HFS severity and sexual dysfunction. This finding indicates that as the severity of HFS increases, sexual dysfunction also increases. This finding is thought to be a result of depression, stigma and negative effects on quality of life as the severity of the disease increases.

A study investigating sexual well-being in Blepharospasm, Spasmodic Torticollis and HFS found that sexual dysfunction was more common in women than in men. In a study published in 2023 by Zhu et al.[14] investigating sexual function in Wilson's Disease, it was found that sexual dysfunction was more common in female patients. In our study, similar to other studies evaluating sexual dysfunction in movement disorders in the literature, sexual dysfunction was more common in women.

The fact that sexual dysfunction decreased as the duration of BoNT treatment was prolonged in the HFS patients included in the study, but no significant relationship was found between the duration of the disease and sexual dysfunction suggests that it may be related to the decrease in depression and anxiety levels as a result of the patient's observation of the decrease in symptoms as a result of treatment after BoNT injections, which is the most practical and effective treatment method of the disease, and getting used to the treatment process that continues in certain periods.

Limitations

Our study has 2 limitations. The first is the lack of a control group and the second is the small number of patients.

CONCLUSION

As a result, our study showed that the frequency of sexual dysfunction was high in patients with HFS. Sexual dysfunction has been shown to increase with depression and severity of HFS. HFS should not only be considered as a motor symptom, it should be considered as a disease that may impair the quality of life including sexual dysfunction because it may also affect body perception and stigma, especially because the facial muscles are affected, and patient evaluation and treatment approaches should be questioned from this point of view.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 12.08.2024, Decision No: 252).

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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Original Article

HEALTH SCIENCES
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Characteristics of pediatric patients with chronic cough: data from a pediatric immunology and allergy outpatient clinic

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ABSTRACT

Aims: Chronic cough is a common complaint in childhood. A differential diagnosis is very important in children with a chronic cough. We aimed to investigate the etiology and underlying risk factors of chronic cough in children.

Methods: Patients aged 1-18 years who were referred to Sincan Training and Research Hospital Pediatric Immunology and Allergy Outpatient Clinic were included. Demographic, clinical and laboratory features of patients were recorded.

Results: The study included 403 children with a median age of 8 years (IQR 6-12) (53% males). 30% of patients had allergic rhinitis (AR), 4.7% of patients had atopic dermatitis (AD), and 2% patients had food allergy (FA) history. 78(19.3%) patients also complained of dyspnea and 9 (2.2%) patients had a diagnosis of cardiovascular disease. 245 (60.8%) asthma-wheezy infant, 107 (26.6%) post-infectious cough, 36 (9%) postnasal drip syndrome, 9 (2.2%) gastroesophageal reflux and 6 (1.5%) psychogenic cough were detected in the whole group. The number of patients with accompanying dyspnea 76 (28.5%) and familial history of atopy 113 (42.3%) were higher in the asthma-wheezy infant group than others group ($p<0.001$ vs. $p<0.001$). Skin prick tests were performed in 273 patients and the presence of aeroallergen sensitivity was shown in 122 (30.2%) patients. Immunoglobulin deficiency was detected in 43 (10.7%) patients. Serum IgG, IgA, and IgM levels were low in 26 (6.5%), 18 (4.4%), and 12 (3%) patients, respectively.

Conclusion: We found the most common reasons are asthma and post-infectious cough in patients. Chronic cough can be the first symptom of primary immunodeficiency diseases and systemic diseases. A detailed history is necessary to avoid unnecessary procedures, treatments and to avoid delay in diagnosis.

Keywords: Asthma, chronic cough, children, immunoglobulin

INTRODUCTION

Chronic cough is a frequent cause of hospital admission and significantly affects the quality of life of the child and parents.[1,2] Chronic cough is considered as a daily cough lasting four or more weeks in children.[3,4] Estimates for the prevalence of chronic cough in school-aged children range as high as 10.4%.[5] The differential diagnosis is extensive. The most common causes of chronic cough include recurrent respiratory tract infections, postinfectious cough, protracted bacterial bronchitis, gastroesophageal reflux disease (GERD), asthma, and upper airway cough syndrome (UACS). The most common cause of chronic specific cough is asthma.[6] Two studies from the USA and Turkiye reported higher percentages of asthma, GERD and UACS diagnoses in children with chronic cough.[7,8]

It is very important to know the history, symptoms and possible related factors to determine the cause of chronic cough. The character of the cough, triggering factors, accompanying symptoms and findings, conditions that increase cough, comorbid diseases, treatments, and family history of atopy should be questioned in detail. The main treatment for chronic cough should be based on the underlying cause.[9]

Due to the high prevalence of chronic cough in children and its burden on quality of life, it is important to identify the most common causes of chronic cough so the present study aimed to define the underlying causes of chronic cough in children.

METHODS

Ethics

The study was conducted in accordance with the principles of the Declaration of Helsinki. The Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee approval was obtained for this retrospective study (Date: 10.09.2024, Decision No: 2024-BÇEK/150).

Study Population and Data Collection

The study included children aged 1-18 years with chronic cough who were being followed at Pediatric Immunology

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and Allergy Outpatient Clinic at Sincan Training and Research Hospital between December 2023 and September 2024. We evaluated demographic information (age, gender, family history, etc.), clinical features and medical history (cough character, wheezing, rhinitis, respiratory tract infection history, exposure to secondhand tobacco smoke and treatments), presence of atopic comorbidities (AR, AD, FA), total serum IgE, Skin prick test (SPT) and Lung function tests (LFTs) (FEV 1%, FEF 25%-75%) results. LFTs were administered to all asthma patients under the participant's supervision, by American Thoracic Society guidelines.[10] The diagnosis of asthma/recurrent wheezing, allergic rhinitis and atopic dermatitis was made according to international guidelines.[11-13] A cough lasting longer than four weeks was diagnosed as chronic cough and we used the "CHEST guideline and expert panel report" guideline for diagnosis, management and treatment methods in chronic cough.[9,14] Serum IgM, IgA, and IgG levels were assessed for primary immunodeficiency diseases (PID) in patients with frequent and severe infections according to age-related reference intervals.[15,16]

Skin Prick Tests

In the routine practice of the pediatric immunology and allergy outpatient clinic, SPT was performed with common aeroallergens [Dermatophagoides pteronyssinus, Dermatophagoides farinea, cat, dog, Alternaria alternata, Cladosporium herbarum, tree pollen mix (Betula pendula, Corylus avellana, Olea europaea, cupressus), weed pollen mix (Artemisia vulgaris, Chenopodium album, Wall pellitory), grass pollen mix (Dactylis glomerata, Lolium perenne, Phleum pratense, Poa pratensis), Cynodon dactylon]. Allergen extracts [Lofarma®, (Italy)] were performed on the volar surface of the forearm with positive and negative controls and measured after 15 minutes. Positive results were defined as a mean wheal diameter 3 mm greater than the negative control.[17,18]

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA). Values are shown as the median and interquartile range for non-normally distributed data. Descriptive analysis was used to characterize the patients. Pearson's Chi-square (χ^2) test was used for between-group comparisons. The Mann-Whitney U test was used to compare values. All statistical tests were two-sided, and the level of statistical significance was set at $p<0.05$.

RESULTS

Study population

The study included 403 children with a median age of 8 years (IQR 6-12) (53% males). 30% of patients had allergic rhinitis, 4.7% of patients had atopic dermatitis history, and 2% of patients had FA. 78(19.3%) patients also complained of dyspnea and 9 (2.2%) patients had a diagnosis of cardiovascular disease. 128 (31.8%) patients had a family history of atopic diseases, and 156 (38.7%) patients had tobacco smoke exposure (Table).

Etiologies of Chronic Cough

When the etiologies of chronic cough were examined; 245 (60.8%) asthma-wheezy infants, 107 (26.6%) post-infectious cough, 36 (9%) postnasal drip syndrome (PNDS), 9 (2.2%) gastroesophageal reflux and 6 (1.5%) psychogenic cough were detected in the whole group. We divided the study group according to age by six years. 78 (19.4%) patients were <6 years and 325 (80.6%) patients were ≥6 years age. In <6 years age group, 47 (60.2%) patients were diagnosed with wheezy infant, 24 (30.8%) patients with post-infectious cough, 4 (5%) patients with postnasal drip syndrome and 3 (3.8%) patients with gastroesophageal reflux. In ≥6 years age group; 198 (61%) patients were diagnosed with asthma, 83 (26%) patients with post-infectious cough, 32 (9.8%) patients with postnasal drip syndrome, 6 (1.8%) patients with psychogenic cough and 6 (1.8%) patients with gastroesophageal reflux (Figure 1). Four patients were diagnosed with bronchiectasis during follow-up.

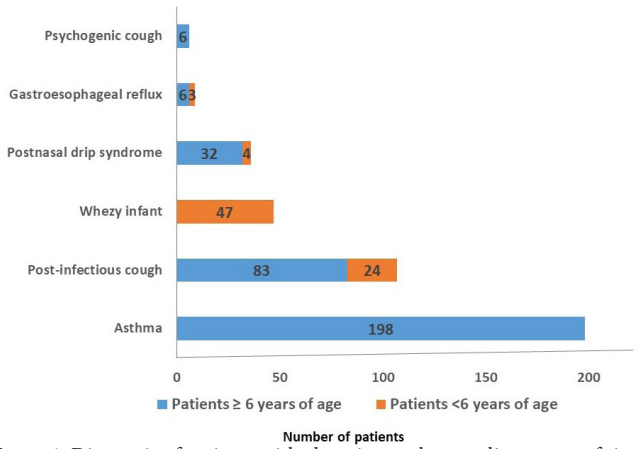

Figure 1. Diagnosis of patients with chronic cough according to age of six years

Table. The characteristics of the study group and its subgroups according to diagnosis of patients

	Whole group (n: 403)	Asthma-wheezy infant (n: 267)	Other diagnoses (n: 136)	p value
Age, year*	8 (6-12)	7 (5-12)	8 (6-11)	NS
Gender-male, n (%)	214 (53)	142 (53.2)	72 (53)	NS
Dispne, n (%)	78 (19.3)	76 (28.5)	2 (1.5)	<0.001
Atopy, n (%)	122 (30.2)	84 (31.5)	38 (28)	NS
AR, n (%)	121 (30)	88 (33)	33 (24.2)	0.072
AD history, n (%)	19 (4.7)	14 (5.2)	5 (3.7)	NS
FA history, n (%)	8 (2)	5 (1.9)	3 (2.2)	NS
Cardiovascular disease, n (%)	9 (2.2)	7 (2.6)	2 (1.5)	NS
Familial history of atopy, n (%)	128 (31.8)	113 (42.3)	15 (11)	<0.001
Tobacco smoke exposure, n (%)	156 (38.7)	104 (39)	52 (38.2)	NS

*Median, IQR: Inter quartile range, NS: Nonsignificant, AR: Allergic rhinitis, AD: Atopic dermatitis, FA: Food allergy

Asthma-Wheezy Infant and Other Groups Comparison

When asthma-wheezy infant and other groups were evaluated; 267 (66.3%) patients were followed with asthma-wheezy infant and 136 (33.7%) patients were followed with other diagnoses. The number of patients with accompanying dyspnea 76 (28.5%) and familial history of atopy 113 (42.3%) were higher in the asthma-wheezy infant group than others group ($p<0.001$ vs. $p<0.001$), respectively. Although, there was no difference in tobacco smoke exposure, age, gender and atopic comorbidities (Table).

Skin Prick Tests

Skin prick tests were performed in 273 patients and the presence of aeroallergen sensitivity was shown in 122 (30.2%) patients. 18.4% of patients were sensitized to grass pollen, 10.4% to weed pollen, 8.4% to cat, and 7.2% to house dust mite. Aeroallergen sensitivities of the patients are shown in Figure 2.

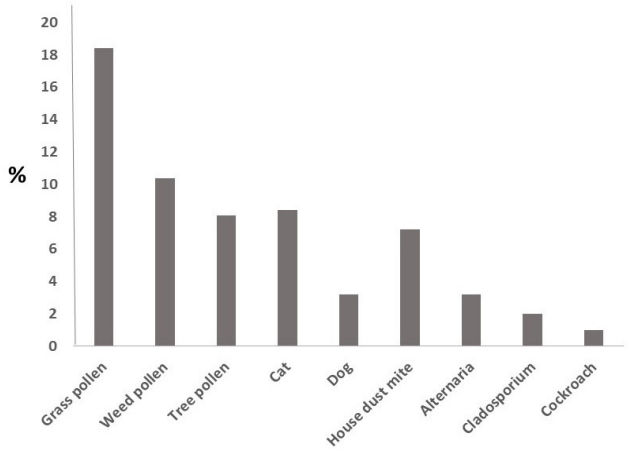

Figure 2. Aeroallergen sensitivites of the study population

Laboratory Characteristics of Study

Immunoglobulin deficiency was detected in 43 (10.7%) patients. Serum IgG, IgA, and IgM levels were low in 26 (6.5%) patients, 18(4.4%) patients, and 12 (3%) patients, respectively (Figure 3). The median level of serum IgE was 54 IU/ml (IQR 22-181). When the spirometric values of the patients were examined, the median value of FEV 1% was 104 (IQR 95.5-116) and for FEF 25%-75% was 105 (IQR 87-116). There was no significant difference in IgE levels and LFTs levels according to asthma-wheezy infant and other groups comparison.

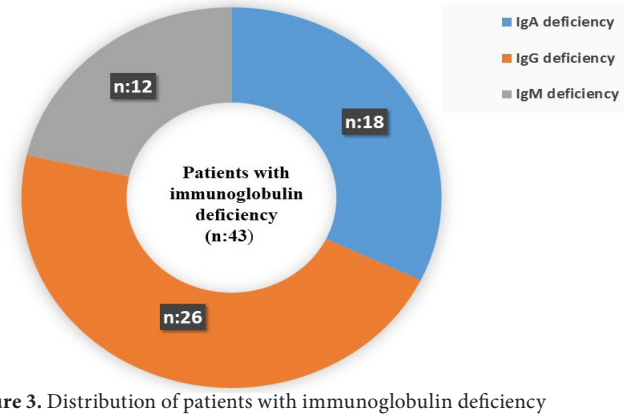

Figure 3. Distribution of patients with immunoglobulin deficiency

Treatment

Antibiotic treatment was started in 81 (20%) patients and inhaled corticosteroids (ICS) treatment was started in 198 (49%) patients. 70/198 (35.4%) of these ICSs were inhaled corticosteroids-long-acting beta agonist combination. 115 (28.5%) patients received leukotriene receptor antagonist treatment. 103 (25.6%) patients were treated with antihistamines and 83 (20.6%) were treated with nasal steroids. Four patients were treated with anti-GERD treatment. Six patients received trimethoprim-sulfamethoxazole prophylaxis because of primer antibody deficiency and recurrent infection. One patient received omalizumab treatment due to severe asthma diagnosis.

DISCUSSION

Chronic cough is one of the most common reasons for referral to the pediatrician in childhood. Chronic cough is distressing and burdensome for patients and their families and it increases health expenditures due to frequent hospital admissions. Coughing can be the first symptom of many systemic diseases or may be caused by a simple disease such as upper respiratory tract infection.[19] Therefore, it is important for the physician to know the appropriate definition of chronic cough and its underlying causes. The study encompassed children aged 1-18 years with chronic cough and investigated the causes of chronic cough in these patients.

In our study, the most common cause of chronic cough was asthma 49%, approximately half of the whole patients group. In most studies on chronic cough etiology, asthma has been found the most common underlying cause.[14,20,21] In our report, 19.3% of patients also complained of dyspnea in whole group, 97% of these patients were in the asthma-wheezy infant group. Asthmatic patients often complain of chest tightness, wheezing, dyspnea and cough. These symptoms may occur alone or in different combinations. Sometimes the only symptom is chronic cough, which is called "cough variant asthma".[22,23] Although nearly 40% of all young children worldwide experience at least one episode of asthmatic symptoms such as wheezing, coughing, dyspnea, only 30% of preschoolers with recurrent wheezing are eventually diagnosed with asthma by the age of six years.[24] We diagnosed wheezy infants in 47 (60.2%) patients in the under 6 age group.

The duration and dose of exposure to allergens and irritant factors, genetic predisposition, and allergen sensitivity may be risk factors for the development of asthma in individuals.[25] We show aeroallergen sensitivity in 30.2% of patients, 69% of them in asthma-wheezy infant group. In our study, 38.7% of patients had tobacco smoke exposure. Exposure to tobacco smoke can negatively affect lung development in infants and cause wheezing, and is a risk factor for the development of asthma in the future. The presence of atopy in parents has been shown a risk factor for the development of asthma in children.[25] In accordance with the literature, we found familial history of atopy were significantly higher in the asthma-wheezy infant group than others group.

We found post-infectious cough, the second cause of chronic cough in our study. Postinfectious cough should be

considered when cough persists after an upper respiratory tract infection. It has been shown that up to 40% of school-age children proceed coughing 10 days after a common cold, with 10% of preschool children having a persistent cough after 25 days.[26] Postinfectious cough is self-limited and will resolve spontaneously, but it may persist for three or more weeks. In the etiology of chronic cough, epithelial disruption and inflammation are suggested to play a main role. Inflammation of the mucosa promotes the production of mucus and in this situation stimulating the cough receptors to clearance airways.[27]

In our study, 9% of the patients were diagnosed with postnasal drip syndrome. PNDS is a clinical condition that develops directly with inflammatory nasal secretions or due to mechanical stimulation and irritation of cough receptors belonging to afferent fibers in the upper airways. The leading causes of PNDS are sinusitis, allergic and non-allergic rhinitis, vasomotor rhinitis, postinfectious rhinitis, and environmental irritants. In treatment, first-generation antihistamines and decongestants were recommended.[3,28] In our study, 25.6% of patients were treated with antihistamines and 20.6% of patients were treated with nasal steroid due to PNDS and AR symptoms.

Gastroesophageal reflux disease should be considered with a prolonged cough or unexplained lung disease or recurrent otitis media attacks in children. Respiratory symptoms can be observed in 10-20% of patients with GERD, and cough may be the only symptom of GERD.[22] In the present report, nine patients were diagnosed with GERD and six patients, all of them adolescents were diagnosed with psychogenic cough, after detailed history and examination. Many patients with psychogenic cough do not cough during sleep, are not awakened by cough, and frequently do not cough during pleasant distractions. Psychogenic cough is a diagnosis of exclusion[29] as we diagnosed six patients in this way.

Recurrent lung infections and chronic cough may be the first warning signs of PID in pediatric patients.[30] Antibody deficiencies are the most common PID group. The subgroup of PID that most frequently presents with pulmonary findings is antibody deficiencies.[30,31] In our study, 10.7% of patients were followed up for immunoglobulin deficiency and trimethoprim-sulfamethoxazole prophylaxis treatment was started in six patients. In primary immunodeficiency diseases, it is important to make early diagnosis, monitor respiratory complications, and provide immunoglobulin replacement therapy as the basic treatment approach and to give prophylactic and therapeutic doses of antimicrobial therapy in case of infection.

Limitations

The main limitation of this retrospective study is that the study was conducted in pediatric immunology and allergy outpatient clinic may not reflect the real population. Although, detection of underlying diseases and determination of risk factors of chronic cough were examined in accordance with the purpose of the study.

CONCLUSION

We found the most common causes are asthma, post-infectious cough and postnasal drip syndrome in children with chronic cough. Factors that may cause or trigger cough should be carefully questioned, and a diagnosis and treatment algorithm in accordance with current guidelines should be followed. A detailed history is necessary to guide further testing, to avoid unnecessary procedures and to avoid delay in diagnosis. Immunoglobulin deficiency was detected in ten percent of our patients. It should not be forgotten that respiratory system symptoms, especially chronic cough, may often be the first presenting symptom in primary immunodeficiency diseases.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee (Date: 10.09.2024, Decision No: 2024-BÇEK/150).

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 in vitro efficacy of ceftazidime-avibactam against *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* isolates from respiratory tract cultures in intensive care units

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ABSTRACT

Aims: Worldwide, an increase in multidrug resistance is observed in *Escherichia coli (E. coli), Klebsiella pneumoniae (K. pneumoniae),* and *Pseudomonas aeruginosa (P. aeruginosa)* isolates, leading to challenges in the treatment of infections caused by these pathogens. This study aims to investigate the in vitro efficacy of ceftazidime-avibactam (CZA) against isolates containing *K. pneumoniae*, *E. coli,* and *P. aeruginosa* strains obtained from respiratory tract samples sent from intensive care units.

Methods: A retrospective analysis was conducted on 653 *Enterobacterales* (*E. coli*, *K. pneumoniae*) and *P. aeruginosa* isolates obtained from respiratory tract cultures, including sputum, tracheal aspirates, and bronchial lavage, from patients over 18 years old admitted to the intensive care units of Ordu University Training and Research Hospital between May 1, 2021, and May 1, 2024. Automated systems were used to identify the pathogens and perform antibiotic susceptibility testing. Discriptive data analysis was conducted using SPSS version 24.0.

Results: A total of 653 isolates from respiratory tract samples were included in the study, consisting of 368 *Enterobacteriaceae* [61 *E. coli* (9.3%) and 307 *K. pneumoniae* (47%)] and 285 *P. aeruginosa* (43.7%). These samples were isolated from endotracheal aspirate (69.5%), sputum (27.9%), and bronchoalveolar lavage (2.6%). Among all isolates, 364 (55.7%) were found to be sensitive to carbapenems, while 289 (44.3%) were carbapenem-resistant. Of the samples, 631 (96.6%) were sensitive to CZA, while 22 (3.4%) were resistant. Although resistance to CZA was detected in 3.6% of *K. pneumoniae* isolates and 3.9% of *P. aeruginosa* isolates, no resistance was detected in *E. coli*. Colistin resistance was observed in 15.3% of *K. pneumoniae* and 5.6% of *P. aeruginosa* isolates, but was absent in *E. coli* isolates. Resistance rates to other antibiotics were as follows for *E. coli*, *K. pneumoniae*, and *P. aeruginosa* isolates, respectively: amikacin (3.3%, 46.6%, 8.1%), ciprofloxacin (73.8%, 73.6%, 85.9%), ceftazidime (67.2%, 77.8%, 35.8%), piperacillin-tazobactam (26.2%, 70%, 37.2%), and trimethoprim-sulfamethoxazole (52.5%, 66.4%, 0%).

Conclusion: In our study, CZA was found to be the most effective antibiotic against multidrug-resistant *Enterobacterales* and *P. aeruginosa* isolates, followed by colistin.

Keywords: Multidrug resistance, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, ceftazidime-avibactam

INTRODUCTION

Concerns regarding antibacterial resistance continue to rise worldwide, and the management of secondary infections caused by multidrug-resistant (MDR) organisms has become a global health issue. The primary pathogens that pose treatment challenges are MDR gram-negative bacteria, and infections caused by these microorganisms are associated with increased mortality and morbidity, especially in patients with significant comorbidities.[1] Furthermore, the increasing prevalence of antibiotic resistance has led to the widespread and often inappropriate use of antibiotics globally. Carbapenems are frequently used as first-line antibiotics in the treatment of infections caused by extended-spectrum beta-lactamase (ESBL)-producing microorganisms isolated from respiratory tract samples, as they are highly effective against these pathogens. However, the rising incidence of infections caused by ESBL-producing *Enterobacteriaceae* over the years has resulted in increased carbapenem usage and higher rates of carbapenem resistance.[2]

In the treatment of carbapenem-resistant microorganisms, ceftazidime-avibactam (CZA), a combination of the third-generation broad-spectrum cephalosporin ceftazidime and

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the β-lactamase inhibitor avibactam, is used as an antibiotic therapy.[3] The use of CZA for gram-negative bacterial infections was approved in 2018. The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have approved it for adult patients with infections caused by aerobic gram-negative bacteria, particularly in cases with limited therapeutic options. In Turkiye, it was licensed for use in October 2019.[4] Recently, the World Health Organization listed the multidrug-resistant *Pseudomonas aeruginosa (*P. *Aeruginosa)*, *Klebsiella pneumoniae (K. Pneumoniae)*, and *Escherichia coli* (*E. Coli)* included in our study among the bacterial species for which the development of new antibiotics is critically needed to treat infections.[5,6]

The aim of this study is to investigate the in vitro efficacy of CZA against carbapenem-resistant *K. pneumoniae*, *E. coli*, and *P. aeruginosa* strains isolated from respiratory tract samples sent from intensive care units to the Microbiology Laboratory of Ordu University Faculty of Medicine Training and Research Hospital. Given the significance of resistance development in combating infections caused by these microorganisms and the limited number of studies in Turkiye examining CZA's activity against MDR strains of these pathogens, further research on this topic is essential.

METHODS

Ethics Approval

This study was approved by the Ordu University Non-interventional Scientific Researches Ethics Committee (Date: 26.07.2024, Decision No: 2024/109). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This retrospective study examined 653 isolates of *E. coli, K. pneumoniae* and *P. aeruginosa* isolated from respiratory culture samples such as sputum, tracheal aspirates, and bronchoalveolar lavage from patients admitted to the intensive care units of Ordu University Training and Research Hospital between May 1, 2021, and May 1, 2024. All patients aged 18 and older were included in the study, and the first culture results from similar clinical samples of the same patient, as well as culture results from different clinical samples, were included in the analysis. Repeated cultures from the same patients were excluded from the study.

Automated systems were used for the identification of pathogens and the results of the antibiograms. In addition to classical methods for species-level identification and antimicrobial susceptibility testing, the BD Phoenix 100 automated system (Becton Dickinson and Company, USA) was utilized to determine the production of extended-spectrum beta-lactamases (ESBL). For ESBL confirmation testing, disk diffusion tests (combined disk method) were performed according to Clinical and Laboratory Standards Institute (CLSI) documents, using both ceftazidime, ceftazidime-clavulanic acid, and cefotaxime, cefotaxime-clavulanic acid disks. Among these, isolates determined to be multidrug-resistant (MDR) were evaluated for susceptibility to ceftazidime-avibactam 10/4 mg (Bioanalyse, Turkiye) using the Kirby-Bauer disk diffusion method. Antimicrobial susceptibility results were reported according to the breakpoints recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Categorical variables are described as frequencies (percentages), while continuous variables are presented as mean and standard deviation. Discriptive data analysis was conducted using SPSS version 24.0.

RESULTS

A total of 653 isolates were included in our study, with 69.5% from endotracheal aspirates, 27.9% from sputum, and 2.6% from bronchoalveolar lavage; of these, 61 (9.3%) were *E. coli* and 307 (47%) were *K. pneumoniae*, resulting in a total of 368 Enterobacteriaceae and 285 (43.7%) *P. aeruginosa* (**Table 1**). All patients from whom respiratory cultures were obtained were adults aged 18 and older who were hospitalized in the intensive care unit.

Table 1. Sample sites of isolated bacterial agents

Sample site	n (%)
Endotracheal aspirate	454 (69.5%)
Sputum	182 (27.9%)
Bronchoalveolar lavage	17 (2.6%)

Among all isolates, 364 (55.7%) were found to be susceptible to carbapenems, while 289 (44.3%) were resistant. Of the *E. coli* isolates, 4.9% (3/61) were resistant to carbapenems, 56% (172/307) of *K. pneumoniae* isolates, and 53% (152/285) of *P. aeruginosa* isolates were found to be carbapenem-resistant.

Of the samples, 631 (96.6%) were susceptible to CZA, while 22 (3.4%) were resistant. Resistance to CZA was found in 3.6% of *K. pneumoniae* isolates and 3.9% of *P. aeruginosa* isolates, while no resistance was detected in *E. coli* isolates. No resistance to CZA was observed in any of the bronchoalveolar lavage samples.

When investigating colistin resistance, 15.3% of *K. pneumoniae* isolates and 5.6% of *P. aeruginosa* isolates were found to be resistant to colistin. No colistin resistance was observed in *E. coli* isolates, similar to the findings for CZA. Among the 63 isolates with detected resistance to colistin, 6 (9.5%) were also resistant to CZA.

Resistance rates were found to be as follows: amikacin 3.3%, 46.6%, and 8.1% for *E. coli*, *K. pneumoniae*, and *P. aeruginosa*, respectively; ciprofloxacin 73.8%, 73.6%, and 85.9%; ceftazidime 67.2%, 77.8%, and 35.8%; piperacillin/tazobactam 26.2%, 70%, and 37.2%; and trimethoprim-sulfamethoxazole 52.5%, 66.4%, and 0%. The detected antibiotic resistances in microorganisms are shown in **Table 2**.

In our study, CZA was found to be the most effective antibiotic against multidrug-resistant Enterobacterales and *P. aeruginosa* isolates, followed by colistin.

DISCUSSION

Members of Enterobacterales are among the primary causes of healthcare-associated and community-acquired infections.

Table 2. Antibiotic resistance rates by microorganism

Microorganism	Carbapenem n (%)	Ceftazidime-avibactam, n (%)	Colistin n (%)	Amikacin n (%)	Ciprofloxacin n (%)	Ceftazidime n (%)	Piperacillin/tazobactam n (%)	Trimethoprim-sulfamethoxazole, n (%)
Klebsiella pneumoniae	172 (56%)	11 (3.6%)	47 (15.3%)	143 (46.6%)	226 (73.6%)	239 (77.8%)	215 (70%)	204 (66.4%)
Escherichia coli	3 (4.9%)	-	-	2 (3.3%)	45 (73.8%)	41 (67.2%)	16 (26.2%)	32 (52.5%)
Pseudomonas aeruginosa	152 (53%)	11 (3.9%)	16 (5.6%)	23 (8.1%)	245 (85.9%)	102 (35.8%)	106 (37.2%)	-
Total	327 (50.0%)	22 (3.3%)	63 (9.6%)	168 (25.7%)	516 (79.0%)	382 (58.5%)	337 (51.6%)	236 (36.1%)

The most frequently isolated Enterobacteriaceae agents from cultures are *K. pneumoniae* and *E. coli*.[7] The most effective treatment for these microorganisms has been carbapenems; however, increased resistance due to their widespread use has posed significant challenges for treatment in clinical practice.[8] Carbapenem antibiotics, which belong to the beta-lactam group, are bactericidal, fast-acting, and have broad-spectrum activity, making them widely used in the treatment of infectious diseases. Carbapenem-resistant bacteria are typically resistant not only to penicillins and cephalosporins but also may carry genes encoding resistance to aminoglycosides and quinolones. Multidrug-resistant Gram-negative bacilli develop resistance mechanisms that lead to resistance against multiple antimicrobial agents, not just a single antibiotic class. Initially, carbapenem resistance was more commonly detected in *Acinetobacter baumannii* and *P. aeruginosa* isolates, but in recent years, *K. pneumoniae* has become the most frequently reported agent of carbapenem resistance and a significant contributor to the spread of carbapenem resistance.[9]

Colistin, tigecycline, and aminoglycosides are nearly the last-line therapeutic agents for treating multidrug-resistant (MDR) isolates.[10] Consequently, there is an increasing need for new antibiotics effective against MDR isolates. In the treatment of carbapenem-resistant microorganisms, CZA, a new antibiotic combining the broad-spectrum cephalosporin ceftazidime with the non-beta-lactam beta-lactamase inhibitor avibactam, is being utilized.

In a study evaluating the antibiotic resistance profiles of *K. pneumoniae*, resistance rates for gentamicin, amikacin, amoxicillin/clavulanate, piperacillin/tazobactam, cefepime, ceftriaxone, and ceftazidime were found to be 37%, 33%, 63%, 53%, 74%, 62%, and 61%, respectively[11]. Another study examining the resistance profiles of carbapenem-resistant Enterobacterales isolates from 2015 to 2018 reported resistance rates in *K. pneumoniae* of 28.10% for amikacin, 51.08% for amoxicillin/clavulanate, 98.37% for ceftazidime, 51.08% for gentamicin, 99.72% for piperacillin/tazobactam, 80.81% for cefepime, and 99.72% for ceftriaxone. The highest resistance rates among carbapenem-resistant *K. pneumoniae* isolates were observed against ceftriaxone and piperacillin/tazobactam (99.72%).[12] In a study conducted by Altay Koçak et al.[13] from 2016 to 2018 on respiratory samples and antibiotic resistance profiles in hospitalized patients, resistance rates in *K. pneumoniae* isolates for amikacin, amoxicillin/clavulanate, gentamicin, colistin, levofloxacin, netilmicin, piperacillin/tazobactam, cefazolin, cefepime, cefoxitin, ceftazidime, ceftriaxone, cefuroxime, ciprofloxacin, and trimethoprim/sulfamethoxazole were reported as 30.6%, 60.9%, 52.9%, 11%, 51.8%, 39.5%, 55.8%, 77.9%, 73.3%, 48.8%, 74.1%, 74.1%, 76.5%, 51.2%, and 65.1%, respectively.

In our study, resistance rates for *K. pneumoniae* isolates were 3.6% for CZA, 15.3% for colistin, 46.6% for amikacin, 73.6% for ciprofloxacin, 77.8% for ceftazidime, 70% for piperacillin/tazobactam, and 66.4% for trimethoprim/sulfamethoxazole. The highest resistance rates in *K. pneumoniae* isolates in our study were observed against ciprofloxacin, ceftazidime, and piperacillin/tazobactam, while the most effective antibiotics were CZA and colistin.

According to a study conducted in İstanbul in 2012, ciprofloxacin, cotrimoxazole, amikacin, and gentamicin resistance rates in ESBL-positive *K. pneumoniae* were reported as 66.2%, 68.6%, 16.2%, and 43.0%, respectively. Resistance rates in ESBL-positive *K. pneumoniae* were reported as 10.5% for imipenem, 7% for meropenem, and 11.6% for ertapenem, with no colistin-resistant isolates detected.[14] The low resistance rates in this study were attributed to its completion in 2012.

In a study conducted in Turkiye, fluoroquinolone resistance was reported at 86.1%, suggesting that empirical use of this class of antibiotics is not recommended.[15] Due to the development of multidrug resistance linked to fluoroquinolone use in gram-negative bacteria, avoiding fluoroquinolones and reverting to other empirical agents is considered one of the most reliable approaches[16]. Similarly, in our study, fluoroquinolone resistance was found to be 79%, and we do not recommend its use in empirical treatment.

In a study by Özkul Koçak et al.,[17] the colistin resistance rate in 81 carbapenem-resistant *K. pneumoniae* isolates was 39.51%. Agyar,[18] in Ankara in 2020, reported colistin resistance of 36.4% in carbapenem-resistant *K. pneumoniae*, while Tartar et al.,[19] in 2017, reported a colistin resistance rate of 5% in *Klebsiella spp.* isolated from endotracheal aspirate samples based on antibiogram results. In our study, colistin resistance in *K. pneumoniae* isolates was detected as 15.3%.

Although studies and case reports on CZA-a combination developed and approved for combating bacterial resistance caused by ESBL and carbapenemases-show promising results, resistance may develop in the near future.[20] Research based on clinical data has shown that CZA is an effective treatment option for MDR gram-negative bacteria, reducing mortality rates and improving quality of life.[21] A recent study conducted in Turkiye reported a CZA susceptibility rate of 95.7% in ESBL-positive strains.[5] Another study found CZA susceptibility rates of 87.5% for *K. pneumoniae* and 95.2% for *E. coli*.[2] As these studies suggest, CZA appears to be a viable option for ESBL-producing and carbapenem-resistant Enterobacteriaceae isolates.[22] Similarly, in our study, 96.6%

of the isolates were susceptible to CZA, while 3.4% showed resistance.

In another study, 22.5% of carbapenem-resistant *K. pneumoniae* isolates were found to be resistant to CZA. Nevertheless, CZA is considered a viable option for suitable cases.[23] Following the use of ceftazidime-avibactam as an alternative therapeutic agent, clinical practice has demonstrated the proliferation of CZA-resistant strains. Given the increase in strains resistant to this antibiotic, it is important to emphasize the prudent use of CZA.[24]

A study conducted in Turkiye found CZA susceptibility rates for *E. coli*, *K. pneumoniae*, and *P. aeruginosa* strains to be 93.8%, 95.7%, and 36.2%, respectively. Despite CZA's introduction in Turkiye in October 2019, the high in vitro resistance rate of MDR *P. aeruginosa* strains (63.8%) found in this study is concerning.[5] Another study in Turkiye determined that, among MDR *P. aeruginosa* strains, colistin was the most effective antibiotic, with similar susceptibility rates to gentamicin, amikacin, and CZA. However, *P. aeruginosa* showed higher resistance rates to CZA than other Gram-negative pathogens.[25] These findings suggest that while CZA may be an alternative for treating infections caused by MDR *Enterobacterales*, susceptibility testing results are critical for MDR *P. aeruginosa* strains. Other studies have similarly shown that the in vitro susceptibility rate of CZA for MDR *P. aeruginosa* is lower than for MDR *Enterobacterales.*[26] In contrast, in our study, 3.6% of *K. pneumoniae* and 3.9% of *P. aeruginosa* isolates were resistant to CZA, with no resistance detected in *E. coli*. Contrary to the literature, our study did not find higher CZA resistance in *P. aeruginosa* isolates compared to other microorganisms.

In a study by Shields et al.,[27] CZA was used to treat carbapenemase-producing, meropenem-resistant *Klebsiella* infections in patients. In recurrent infections, the same patients developed meropenem-susceptible, CZA-resistant *Klebsiella*, showing both beneficial and adverse impacts of CZA on antibiotic resistance genes. The absence of CZA resistance is thought to be related to naive strains that had not previously encountered this antibiotic.[15]

In the study by Hoşbul et al.,[28] susceptibility results for 100 *Pseudomonas* strains were 100% for colistin and 90% for CZA, respectively. In our study, similar results were observed, with *P. aeruginosa* isolates showing 94.4% and 96.1% susceptibility to colistin and CZA, respectively. Studies by Camargo et al.[29] and Wu et al.[30] observed successful treatment and microbiological cure in cases unresponsive to alternative treatments, including combinations of colistin and carbapenems, when treated with CZA. The rational use of CZA, along with older antibiotics such as colistin and meropenem, forms an essential part of infection control and antimicrobial stewardship.[31] Therefore, in vivo studies are needed to evaluate the antimicrobial activity of CZA in combination therapies, particularly in bacteria with various resistance genes.

Limitations

The main limitation of our study is that it was conducted in a single center, which restricts its generalizability to national data. Another important limitation is the lack of genomic analysis and molecular testing in evaluating antibiotic susceptibilities. Limiting the study to carbapenem-resistant bacterial strains reduced the number of bacterial species included in the study. Additionally, clinical patient data and treatment outcomes were not analyzed.

CONCLUSION

Surveillance of local epidemiology and antimicrobial susceptibility is a crucial step in determining empirical treatment options to combat infections. Increasing the use of narrow-spectrum antibiotics minimizes the development of resistance mechanisms associated with antibiotic use. Regular monitoring of antibiotic resistance patterns is essential to guide future antibiotic choices. Similar to other studies, our findings confirm the in vitro activity of CZA against MDR *K. pneumoniae*, *E. coli*, and *P. aeruginosa* strains.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ordu University Non-interventional Scientific Researches Ethics Committee (Date: 26.07.2024, Decision No: 2024/109).

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

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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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Efficacy of serum lactate/albumin ratio as a prognostic biomarker in patients with ventilator-associated pneumonia

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ABSTRACT

Aims: This study aims to evaluate the efficacy of the serum lactate/albumin ratio (LAR) as a prognostic marker in patients with ventilator-associated pneumonia (VAP) who are hospitalized in the intensive care unit (ICU).

Methods: This single-center retrospective observational clinical study was conducted between January 1, 2022, and October 1, 2024. The study group comprised 58 patients admitted to the ICUs of Malatya Training and Research Hospital, Turkiye, with intubation but without a diagnosis of pneumonia at the time of admission. These patients were diagnosed with VAP 48 hours after intubation. The serum LAR was calculated within the first 24 hours after admission to the ICU and correlated with mortality and morbidity.

Results: The mean age of the patients was 68 years, with the majority being over 65 years of age. Of the 58 patients included in the study, 43 (74.1%) ultimately succumbed to their illness. The LAR of those who died in the study was significantly higher than that of those who survived. The LAR was identified as a reliable predictor, exhibiting a sensitivity of 83.7% and a specificity of 60% when a cutoff value of 1.13 was applied. The survival time of patients with a LAR of ≤1.13 was significantly longer than that of patients with a ratio of >1.13.

Conclusion: In our study, the mortality prediction performance of the LAR in patients with VAP was superior to that of the serum lactate level or serum albumin level alone. Therefore, the LAR may be a useful and readily available prognostic factor for early risk stratification of VAP patients.

Keywords: Ventilator-associated pneumonia, biomarker, lactate/albumin ratio, prognostic factor

INTRODUCTION

Ventilator-associated pneumonia (VAP) is defined as the occurrence of new pneumonia in the lung parenchyma in patients who require invasive mechanical ventilation for a minimum of 48 hours in the intensive care unit (ICU).[1] VAP represents a significant complication in patients who are mechanically ventilated. In patients on mechanical ventilators in intensive care, the incidence of VAP was found to be between 15% and 60%, with a mortality rate between 25% and 76%.[2] Additionally, the prevalence of underlying disease states, including sepsis, trauma, central nervous system, and respiratory diseases, was demonstrated to elevate the incidence of VAP.[3] Patients with VAP have longer hospital stays and higher hospitalization costs.[4] Serum albumin is a major plasma protein that is produced in the liver and is a negative acute-phase reactant.[5] In a study by Kendall et al.,[6] low serum albumin levels were found to be associated with mortality in patients admitted to the ICU with sepsis. In numerous clinical studies conducted in medical settings, including those examining sepsis, traumatic brain injury, decompensated heart failure, and Coronavirus disease 2019 (COVID-19), hypoalbuminemia was linked to unfavorable outcomes and a shorter survival period.[7,8] As a consequence of cellular dysfunction, tissue hypoxia, mitochondrial defect in oxygen utilization, impaired pyruvate dehydrogenase function, and increased aerobic glycolysis activity, high serum lactate levels (>10 mmol/L) and lactic acidosis (pH <7.35) occur, which is associated with significant morbidity and mortality.[9,10] In clinical studies conducted on patients with septic shock, heart failure, cardiac arrest, and those with COVID-19, the lactate/albumin ratio (LAR) was identified as a crucial prognostic indicator for mortality prediction.[11-14] The prognostic role of the LAR in patients with VAP remains to be

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elucidated. With this in mind, the present study was designed to investigate whether the serum LAR at admission can serve as an early prognostic biomarker of mortality in ICU patients diagnosed with VAP. We hope that the findings of this study will contribute to the existing literature on this topic (deleted).

METHODS

Ethics

The study was conducted following the Declaration of Helsinki and received approval from the Malatya Turgut Özal University Ethics Committee (Date: 11/07/2024, Decision No: E-30785963-020-262686).

Design of the Study and the Subjects

This single-center retrospective observational clinical study was conducted between January 1, 2022, and October 1, 2024. The data of 1436 patients who were hospitalized, followed up, and treated in the ICUs were obtained. The study population consisted of patients from Malatya Training and Research Hospital, Turkiye, who were diagnosed with VAP according to the National Healthcare Safety Network (NHSN) criteria 48 hours after intubation between January 1, 2022, and October 1, 2024. The study included patients aged 18 to 85 years. Patients under the age of 18 or over the age of 85, patients with a diagnosis of pneumonia at the time of hospitalization, patients diagnosed with sepsis, trauma patients, patients who died within 30 days of hospitalization, patients with multiple consecutive diagnoses of VAP during long hospitalizations, patients who had reached the point of brain death and multi-organ failure were excluded from the study. A total of 120 patients who were intubated at the time of hospitalization and subsequently admitted to the ICUs were identified through a retrospective review of the hospital's data processing system. The data of 58 patients who met the criteria for VAP were subjected to analysis.

Data Collection and Definitions

The following demographic and clinic variables were collected from all patients: age, gender, comorbidities, microorganisms, C-reactive protein (CRP), procalcitonin (PCT), ferritin, lactate, albumin, LAR, leukocyte (Leu), neutrophil percentage (Neu %), platelet (Plt), platelet distribution width (PDW), length of ICU stay, and survival status. The clinical and laboratory variables were evaluated within the first 24 hours following admission to the ICU. Additionally, data were collected from 58 patients with a diagnosis of VAP according to the NHSN criteria. All patients were monitored in the ICU throughout their stay or until death. Patients were classified as either survivors (i.e., those who survived the observation period) or non-survivors (i.e., those who died during the observation period). The term "30-day mortality" was defined as the mortality rate occurring on or after the 30th day of hospitalization. All patients' mortality data were retrieved from the hospital's medical record system.

The most recent studies have established a standardized diagnostic algorithm for VAP according to the National Healthcare Safety Network (NHSN) criteria.[15] This definition was utilized in the diagnosis of VAP.

The diagnostic criteria for VAP according to the National Healthcare Safety Network (NHSN) are as follows:

- Minimum positive end-expiratory pressure (PEEP) ≥3 cm H_2O or minimum fraction of inspired oxygen (FIO_2) >20 cm H_2O for at least two consecutive days.
- A fever of less than or equal to 36.0°C or greater than 38.0°C, a leukocyte count of less than or equal to 4000 or greater than 12000 cells/mm^3, and the continuation of one or more new antibiotics for four days.
- A gram stain, endotracheal aspirate, or bronchoalveolar lavage (BAL) with a neutrophil count of ≥25 and an epithelial cell area of ≤10, or a positive sputum culture, endotracheal aspirate, BAL, or lung tissue sample, is indicative of the presence of the disease.
- A positive endotracheal aspirate culture of at least 105 colony-forming units (CFU) per milliliter, or a positive BAL culture of at least 104 CFU/ml, is indicative of the presence of the pathogen. A positive culture of a sterile specimen of at least 103 CFU/ml is also diagnostic.

Alternatively, one of the following criteria may be met in the absence of purulent secretion:

- A positive pleural fluid culture (thoracentesis or chest tube),
- A positive lung histopathology,
- A positive diagnostic test for *Legionella*,
- *Influenza* virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human positive diagnostic test in respiratory secretion for metapneumovirus, coronavirus.

Statistical Analysis

The statistical analysis was conducted using the SPSS (statistical package for social sciences) 22 package program. Descriptive data were presented as absolute and relative frequencies for categorical variables and as mean±standard deviation (M±SD) and median interquartile range (25th-75th percentile) for continuous variables. A Chi-square analysis (Pearson Chi-square) was employed to ascertain the significance of the observed differences between the categorical variables within the various groups. The compliance of continuous variables with a normal distribution was evaluated using the Kolmogorov-Smirnov test. The student t-test was employed for variables exhibiting a normal distribution, whereas the Mann-Whitney U test was utilized for variables lacking a normal distribution. Overall survival was assessed with Kaplan-Meier for univariate analysis. Log-rank (Mantel-Cox) analysis was employed to compare survival time between categorical variables. The optimal cut-off value of the LAR was determined with the use of a receiver operating characteristic (ROC) curve. The statistical significance level was set at $p<0.05$ for all analyses.

RESULTS

Key Features of the Study

The study included a total of 58 patients aged 18 years and older, of whom 26 (44.8%) were female and 32 (55.2%) were male. The mean age of the patients was 68 years. Of the patients 36.2% had COPD, 39.7% had CVD, 41.4% had HT,

15.5% had DM and 12.1% had trauma. The most prevalent microorganisms isolated from patients with VAP were *Acinetobacter baumannii* (21 patients, 36.2%), *Klebsiella pneumonia* (12 patients, 20.7%), and *Pseudomonas aeruginosa* (6 patients,10.3%) (Table 1).

Comparison of Key Clinical Characteristics between Survivors and Non-survivors

A comparison of key clinical characteristics between survivors and non-survivors of the total 58 patients who participated in the study revealed that 43 (74.1%) had mortality, while 15 (25.9%) did not. The mortality rate was 80.8% among women and 68.8% among men, with no statistically significant difference between the two groups (p=0.299). The mean age of those who died was significantly higher than the mean age of those who did not (p=0.038). The mortality rate for individuals aged 65 years and above (83.3%) was significantly higher than that observed in individuals under 65 years of age (59.1%) (p=0.041). The lactate dehydrogenase (LDH) rate of patients who died was found to be significantly higher than the LDH rate of patients who survived (p=0.008) (Table 1).

The capacity of the LAR to predict 30-day mortality was examined through the use of ROC analysis, resulting in the determination of optimal cut-off values. Upon establishing a cut-off value of 1.13 for LAR, a sensitivity of 83.7% and a specificity of 60% were observed, indicating that this metric possesses satisfactory predictive efficacy (Figure 1).

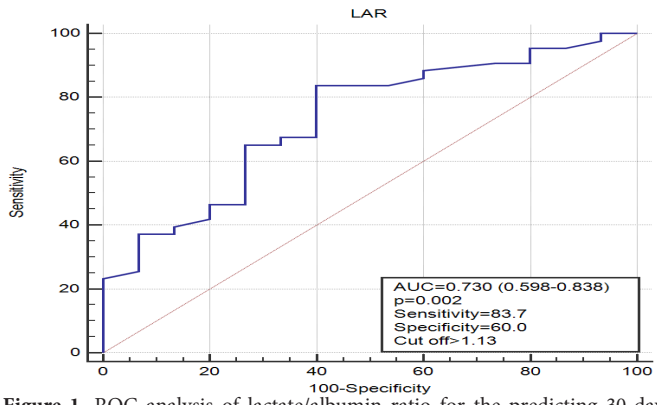

Figure 1. ROC analysis of lactate/albumin ratio for the predicting 30-day mortality

LAR: Lactate/albumin ratio, ROC: Receiver operating characteristic

Table 1. Comparison of mortality according to all data

		Total (n=58)	Non-survivors (n=43)	Survivors (n=15)	
		n (%)	n (%)	n (%)	p*
Gender	Female	26 (44.8)	21 (80.8)	5 (19.2)	0.299
	Male	32 (55.2)	22 (68.8)	10 (31.2)	
Age		68.00 (60.00-80.00)	69.00 (64.00-83.00)	63.00 (45.00-73.00)	0.038**
Age group	≥65	36 (62.1)	30 (83.3)	6 (16.7)	0.041
	<65	22 (37.9)	13 (59.1)	9 (40.9)	
COPD	Present	21 (36.2)	16 (76.2)	5 (23.8)	0.788
	Absent	37 (63.8)	27 (73.9)	10 (27.0)	
CVH	Present	23 (39.7)	18 (78.3)	5 (21.7)	0.561
	Absent	35 (60.3)	25 (71.4)	10 (28.6)	
HT	Present	24 (41.4)	19 (79.2)	5 (20.8)	0.462
	Absent	34 (58.6)	24 (70.6)	10 (29.4)	
DM	Present	9 (15.5)	7 (77.8)	2 (22.2)	0.786
	Absent	49 (84.5)	36 (73.5)	13 (26.5)	
Microorganism	*Acinetobacter baumannii*	21 (36.2)	17 (81.0)	4 (19.0)	0.528
	Klebsiella pneumoniae	12 (20.7)	9 (75.0)	3 (25.0)	
	Pseudomonas aeruginosa	19 (32.8)	14 (73.7)	5 (26.3)	
	Other	6 (10.3)	3 (50.0)	3 (50.0)	
CRP, mg/dl		15.63±9.21	15.75±9.73	15.29±7.82	0.870***
PCT, µg/l		1.18 (32-6.30)	1.08 (0.29-6.30)	1.27 (0.39-6.55)	0.770**
Ferritin, ng/ml		320.50 (132.00-775.00)	365.00 (155.00-765.00)	158.00 (77.60-905.00)	0.311**
Lactate, mmol/L		3.01±1.16	3.18±1.11	2.55±1.23	0.074***
Albumin, g/dl		2.01±0.51	1.93±0.53	2.21±0.41	0.066***
LAR		1.59±0.73	1.74±0.73	1.17±0.55	0.008***
Leu, 10^3 /µl		13.23 (10.42-17.50)	13.40 (10.18-17.50)	12.64 (11.20-17.78)	0.929**
Percent neutrophils, %		84.02±7.90	84.24±8.46	83.40±6.20	0.726***
Plt, 10^3 /µl		211.00 (164.00-328.00)	225.00 (146.00-325.00)	211.00 (165.00-362.00)	0.873**
PDW, %		13.98±3.44	14.01±3.56	13.86±3.16	0.891***

*Chi-square analysis, **Mann-Whitney U test, ***Student T test were applied, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular diseases, HT: Hypertension, DM: Diabetes Mellitus, CRP: C-reactive protein, PCT: Procalcitonin, LAR: Lactate/albumin ratio, Leu: Leukocyte, Neu %: Neutrophil percentage, Plt: Platelet, PDW: Platelet distribution range

Of the 58 patients included in the study, 43 died, yielding an overall survival rate of 25.9%. When all patients were evaluated together, the mean survival time was 65.3 days. Patients with LAR level ≤1.13 exhibited a significantly higher survival time than patients with LAR level >1.13 (p=0.016) (Table 2, Figure 2).

Table 2. Comparison of overall survival and LAR level

		Survival rate	Mean	SE	95% CI	p*
LAR	≤1.13	56.3	115.2	18.7	78.5-151.8	0.016
	>1.13	14.3	51.9	3.9	44.1-59.7	
Total		25.9	65.3	7.3	50.9-79.6	

*A log rank (Mantel-Cox) analysis was performed, LAR: Lactate/albumin ratio, SE: Standard error, CI: Confidence interval

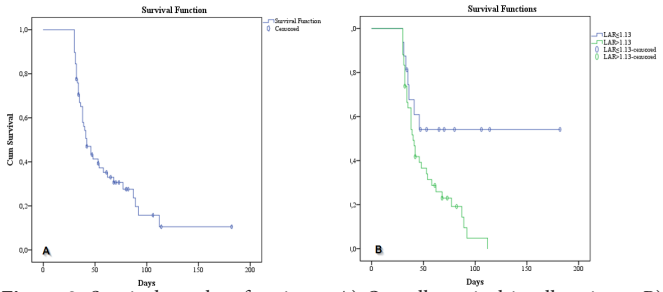

Figure 2. Survival graphs of patients, A) Overall survival in all patients, B) Overall survival curve according to LAR group

LAR: Lactate/albumin ratio

A comparison of the LAR group according to all data revealed a significantly higher rate of LAR values above 1.13 in those with CVH (87%) compared to those without CVH (62.9%) (p=0.045) (Table 3).

DISCUSSION

In our study, which analyzed the prognostic factor of LAR in patients with VAP who were followed up in the ICU, we found that the survival time of those with serum LAR levels ≤1.13 was significantly higher than the survival time of those with LAR levels >1.13. Furthermore, the LAR cut-off value of 1.13 exhibited 83.7% sensitivity and 60% specificity in predicting mortality beyond the 30th day. These findings indicate that LAR is a reliable biomarker for predicting mortality.

Patients hospitalized and critically ill with VAP have a high mortality and morbidity rate. In light of these considerations, several studies have recently been conducted to predict the severity and prognosis of the disease employing various factors, including laboratory and clinical variables. For example (deleted) In a study of patients with sepsis, it was demonstrated that the predictive value of LAR was superior to that of lactate and albumin alone in predicting mortality and length of hospital stay (discharge). The sensitivity and specificity of LAR were 100% and 88%, respectively.[16] In a study conducted by Jia Liang Zhu et al.,[17] LAR was found to have predictive value in predicting 30-day mortality in patients with severe acute myocardial infarction.

Table 3. Comparison of the LAR group according to all data

		LAR ≤1.13 (n=16)	LAR >1.13 (n=42)	p*
		n (%)	n (%)	
Gender	Female	8 (30.8)	18 (69.2)	0.625
	Male	8 (25.0)	24 (75.0)	
Age		68.00 (55.00-76.00)	68.00 (60.00-81.00)	0.761**
Age group	≥65	10 (27.8)	26 (72.2)	0.967
	<65	6 (27.3)	16 (72.7)	
COPD	Present	6 (28.6)	15 (71.4)	0.899
	Absent	10 (27.0)	27 (73.0)	
CVH	Present	3 (13.0)	20 (87.0)	0.045
	Absent	13 (37.1)	22 (62.9)	
HT	Present	6 (25.0)	18 (75.0)	0.711
	Absent	10 (29.4)	24 (70.6)	
DM	Present	3 (33.3)	6 (66.7)	0.696
	Absent	13 (26.5)	36 (73.5)	
Trauma	Present	3 (42.9)	4 (57.1)	0.381
	Absent	13 (25.5)	38 (74.5)	
Microorganism	*Acinetobacter baumannii*	5 (23.8)	16 (76.2)	0.229
	Klebsiella pneumoniae	5 (41.7)	7 (58.3)	
	Pseudomonas aeruginosa	3 (15.8)	16 (84.2)	
	Other	3 (50.0)	3 (50.0)	
CRP		12.46±6.72	16.84±9.80	0.106***
PCT		2.74 (0.34-7.74)	1.12 (0.32-4.32)	0.476**
Ferritin		217.00 (134.00-624.00)	352,00 (128.00-785.00)	0.476**
Leu		13.17 (11.68-17.14)	13.31 (10.20-17.50)	0.670**
Neu		84.70±7.18	83.76±8.22	0.690***
Plt		218.00 (166.50-347.50)	200.00 (146.00-318.00)	0.439**
PDW		12.69±4.53	14.48±2.82	0.079***

*Chi-square analysis, **Mann-Whitney U test, ***Student T test were conducted, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular diseases, HT: Hypertension, DM: Diabetes mellitus, CRP: C-reactive protein, PCT: Procalcitonin, LAR: Lactate/albumin ratio, Leu: Leukocyte, Neu %: Neutrophil percentage, Plt: Platelet, PDW: Platelet distribution range

The correlation between age and risk appears to be inconclusive, particularly in the context of VAP. In a multicenter cohort study, the incidence of VAP was 13.7% in middle-aged patients (45-64 years), 16.6% in elderly patients (65-74 years), and 13.0% in very elderly patients (≥75 years). The logistic regression analysis did not identify a heightened risk of VAP among older patients. However, elevated mortality rates were observed in the very old (aged 85 and above).[18] Our study revealed a higher mortality rate among elderly patients (aged 65 and above), with a death rate of 83.3% compared to 59.1% in patients below the age of 65.

In recent studies, the prognostic value of LAR has been subjected to analysis. In a study by Shin et al.,[11] it was demonstrated that LAR was a predictor of 28-day mortality in patients with critical sepsis. In a separate study by Kong et al.,[12] it was indicated that LAR serves as a prognostic marker for neurogenic outcome and survival in patients whose spontaneous circulation was restored following out-of-hospital cardiac arrest. In a study, LAR was identified as an indicator of short- and long-term mortality in critically ill patients with heart failure.[13] Additionally, LAR was reported as a prognostic marker for predicting 30-day mortality in critically ill patients diagnosed with COVID-19.[12] The available evidence indicates that LAR is a novel clinical biomarker with prognostic significance in a range of diseases. A review of the literature revealed no studies indicating that LAR is a prognostic biomarker in patients with VAP. Accordingly, the present clinical retrospective study was designed to examine patients with VAP. As with the aforementioned studies, our findings revealed that serum LAR levels were markedly elevated in patients who succumbed to their illnesses compared to those who survived. A study conducted on patients with acute ischemic stroke and low-attenuation signals on brain imaging (LAR) revealed a linear correlation between LAR and mortality risk. It was identified as a predictor of all-cause mortality within 28 days of the onset of acute ischemic stroke.[19] In a separate clinical investigation conducted on patients with spontaneous subarachnoid hemorrhage, LAR was identified as a significant predictor of in-hospital mortality.[20] In our study, a comparison of LAR levels between patients with and without cerebrovascular disease (CVD) revealed a significantly higher prevalence of LAR in patients with CVD (87%) compared to those without CVD (62.9%). These findings suggest that LAR level may serve as a potential biomarker for mortality in patients with VAP and CVD, given the high prevalence of CVD among other comorbidities.

Limitations

However, this study is not without limitations. The current study was retrospective and had a relatively small sample size, which precluded the ability to correlate clinical data with disease prognosis. To confirm these results, larger sample sizes are needed, ideally from multicenter prospective studies.

CONCLUSION

The primary outcome of this study was that a LAR result greater than 1.13 was associated with survival. As the LAR level increases, the survival time decreases. The LAR was identified as an independent and significant predictor of mortality, exhibiting a sensitivity of 83.7% and a specificity of 60% when the cut-off value for predicting mortality was 1.13. Furthermore, in patients with VAP, the LAR proved to be a more effective predictor of mortality than either the serum lactate level or the serum albumin level alone. Consequently, the LAR may serve as a valuable and readily accessible prognostic biomarker for early risk stratification of VAP patients, facilitating mortality prediction and more optimal management of VAP patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Malatya Turgut Özal University Faculty of Medicine Clinical Researches Ethics Committee (Date: /06/2024, Decision No: 2024/5038).

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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Analysis of the Turkish informative videos for gambling disorder on YouTube

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ABSTRACT

Aims: The low rates of treatment seeking in gambling disorder (GD) and the popularization of online gambling increase the importance of informative videos on digital platforms. We aimed to evaluate the characteristics and quality of Turkish informative videos for GD on YouTube.

Methods: A total of 116 videos that met the study criteria were examined by two independent psychiatrists. In addition to quantitative characteristics such as the speakers, video duration, number of the views, likes, and comments, the quality and reliability of the videos were evaluated using the Global Quality Scale (GQS) and modified DISCERN scale.

Results: 46.6% of the videos were in the professional group (featuring a speaker who is a physician, psychologist, or another mental health professional, or voice-over videos uploaded by health/academic channels). According to GQS scores, 58.6% of the videos were of low quality, 24.1% were of medium quality, and 17.2% were of good/excellent quality. Despite higher quality scores for professional videos (GQS scores: 3.24±0.79, 1.90±0.46, respectively), non-professional videos had higher daily average views, likes, and comments. It was found that there was a negative correlation between the GQS scores and the average daily views, likes, and comments, whereas only video duration showed a positive correlation with the modified DISCERN scores.

Conclusion: When creating informative videos for GD, including experiences shared by patients, their relatives, or celebrities along with the medical information presented by mental health professionals can ensure high quality and reliability while also providing higher levels of interaction, thereby reaching a wider audience.

Keywords: Gambling, gambling disorder, YouTube, behavioral addictions

INTRODUCTION

Gambling, defined as taking a risk with something of value in the hope of achieving a higher gain, involves uncertainty and the role of chance; it spans the spectrum from social gambling, problematic gambling, to gambling disorder (GD).[1] In social gambling, the purpose is entertainment, and there is no loss of control over the gambling behavior, with losses being controlled. Although not included in international diagnostic systems, the term 'problematic gambling' is used in the literature to describe gambling behavior that goes beyond social limits, with increasing risks and unpredictable losses. In problematic gambling, although gambling causes problems in people's lives, these individuals do not meet the diagnostic criteria for GD.[1,2]

Gambling stretches back to the depths of human history, but considering maladaptive gambling as a psychiatric disorder is relatively recent. This disorder was first included under the name 'pathological gambling' in the 3rd edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III), published by the American Psychiatric Association in 1980, under the category of impulse control disorders. The diagnostic criteria for pathological gambling were reviewed in the DSM-IV, published in 1994, and it was included in the addiction category with the DSM-5 in 2013, being renamed as GD in this edition.[1,3,4]

The prevalence of GD in the United States is estimated to be 0.5% of the adult population, also similar or slightly higher estimates in other countries.[5] Recognized as a complex psychiatric disorder influenced by environmental and genetic factors, the risk factors for GD include male gender, being single, young age, living alone, low education level, and financial difficulties.[6] One of the significant clinical features of GD is its high comorbidity with other psychiatric disorders. In a study conducted on 2099 individuals receiving treatment for GD, the rate of coexisting psychiatric disorders was reported to be 73%, while another study in the United States found that 96.3% of individuals diagnosed with GD met the diagnostic criteria for at least one psychiatric disorder during their lifespan.[7,8] It is noted that a range of psychiatric

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disorders, such as substance use disorders (SUD), impulse control disorders, major depression and other mood disorders, anxiety disorders, post-traumatic stress disorder, and attention deficit hyperactivity disorder, are highly comorbid with GD.[1,3,5,7] In addition to these disorders, increased suicide rates in GD compared to the general population have also been demonstrated in various studies.[9,10]

Technological developments have brought a new dimension to GD, which negatively affects the individual, their family, and society in various ways. Online gambling, with its unique features, has rapidly become a significant and growing problem worldwide in recent years. Factors such as its easy accessibility, flexibility in timing, higher interaction, anonymity, and variety of games have played a significant role in the spread of online gambling.[11] Despite the serious problems it creates, studies have shown that the rate of seeking treatment for GD is quite low. Various reasons such as individuals' tendencies to deny, feel ashamed, hide the situation, and desire to handle the problem alone play a role in the low treatment application rates.[12,13] Considering this situation, easily accessible and accurate information sources can provide significant benefits for informing and educating individuals with gambling problems and their relatives, as well as especially young people, who are identified as a risk group.

As the internet develops and becomes widespread, sources of health information are shifting from traditional media to digital media.[14] In a 2014 report on the digital health literacy of European citizens, more than 75% of participants indicated that they considered the internet to be a good source for searching health information, and 60% reported using the internet to search for health information.[15] The digital media platform YouTube, which was established approximately 19 years ago, is now one of the most visited video-sharing sites, with over 500 videos uploaded per minute. YouTube, a platform where anyone can upload videos for free at any time, has become a resource for health information as well as other fields. However, misleading and low-quality videos pose the risk of negatively influencing individuals' decisions on health-related issues.[16] Concerns about the accuracy and quality of videos uploaded in the health field, especially due to the lack of content moderation, have laid the groundwork for studies in this area.[16-18] Considering the financial, familial, social, professional, and legal problems, as well as the high psychiatric comorbidity intertwined with GD, we believe that the low rates of treatment applications for GD and the widespread prevalence of online gambling increase the importance of informative videos on digital platforms. In this context, our study aimed to analyze the quality and reliability, along with other quantitative characteristics, of Turkish informative videos about GD on YouTube, a topic that has not yet been addressed in the literature.

METHODS

Study Design

In this study, similar to previous studies with a similar design, no ethics committee approval was required as publicly available videos were used and no human or animal data were used.[16-18] All procedures were carried out in accordance with the ethical rules and the principles.

To access the videos on YouTube, the search history was cleared. In incognito mode and without logging into personal accounts, the terms 'gambling disorder' and 'gambling addiction' were separately entered into the YouTube (https://www.youtube.com) search bar, and the search was conducted on August 30, 2024. Studies on internet search engines have indicated that more than 90% of search engine users click on a result on the first three pages of search results.[17] Therefore, in our study, the first 100 videos listed for each term were evaluated for suitability according to the study criteria by two psychiatrists (H.İ.Ö., F.S.). Videos without sound, repetitive, unrelated, requiring a paid subscription for access, intended for humor, film/music/advertisements, and news videos were excluded from the study. Videos divided into multiple parts were considered as a single video, and their average values were used for analysis. According to these criteria, a total of 116 videos included in the study were reviewed by two independent psychiatrists (Figure).

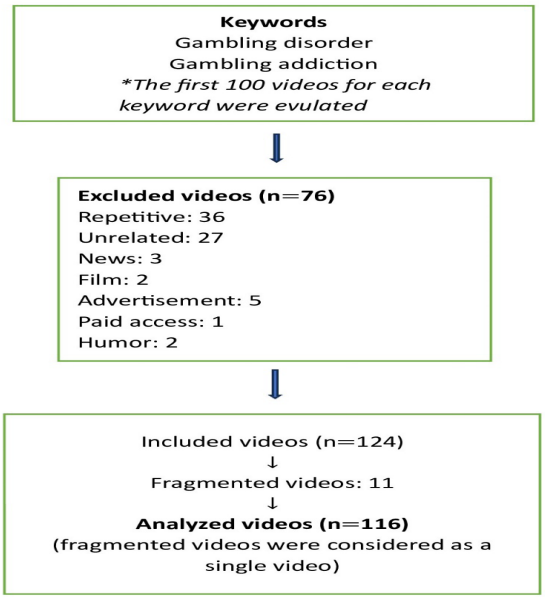

Figure. The flowchart of the videos selection

Information regarding the speaker in the video (physician, psychologist, or other mental health professional, voice-over, patient or their relative, individual/celebrity or youtuber), the video's length (seconds), the time elapsed since the upload date on YouTube (days), average daily views [total views/time elapsed since the upload date on YouTube (days)], average daily likes [total likes/time elapsed since the upload date on YouTube (days)], and average daily comments [total comments/time elapsed since the upload date on YouTube (days)] was identified and recorded. In addition to these variables, the videos were classified as professional and non-professional. The professional videos group consisted of videos featuring physicians, psychologists, and other mental health professionals as speakers, as well as voice-over videos uploaded by health or academic channels. The non-professional videos group included videos featuring personal experiences of patients or their relatives, videos with individuals/celebrities

or youtubers as speakers, and voice-over videos uploaded by channels other than health or academic ones.

The overall quality of the videos was evaluated by two independent psychiatrists using the Global Quality Scale (GQS).[19] Additionally, the comprehensiveness and reliability of the videos in the professional group were scored using the modified DISCERN scale.[17,20]

Global Quality Scale (GQS)

It was developed by Bernard et al.[19] to evaluate the quality of health information presented online. The scale is rated between 1 to 5. The scoring is done by considering the flow of information, adequacy, and usefulness for patients. A score of 1 indicates the lowest quality, 3 indicates average quality, and 5 indicates the highest quality. It has been widely used in studies evaluating health videos broadcasted online in English, Turkish, or other languages.[16-18,21-24]

Modified DISCERN

It is a modified version of the original DISCERN scale developed by Charnock et al.,[20] which consists of 16 questions.[17] It consists of a total of 5 questions. The health information provided is scored as no (0) and yes (1) in response to each question in the scale. The total score of the scale can vary between 0 and 5. It has been used in many studies to assess the reliability of health videos on YouTube in English, Turkish or other languages.[16,17,21,22,25,26]

Statistical Analysis

Numerical variables were given as mean±standard deviation or median (interquartile range) depending on their distribution, and categorical variables were given as frequencies and percentages in descriptive statistics. The normality of the distribution was evaluated using the Shapiro-Wilk test. The inter-rater agreement for the GQS and Modified DISCERN scales was assessed using Cohen's kappa (κ) coefficient. For comparing professional and non-professional video groups, the t-test was used for normally distributed numerical data, and the Mann Whitney U test was used when normal distribution was not met. The direction and level of relationships between the GQS and modified DISCERN scores and the independent variables studied were examined using Spearman correlation analysis. The significance level in the analyses was set at $p<0.05$. Statistical Package for the Social Sciences (SPSS; IBM Corp., Armonk, NY) version 23.0 software package was used for data analysis.

RESULTS

Of the 116 videos included in the study, 46.6% (n=54) were in the professional group (featuring a speaker who is a physician, psychologist, or another mental health professional, or voice-over videos uploaded by health/academic channels). The majority of the speakers in the videos were physicians and patients or their relatives. While the number of videos sharing the experiences of patients or their relatives was 35 (30.2%), the number of videos featuring physicians as speakers was 34 (29.3%). The median duration of the reviewed videos was found to be 866 seconds (25^{th}-75^{th} percentile: 424-1631), and the median daily view count was 26.7 (25^{th}-75^{th} percentile: 3.97-90.1). The average GQS score of the videos, evaluated by two independent psychiatrists, was calculated as 2.52±0.92. According to GQS scores, 58.6% (n=68) of the videos were of low quality, 24.1% (n=28) were of medium quality, and 17.2% (n=20) were of good to excellent quality. The average modified DISCERN score of the videos in the professional group was found to be 2.90±0.48. The characteristics and quality evaluations of the videos are presented in detail in Table 1.

Table 1. The characteristics and quality evaluations of the videos (n=116)

Videos category	
Professional, n (%)	54 (46.6%)
Non-professional, n (%)	62 (53.4%)
Speakers in the videos	
Physicians, n (%)	34 (29.3%)
Psychologists/other mental health professionals, n (%)	20 (17.2%)
Patients/their relatives, n (%)	35 (30.2%)
Individuals/celebrities/youtubers, n (%)	19 (16.4%)
Voice-over, n (%)	8 (6.9%)
Video duration (seconds)	866 (424-1631)
Duration of YouTube presence (days)	653 (122-1010)
Average number of daily views	26.7 (3.97-90.1)
Average number of daily likes	0.27 (0.01-1.44)
Average number of daily comments	0.15 (0.0-0.92)
GQS	
GQS, mean±SD	2.52±0.92
Poor quality (1-2), n (%)	68 (58.6%)
Moderate quality (3), n (%)	28 (24.1%)
Good/excellent quality (4-5), n (%)	20 (17.2%)
Modified DISCERN, mean±SD	2.90±0.48

Note: Data is presented as mean±SD or median (25^{th}-75^{th} percentile) for numerical variables, and as count (n) and percentage (%) for categorical variables, SD: Standard deviation, GQS: Global Quality Scale

In determining the inter-rater agreement, the κ coefficient was calculated as 0.946 for the GQS scale and 0.884 for the modified DISCERN scale ($p<0.001$) (Table 2). These results indicate a high level of agreement between the raters.[27]

Table 2. Inter-rater agreement

	Mean±SD	z	p	Cohen κ
GQS				
GQS1	2.48±0.91	10.2	<0.001	0.946
GQS2	2.56±0.96			
Modified DISCERN				
Modified DISCERN1	2.87±0.48	6.55	<0.001	0.884
Modified DISCERN2	2.93±0.51			

Abbreviations: SD: Standard deviaiton, GQS1: First rater score, GQS2: Second rater score, modified DISCERN1: First rater score, modified DISCERN2: Second rater score, SD: Standard deviation, κ: Kappa, $p<0.05$ statistical significance level, GQS: Global Quality Scale

When comparing professional and non-professional videos, it was found that the average GQS scores of professional videos were higher (3.24±0.79, 1.90±0.46, respectively, $p<0.001$). However, non-professional videos had higher daily average

views, daily average likes, and daily average comments compared to professional videos (p<0.001). Comparisons between professional and non-professional video groups are presented in Table 3.

The direction and level of relationships between the GQS and modified DISCERN scores and the independent variables investigated in the study are presented in Table 4. It was found that the GQS score showed a low positive correlation with video duration and the time the video had been on YouTube (days), while it had a negative correlation with average daily views, likes, and comments (p<0.05). The modified DISCERN score only showed a significant correlation with video duration (rs=0.72, p<0.05).

DISCUSSION

To the best of our knowledge, this is the first study to analyze the Turkish informative videos for GD on YouTube. The main finding was that the majority of the videos were of low quality, and most of the videos featured speakers who were not mental health professionals. Another significant finding was that videos with mental health professionals as speakers had higher quality, but non-professional videos had higher daily view counts, daily comment counts, and daily like counts, which are parameters indicating video interaction.

The development of technology and the widespread use of the internet have made digital platforms one of the main sources people use to obtain information about health issues.[27,28] YouTube, one of the most preferred video-sharing platforms, hosts many videos about general information, experiences, diagnosis, treatment, and coping methods for various diseases. However, YouTube does not guarantee the quality or reliability of these videos for its users.[16] This situation carries the risk of patients and their relatives obtaining incomplete, misleading, or incorrect medical information, which has the potential to negatively impact their health. In a pioneering study by Keelan et al.,[29] it was reported that there are numerous anti-immunization videos on YouTube, and that the content of these videos contradicts reference sources. They recommended that clinicians should be aware of online video-sharing sites and be prepared to respond to patients seeking health information from these sources. Similar to our study results, numerous studies analyzing YouTube videos on different diseases have reported that the majority of informative videos on YouTube are of low quality.[18,24,30-33]

The majority of the videos analyzed in our study were non-professional videos. In the literature, studies conducted with similar methodologies for different diseases show that there are varying proportions of professional and non-professional videos.[16-18,32-35] This proportional difference between studies may be due to the prevalence of diseases, the level of awareness in the community, or other disease-specific characteristics. However, consistent with our study, previous studies found that professional videos were of higher quality.[16,32,36-41] The higher quality and reliability of video content uploaded by health professionals and health channels indicates their competence and sense of responsibility towards their profession, institutions and their community.

Despite professional videos being of higher quality, the average daily views, average daily likes, and average daily comments were lower compared to non-professional videos. Furthermore, in the correlation analysis that included all videos in the study, a negative correlation was found between GQS scores and average daily views, average daily likes, and average daily comments. In addition, no significant relationship was found between the modified DISCERN scale scores, used to evaluate the comprehensiveness and reliability of professional videos, and the average daily views, average daily likes, and average daily comments. There was a positive correlation only between the modified DISCERN scale scores and video duration. It is expected that longer videos can convey information more comprehensively and holistically. Consistent with our study results, a study analyzing YouTube videos about agoraphobia also highlighted that the average

Table 3. Comparison of professional and non-professional videos

	Professional (n=54)	Non-professional (n=62)	Effect size	p
Video duration (s)	606 (228-1629)	1009 (613-1609)		0.07
Duration of YouTube presence (d)	857 (334-1289)	173 (67.5-464)	0.498	<0.001
Average number of daily views	3.91 (0.49-26.4)	55 (24.3-179)	0.663	<0.001
Average number of daily likes	0.03 (0.0-0.21)	1.06 (0.20-2.74)	0.559	<0.001
Average number of daily comments	0.0 (0.0-0.04)	0.64 (0.26-2.42)	0.759	<0.001
GQS (Mean±SD)	3.24±0.79	1.90±0.46	0.813	<0.001

Note. Data is presented as mean±standard deviation or median (25^{th}-75^{th} percentile) for numerical variables, rank biserial correlation, p<0.05 statistical significance level, s: Seconds, d: Days, SD: Standard deviation, GQS: Global Quality Scale

Table 4. Correlation between GQS and modified DISCERN scores and video characteristics

		Video duration (seconds)	Duration of YouTube presence (days)	Average number of daily views	Average number of daily likes	Average number of daily comments
GQS	rs	0.29*	0.26*	-0.43*	-0.31*	-0.41*
modified DISCERN	rs	0.72*	0.01	-0.01	0.24	0.11

Abbreviations. GQS: Global Quality Scale, rs: Spearman correlation coefficient, *significant relationship at p<0.05 level (two-tailed)

number of likes and views of the included videos did not reflect professionalism, quality or reliable content.[16] Another study analyzing YouTube videos on essential tremor reported that the correlation analysis showed a significant negative correlation between average DISCERN and GQS scores and viewer interaction parameters (video power index, like ratio, etc.).[18] A review of the literature analyzing health-related content on YouTube reveals that many studies report higher interaction parameters-such as views, likes, and comments-for the videos of low quality and reliability. In a systematic review study conducted in this field, it was reported that 13 studies found a negative correlation between video quality and the number of views, and 6 studies found a negative correlation between video quality and the number of likes.[42] This may be due to the recognizability of the speakers (individuals, celebrities, youtubers, etc.) in the videos and/or the fact that they share engaging content due to interaction concerns. On the other hand, professional videos may have been less popular among YouTube users due to their preference for medical and formal language/flow. Regardless of the reason, the fact that low-quality videos have higher interaction (average daily views, likes, and comments) in a serious psychiatric disorder like GD, where treatment seeking rates are already quite low, poses a risk of negatively impacting health. In addition, we encountered 5 advertisements for illegal gambling sites or gambling videos, which were excluded from our study. These results highlight a significant issue that policymakers in our country should address, while also underscoring the necessity for YouTube officials to act responsibly.

Limitations

Our current study has some significant limitations. Firstly, the choice of keywords (gambling addiction, gambling disorder) and the evaluation of the first 100 videos for each keyword may have excluded other videos related to GD. Additionally, YouTube is a dynamic video-sharing platform with variability. Factors such as the number of likes and views can alter the visibility of videos, and existing videos can be removed while new videos can be added. Finally, the limitation of including only videos in the Turkish language can also be considered a limitation.

CONCLUSION

Considering the online gambling dimension brought by technological changes and the low treatment seeking rates in GD, video-sharing platforms like YouTube can be an important source of information. In this context, the potential negative impact of incomplete/misleading information and guidance on individuals' treatment adherence and prognosis should be considered by both policymakers and YouTube officials. When creating informative videos for GD, including experiences shared by patients, their relatives, or celebrities along with the medical information presented by mental health professionals can ensure high quality and reliability while also providing higher levels of interaction, thereby reaching a wider audience. Considering YouTube's dynamic nature, replicating a study with a similar design in the coming years could be useful to assess any changes in the reliability, quality, and interaction parameters of videos related to GD. Additionally, there is a need for studies that evaluate and compare the Turkish and English informative videos about GD.

ETHICAL DECLARATIONS

Ethics Committee Approval

As in previous studies with a similar design, no ethics committee approval was required as publicly available videos were used and no human or animal data were used in this study.

Informed Consent

This study did not require informed consent as it did not involve any human subjects or animal experiments.

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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Voices from a healthy life centre: a qualitative investigation of clients' nutrition and physical activity experiences

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ABSTRACT

Aims: This study aimed to investigate the perceptions and experiences of clients attending a healthy life centre in Amasya for weight management and physical activity counselling.

Methods: This qualitative study was conducted through telephone interviews with 23 individuals who had attended weight management counseling. Participants were adults aged 18 years and over who attended the healthy life centre in Amasya for weight management and were randomly selected from those who received weight management services. Semi-structured interviews were conducted to explore participants' experiences with the healthy life centre, including their reasons for applying, their access to and satisfaction with the services, and changes in their wellbeing. Using NVivo12, transcripts were analysed thematically based on grounded theory.

Results: The mean age of participants was 32.57 years (±6.1), with weight loss being a common reason for attending. The majority of participants attended a single session (n=9), and the primary sources of awareness about the center were friends (n=6) and family (n=3).The thematic analysis revealed five major themes: 1) impact on healthy living, 2) lack of promotion, 3) satisfaction, 4) reason for ceasing, and 5) suggestions for the future.

Conclusion: This study emphasises the positive impact of healthy life centres on clients' health and lifestyle behaviors, with patients reporting significant improvements in their nutritional habits and increased physical activity levels due to the counseling they received. However, the study also showed that people are unaware of the existence of healthy life centres, and that these services are not sufficiently promoted. Therefore, there is a need for the greater promotion of healthy life centres in Turkiye to improve public health.

Keywords: Health promotion, healthy life centre, qualitative research, weight management

INTRODUCTION

One of the main causes of morbidity brought on by the emergence of noncommunicable diseases (NCDs) is negative health behaviours, such as lack of physical activity, unhealthly eating habits, smoking, and excessive alcohol consumption. The World Health Organization (WHO) global plan of action encourages national governments to develop public health strategies to improve human health.[1] The burden of NCDs is a global public health problem that jeopardizes socioeconomic development.[2] In developing nations, where noncommunicable illnesses account for 71% of all causes of mortality, this figure is projected to rise to 55 million by 2030, with about 41 million fatalities globally.[3] According to the status report published by WHO for Turkiye, 34% of these deaths are due to cardiovascular diseases, 23% cancers, 7% chronic respiratory diseases, 5% diabetes, and 21% other noncommunicable diseases.[4]

A combined diet and exercise approach, more commonly known as a lifestyle intervention, has been shown in clinical trials to reverse metabolic abnormalities, reduce dependence on pharmacotherapy, and prevent the progression of diabetes and cardiovascular disease.[5,6] A growing body of literature recognises that the majority of heart disease, stroke, type 2 diabetes, and a significant percentage of cancers could be prevented through healthy dietary choices and lifestyle improvements.[7-11] Community-based interventions and public health policies are needed to combat this rising mortality rates from NCDs in preventive medicine and public health.[12] One of these policies is primary health care. Patients are more likely to modify their behaviour when professionals encourage them. Therefore, primary health care services are ideal environments for behaviour modification-based counselling.[13] Counselling patients on lifestyle change is a key

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task for primary care clinicians.[14] Considering both the direct (e.g. medical care) and indirect (e.g. sickness absenteeism or presenteeism and physical inability) cost of obesity on health systems, weight management programs which encourage people to eat a healthier diet and become more physically active could be cost effective.[15] People who have a low income tend to claim high costs as a barrier to engagement.[16] Individuals could not attend due to the cost of participation, transport and/or childcare.[17] Therefore, it is important to provide such interventions free of cost.

In Turkiye, healthy life centers (HLC) have been established in all 81 provinces to protect individuals and society from risky conditions for health, to strengthen primary healthcare services and to make these services easily accessible, and to encourage a healthy lifestyle. These facilities' target population includes both healthy people and ill people. In Turkiye, Healthy Life Centres provides solutions combating risk factors of NCDs, nutritional counselling, psycho social counselling, oral and dental health, injection services, women's and reproductive health, school health, cancer early diagnosis and screening and education, smoking cessation counselling, counselling for drug users and their relatives, infectious diseases services including control and management.[18]

Few studies have evaluated the efficacy of the services offered in HLCs because these facilities are relatively new and poorly known. In 2017, an HLC was established in Amasya, and this qualitative study aimed to investigate the views and experiences of the citizens who received services at the HLC.

METHODS

Design

This study was approved by Amasya University Ethics Committee (Date: 25.06.2020, Decision No: 89). The study was conducted in accordance with the guidelines of the Declaration of Helsinki. Written consent was obtained during phone conversations by first explaining the study's purpose, procedures, potential risks, and benefits to the participants in detail. Participants were then given the opportunity to ask questions and clarify any concerns. Following verbal agreement, a consent form was sent to them electronically, which they signed and returned via email. This process ensured transparency, informed decision-making, and adherence to ethical standards.

Qualitative research methods focus on exploring and understanding individuals' experiences, perspectives, and behaviors in depth, often through data collection methods including interviews, focus groups, and content analysis. These methods allow researchers to capture rich, contextualised insights that may not be achievable through quantitative approaches.[19-21] This study employed a qualitative research design that utilised telephone interviews to gather in-depth insights.

Telephone interviews were selected to address potential difficulties in transportation, ensuring convenience and accessibility for all participants. This method facilitated open-ended discussions, enabling the collection of rich, detailed data that provided a nuanced understanding of the research topic. The interviews were guided in a semi-structured format, allowing for consistency in questioning and the opportunity to probe deeper into emerging themes.

Subjects and Settings

This qualitative study was conducted from July to September 2020 through telephone interviews to explore the views and experiences of the services offered. Telephone interviewing was determined to be an appropriate data collection method, considering COVID 19 pandemic restrictions.

Amasya is a city located in the north of Turkiye with a population of 339.529 as of the end of 2023.[22] The participants consisted of adults aged 18 years and over who attended the HLC in Amasya for weight management. Pregnant women were excluded from this study.

Participants for the telephone interviews were randomly selected from the data received from the bioelectrical impedance scale (Tanita-BC 418). The Tanita measurements were initially used to identify individuals attending the center for weight management or physical activity, as all participants' data were recorded on Tanita-BC 418. However, no weight-related data from the measurements were utilised in the study. The only information extracted from the records was participants' telephone numbers, which were used solely for recruiting participants for the telephone interviews.

Randomisation was managed by the lead researcher using the identification numbers of the clients through an online random drawing generator. 2652 adults whose attendance frequency ranged from one to 12, were entered into the generator. When the generator provided potential participants, they were contacted, and those who volunteered to be interviewed were included in the study. The sample size was specified by data saturation when no new themes emerged from participants' experiences. In qualitative research, the goal is not to calculate sample size based on statistical power but to achieve data fullness and saturation, where no new information is emerging from additional participants.[20,21] The sample size in qualitative studies is determined by the point of saturation, ensuring the depth and richness of the data are adequately captured to address the research questions.[21,23]

All telephone interviews were conducted by a doctoral student (EDK). At the beginning of each telephone conversation, the aim of the interview was explained, and verbal consent was obtained for the interview to be recorded using a voice recording application.

Data Collection

Semi-structured interviews were conducted based on the flexible study design of a qualitative approach. An interview guide was developed based on previous literature and expert and health practitioner opinions (appendix), but the questions were not restricted to the order in the guide to allow a natural discussion. The interview guide was piloted with two participants in the target population and two experts in the health sciences to assess its clarity and comprehensiveness. No significant changes were deemed necessary, as all the questions were clear and easy to understand. This feedback was used to confirm the suitability of the interview schedule

for the main study, ensuring that it adequately captured the experiences and perspectives of the HLC attendees.

The interviews started with the following questions: "How did you first hear about the centre?" and "How did you access the centre (transportation)?". The interview then continued with the main questions, exploring the experiences of participants regarding the services, and concluded by asking their suggestions on how to improve the services. Prompts such as "Can you tell me more about this?" and "Can you tell me the reason behind your answer?" were used as appropriate to receive more depth from the responses. Telephone interviews were completed when clear patterns and data saturation emerged. Each telephone interview lasted between 6-8 minutes.

Appendix: Semi-structured Interview Guide

Introduction

Hello (the researcher introduces himself), we are interviewing you to better understand what clients think about Healthy Life Centre (HLC) in Amasya and how the services could be improved. So there are no right or wrong answers to any of our questions, we are interested in your own experiences.

Participation in this study is voluntary and your decision to participate, or not participate, will not affect the services you currently receive from the HLC. The interview will take approximately 8-10 minutes. I would like to audio record the interview with your permission; however all responses will be kept confidential. All information will be anonymised (will only be shared with research team members).

You may decline to answer any question or stop the interview at any time and for any reason. Are there any questions about what I have just explained?

May I turn on the digital recorder?

Age: Gender: Weight: Height:

How did you first get connected with HLC? (How did you hear about it? Were you referred; If so, by whom?)

What was the reason for applying the HLC? (Which services did you receive?; If attended various services, following questions will be asked for the services attended.)

When did you attend the services? (How long have you been involved?; If you cease the services, what is the reason/ reasons?)

How did you access the HLC? (Was it easy or hard?; What kind of transportation vehicle did you use?; How long did it take to access the HLC?)

How would you describe your wellbeing since receiving services from HLC? (Has your general well-being improved, declined, or remained the same? What do you think are the reasons for any changes in your health? If your health has improved, what are your thoughts on maintaining this improvement? How likely are you to follow the advice given to you?)

Can you tell me about the services that you are involved? (Was there anything you particularly liked?; Was there anything you didn't like?; What are the reasons?)

Can you tell me your suggestions about how to improve the services? (Are there any other services that you wish to be involved in future?; Why or why not?; Would you recommend HLC to a person with similar needs as you?)

Thank you very much for your time and the information you shared today.

Note: Prompts such as "Can you give an example?", "Can you please tell me more about this?" or "Can you tell me the reasons behind your answer? will be used, as appropriate.

Statistical Analysis

The recorded interviews were stored using identifying numbers (e.g., P01, P02, P03, etc.). The researcher listened to the recordings carefully and transcribed them verbatim using Microsoft Word 2020. The transcripts were analysed using a thematic analysis approach based on grounded theory using a qualitative data management software tool (NVivo12). The analysis process started by coding and labelling similar topics after reading the transcripts several times. Themes were formed using groups that included the same labels and topics. The frequency of words or phrases has also been reported to reflect the importance of a theme based on a quasi-statistical approach.

RESULTS

In total, 23 adults (20 female; 3 male) who attended nutrition and physical activity counselling were interviewed via telephone. The gender ratio of the population represents the gender ratio of adults who attended nutrition counselling over the last two years (2327 female; 325 male). The mean age of the participants was 32.57±6.1, with a minimum age of 21 and a maximum age of 42. A common reason for attendance to the counselling among interviewees was losing weight.

Interviewees' first attendance dates ranged from when the centre was first launched to when the centre was suspended due to the COVID-19 pandemic (July 2020). Of those reporting the duration of their attendance, the majority (n=9) received services from the centre only once. Other interviewees reported attending twice (n=3), three times (n=3), four times (n=1) and regularly once a month during a year (n=3).

When the participants were asked how they heard about the HLC, of those who answered this question, the majority (n=6) reported that they heard of the centre from their friends, and others (n=3) heard from a family member. A small number of participants emphasised that they attended the centre to accompany their friends (n=3) or one of their family members (n=1).

The following five broad themes emerged from the thematic analysis: 1) impacts on healthy living, 2) lack of promotion, 3) satisfaction, 4) reason for ceasing, 5) suggestions for the future.

Impacts on Healthy Living

Among many interviewees, there was the perception that the services in HLC Amasya had favourable impacts on their lifestyles, as indicated; "In fact, I learned once again how to eat…. I maintain (the behaviours that I gained from the nutrition counselling). Sometimes I gained some weight, then

I tend to lose that weight when I applied her (the dietitian) eating advice." (P08). However, a minority of the participants mentioned that they did not put the advice given by the experts in the centre into practice, as one interviewee said: "Unfortunately, it did not have any impact on my lifestyle in only one session. If I continued, it would probably have an impact." (P19).

A new subtheme emerged in discussions of impact on individuals' lifestyles: weight loss. Several participants (n=7) expressed their experiences with weight loss.

For example, one interviewee said: "I reached my target weight." (P13), and another reported: "Before, I was unable to lose weight. I lost weight thanks to her (the dietitian)." (P07).

Lack of Promotion

An interesting theme to emerge was the centre's failure to publicise its services. The participants were unanimous in that many people living in Amasya were not aware of the existence of this centre. When asked whether the participants attended physical activity counselling when it is available, one participant said: "No, I did not. Personally, I did not even know about it." (P08).

Satisfaction

With respect to satisfaction, pleasure was a sense amongst all interviewees. In one case, the participant thought that the group physical activity session was great (P02). Another interviewee quoted; "It was a very good opportunity for us." (P03). This view was agreed with the statement that the services provided in this centre were almost the same as private centres but were free. Some interviewees reported that they recommended the services in the HLC Amasya to the people around them.

One concern was expressed regarding the accessibility of the centre, as reported; "The centre is far from my house, I wish there was another near to my area." (P21). This view was echoed by another interviewee who said "I wish there were more centres in the locations where everyone could go." (P10).

Reason for Ceasing

Reasons expressed by the interviewees for not continuing to attend the services included reaching the target weight, a busy schedule and moving from the city (Amasya). In addition to these reasons, the COVID-19 pandemic was mentioned by many interviewees for ceasing attendance.

Suggestions for Future Improvements

The interviewees were asked for their suggestions and expectations regarding the HLC. Their views included:

- The number of centres should be increased.
- The services in the centre should be publicised more effectively through social media and leaflets.
- There should be more practitioners (dietitians and physiotherapists) in the centre.
- The clients should be given more detail about their measurements, such as an abdominal fat percentage.
- Group sessions, including walking and running for different gender and age groups, should be organised.

DISCUSSION

This study explored the effectiveness of nutritional and physical activity counselling provided by HLCs, a component of primary healthcare services. To the best of our knowledge, as the first qualitative study in Turkiye to document participants' experiences with HLCs, this research provides novel insights into their impact to the existing literature. Quantitative research has consistently demonstrated the benefits of counselling in primary healthcare settings. For example, Zynk et al.[24] found that nutritional and physical activity counselling for patients with obesity significantly improved health outcomes. Similarly, Reynolds et al.[25] reported that tailored counselling interventions in primary care settings led to better management of chronic conditions.

Despite these positive outcomes, our study also identified challenges related to the COVID-19 pandemic, that led to the suspension of services. The temporary disruption in HLC services impacted program continuity, but did not diminish overall participant satisfaction with the counselling received before the pandemic. This mirrors the findings of other studies that have assessed the impact of pandemic-related interruptions on healthcare services globally.[26,27] Studies have reported reduced access to services for patients with chronic and rare diseases,[28] and an increased workload for healthcare providers.[29]

The participants in our study appreciated the free nature of HLC services, which aligns with recent evidence that cost-free health interventions can enhance participation and satisfaction. Studies by Dhillon et al.[28] and Murayama et al.[29] found that removing financial barriers significantly improves the uptake and effectiveness of health programs. While removing financial barriers can increase service utilisation, it may also increase workloads for health staff and affect their remuneration.[30] Coordinating health financing and human resource policies is essential to address these challenges and ensure sustainable improvements in healthcare access and outcomes.

The Ministry of Health established HLCs in 2018 to improve public health through accessible health-related counselling.[18] However, our study revealed that inadequate promotion of these centres limits public awareness and utilisation. Research indicates that while awareness of primary healthcare centres is generally high among rural populations, the utilisation of their services remains low.[31,32] To improve primary healthcare centre utilisation, researchers recommend regular assessments of patient satisfaction, collaborative efforts between primary healthcare centre staff and communities, and public awareness campaigns through information, education, and communication activities.[31,32] Enhancing the promotion of HLCs through public service announcements, social media campaigns, and community outreach could address these challenges and improve service utilisation.

Patient satisfaction, a key quality indicator in healthcare, was notably high in the present study. Research on patient satisfaction in healthcare settings has consistently shown high levels of contentment with counselling services. Patients value comprehensive care that addresses their specific needs, as seen in cancer patients' positive experiences with interprofessional

complementary and integrative healthcare counselling.[33] Patients with asthma reported satisfaction with primary care counselling, particularly when it was client-oriented and supported self-care adherence.[34] Similarly, patients at a nurse practitioner-led clinic reported high satisfaction with services, especially appreciating the lifestyle counselling that led to positive behavioural changes.[35] Across these studies, patients valued the comprehensive nature of counselling, the expertise of healthcare professionals, and a personalised approach to addressing their health concerns.

Limitations

A limitation of this study is that only telephone interviews were used for data collection. This was because there was a lockdown in Turkiye due to the COVID-19 pandemic and it was not possible to conduct face-to-face interviews, which may have resulted in missing non-verbal expressions, mutual relationships, or trust between participants and the researcher. Future research could benefit from incorporating diverse data collection methods, including in-person interviews, to capture a more comprehensive view of participant experiences. Another limitation of this study is the absence of detailed demographic data, including range, economic status, and education level, which could have provided valuable context for understanding the participants' experiences, perspectives, and behaviors. These factors can influence individuals' responses and may have added depth to the analysis. Future studies may benefit from including such demographic variables to enhance the comprehensiveness and applicability of the findings. Additionaly, lack of gender balance in this study may limit the generalisability of the findings and introduce potential bias in understanding the experiences and perspectives of different genders. While we made efforts to capture diverse viewpoints, the underrepresentation of males may have resulted in an incomplete understanding of their experiences. Future studies should aim for a more gender-balanced sample to ensure a broader and more representative perspective on the topic.

CONCLUSION

In conclusion, this study provides valuable insights into the effectiveness of nutritional and physical activity counselling provided for HLC in Turkiye. This study highlights the positive impact of HLCs on clients' health and lifestyle behaviours. Patients reported improved nutritional habits and increased physical activity levels as a result of the counselling provided by HLCs. Nevertheless, the study also indicated that HLCs are not sufficiently promoted and that patients are not adequately informed of the availability of these services. Therefore, there is a need for increased promotion of HLCs and collaboration between nutritional and physical activity counsellors and primary healthcare physicians. This study contributes to the growing body of research on the importance of primary healthcare services in promoting healthy behaviours and improving public health. Despite the limitation of using only telephone interviews due to the COVID-19 pandemic, the findings of this study suggest that HLCs can be a valuable resource for individuals seeking to improve their health and wellbeing.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Amasya University Ethics Committee (Date: 25.06.2020, Decision No: 89).

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

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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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Effect of suprainguinal fascia iliaca block on recovery quality after total knee arthroplasty: a prospective, randomized controlled, double-blind, multicenter study

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ABSTRACT

Aims: Total knee arthroplasty (TKA) is a common procedure for patients with advanced gonarthrosis, often leading to significant postoperative pain. Effective pain management, including multimodal analgesia with peripheral nerve blocks, is essential. The suprainguinal fascia iliaca block is a technique that targets key nerves responsible for knee sensation and is similar in effect to the lumbar plexus block. This research aims to evaluate whether suprainguinal fascia iliaca block improves the quality of recovery-15 scores in TKA patients.

Methods: A randomized, prospective, controlled, multicenter study was conducted with 60 patients undergoing TKA. Participants were allocated to either group S (received SIFIB with local anesthetic) or group C (received SIFIB with saline solution). The primary outcome measured was the quality of recovery-15 (QoR-15) score 24 hours post-surgery. Secondary outcomes included postoperative numeric rating scale scores, the requirement for rescue analgesia, time to first rescue analgesia, postoperative complications (nausea and vomiting), the necessity for antiemetics, and patient satisfaction.

Results: Group S had significantly higher QoR-15 scores [124 (121-129) vs. 98 (92-101); p<0.001] and lower numerical rating scale scores at all time points compared with group C (p<0.001). The total amount of tramadol consumed within the first 24 hours postoperatively was higher in group C [145 (80-225) mg vs. 0 (0-0) mg; p<0.001].

Conclusion: Suprainguinal fascia iliaca block significantly enhances postoperative recovery and pain management in TKA patients, presenting a viable alternative to other regional blocks for knee surgery.

Keywords: Multimodal analgesia, postoperative recovery, quality of recovery-15 score, Suprainguinal fascia iliaca block

INTRODUCTION

Total knee arthroplasty (TKA) is a predominant orthopedic procedure, particularly in individuals with advanced gonarthrosis and restricted joint mobility.[1] After TKA, patients experience severe pain, which could be successfully treated with various variants of multimodal analgesics.[2,3] With the extensive adoption of ultrasound (US) technology, peripheral nerve blocks have been widely utilized as a component of multimodal analgesia.[4,5] The sensory innervation of the knee region is provided by the femoral, obturator, and lateral femoral cutaneous nerves that originate from the lumbar plexus, as well as the sciatic nerve that originates from the sacral plexus.[6,7] These nerves need to be targeted to provide analgesia in knee surgeries.[8] Peripheral nerve blocks and fascia iliaca blocks are frequently used for analgesic purposes in lower extremity surgeries, such as knee surgery.[9-11] This block can be performed in two ways: suprainguinal and infrainguinal, which target the femoral nerve, obturator nerve, and lateral femoral cutaneous nerve.[12,13] The suprainguinal fascia iliaca block (SIFIB) shows a similar effect to the lumbar plexus block that targets the femoral nerve, obturator nerve, and lateral femoral cutaneous nerve.[14] Some studies show that SIFIB was applied for postoperative analgesia in TKA. However, none of these studies evaluated the quality of recovery.[9-11]

In this study, we proposed that patients undergoing TKA who receive the SIFIB will show improved quality of recovery-15 (QoR-15) scores and aimed to evaluate the effect of SIFIB on postoperative recovery by using the QoR-15 score, while also assessing secondary outcomes, such as postoperative Numerical Rating Scale (NRS) scores at rest and during movement, patient satisfaction levels, time to first request for rescue analgesia, number of patients requiring rescue analgesia, total consumption of rescue analgesics, antiemetic use, and incidence of complications, including nausea, vomiting.

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METHODS

Ethics Approval and Registration

The Harran University Faculty of Medicine Ethics Committee (Date: 12.02.2024, Decision No: 24.01.42) approved this study. This study was registered in the ClinicalTrials.gov database (number NCT06386575, date: April 15, 2024). The study followed the ethical criteria outlined in the Declaration of Helsinki. We strictly applied the guidelines outlined in the Consolidated Standards of Reporting Trials (CONSORT) statement.[15] We obtained written and verbal consent from patients.

Patient Population and Inclusion/Exclusion Criteria

This research was conducted from April 2024 to July 2024 at Şanlıurfa City Hospital and Harran University Faculty of Medicine. The study included patients aged between 18 and 65, classified as ASA I-III, undergoing unilateral TKA, and hospitalized for a minimum of 24 hours. We excluded patients who did not provide consent, those who refused spinal anesthesia, individuals for whom regional anesthesia was contra-indicated, those with bleeding disorders, patients on anticoagulants, individuals with infections at the peripheral nerve block site, those allergic to local anesthetic (LA), and emergency cases

Randomization

The investigation was conducted as a prospective, randomized controlled, double-blind, multicenter trial. We obtained written and verbal consent from patients before randomization. Randomization was performed in the operating room on the day of surgery. SPSS V.26.0 was used to generate numbers from 1 to 60. The results were placed in a sealed opaque envelope with the same serial number. Each patient was given a random ID throughout the study. All patients were randomized 1:1 into two groups of 30 people: group C (received SIFIB with saline solution) and group S (received SIFIB with LA). The physician providing randomization was blinded to other study phases. After this stage, a different researcher opened the envelopes and was removed from the study. The investigator who performed the block was blinded to the patients regarding LA or saline solution and did not participate in data collection and evaluation. An anesthesiologist with at least five years of experience in both centers performed SIFIB. These individuals did not participate in other study stages. Two anesthesia doctors recorded the results.

Standard Anaesthesia and Postoperative Analgesia Protocol

Each patient received standard monitoring and anesthesia management. The patients were given 20-gauge intravenous (IV) cannulation, and 15 ml/kg/h isotonic fluid was started. Before spinal anesthesia, 0.02 mg/kg midazolam was administered for sedation. Spinal anesthesia was administered using 3 ml of 0.5% heavy marcaine through a 26-gauge needle through the L3-L4 or L4-L5 intervertebral space in a sitting position. Subsequently, the patients were left to the surgical team for TKA. Postoperatively, all patients were administered IV 1 g paracetamol +IV 20 mg tenoxicam +IV dexamethasone 8 mg for postoperative analgesia in the postanesthetic care unit (PACU). Paracetamol 3×1 g+tenoxicam 2×20 mg were administered continuously. SIFIB was applied to all patients in the PACU. However, the patients in group C were administered 40 ml of saline solution during SIFIB administration, whereas the patients in group S were administered 40 ml of 0.25% marcaine. All patients were administered IV 1 mg/kg tramadol as a rescue analgesic when the NRS scores were ≥4. All patients with nausea and vomiting were administered 4 mg IV ondasetron.

Ultrasound-Guided Suprainguinal Fascia Iliaca Block

SIFIB was conducted immediately postoperatively in the block performance room that utilized an in-plane technique with a high-frequency linear transducer (10-18 MHz, MyLabFive; Esaote Europe BV, Philipsweg 1, 6227 AJ, Maastricht, Netherlands). The transducer was placed on the femoral crest to sonographically visualize the femoral artery, femoral nerve, fascia iliaca, and iliacus muscle. The continuity of the fascia iliaca between the iliacus and sartorius muscles was observed by moving the transducer laterally. Subsequently, the transducer was rotated superolateral to the oblique plane and positioned just medial to the anterior superior iliac spine. Sonoanatomically, the abdominal muscles, deep circumflex artery, iliacus muscle, sartorius muscle, and fascia iliaca were identified within the same image. Utilizing the in-plane technique, an 80-mm peripheral block needle (B. Braun, Melsungen AG, Germany, 80 mm, 21 G) was advanced from caudal to cephalad into the space between the fascia iliaca and iliacus muscle. After the needle tip position was confirmed by injecting 1 ml of isotonic fluid, 40 ml of 0.25% bupivacaine or 40 ml of saline solution was slowly administered into the area.

Outcome Measures

24 hours following surgery, the patient's quality of recovery was gauged by recording their QoR-15 scores, which served as the primary outcome measure. The QoR-15 score is composed of fifteen questions for a total of 150 points. The five domains include pain (n=2), physical comfort (n=5), physical independence (n=2), psychological support (n=2), and emotional state (n=4). The questions range in score from 1 to 10.[16,17]

Secondary outcome assessments were postoperative NRS ratings at rest and during mobility at 3, 6, 9, 12, 18, and 24 hours postoperatively. A score of 0 indicates no pain, while 10 indicates the most severe pain. In addition, the research measured patient satisfaction using a Likert scale 24 hours after surgery, the total quantity of rescue analgesia used, the duration until the initial administration of rescue analgesics, problems such as nausea and vomiting, and the need for antiemetics. We recorded the age, weight, height, laboratory findings, and duration of surgery for patients in both groups.

Patient satisfaction was assessed using a Likert scale, with a score of 1 representing "not satisfied at all," 2 representing "unsatisfied," 3 representing "neutral," 4 representing "satisfied," and 5 representing "very satisfied."

Sample Size

A minimal clinically important difference (MCID) in the quality of recovery after surgery and anesthesia is defined as

a change of ≥8 points in the global QoR-15 score.[18] In the pilot study, including 10 patients, the global QoR-15 score in the control group at 24 hours postoperatively was 100.3±11.49. Based on this data and using a Cohen's D effect size of 0.696 in an independent groups T test model, it was determined that 27 patients per group were needed to achieve 80% power with a maximum type I error of 5%. Taking into account the potential dropout rate, the required sample size for each group was calculated to be 30 patients, resulting in a total of 60 patients for the study.

Statistical Analysis

The IBM Statistical Pack Age for Social Sciences (IBM-SPSS Inc., Chicago, IL, USA) 22.0 program was used for analysis. Data conformity to the normal distribution was examined using the Shapiro-Wilk test. Continuous variables were expressed as mean, standard deviation, or (median 25-75 percentile) based on their distribution status, and categorical variables were expressed as numbers and percentages. In the analysis of continuous variables, the independent sample student's T test was applied after meeting parametric test assumptions. Otherwise, the Mann-Whitney U test was used. The Fisher exact test and Chi-square test were used to analyze categorical variables. Analysis of variance (ANOVA) was utilized for repeated measurements between groups at different times. A Kaplan-Meier curve was constructed for time to the first analgesic medication requirement, and the groups were compared using the log-rank test. Statistical significance was accepted as p<0.05.

RESULTS

We initially assessed 65 patients for eligibility; however, we excluded five patients due to their refusal to participate. The remaining 60 patients were randomized and treated based on the protocol (group C, n=30; group S, n=30) (Figure 1). Patient characteristics and duration of surgery were similar between the groups (Table 1).

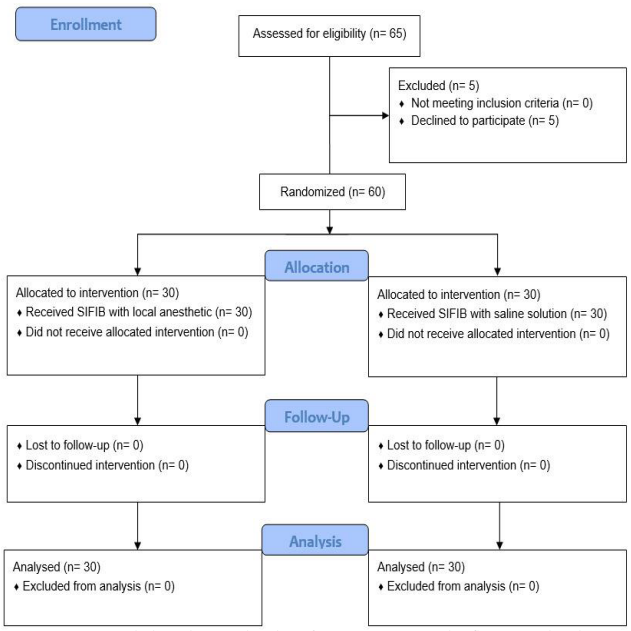

Figure 1. Consolidated standards of reporting trials flow study diagram describing patient progress through the study. SIFIB, Suprainguinal fascia iliaca block

SIFIB: Suprainguinal fascia iliaca block

Table 1. Baseline characteristics by groups

Factors	Group C (n=30)	Group S (n=30)
Age (year)	58±8	58±5
Female	23 (76.7%)	22 (73.3%)
ASA		
1	2 (6.7%)	4 (13.3%)
2	21 (70%)	20 (66.7%)
3	7 (23.3%)	6 (20%)
Smoking	6 (20%)	3 (10%)
Coronary artery disease	4 (13.3%)	4 (13.3%)
Hypertension	11 (36.7%)	11 (36.7%)
Lung disase	3 (10%)	8 (26.7%)
Height (cm)	164±7	165±7
Weight (kg)	72±11	72±10
Surgery time (min)	103 (90-120)	103 (90-120)

Data presented as mean±standard deviation, median (Q1-Q3), or n (%), cm: Centimeter, Kg: Kilogram, min: Minutes, ASA: American Society of Anesthesiologists physical status

Primary Outcome

We compared two randomized assigned groups who underwent knee arthroscopy, focusing on their postoperative recovery measured by the QoR-15 score. Group S had significantly higher QoR-15 scores than group C [124 (121-129) vs 98 (92-101); p<0.001]. Group S had considerably higher scores in postoperative pain, physical comfort, physical independence, psychological support, and emotional state than another area to other group (p<0.001 for each) (Table 2).

Table 2. Total and dimensional QoR-15 scores of the participants

Quality of recovery	Group C (n=30)	Group S (n=30)	p value
Pain	12 (10-14)	19 (19-20)	<0.001
Physical comfort	34 (32-36)	44 (43-45)	<0.001
Physical independence	8 (6-8)	10 (8-10)	<0.001
Psychological support	13 (13-14)	17 (16-18)	<0.001
Emotional state	30 (28-32)	36 (33-36)	<0.001
Total QoR-15 score	98 (92-101)	124 (121-129)	<0.001

Data presented as median (Q1-Q3), QoR-15: Quality of recovery-15

Secondary Outcomes

Pain scores: At 24 h postoperatively, the NRS scores at rest and during movement were consistently smaller in group S at all time points, and this difference was statistically significant at 3, 6, 9, 12, and 24 hours postoperatively. In addition, when the change over time of the NRS scores at 24 hours postoperatively was evaluated for rest and movement, the time-group interaction was statistically significant for NRS scores during rest and movement. (p<0.001 and p<0.001, respectively) (Figure 2 a, b).

Rescue analgesia requirement: Rescue analgesia was administered to group C, whereas 25 patients in group S did not require rescue analgesia (p<0.001). The number of patients requiring rescue analgesia was significantly higher in the control group at all time intervals. The difference between the groups was statistically significant for the "0-6" and "6-12" time intervals (p<0.001 for both), but it was not statistically significant in the "12-24" time interval (p=0.706) (Table 3).

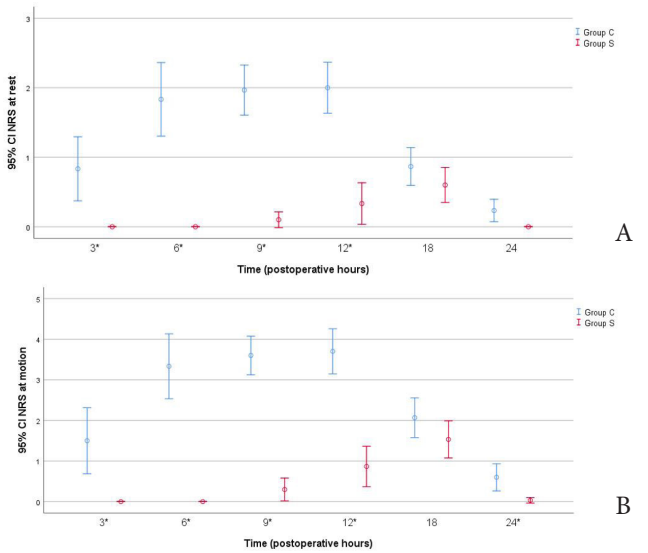

Figure 2. a) Postoperative numerical rating scores at rest with 95% CI, *p<0.05, b) Postoperative numerical rating scores at motion with 95% CI

CI: Confidence interval, NRS: Numerical Rating Scale

The total amount of tramadol consumed within the first 24 hours postoperatively was higher in group C [145 (80-225) mg vs 0 (0-0) mg; p<0.001] (Table 3). The median time to administer rescue analgesics was 6 (3-9) and 18 (18-18) h in groups C and S, respectively (p<0.001) (Table 3). Patients in the control group requested analgesia significantly earlier compared with group S (p<0.001) (Figure. 3).

Table 3. Postoperative rescue analgesic characteristics among groups

Factors	Group C (n=30)	Group S (n=30)	p value
First rescue analgesic time (h)	6 (3-9)	18 (18-18)	<0.001
Tramadol consumption (mg)	145 (80-225)	0 (0-0)	<0.001
Rescue analgesic usage, time frame (h)			
0-6	19 (63.3%)	0 (0%)	<0.001
6-12	30 (100%)	2 (6.7%)	<0.001
12-24	5 (16.7%)	3 (10%)	0.706
0-24	30 (100%)	5 (16.7%)	<0.001

Data are presented as median (Q1-Q3), or n (%)

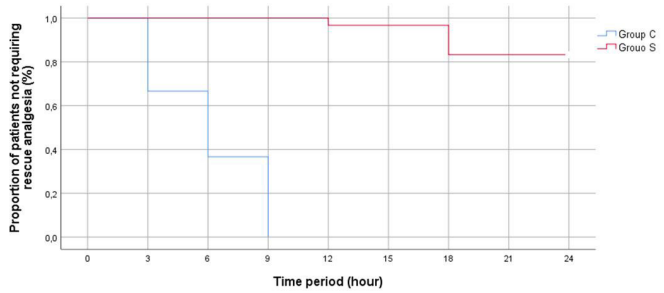

Figure 3. Kaplan Meier plot showing the percentage of patients not requiring rescue analgesia over time

Advers Events, and Likert Scale: In the postoperative 24-hour period, postoperative nausea and vomiting (PONV) was observed in 9 (30%) and 1 (3.3%) patient in groups C and S, respectively (p=0.006). The requirement for antiemetic drugs was significantly lower in group S (1 vs. 9 patients, p=0.006). Additionally, patient satisfaction scores on the Likert scale were significantly higher in group S [5 (5-5) vs. 3 (3-4); p<0.001].

DISCUSSION

This prospective, randomized, controlled, multicenter, double-blind study of patients undergoing TKA showed that SIFIB significantly improved postoperative recovery, evidenced by higher QoR-15 scores, lower pain scores, lower need for rescue analgesia, fewer side effects, and higher patient satisfaction in group S. This study is the first to comprehensively investigate the use of SIFIB in TKA using the QoR-15 scores.

Although SIFIB was initially widely applied in hip surgery, subsequent studies have emphasized that SIFIB for postoperative analgesia in knee surgeries is an integral part of multimodal analgesia.[19] A study reported that SIFIB in hip surgery increased QoR-15 scores.[20] In another study, QoR-15 scores were evaluated postoperatively in patients who underwent knee arthroplasty after IV magnesium sulfate. In this study, QoR-15 scores were higher than the control group. Lower pain levels, higher emotional states, and greater physical comfort were also exhibited.[21] In our study, QoR-15 scores were higher in patients treated with SIFIB 24 hours postoperatively than those in the control group. Patients treated with SIFIB had higher postoperative pain, physical comfort, physical support, physical independence, and emotional state scores. The QoR-15 score is a validated measure evaluating the quality of postoperative recovery and includes pain, physical comfort, physical independence, psychological support, and emotional state. Furthermore, the overall improvement in these recovery parameters was consistent with previous studies that emphasize the benefits of regional anesthesia techniques in improving the quality of postoperative recovery.[22]

The literature reported an eight-point difference as MCID for the QoR-15 score.[18] Our study's MCID for QoR-15 score was >8 points and was statistically significant, indicating that SIFIB in knee arthroplasty speeds up recovery and makes the postoperative experience more comfortable.

In patients undergoing TKA treated with SIFIB, pain scores and amount of rescue analgesia were low, and the duration of initial rescue analgesia application was long.[9-11,20,23] A study highlighted the potential impact of the combination of an adductor canal block and infiltration of local anesthetic between the popliteal artery and the capsule of the knee (IPACK) in patients undergoing knee arthroscopy. This technique resulted in higher QoR-15 scores at 24 hours, along with lower rescue analgesia consumption and reduced pain scores.[24] Similarly, a meta-analysis emphasized the potential of various peripheral nerve blocks to significantly decrease pain scores and rescue analgesia requirements in patients following knee arthroplasty.[25] Another study reported the potential of femoral and adductor canal blocks to reduce the consumption of rescue analgesia in knee arthroplasty patients.[26] Additionally, it has been documented that the potential for pain reduction in patients undergoing lower extremity surgery is significant after applying a selective SIFIB.[27]

Our study showed that NRS scores were consistently lower at rest and during movement in patients undergoing SIFIB at all postoperative time points, highlighting the sustained analgesic efficacy of the intervention. Additionally, the significant time-group interaction for NRS scores indicates that the technique reduces immediate postoperative pain and positively affects pain progression over time. The amount of rescue analgesia was considerably higher in the control group at 24 h. In the 24 hours, rescue analgesia was administered to all patients in group C, whereas only five patients in group S required rescue analgesia. Patients in the control group requested analgesia earlier. Group S had a significantly longer time to first request rescue analgesia, indicating the long-term analgesic effect of the advanced technique. Our results were consistent with existing literature advocating multimodal analgesia to reduce opioid requirements and improve pain management outcomes.

Our study showed that the rates of nausea and vomiting due to tramadol use were significantly higher in the control group, significantly increasing the need for antiemetic drugs in this group. Similar mobilization times between both groups indicate that the effects of spinal anesthesia diminished similarly over time. Simultaneously, the high efficacy of SIFIB resulted in patients in group S achieving higher scores on the Likert satisfaction scale, emphasizing improved patient well-being in the postoperative period, showing the clinical benefits of SIFIB.

Limitations

Limitations of this study, we did not evaluate the combinations of SIFIB with other anesthesia techniques or its long-term effects. Future research should investigate the long-term outcomes of SIFIB and its effectiveness when used in combination with different peripheral nerve blocks, which will offer valuable insights into the long-term benefits and broader applications of SIFIB in various surgical settings.

CONCLUSION

The SIFIB has been demonstrated to significantly improve postoperative recovery and pain management in patients undergoing TKA. This technique provides effective analgesia, contributing to enhanced patient comfort and a reduction in the need for additional pain medications. Given its efficacy and favorable safety profile, the SIFIB represents a promising alternative to other regional anesthesia techniques commonly used in knee surgery. Its potential to minimize complications associated with certain blocks further underscores its utility in optimizing perioperative care and promoting faster functional recovery.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ethics Committee of Harran University Faculty of Medicine (Date: 12.02.2024; Decision No: 24.01.42).

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.

Registered Database

The study was registered on the ClinicalTrials.gov database under the identifier NCT06386575.

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Original Article

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Incidental focal 18F-FDG uptake in colorectal locations on PET/CT for oncologic reasons: pathologic correlation with endoscopic finding

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ABSTRACT

Aims: Incidental focal 18-fluorodeoxyglucose (18F-FDG) uptake in the colorectal region on positron emission tomography/computed tomography (PET/CT) may indicate premalignant lesions, such as adenomas or malignancies. Early detection and diagnosis are crucial for cancer prevention. This study aimed to assess the characteristics of incidental focal colonic FDG uptake associated with benign, premalignant, and malignant lesions, and to determine when colonoscopy is necessary.

Methods: A retrospective review of PET/CT reports was conducted on 5.380 patients with confirmed or suspected malignancies who underwent whole-body 18F-FDG PET/CT between January 2019 and April 2024. Patients exhibiting focal colonic 18F-FDG uptake and subsequently referred for colonoscopy were included in this study.

Results: Among 110 patients who underwent colonoscopy, 63 (57.3%) had adenomas and 14 (12.7%) had malignant tumors. The receiver operating characteristic (ROC) curve based on the maximum standardized uptake value (SUVmax) showed an AUC of 0.958. A cutoff value of 13.80 was optimal for distinguishing malignant lesions from nonmalignant lesions, with a sensitivity of 92%, specificity of 89%, positive predictive value of 56%, and negative predictive value of 98%. The SUVmax significantly differentiated malignancy from other colonoscopic findings ($p<0.001$). No significant differences were observed between adenomas and benign or physiological findings ($p>0.05$).

Conclusion: The colonoscopy results indicated that malignant lesions had significantly elevated SUVmax values compared to other lesion types or physiological uptake. However, the SUVmax was not sufficient to distinguish benign lesions from adenomas. Therefore, all incidental colonic findings should be thoroughly assessed, and lesions with SUVmax ≥13.80 should be promptly evaluated.

Keywords: PET/CT, focal uptake, SUVmax, colonoscopy, malignancy

INTRODUCTION

With its expanding role in diagnosing, staging, and evaluating treatment responses for a range of cancers, 18F-fluorodeoxyglucose (18-FDG) positron emission tomography/computed tomography (FDG PET/CT) has established itself as an invaluable tool.[1,2] The main radiotracer used in PET scans, 18F-fluorodeoxyglucose, is absorbed by different body tissues via glucose metabolism.

FDG PET/CT relies on the principle that cancer cells metabolize glucose more quickly than healthy cells, which serves as the foundation for its effectiveness in detecting malignant tissues.[3,4] However, malignancy is only one of the possible reasons for FDG uptake. Increased FDG uptake, which signals hypermetabolic activity, may also occur in nonmalignant conditions such as inflammation, infections, hyperplasia, and gastrointestinal polyps.[5] PET/CT scans conducted for different medical reasons may sometimes identify unexpected regions of elevated radiopharmaceutical uptake in the large intestine. Colorectal FDG uptake may occur in focal, segmental, and diffuse patterns. Focal uptake seen in the colorectal region is more often an indicator of actual lesions than physiological uptake, which usually appears as long-segment diffuse activity.[6] The early detection of 18F-FDG-avid lesions, whether neoplastic, preneoplastic, or related to inflammatory bowel disease, can significantly influence patient management and outcomes. Specifically, colonic adenomas have the potential to transition from benign to carcinoma, gradually advancing in asymptomatic patients.[7] The integrated PET/CT approach may enable the precise localization and characterization of abdominal FDG uptake, particularly in the intestine.

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A detailed meta-analysis, that examined 89.061 patients who underwent PET/CT for various reasons found that approximately 3.6% of the patients had incidental focal colonic uptake. Approximately one-third of the patients (n=1.044) underwent either colonoscopy or histopathological examination. The average risk of detecting premalignant and malignant lesions during colonoscopy was 68% (95% CI: 60-75%). Nevertheless, when evaluating the maximum standardized uptake value (SUVmax), there was a significant overlap in the mean values across benign, premalignant, and malignant lesions.[8]

Given the frequent discrepancy between focal colonic FDG uptake and the corresponding histopathological findings in previous studies, determining the need for additional diagnostic evaluations is challenging. Colonoscopy is an invasive medical procedure that carries potential risks such as bowel perforation, bleeding, and complications related to anesthesia.[9] A predictor of malignancy risk would be useful for assessing the urgency of performing colonoscopy. The SUVmax, which reflects the level of FDG uptake intensity, can be crucial for differentiating between nonmalignant and malignant lesions. Therefore, this study sought to evaluate PET-positive focal colonic uptake in a substantial patient population and to examine the relationship between the SUVmax and the results of the corresponding colonoscopy.

METHODS

Ethics

The Institutional of the Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Non-interventional Clinical Researches Ethics Committee approved this study (Date: 28.12.2023, Decision No: 2023-12/118). For this retrospective study, informed consent was deemed unnecessary, and no personal data were exposed. All research followed the principles outlined in the Declaration of Helsinki.

Study Design and Patient Data

The electronic records of 5.380 patients aged ≥18 years who visited the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between January 2019 and April 2024 were retrospectively reviewed. The reason for PET/CT application in these patients was either to stage existing malignant diseases or to investigate primary cancers when metastatic sites were found in imaging studies. Patients diagnosed with colorectal cancer or with a known history of inflammatory bowel disease were excluded from this study. All PET/CT records reported by nuclear medicine specialists with more than a decade of experience were reviewed for incidental focal uptake in the colorectal region. Focal radiotracer accumulation between the anus and cecum was characterized as colonic 18-FDG uptake. Patients who underwent colonoscopy within the 90-day period following their PET/CT scans were documented. An independent researcher recorded data from the hospital system, including various factors such as age, sex, reason for undergoing a PET scan, type andz diagnosis of primary cancer, location of colonic findings, SUVmax of FDG, lesion size, and histological findings.

PET/CT Acquisition

Patients were advised to abstain from consuming any oral fluid containing glucose for six hours prior to FDG injection. Diabetic patients were instructed to discontinue oral hypoglycemic medications containing metformin for 48 hours before the scan in accordance with European Association of Nuclear Medicine (EANM) guidelines. Before the injection, the blood glucose levels were checked, and if values exceeding 200 mg/dl were detected, their appointments were rescheduled. The patient was administered an intravenous injection of 18F-FDG at a dose of 3.2-5.3 MBq/kg based on weight. PET/CT imaging was performed one hour after the injection of 18F-FDG, using a Siemens Biograph TruePoint 6 PET/CT system (Siemens Healthcare, USA) with three-dimensional capabilities. During the same session, simultaneous images were taken with a 3 mm sliced multidetector CT scanner and PET scanner. Attenuation correction and anatomical correlation were performed by using low-dose CT scans that did not require intravenous iodinated contrast.

Image Data Analysis and Endoscopic Correlation

The nuclear medicine specialists assessed both the PET and CT components utilized in this study. The axial, sagittal and coronal views of the PET and fused images were examined by readers. Intense focal bowel uptake was defined as any metabolic activity in the bowel that surpassed that observed in the normal hepatic tissue. The CT component of this study was used to evaluate any soft tissue abnormalities associated with regions that exhibited focal colorectal uptake. The SUVmax within a defined region of interest was measured using the attenuation-corrected PET component. In our study, histopathological diagnoses were categorized into three groups: malignant lesions, comprising primary carcinoma and metastatic gastrointestinal tract disease; premalignant lesions, encompassing adenomas with varying levels of dysplasia; and benign lesions, involving radiation proctitis and hyperplastic polyps. Physiological uptake was determined when focal bowel activity increased without any detectable mucosal or structural abnormalities during the colonoscopy. Uptake detected on PET/CT was confirmed as true-positive if it corresponded to an abnormality identified during colonoscopy. The true-positive results included benign, premalignant, and malignant lesions. In contrast, a false-positive result was identified as FDG uptake that did not correlate with an abnormality detected during colonoscopy, which was interpreted as a benign or physiological uptake. The size of the lesions detected during colonoscopy was also recorded.

Statistical Analysis

Data are presented as numerical values (percentages), mean ±standard deviation, and median (minimum-maximum). Differences in colonoscopic findings based on the SUVmax were evaluated using ANOVA and the Bonferroni posthoc test. To determine the ideal threshold for differentiating between malignant and nonmalignant lesions, a receiver operating characteristic (ROC) curve was employed. The SPSS software, version 27, was used for all statistical analyses. Statistical significance was set at $p<0.05$.

RESULTS

Between January 2019 and March 2024, 5.380 patients underwent PET/CT at the Abdurrahman Yurtaslan Oncology

Training and Research Hospital. Unexpected focal FDG uptake in the colon was observed in 211 (3.9%) patients. Of whom 163 (77%) underwent colonoscopy within 90 days of scanning. In total, 53 of 163 patients were excluded from our study because of a previously known colorectal malignancy or inflammatory bowel disease (Figure 1). Among the remaining 110 patients with focal FDG uptake, 88 (80%) had corresponding lesions identified during colonoscopy.

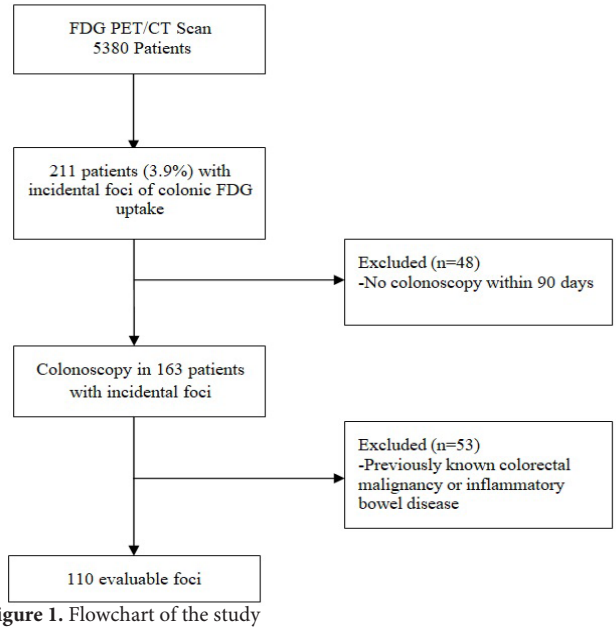

Figure 1. Flowchart of the study

Table 1 presents the baseline characteristics of the 110 patients with colonic FDG uptake along with the results of their corresponding colonoscopies and histopathological findings. Colorectal uptake was predominantly observed in the rectum (36.4%) and the sigmoid colon (35.5%). Histopathological examination of 18F-FDG uptake sites revealed that 22 patients (20%) had no corresponding lesions, 11 (10%) had benign lesions, 50 (45.5%) had adenomas with low-grade dysplasia (LGD), 13 (11.8%) had adenomas with high-grade dysplasia (HGD), and 14 (12.7%) had malignant lesions (Figure 2, 3). Therefore, 77 cases (70%) of incidental hypermetabolic foci were found to be premalignant (polyps with dysplasia) or malignant. In 9 of the 14 patients with malignancy, malignant lesions were determined either by measuring the long axis during colonoscopy or with histopathological assessment following surgery in patients with obstructive masses. The lesion sizes for the remaining five malignant cases could not be determined because of either obstruction caused by the mass during colonoscopy or inoperability of the patient. The average longest dimension of malignant lesions was measured as 43.13±12.98 mm.

To assess the efficacy of SUVmax in differentiating between malignant and nonmalignant lesions, an ROC curve was constructed. The optimal cutoff SUVmax was 13.80, with a sensitivity of 92%, specificity of 89%, positive predictive value of 56%, and negative predictive value of 98%. The area under the curve was 0.958 (standard deviation ±0.018). Focal uptake with SUVmax ≥13.80 was strongly correlated with a high risk of malignancy (Figure 4).

Table 1. Characteristics of patients and their incidental lesions at baseline (n=110)

		n (%)
Age(years)	Min-max	35-85
	Mean±SD	66.56±8.58
Sex	Male	61 (55.5)
	Female	49 (44.5)
Location	Rectum	40 (36.4)
	Sigmoid colon	39 (35.5)
	Descending colon	7 (6.4)
	Splenic flexure	3 (2.7)
	Transvers colon	4 (3.6)
	Hepatic flexure	5 (4.5)
	Ascending colon	9 (8.2)
	Cecum	3 (2.7)
SUVmax	Min-max	3.02-27.96
	Mean±SD	11.30±5.70
Histopathology	Physiologic	22 (20)
	Benign*	11 (10)
	Malignant	14 (12.7)
	Adenoma with LGD	50 (45.5)
	Adenoma with HGD	13 (11.8)
Size (mm, mean±SD)	Malignant†	43.13±12.98
	Adenoma with LGD	12.08±9.56
	Adenoma with HGD	27.92±11.37
Primary malignancy	Lung cancer	25 (22.7)
	Skin cancer	9 (8.2)
	Pituitary gland tumor	1 (0.9)
	Larynx carcinoma	5 (4.5)
	Lymphoma	2 (1.8)
	Carcinoma of unknown primary	28 (25.5)
	Breast carcinoma	17 (15.5)
	Gastric carcinoma	7 (6.4)
	Multiple myeloma	4 (3.6)
	Ovarian carcinoma	5 (4.5)
	Pancreas carcinoma	4 (3.6)
	Renal cell carcinoma	1 (0.9)
	Cervix carcinoma	1 (0.9)
	Thyroid carcinoma	1 (0.9)

Min: Minimum, Max: Maximum, SD: Standard deviation, SUVmax: Maximum standardized uptake value, LGD: Low-grade dysplasia, HGD: High-grade dysplasia, *Benign: Hyperplastic polyp (n=6), radiation proctitis (n=2), solitary rectal ulcer syndrome (n=2), diverticulosis (n=1), †n=9

Table 2 shows the SUVmax values for lesions observed during colonoscopy. The SUVmax was significantly associated with distinguishing malignancy from other colonoscopic findings ($p<0.001$). Statistical significance was not observed between adenomas, regardless of the degree of dysplasia, or benign and physiological findings ($p>0.05$). The average SUVmax threshold indicative of colorectal cancer was determined to be 16.99±2.76 ($p<0.001$).

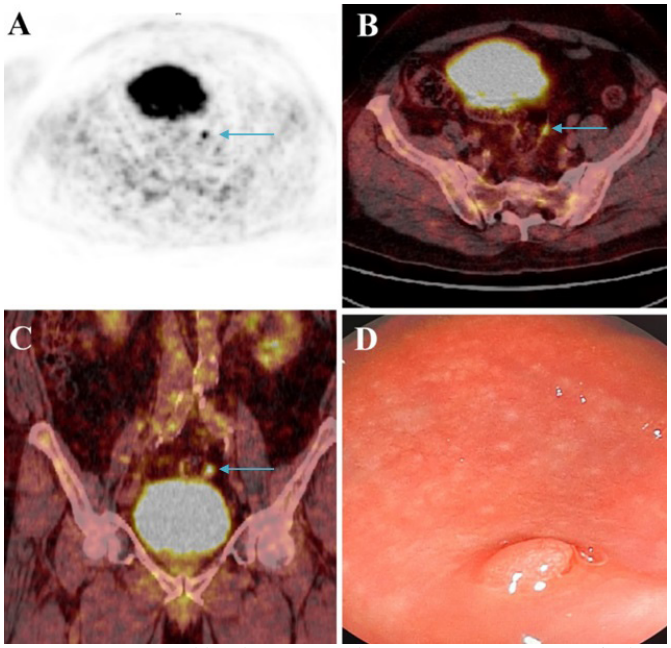

Figure 2. A 70-year-old male patient undergoing 18F-FDG PET/CT for lung cancer staging. (A-C) (blue arrows). Abnormal 18F-FDG PET/CT uptake in the sigmoid colon (SUVmax: 7.39). (D) Colonoscopy revealed a sessile polyp, and pathology confirmed the diagnosis of an adenomatous polyp with low-grade dysplasia

FDG: Fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, SUVmax: Maximum standardized uptake value

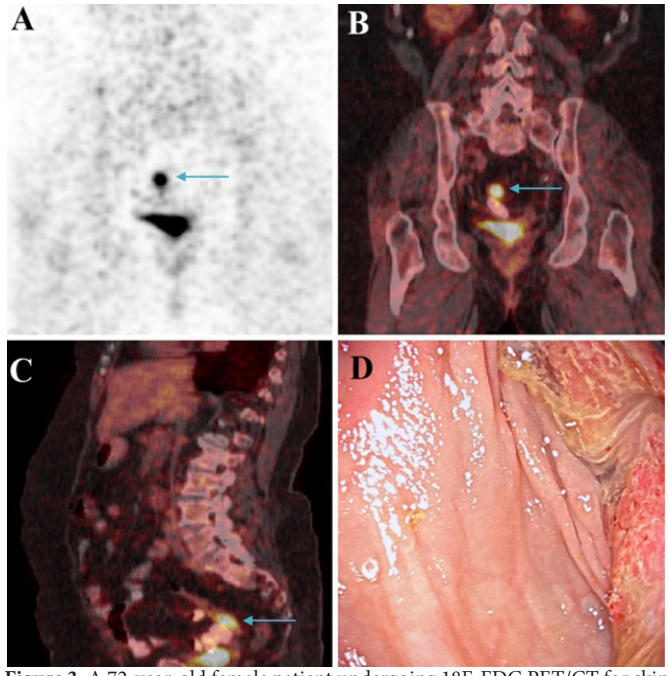

Figure 3. A 72-year-old female patient undergoing 18F-FDG PET/CT for skin cancer staging (A-C) (blue arrows). Abnormal 18F-FDG PET/CT uptake in the sigmoid colon (SUVmax: 18.01). (D) Colonoscopy revealed a mass in the sigmoid colon, and the pathological diagnosis confirmed adenocarcinoma

FDG: Fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, SUVmax: Maximum standardized uptake value

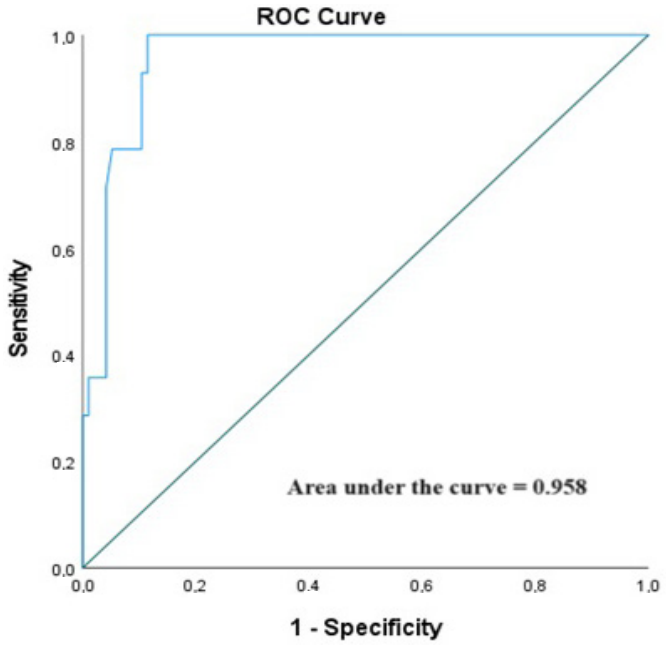

Figure 4. ROC curve analysis for differentiating malignant from nonmalignant incidental FDG-avid lesions in the colon on PET/CT, showing an area under the curve of 0.922. The optimal SUVmax threshold for distinguishing between malignant and nonmalignant incidental colonic lesions is 13.80, with a sensitivity of 92%, specificity of 88%, positive predictive value of 56%, and negative predictive value of 98%

ROC: Receiver operating characteristic, FDG: Fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, SUVmax: Maximum standardized uptake value

DISCUSSION

PET/CT is a noninvasive imaging technique used to diagnose and stage diseases, monitor treatment effectiveness, assess tumor aggressiveness, and delineate areas for radiotherapy.[10] Colonoscopy continues to be the leading screening method for colorectal cancer given its high sensitivity and specificity, enabling the early identification and removal of precursor lesions.[11] However, colonoscopy is a challenging procedure, given the associated risks and the demanding bowel preparation required. Therefore, determining which patients with focal colorectal 18F-FDG uptake on PET/CT scans should undergo further colonoscopic evaluation remains an ongoing debate.[12] Our study is one of the most extensive investigations of incidental focal colorectal uptake and its associated endoscopic findings.

In our investigation, the prevalence of incidental focal colorectal uptake was 3.9% (211/5.380), consistent with the 0.5%-3.6% range reported in other studies.[8,13] In a meta-analysis of 32 studies using colonoscopic or histopathological confirmation as the reference standard, focal FDG uptake was strongly associated with premalignant or malignant lesions (68%). Therefore, colonoscopy is recommended when a focal uptake is detected.[8] Similarly, in our study, 70% of 110 eligible lesions were malignant (12.7%, 14/110) or premalignant (57.3%, 63/110). The higher percentage of premalignant lesions

Table 2. Analysis of SUVmax based on colonoscopic findings

Variable	Colonoscopic findings			
	Benign + physiologic	Adenoma with LGD	Adenoma with HGD	Malignant
SUVmax	8.26±3.44	9.34±3.49	9.84±2.70	16.99±2.76[abc]

Data are presented as mean ± SD, SUVmax: Maximum standardized uptake value, SD: Standard deviation, LGD: Low-grade dysplasia, HGD: High-grade dysplasia, [a]Significantly different from benign + physiologic, [b]Significantly different from low-grade adenoma, [c] Significantly different from high-grade adenoma

compared to malignant lesions aligns with other studies, suggesting that colonoscopy should be performed for further assessment of focal hypermetabolism.[14,15]

Previous studies have reported that 14-38% of patients with focal colorectal FDG uptake who underwent colonoscopy showed no corresponding lesions during endoscopic examination.[16-18] In our study, while 80% of the 110 patients with focal FDG uptake had corresponding benign or malignant lesions detected during colonoscopy, 22 patients (20%) had no lesions despite thorough endoscopic examination, resulting in a false-positive rate of 20% for PET/CT lesions. Physiological uptake, transient inflammation, or FDG accumulation in gastrointestinal lymphoid tissue is a possible cause of false-positive lesions on PET/CT.[19] In cases of physiological uptake, FDG usually shows diffuse uptake in the gastrointestinal system; however, focal uptake can also occur. Physiological uptake in the colon may originate from factors such as smooth muscle contractions, activity in mucosa-associated lymphoid tissue, secretions, microbial metabolism, and FDG excretion.[20]

Adenomatous polyps in the colon are considered premalignant lesions, and their identification is crucial because early removal has been proven to greatly decrease the occurrence and fatality rates of colon cancer.[21] Traglia et al.[22] reported SUVmax values of 9.6±4.7 for malignant disease (n=12), 8.5±5.2 for adenomas (n=19), 6.5±3.6 for benign lesions (n=6), and 8.3±3.6 for normal colonoscopy groups (n=11). In a study by Gutman et al.,[23] SUVmax values were reported as 15±11.6 for malignant lesions (n=3), 12±3.7 for adenomatous polyps with HGD (n=4), 8.8±4.9 for adenomatous polyps with LGD (n=6), and 7.1±3.3 for lesions with negative colonoscopic findings (n=7). In a different study, Luboldt et al.[24] found that the SUVmax values for malignancy (n=23), adenomatous polyps with HGD (n=10), adenomatous polyps with LGD (n=25), and benign uptakes (n=48) were 11.9±6.8 and 11.6±4.1. In these studies, although SUVmax generally increased with progression from benign conditions to dysplasia, as well as from dysplasia to malignancy, the SUVmax values for various colonic lesions often overlapped significantly, making the differences between them statistically insignificant. According to our study, the mean SUVmax of colorectal malignancies was noticeably higher than that of all the other lesions. When comparing the benign-physiological and premalignant groups, statistical analysis revealed no significant difference in the SUVmax. Consistent with our findings, a study by Özarslan et al.[25] reported that among 84 patients with focal colonic uptake on PET/CT who underwent follow-up colonoscopy, the SUVmax was 15.0±10.6 for malignant disease, 10.2±4.3 for adenomas, 7.3±3.6 for inflammation, and 9.8±4.2 for normal endoscopy groups ($p<0.001$). Consequently, the overlap of SUVmax values among the different groups suggests that SUVmax is particularly crucial for diagnosing malignant diseases.

In a study conducted by Hosni et al.,[3] involving 32 individuals with focal uptake on PET/CT scans, an SUVmax value of 9.2 or higher demonstrated a high sensitivity (0.76) and specificity (0.885) for distinguishing malignant and premalignant lesions from benign uptakes. Lee et al.[13] reported that using an SUVmax threshold of 7.6 yielded a sensitivity of 0.686 and a specificity of 0.688 for distinguishing benign from cancer/precancerous lesions. In a study of 36 patients with focal uptake, Esmer et al.[26] identified an SUVmax cutoff point of 11.1 (sensitivity, 83.3%; specificity, 90%) using an ROC curve to distinguish benign from premalignant or malignant lesions. These studies showed no statistically significant differences in the average SUVmax values when comparing malignant and premalignant lesions. In our study, the absence of a significant difference in SUVmax between adenomas and benign-physiological uptake prevented the establishment of an effective SUVmax threshold for distinguishing cancer or precancerous lesions from benign lesions. Our findings suggest that focal colorectal uptakes with SUVmax ≥13.80 are significantly linked to an increased risk of malignancy and should be urgently assessed with colonoscopy, given their high sensitivity (92%) and specificity (89%). In a study by Van Hoeijet et al.[18] evaluating incidental focal colonic uptake detected by PET/CT in 7.318 patients, including 242 who underwent colonoscopy, it was emphasized that colonic focal uptakes with an SUVmax of ≥11.4 carry a high risk of malignancy, with 80% sensitivity and 82% specificity, and should be urgently evaluated with colonoscopy.

Limitations

A major strength of our study is that it has a larger sample size than most previous studies. However, its single-center design poses a limitation, potentially impacting the generalizability of the results. To minimize the heterogeneity among studies, a multicenter prospective study with uniform imaging protocols is required.

CONCLUSION

Our study revealed that colon malignancies had significantly higher SUVmax on FDG PET/CT than other lesion types, with a threshold of ≥13.80 effectively distinguishing malignant from benign lesions. However, as SUVmax cannot differentiate noncancerous uptake from adenomas, colonoscopy remains essential for evaluating incidental colonic hotspots, highlighting the need for advanced molecular probes in PET/CT imaging.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 28.12.2023, Decision No: 2023-12/118).

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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Investigation of the effect of video-based game application on acute pain in children under surgery

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ABSTRACT

Aims: The aim of this study is to investigate whether video-based game application is effective on post-surgical acute pain in children.

Methods: A randomized controlled trial was conducted between September 2022 and February 2023 in the department of pediatric surgery at a research and practice hospital affiliated with the university. Eighteen children aged 2-4 who were hospitalized after undergoing surgery due to illness and/or trauma, who did not have any problems grasping the upper extremity, and whose parents allowed them to participate in the study were included in the study. Children who had chronic pain complaints for more than 3 months, regardless of the pathology requiring surgery, and children who needed to be given painkillers in the postoperative period were excluded from the study. In our study, the Postoperative Pain Scale for preschool children was applied to all children after the effect of anesthesia wore off. Children in the game group were allowed to play video-based games for 30 minutes via a handheld game console called Nintendo Switch Lite. Pain assessment was performed three times before starting the game, at the 15th minute, and at the end of the 30th minute. Children in the control group were assessed for pain three times at 15-minute intervals within 30 minutes after the effect of anesthesia wore off without any intervention. The result was calculated by taking the average of 3 evaluations in both groups.

Results: 18 children with an mean age of 3.05±0.89 years, 4 girls and 5 boys in the game group and 9 boys in the control group, were included in the study. The age and preoperative pain values were similar between the two groups ($p>0.05$). In the post-surgical pain evaluation, the pain mean of the play group was 1.72±0.89, while the pain mean of the control group was 4.03±1.25. A statistically significant difference was found in post-surgical pain values between the two groups ($p=0.003$).

Conclusion: As a result of our study, it was determined that video-based game application had a positive effect on acute pain in children undergoing surgery.

Keywords: General surgery, pain, video game

INTRODUCTION

Pain is a sensory and emotional symptom caused by the perception in the brain of signals that reach the medulla spinalis through tissue receptors and peripheral nerves as a result of tissue damage that occurs in many orthopedic and/or neurological diseases.[1] Many conditions such as foreign body aspiration, anterior chest wall deformities, inguinal hernia, umbilical hernia, gastroesophageal reflux, constipation, undescended testicle, circumcision, and trauma require surgical intervention in childhood.[2] Since surgical intervention involves procedures that cause trauma to tissues, moderate to severe pain has been reported in children after surgery.[3] Pain delays recovery, leading to family and child unhappiness, increased incidence of post-surgical complications and increased length of hospital stay, and thus higher costs. In addition, pain has been shown to be associated with sleep and eating disorders, avoidance of medical interventions and anxiety during hospitalization in children.[4] Studies have reported that pain memory, which develops early in children, will emerge during all future experiences involving pain and will play an important role in quality of life.[5] It has been reported that children who experience postoperative pain recall more pain-related words, experience anxiety in adulthood, and try to avoid medical interventions when compared with their healthy peers.[6] Determining the level of pain and treating it with the right approaches is very important to prevent other pain-related symptoms, reduce the duration of hospitalization, and prevent psychological trauma.[7]

After surgical interventions, as the anesthesia wears off, children begin to feel pain at the incision site. Since it is difficult for children, especially in the younger age group, to perceive

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pain locally, they may experience general restlessness, and it becomes difficult to comfort them. In such cases, it is very important to identify alternative methods to reduce children's restlessness in order to minimize the effects of using higher doses of medication to reduce the pain felt. Video-based gaming applications are known to be effective in creating a positive emotional state in players.[8] Many methods are used to minimize the sensation of pain in children undergoing medical procedures. Distraction is a method that aims to control the sensation by directing the patient's attention to something else. Although it is not possible to eliminate pain with this method, pain tolerance is increased.[9] Active methods such as inflating balloons, squeezing plastic balls, breathing exercises, singing, playing video-based games, as well as passive methods such as watching videos, listening to songs and audio stories are also preferred for distraction.[10]

Video-based gaming applications are known to be used as an active distraction method to reduce stress and anxiety in children during pain-inducing hospital stays such as blood draws, dental procedures, and burns and cancer treatment.[11] Distraction is a non-pharmacological intervention that has been recognized as a useful approach to improve the child's experienceduringpainfulprocedures,isasafe,easy,inexpensive, effective and practical psychological pain management strategy for brief painful procedures, and is clearly effective in improving pain control during invasive procedures.[12]

The aim of this study was to investigate whether video-based gaming is effective on acute postoperative pain in children.

METHODS

Ethics

Ethics committee approval for the study was obtained from Hatay Mustafa Kemal University Clinical Researches Ethics Committee (Date: 27.06.2022, Decision No: 04). A signed parental informed consent form was obtained from the families of all children participating in the study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

This study was conducted in the Department of Pediatric Surgery, Hatay Mustafa Kemal University Hospital between September 2022 and February 2023. The study included children between the ages of 2-4 years who were hospitalized in the hospital because of a surgical operation due to a disease and/or trauma, who did not have problems with grip in the upper extremity and whose parents consented to participate in the study. Children with chronic pain complaints for more than three months and children who underwent surgery for diseases requiring analgesic administration in the postoperative period were excluded from the study. In the post-hoc power analysis, when the statistical significance of alpha was found to be 5% and the confidence interval was taken as 95%, the power (1-β) of the study was found to be 99%.

Randomization

Surgery dates and list order were determined before the study. A randomization scheme was created using a computer program. Study consents were obtained from the families and the group they would be in was determined according to the randomization list. Eighteen children who met the inclusion criteria were randomly divided into two groups.

Assessments

In our study, the Postoperative Pain Scale in preschool children was administered to all children after the effect of anesthesia wore off.[13] The Postoperative Pain Scale in preschool children is a seven-item scale developed by Tarbell et al.[14] in 1992 to assess the postoperative pain of preschool children. It consists of seven items in three behavioral categories: vocal pain expression, facial pain expression, and bodily pain expression. The Cronbach alpha coefficient of the scale was found to be 0.88 in the total three behavioral categories. It was chosen because it is a highly reliable, simple and applicable scale that uses both self-report and behavioral measurements in the assessment of pain. The score obtained varies between 0 and 7. The higher the score, the more severe the pain. The children were assessed three times at intervals after the effect of anesthesia wore off and the scores obtained were averaged to calculate the evaluation score.

Intervention

All children stayed in a standard two-person hospital room. The hospital rooms where the children were located after surgery were similar in terms of sound, human density and light. During the study, children in the control group were informed not to use the companions' phones or watch the hospital television. Children in the control group were comforted in bed or by being held in their arms. Children in the play group played video-based games for 30 minutes after anesthesia wore off, while children in the control group spent time in or out of bed without any technological devices. The Nintendo Switch Lite was used for playgroup children to play video-based games. The Nintendo Switch is a recently released video game console. It can be used as both a stationary and portable device; it is handheld, has a joystick, buttons and a screen. The children in the play group played a video-based game of their choice for 30 minutes. Since the mean age of the sample group is small and car racing games such as Asphalt and Season 7 were preferred in our study.

Pain assessment was performed 3 times before starting the game, at 15 minutes and at the end of 30 minutes. Children in the control group underwent pain assessment three times in 30 minutes at 15-minute intervals without any intervention after the effect of anesthesia wore off.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS inc., Chicago, IL, USA) was used for statistical analysis. The conformity of the variables to normal distribution was examined visually (histograms and probability plots) and analytically (Kolmogorov-Smirnov/ Shapiro-Wilk tests). Descriptive analyses were expressed as mean and standard deviations and categorical variables were expressed as numbers and percentages. Since parametric test assumptions were not met, Mann-Whitney U test was used to compare independent group differences. A value of $p<0.05$ was considered statistically significant in all analyses.

RESULTS

Eighteen children, 4 girls and 5 boys in the play group and 9 boys in the control group, with a mean age of 3.05±0.89 years, were included in the study. There was no significant difference between the two groups in terms of age (p=0.165) (Table 1). All children were discharged on the same day after surgery.

Table 1. Demographic characteristics of the groups

	Play group	Control group	p
Age (mean±SD) (year)	3.33±1.0	2.75±0.70	0.165
Gender [G (B)] (n)	4 (5)	(9)	
Surgical interventions (n)			
Distal hypospadias	3	3	
Circumcision	1	1	
Undescended testicle	4	3	
Inguinal hernia	1	2	

n: Number of children

There was no difference between the preoperative pain values of the two groups (p>0.05). A statistically significant difference was found in postoperative pain values between the two groups (p=0.003). Accordingly, the pain values of the children in the play group were significantly lower than those in the control group (Table 2).

Table 2. Postoperative pain values of the groups

	Postoperative pain	p
Play group	1.72±0.89	0.003*
Control group	4.03±1.25	

*: p<0.05

DISCUSSION

As a result of our study, it was determined that video-based game application had a positive effect on acute postoperative pain in children. When the results of studies on video-based gaming applications are examined, it is reported that it has positive results on anxiety and pain and that its use before or during applications involving pain in children will be beneficial.[15,16] It is also known that video-based play increases psychosocial well-being in children and helps children feel happier.[17] Dwairej et al.[18] examined the effects of video-based games on children's anxiety in preparation for surgery and emphasized that distraction through video games is a reliable method that can be used to reduce anxiety in children. Demeter et al.[19] reported that the pain score in the virtual reality group was significantly lower than the control group as a result of their study on the effects of virtual reality application in acute pain control in 2015.

Playing video-based games includes elements that will trigger fun and positive mood in children. Video-based game-based interventions are effective in reducing traditional pain and anxiety by distracting attention.[20] They can also improve social and communication skills, help reflect fears, feelings and emotions, and promote cooperation during medical procedures.[21] The fact that the games are constantly oriented towards moving to the next level also allows players to quickly develop new strategies without experiencing anxiety and frustration. This has been shown to help them feel more positive.[22,23] As a result of a systematic review and meta-analysis investigating the effect of play-based approaches on preoperative pain in children, Suleiman-Martos et al.[24] emphasized that the management of the preoperative process in children is quite challenging for healthcare professionals. They emphasized that game-based strategies can improve the emotional health of patients and accelerate postoperative recovery.

Our study is a randomized controlled trial including the results of pain management during hospital stay in children who underwent surgical procedures in preschool period. The results showed that pain was reduced with video-based game application during the hospital stay after surgery in children. The results obtained will be useful for families and healthcare professionals to use this simple, easily applicable and effective method to reduce pain during hospital stay after surgical procedures in preschool children.

Limitations

One of the limitations of our study is that pain was evaluated with a single scale. In addition, sociocultural characteristics that may affect pain were not evaluated in this study. In future studies, it is recommended to evaluate other factors that may affect pain in addition to objective assessment of pain. In addition, it is recommended to plan the study with larger sample groups to make the results more widespread.

CONCLUSION

As a result of our study, it was determined that video-based game application had a positive effect on acute pain in children undergoing surgery. Accordingly, it can be said that video-based game applications can be utilized during hospitalization after surgery.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Hatay Mustafa Kemal University Clinical Researches Ethics Committee (Date: 27.06.2022, Decision No: 04).

Informed Consent

A signed parental informed consent form was obtained from the families of all children participating in the study.

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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Original Article

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The impact of hyperglycemia on mortality in the emergency department: a comparison of diabetic and non-diabetic patients

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ABSTRACT

Aims: Hyperglycemia is a common cause of emergency department visits and can be life-threatening. Chronic hyperglycemia results in complications including neuropathy, cardiovascular diseases, and kidney failure that are commonly found among diabetic patients while acute stress hyperglycemia induced by trauma, infection, and cardiovascular events is more often seen in non-diabetic individuals. They need to be managed in unique ways. We attempt to quantify the mortality risks of hyperglycemia in diabetic and non-diabetic emergency department patients respectively, and then use these data as a basis for management strategies.

Methods: A retrospective analysis of 1,000 patients who were admitted to Esenyurt Necmi Kadıoğlu State Hospital between January 1, 2024, and June 30, 2024. Biochemical parameters and mortality were compared between diabetic and non-diabetic patients.

Results: Diabetic patients had high mortality. Elevated CRP and glucose levels increase mortality risk, stress hyperglycemia was found to predict short-term risk in non-diabetic patients. The findings suggest that emergency departments should integrate hyperglycemia-related mortality risk assessment into triage protocols and consider tailored treatment strategies for diabetic and non-diabetic patients.

Conclusion: This research highlights that diabetes significantly influences mortality among patients with hyperglycemia, necessitating tailored management strategies for diabetic and non-diabetic groups.

Keywords: Hyperglycemia, diabetes, mortality, emergency department, stress hyperglycemia

INTRODUCTION

Hyperglycemia is one of the most common metabolic disorders in patients presenting to emergency departments. Among emergency conditions, hyperglycemia significantly influences morbidity and mortality. Acute hyperglycemia, in particular, is closely associated with cardiovascular events, organ damage, and an increased risk of death. The causes of hyperglycemia in diabetic and non-diabetic individuals stem from different pathophysiological mechanisms. This difference also affects clinical outcomes. In diabetic patients, long-term hyperglycemia due to chronic hyperglycemia results in chronic complications such as chronic kidney failure, cardiovascular diseases, and neuropathy. Conditions like thrombosis tendency and acute oxidative stress are more commonly seen as a result of acute hyperglycemia in non-diabetic individuals. These factors can worsen prognosis, especially in acute events such as myocardial infarction.[1]

Hyperglycemia resulting from the stress response is observed in non-diabetic individuals and is referred to as stress hyperglycemia. In response to sudden stress, catecholamine and cortisol discharge occurs. Elevated levels of cortisol and catecholamines increase gluconeogenesis, leading to hyperglycemia. In the literature, stress hyperglycemia has been shown to reflect the severity of the underlying condition and is closely associated with mortality, especially in cases such as sepsis or trauma.[2]

Studies examining the impact of hyperglycemia on mortality in special patient groups or intensive care patients demonstrate the effect of hyperglycemia on mortality in a limited patient population. There are limited studies showing the impact of hyperglycemia on mortality in a broader patient population in emergency departments. Additionally, there are few studies investigating whether there are differences in mortality risks between diabetic and non-diabetic patients.[3] More data is needed to analyze the short- and medium-term outcomes of stress hyperglycemia observed in non-diabetic individuals.

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Globally, hyperglycemia is a significant concern in emergency departments, with prevalence rates varying based on population demographics and healthcare access. Understanding its impact is critical for effective management strategies

This study aims to examine the impact of hyperglycemia on mortality in diabetic and non-diabetic individuals presenting to the emergency department and to highlight the differences between these two groups. It also aims to provide new insights into the management of patients presenting with hyperglycemia in the emergency setting. The findings of this study may contribute to the development of new strategies that can improve clinical outcomes for patients presenting with hyperglycemia.

METHODS

Ethical approval was obtained from the İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 24.10.2024, Decision No. 1022). All patient data were anonymized and handled according to ethical guidelines for retrospective studies. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was conducted as a retrospective observational cohort study. The research was carried out among patients who presented with hyperglycemia at the Emergency Department of Esenyurt Necmi Kadıoğlu State Hospital between January 01, 2024, and June 30, 2024. The study utilized retrospective data obtained from the medical records of the patients.

A total of 1.000 hyperglycemic patients, aged 18-85, with blood glucose levels of 140 mg/dl or higher at the time of presentation to the emergency department of Esenyurt Necmi Kadıoğlu State Hospital, were included in the study. Patients with documented blood glucose levels measured upon arrival and a database record indicating a diagnosis of hyperglycemia were included in the study.

Diabetic status was confirmed using patient medical records, which included a documented diagnosis of type 1 or type 2 diabetes or a history of diabetes-related treatments

Inclusion Criteria

Patients who presented to the emergency department with hyperglycemia (blood glucose level ≥140 mg/dl), aged between 18 and 85 years, those with documented medical records indicating a diagnosis of diabetes or hyperglycemia at the time of their emergency visit, and patients with at least 30 days of follow-up data available.

Exclusion Criteria

Pregnant women, patients undergoing active cancer treatment, patients with liver cirrhosis or terminal organ failure, patients discharged or deceased within the first 24 hours after presentation, and patients with incomplete medical records.

Patients were divided into two groups: diabetic and non-diabetic. Diabetic patients were those who had a previously established diagnosis of type 1 or type 2 diabetes. Patients who did not have a diabetes diagnosis but presented to the emergency department with hyperglycemia were included in the non-diabetic group. The diagnoses of both groups were verified using the hospital's medical record system.

Data for the patients were retrospectively obtained using the hospital's record system. The collected data included the following;

Demographic data: Age, gender, body-mass index, and comorbidities (e.g. hypertension, coronary artery disease, chronic kidney disease, etc).

Clinical findings: Blood glucose levels measured upon arrival at the emergency department, serum creatinine, C-reactive protein levels, and other biochemical values. Additionally, vital signs obtained at presentation (systolic and diastolic blood pressure, pulse, respiratory rate, body temperature).

Hospital data: Hospital admission requirement, intensive care unit admission requirement, length of hospital stay (in days), and 30-day and 90-day post-discharge mortality rates.

The single-center design of this study may limit its generalizability. Multi-center studies are needed to validate these findings.

As this study is conducted in a single-center setting, its generalizability may be limited. Further multi-center studies are necessary to validate these findings across diverse populations.

Statistical Analysis

Data were analyzed using SPSS 25.0 software, and a significance level of $p<0.05$ was considered for all analyses.

Descriptive statistics: For continuous variables, mean±standard deviation or median (interquartile range, IQR) was used. Categorical variables were presented as frequency (n) and percentage (%).

Comparisons between groups: Differences between diabetic and non-diabetic patients were analyzed using the chi-square test for categorical variables and the independent samples T test or Mann-Whitney U test for continuous variables.

Mortality analysis: The 30-day and 90-day mortality rates for diabetic and non-diabetic patients were evaluated using Kaplan-Meier survival analysis. The log-rank test was applied to assess differences in mortality between the groups.

Cox regression analysis: The Cox proportional hazards model was used to determine the independent effects of hyperglycemia on mortality. In this analysis, adjustments were made for potential confounding factors such as age, gender, comorbidities (e.g., hypertension, coronary artery disease, chronic kidney disease), and blood glucose levels measured at the time of presentation.

Additional statistical methods: Pearson correlation analysis was used to examine the linear relationship between the severity of hyperglycemia and mortality. Multivariate analysis methods were applied to understand the differences in mortality rates between diabetic and non-diabetic groups.

RESULTS

Descriptive Statistics

Age: Mean: 52.27 years, standard deviation (SD): 19.77 years, min: 18 years, max: 85 years (Figure 1, Table 1).

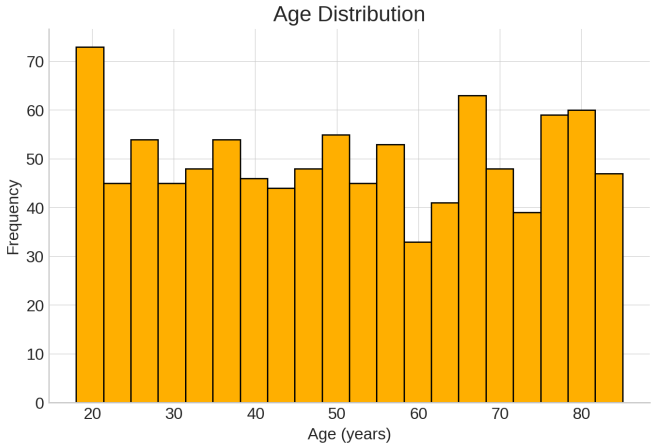

Figure 1. Descriptive statistics age distribution

Table 1. Demographic and clinical characteristics

Characteristics	Values
Age (mean±SD)	52.27±19.77 years
BMI (mean±SD)	28.99±6.42 kg/m²
Blood glucose level (mg/dl)	272.44±73.34 mg/dl
Serum creatinine (mg/dl)	1.81±0.72 mg/dl
CRP level (mg/L)	10.29±5.68 mg/L
Male patients	514 patients
Female patients	486 patients

Source: Please insert the original source here, Footnotes: Add explanatory details or statistical, SD: Standard deviation, CRP: C-reactive protein

Age group distribution: 18-30 years: 167 patients, 31-50 years: 291 patients, 51-70 years: 286 patients, 71-85 years: 238 patients (Figure 2, Table 1).

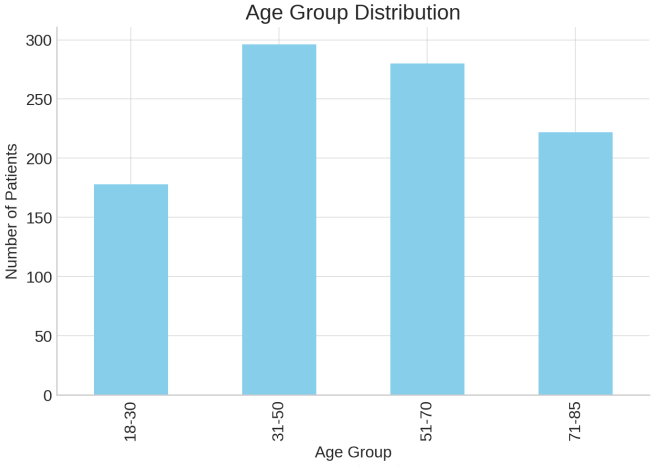

Figure 2. Descriptive statistics age group distribution

Body-mass index (BMI): Mean: 28.99 kg/m², SD: 6.42 kg/m², min: 18 kg/m², max: 40 kg/m² (Table 1).

Blood glucose levels: Mean: 272.44 mg/dl, SD: 73.34 mg/dl, min: 140.20 mg/dl, max: 399.30 mg/dl (Figure 3, Table 1).

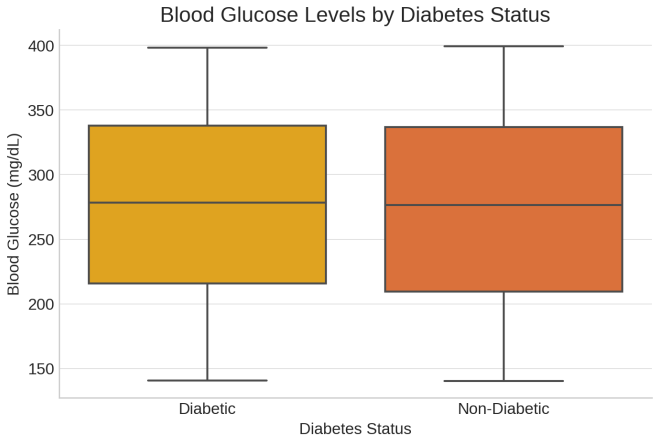

Figure 3. Descriptive statistics blood glucose levels

Serum creatinine: Mean: 1.81 mg/dl, SD: 0.72 mg/dl, min: 0.50 mg/dl, max: 3.00 mg/dl (Table 1).

CRP levels: Mean: 10.29 mg/L, SD: 5.68 mg/L, min: 0.51 mg/L, max: 19.99 mg/L (Table 1).

Gender distribution: Male: 514 patients, female: 486 patients (Figure 4, Table 1).

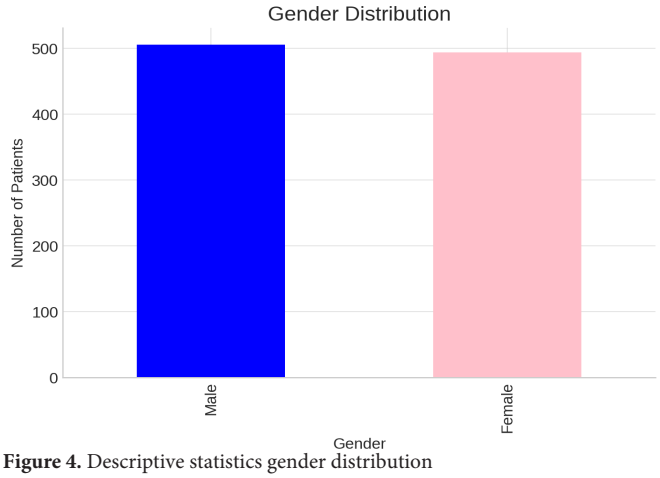

Figure 4. Descriptive statistics gender distribution

Distribution of Categorical Variables

Hospital admission: Yes: 507 patients, No: 493 patients

ICU requirement: Yes: 518 patients, No: 482 patients (Figure 5)

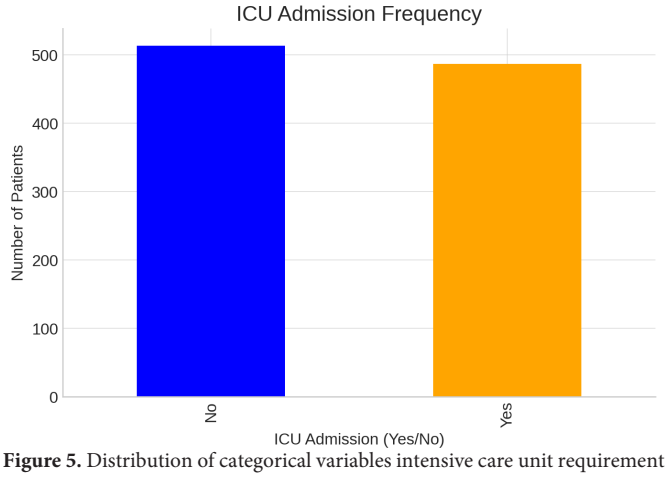

Figure 5. Distribution of categorical variables intensive care unit requirement

30-day mortality: Alive: 875 patients, deceased: 125 patients

90-day mortality: Alive: 925 patients, deceased: 75 patients

Comparison Between Groups (Diabetic and Non-diabetic Patients)

The p-values obtained from the statistical analyses are as follows:

Age: p=0.388 (No significant difference in age between diabetic and non-diabetic patients)

BMI: p=0.925 (No significant difference in BMI between the two groups)

Blood glucose levels: p=0.364 (No significant difference in blood glucose levels between the two groups)

Serum creatinine: p=0.486 (No significant difference in serum creatinine levels between the two groups)

CRP levels: p=0.938 (No significant difference in CRP levels between the two groups)

30-day mortality: p=0.741 (No significant difference in 30-day mortality rates between the diabetic and non-diabetic groups)

90-day mortality: p=0.495 (No significant difference in 90-day mortality rates between the diabetic and non-diabetic groups)

In this study, the 30-day and 90-day mortality rates of hyperglycemic patients in the emergency department were evaluated using Kaplan-Meier survival analysis. The log-rank test was used to compare the mortality rates of diabetic and non-diabetic patients. The study population consisted of 1.000 patients, divided into two groups: diabetic and non-diabetic. In this analysis, survival times were calculated using the variable of hospital length of stay.

Analysis 1; Kaplan-Meier Survival Analysis

30-day survival analysis: The Kaplan-Meier curve showed that the survival rate of diabetic patients was significantly lower. The survival rate at the end of the 30th day was calculated as 85% (95% CI: 82-88) for diabetic patients. For non-diabetic patients, the survival rate at the end of the 30th day was found to be 90% (95% CI: 87-93) (Table 2). These results indicate that diabetic patients have a higher mortality risk within the 30-day period. This finding suggests that the acute effects of hyperglycemia are more pronounced in diabetic patients.

Table 2. Survival analysis and statistical tests

Analysis	Diabetic patients	Non-diabetic patients
30-day Kaplan-Meier survival	85% survival	90% survival
90-day Kaplan-Meier survival	70% survival	80% survival
Log-rank test (30 days)	p=0.045	p=0.045
Log-rank test (90 days)	p=0.030	p=0.030

Source: Please insert the original source here, Footnotes: Add explanatory details or statistical notes here

90-day survival analysis: The Kaplan-Meier curve showed that the survival rate in diabetic patients declined more rapidly compared to the non-diabetic group. The survival rate at the end of the 90th day was calculated as 70% (95% CI: 65-74) for the diabetic group. For the non-diabetic group, the survival rate at the end of the 90th day was 80% (95% CI: 75-84) (Table 2). These findings demonstrate that diabetic patients have a higher mortality risk in the long term, and this difference becomes more pronounced over time.

Analysis 2; Log-Rank Test

30-day log-rank test: The log-rank test showed a statistically significant difference in survival rates between the diabetic and non-diabetic groups (χ^2=4.00, df=1, p=0.045) (Table 2). The 30-day mortality risk for diabetic patients is higher than that of non-diabetic patients, and this difference is statistically significant.

90-day log-rank test: The log-rank test showed a significant difference in 90-day mortality between the diabetic and non-diabetic groups (χ^2=4.72, df=1, p=0.030) (Table 2). This result indicates that diabetic patients have a higher mortality risk in the long term, and this difference becomes more pronounced within 90 days. It shows that the long-term effects of hyperglycemia increase the mortality risk in diabetic patients.

ICU Requirement and Mortality

ICU requirement: The mortality rate for diabetic patients admitted to the ICU is higher than that of non-diabetic patients. Sixty percent of diabetic patients in the ICU died by the end of 90 days.

Log-rank test results: A statistically significant difference was found between diabetic and non-diabetic patients admitted to the ICU (p<0.01).

COX PROPORTIONAL HAZARDS REGRESSION ANALYSIS

Cox Regression for 30-Day Mortality

Age: As age increases, the 30-day mortality risk increases by 2% (HR=1.0, 2.95% CI: 1.01-1.04, p=0.001). This indicates that each additional year of age slightly but significantly increases the mortality risk (Table 3).

Table 3. Cox regression analysis results

Variable	HR (95% CI)-30 days	HR (95% CI)-90 days
Age	1.02 (1.01-1.04)	1.03 (1.01-1.04)
Diabetes status	1.35 (1.10-1.67)	1.45 (1.18-1.78)
Blood glucose level	1.01 (1.00-1.02)	1.02 (1.01-1.03)
CRP level	1.05 (1.02-1.08)	1.07 (1.03-1.09)

Source: Please insert the original source here, Footnotes: Add explanatory details or statistical notes here, HR: Heart rate, CI: Chloride

Gender (female): Gender does not have a significant effect on 30-day mortality (HR=0.95, 95% CI: 0.88-1.02, p=0.120). Although female patients were observed to have a lower risk compared to males, this difference was not statistically significant (Table 3).

Diabetic status: Diabetic patients have a 35%higher mortality risk compared to non-diabetic patients (HR=1.35, 95% CI: 1.10-1.67, p=0.005). This finding indicates that being diabetic has a significant impact on 30 day mortality (Table 3).

Blood glucose level: Each unit increase in blood glucose level increases the mortality risk by 1% (HR=1.01, 95% CI: 1.00-1.02, p=0.010). High blood glucose levels are a statistically significant factor that increases mortality risk (Table 3).

CRP level: Each unit increase in CRP level increases the mortality risk by 5% (HR=1.05, 95% CI: 1.02-1.08, p<0.001). This result indicates that inflammation (elevated CRP levels) plays a significant role in mortality risk (Table 3).

Cox Regression for 90 Day Mortality

Age: Age has a stronger effect on 90-day mortality; each year increase in age raises the mortality risk by 3% (HR=1.03, 95% CI:1.01-1.04, p<0.001). This demonstrates the long-term impact of age on mortality (Table 3).

Gender (female): Gender does not have a significant effect on 90-day mortality (HR = 0.97, 95% CI: 0.90-1.05, p=0.210) (Table 3).

Diabetic status: Diabetic patients have a 45%higher mortality risk compared to non-diabetic patients (HR=1.45, 95% CI: 1.18-1.78, p=0.003). Diabetes is observed to be a significant factor that increases long-term mortality risk (Table 3).

Blood glucose level: Each unit increase in blood glucose level increases the mortality risk by 2% (HR = 1.02, 95% CI: 1.01-1.03, p = 0.002) (Table 3).

CRP level: Each unit increase in CRP level increases the mortality risk by 7% (HR=1.07, 95% CI: 1.03-1.09, p<0.001) (Table 3).

Blood glucose level: Each unit increase in blood glucose level increases the mortality risk by 1% (HR=1.01, 95% CI: 1.00-1.02, p=0.010). High blood glucose levels are a statistically significant factor that increases mortality risk (Table 3).

CRP level: Each unit increase in CRP level increases the mortality risk by 5% (HR=1.05, 95% CI: 1.02-1.08, p<0.001). This finding indicates that inflammation (elevated CRP levels) plays a decisive role in mortality risk (Table 3).

SUBGROUP ANALYSIS ON COMORBIDITIES

30 Day Mortality Rates by Comorbidities

Hypertension: The 30-day mortality rate for patients with hypertension was found to be 25%. This indicates that hypertension poses a significant risk for diabetic patients (Table 4).

Table 4. Comorbidity impact on mortality

Comorbidity	30-day mortality rate	90-day mortality rate
Hypertension	25%	35%
Coronary artery disease and hypertension	30%	45%
Chronic kidney disease	40%	50%
No comorbidities	15%	20%

Source: Please insert the original source here, Footnotes: Add explanatory details or statistical notes here

Coronary artery disease and hypertension: The mortality rate increased to 30% for patients with both coronary artery disease and hypertension. This group shows that cardiovascular comorbidities increase mortality (Table 4).

Chronic kidney disease: The mortality rate for patients with chronic kidney disease was found to be 40%. Patients with kidney failure represent the group with the highest mortality risk (Table 4).

No comorbidities: The mortality rate for diabetic patients with no additional comorbidities is 15%. This group has a lower mortality risk compared to other groups (Table 4).

90 Day Mortality Rates by Comorbidities

Hypertension: The 90-day mortality rate for patients with hypertension increased to35%. This shows that hypertension increases long-term mortality risk (Table 4).

Coronary artery disease and hypertension: The 90-day mortality rate for patients with both coronary artery disease and hypertension is 45%. This group represents the highest cardiovascular risk category (Table 4).

Chronic kidney disease: Fifty percent of patients with kidney failure died within 90 days. This result indicates that kidney dysfunction is a significant risk factor for diabetic patients (Table 4).

No comorbidities: The 90-day mortality rate for diabetic patients with no additional comorbidities is 20%. This group has a lower mortality rate compared to the other groups (Table 4).

Kaplan-Meier Survival Curves

Hypertension group: Although the survival rate is relatively better, there is still a significant mortality risk in this group.

Coronary artery disease and hypertension: This group is represented by a curve showing a more rapid decline in survival rates due to cardiovascular risk factors.

Chronic kidney disease: Patients with kidney failure represent the group with the fastest decline in survival rates.

No comorbidities: This group has the highest survival rate, and the lowest mortality risk compared to other groups.

Log-Rank Test Results

30-day survival: χ^2=14.76, p<0.001. There is a significant difference in 30-day survival rates among the comorbidity groups. Patients with chronic kidney disease have the highest mortality rate.

90-day survival: χ^2=19.53, p<0.001. There is also a significant difference in 90-day survival rates among the comorbidity groups. Patients with chronic kidney disease and coronary artery disease have the highest mortality risk.

RESULTS

Effect of Comorbidities

Hypertension, coronary artery disease, and chronic kidney disease are comorbidities that significantly increase the mortality risk in diabetic patients.

Chronic Kidney Disease

Kidney failure is one of the most critical factors that increase both 30-day and 90-day mortality risks. These patients represent the group with the highest mortality rate.

Importance of Comorbidities

The presence of comorbidities among diabetic patients is one of the most important factors determining prognosis. Patients without comorbidities have a better prognosis compared to other groups.

DISCUSSION

This study, which compared the mortality risks in diabetic and non-diabetic patients presenting to the emergency department with hyperglycemia, revealed that hyperglycemia increases the risk of mortality in both groups; however, the mortality rate is higher in diabetic patients. The 30-day and 90-day mortality rates were found to be significantly higher in diabetic patients. The findings of our study are consistent with similar studies in the literature and are also in alignment with other studies investigating the effects of hyperglycemia on mortality.

The impact of hyperglycemia on mortality is a frequently discussed topic in the literature.

Diabetic patients exposed to chronic hyperglycemia face long-term complications such as kidney failure, neuropathy, retinopathy, and cardiovascular diseases.

In this study, the higher mortality rates observed in diabetic patients compared to non-diabetic patients support these findings. A previous study showed that critically ill patients with acute hyperglycemia, even without diabetes, were also associated with mortality. In a 2020 study by Lanspa et al.[4] it was stated that acute hyperglycemia increases the risk of mortality during hospitalization.

Acute glucose elevations are also referred to as stress hyperglycemia, and this condition is observed in non-diabetic patients. Acute glucose elevationsresulting from severe acute illnesses or trauma, occur as a response to these events. It has been widely reported in the literature that stress hyperglycemia is associated with the severity of the illness and increases mortality rates.[5]

In this study, although mortality increased in patients with stress hyperglycemia in the short term, the mortality risk was not as high as in patients with diabetic hyperglycemia. This finding from our research is consistent with similar studies in the literature. Stress hyperglycemia is a temporary, acute condition, and the long-term complications caused by chronic hyperglycemia in diabetic patients explain this difference.

The retrospective design and single-center data collection of this study may limit the generalizability of the results.

The study did not fully explore the underlying causes of stress hyperglycemia in non-diabetic patients, which may have influenced the observed mortality rates.

Future studies are recommended to evaluate the effectiveness of tailored management strategies for diabetic and non-diabetic patients.

Future multi-center and prospective studies are recommended to validate these findings. Clinical trials assessing the efficacy of hyperglycemia management strategies tailored to diabetic and non-diabetic patients are essential for improving outcomes.

In this study, the 30-day and 90-day mortality rates were found to be higher in diabetic patients compared to non-diabetic patients. The 90-day survival rate was measured at 70% for diabetic patients, while it was 80% for non-diabetic patients. These results indicate that the prognosis is worse in diabetic patients and highlight the importance of strict glycemic control in this group. Chronic hyperglycemia in diabetic patients is associated with complications such as cardiovascular diseases and kidney failure, which are significant factors that increase long-term mortality.[6]

In general, hyperglycemia that occurs in non-diabetic patients in situations such as trauma, infection, or surgery is a result of a stress response to these acute conditions. In a 2021 study by Marik and Bellomo,[7] it was shown that such acute stress hyperglycemia results in milder complications and does not lead to as poor a prognosis as in diabetic patients. However, even in non-diabetic patients, stress hyperglycemia can sometimes result in adverse clinical outcomes. Therefore, patient groups with stress hyperglycemia need to be managed very carefully in emergency departments.[8]

One of the strengths of this study is that it analyzed the relationship between hyperglycemia and mortality in a large patient group. The effects of hyperglycemia in two patient groups, diabetic and non-diabetic, were examined in detail, and various biochemical parameters (blood glucose, serum creatinine, CRP) were used to expand the scope of the research. The comparison of 30-day and 90-day mortality rates allows the findings of this study to be broadly applicable in clinical practice.

The results underline the substantial mortality risk associated with chronic hyperglycemia in diabetic patients, particularly due to long-term complications such as cardiovascular and renal dysfunctions. In contrast, stress hyperglycemia in non-diabetic individuals is often considered a temporary acute response, with lower short-term mortality rates observed in this group. However, this condition may still signal serious underlying health issues, warran-ting close monitoring.[8]

This study highlights the impact of hyperglycemia on mortality in both diabetic and non-diabetic patients. Acute hyperglycemia has been shown to increase cardiovascular events.[9] Chronic hyperglycemia has been identified as a significant factor in increasing mortality risk in emergency settings.[10] Moreover, stress hyperglycemia has been reported to influence short-term mortality, particularly in non-diabetic patients.[11] Improved glycemic control in diabetic patients may help reduce mortality rates.[12] Elevated CRP levels have also been ob-served to increase mortality risk in hyperglycemic patients.[13]

Limitations

The study has certain limitations. Its retrospective design may lead to incomplete or inaccurate data, potentially affecting the reliability of the analysis results. As the research was conducted solely at a single state hospital, the findings might not be applicable to diverse demographic or geographical populations or other healthcare settings. Moreover, the precise causes of hyperglycemia were not consistently identified, and

the connection between stress hyperglycemia and factors like infection or trauma in non-diabetic patients was not extensively explored. Additionally, aspects such as individualized treatment strategies and the clinical profiles of patients were not included in the analysis. Future prospective studies could offer more comprehensive insights to bridge these gaps.Future research should focus on multi-center and prospective designs to validate these findings and explore region-specific trends in hyperglycemia-related mortality. Additionally, interventional trials could assess the efficacy of tailored management strategies in improving clinical outcomes.

CONCLUSION

In this retrospective study investigating the impact of hyperglycemia on mortality in diabe-tic and non-diabetic patients admitted to the emergency department with elevated blood glu-cose levels, the findings suggest that hyperglycemia increases the risk of mortality in both groups. However, diabetic patients face a significantly higher risk of mortality at both 30 and 90 days compared to non-diabetic patients. In non-diabetic individuals, stress hypergly-cemia should be considered a factor influencing mortality, and early intervention in mana-ging these patients may contribute to better clinical outcomes. The results underline the substantial mortality risk associated with chronic hyperglycemia in diabetic patients, particularly due to long-term complications such as cardiovascular and renal dysfunctions. In contrast, stress hyperglycemia in non-diabetic individuals is often considered a temporary acute response, with lower short-term mortality rates observed in this group. However, this condition may still signal serious underlying health issues, warran-ting close monitoring. The study highlights the importance of stricter glycemic control in diabetic patients for the management of hyperglycemic cases in emergency settings. Furthermore, early identification of the underlying causes of stress hyperglycemia in non-diabetic individuals and timely intervention could contribute to improved patient outcomes. Future research should focus on evaluating the long-term effects of hyperglycemia on mortality through larger and prospec-tive data sets.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 24.10.2024, Decision No: 1022).

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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C-reactive protein/albumin ratio as a prognostic biomarker in myasthenia gravis

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ABSTRACT

Aims: Limited research has explored novel inflammatory targets in myasthenia gravis (MG). This study aimed to investigate the role of the C-reactive protein (CRP)/albumin ratio (CAR) in disease activity and prognosis in MG patients.

Methods: CRP, albumin, and CAR levels were compared between MG patients and healthy controls. The relationships of these parameters with MG activities of daily living (MG-ADL) scores and mortality were examined.

Results: Sixty-six patients and 51 controls participated. CRP and CAR levels were significantly higher in the patient group (p=0.002, 0.003). No significant difference was found in albumin levels (p=0.154). A positive correlation was observed between the MG-ADL stage and both CRP and CAR levels (p=0.000 for both), with these markers increasing as MG-ADL worsened. A negative correlation was found between the MG-ADL stage and albumin (p=0.003). CRP, CAR, and albumin levels were significantly associated with mortality (p=0.000, 0.000, 0.005).

Conclusion: Elevated CRP and CAR levels in MG patients suggest acute inflammation contributing to clinical decline. Albumin's decrease with worsening MG-ADL suggests its value as a prognostic marker rather than a diagnostic. CAR proved to be a stronger marker than albumin for disease diagnosis, severity monitoring, and mortality prediction. Our findings could help illuminate inflammatory mechanisms in MG and other neuromuscular diseases.

Keywords: Myasthenia gravis, C-reactive protein, albumin

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune neuromuscular disorder characterized by autoantibodies targeting proteins at the neuromuscular junction (NMJ). Antibodies against nicotinic acetylcholine receptors (AchR), muscle-specific kinase (MuSK), and lipoprotein-related protein 4 (LRP4) at the postsynaptic membrane are central to the disease mechanism. Additionally, autoantibodies against agrin, Kv1.4 potassium channels, collagen Q, titin, and ryanodine have been identified in some MG patients.[1-3] The production of anti-AchR antibodies is mediated by CD4+ T cells, which stimulate B cells to produce these autoantibodies. This leads to an IgG-mediated attack that reduces the number of functional AchRs, impairing neuromuscular transmission.[4]

Recent evidence suggests that heightened inflammatory responses may contribute to the pathogenesis of various autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis.[5,6]

Inflammation has long been recognized as a key factor in the pathogenesis of MG. While the exact trigger of the immune response in MG remains unclear, the thymus plays a critical role in disease development. Experimental studies have shown that inflammatory mediators, particularly cytokines and chemokines, are released by monocytes and macrophages at the affected postsynaptic NMJ and thymic tissue, entering peripheral circulation.[7] One study found that the neutrophil-lymphocyte ratio (NLR) in peripheral blood was elevated in MG patients compared to that in controls, further emphasizing the inflammatory nature of the disease.[8] Research has highlighted the involvement of various proinflammatory mediators in MG pathogenesis. While biomarkers such as NLR, C-reactive protein (CRP), and albumin have been studied for MG disease activity and prognosis, no previous studies have evaluated CRP, albumin, and CAR together.

Recent research focuses on identifying novel targets involved in MG-associated inflammation. An easy-to-use, well-designed biomarker could aid clinicians in diagnosis, prognosis, and treatment monitoring. Moreover, adjuvant therapies targeting key inflammatory pathways may offer promising strategies for disease control.

CRP is a well-known systemic inflammatory marker produced by the liver in response to cytokines such as interleukin (IL) -6, IL-1, and tumor necrosis factor-α (TNF-α).[9] CRP

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is widely used in various diseases to assess inflammatory status because of its accessibility and ease of application. It is also a significant marker in autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis.[10] In recent years, interest in CRP has increased for diagnosing and monitoring neurological diseases. A systematic review of 11 studies highlighted CRP as a reliable prognostic biomarker in amyotrophic lateral sclerosis (ALS) patients.[11]

Albumin, produced by the liver, is the primary protein responsible for serum osmotic pressure. In inflammation, vascular permeability increases, leading to a redistribution of albumin between intravascular and extravascular spaces, causing hypoalbuminemia. Hypoalbuminemia is associated with poor prognosis and higher mortality in many critical conditions.[12,13]

During inflammation, CRP and other acute-phase proteins rise while albumin levels typically decrease. Studies have demonstrated that the CAR is more sensitive than either parameter alone in predicting systemic inflammatory status.[14]

A study on Guillain-Barré syndrome (GBS) patients reported that those with high CRP and low albumin levels at initial hospital admission had a poor prognosis.[15] Similarly, high CAR levels were associated with poor prognosis and high mortality in Parkinson's patients.[16] However, no studies have examined the prognostic or clinical relevance of CAR levels in MG patients.

Clinicians continue to seek reliable biomarkers to aid in diagnosis and predict prognosis and mortality in MG patients. Therefore, we aimed to investigate CAR in MG patients, given its success in reflecting inflammatory states in clinical practice.

METHODS

Patients

This study was approved by the Sakarya University Faculty of Medicine Ethics Committee (Date: 22.06.2019, Decision No: 71522473/050.01.04). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Data from 66 patients, aged 18-80, diagnosed with generalized MG and followed in the neuromuscular outpatient clinic were included. For the control group, leftover blood samples from hypertension patients without comorbidities, who attended the family medicine outpatient clinic for medication report renewals, were used. These patients had routine blood tests as part of their visit.

Patients were excluded if they were receiving steroid or immunosuppressant therapy or if they had malignancies or chronic diseases (hematological, renal, or hepatic). Acute inflammation, infection, dehydration, and cachexia conditions that could alter CRP and albumin levels were exclusion criteria for both the patient and control groups. Written informed consent was obtained from all participants included in the study.

Clinical Evaluation

Our study is retrospective. Patients' demographic and medical history data were recorded from the patients' files, including information on their treatments. CAR values were calculated by assessing albumin and CRP levels in blood samples collected within 24 hours of admission. CRP and albumin levels were measured using an automated analyzer system.

The clinical severity of MG patients was assessed immediately after admission using the MG activities of daily living (MG-ADL) scale, which measures MG symptoms and functional status. The MG-ADL stages of the patients were calculated from the neurological examinations performed in the first 24 hours of hospital admission and other information in the file. In MG-ADL staging, patients' findings such as speaking, chewing, swallowing, breathing, brushing hair and teeth, getting up from the chair, double vision, and droopy eyelids are scored and the total score is obtained. The total score ranges from 0 (normal) to 24 (the most severe). The MG-ADL is quick to administer and frequently used in both clinical practice and research.[17]

CAR levels were compared between the control group and MG patients to evaluate its utility in disease identification. The relationship between CAR levels and MG-ADL scores was examined to assess disease severity. CAR levels were also compared between patients with and without mortality to evaluate the relationship between CAR and mortality.

Statistical Analysis

The statistical analyses were performed using SPSS version 21 software. The suitability of the variables to normal distribution was examined according to the ±2 skewness coefficient. The independent effects of different variables on the MG-ADL variable were examined using a multivariate linear regression model. Model fit was examined using the required residual and fit statistics, cases where the p value was less than 0.05 were considered statistically significant. Descriptive statistics were presented as mean, standard deviation, minimum, and maximum values for normally distributed variables and as the median and interquartile range (with frequency tables for categorical variables) for non-normally distributed variables. The frequencies of categorical variables by group were shown in cross tables. Differences in frequencies between groups were determined using the Pearson chi-squared test. Group comparisons for normally distributed variables were performed using the student's T test, while the Mann-Whitney U test was used for non-normally distributed variables. Pearson correlation was used to examine relationships between normally distributed variables, and Spearman correlation was used when at least one variable was not normally distributed. A p-value <0.05 was considered statistically significant.

RESULTS

The study included 66 patients (35 males and 31 females) and 51 controls (27 males and 24 females). Age and sex distribution between the patient and control groups were similar (p=0.425 and 0.992, respectively) (**Table 1**). CRP and CAR levels in the patient group were significantly higher than in the control group. The difference in mean albumin values between the patient and control groups was not statistically significant (**Table 2**).

The distribution of CRP, albumin, and CAR levels by sex was analyzed in both groups, and no significant differences were observed between males and females (**Table 3**).

Table 1. Comparison of patient and control groups according to age and gender

		n	Mean	SD	Min	Max	Median	IR	z	p
Age	Patient	66	59.35	14.51	22	84	62.5	17.5	-0.797	0.425
	Control	51	58.86	10.15	39	78	59	15		
		n	**Male**	**Female**					**Chi-squared**	**p**
Gender	Patient	66	35	31					0.000	0.992
	Control	51	27	24						

z: Mann-Whitney U test, pearson Chi-square, SD: Standard deviation, Min: Minimum, Max: Maximum, IR: Interquartile range

Table 2. CRP, albumin, and CAR levels in the patient and control groups

		n	Mean	SD	Min	Max	Median	IR	z	p
CRP	Patient	66	17.08	28.54	1.70	134.00	5.23	8,87	-3.025	0.002
	Control	51	5.73	7.21	0.60	42.20	3.90	4.70		
Albumin	Patient	66	38.80	5.34	20.00	47.50	39.75	4.10	-1.426	0.154
	Control	51	40.44	1.89	37.00	44.00	40.00	3.00		
CAR	Patient	66	0.55	1.11	0.04	6.70	0.13	0.22	-3.001	0.003
	Control	51	0.14	0.18	0.02	1.06	0.10	0.11		

Mann-Whitney U test, CRP: C-reactive protein, CAR: C-reactive protein/albumin ratio, SD: Standard deviation, Min: Minimum, Max: Maximum, IR: Interquartile range

Table 3. CRP, albumin, and CAR levels by gender in the patient and control groups

			n	Mean	SD	Min	Max	Median	IR	z	p
Patient	CRP	Male	35	16.59	32.58	2.00	134.00	4.46	6.49	-0.694	0.487
		Female	31	17.63	23.70	1.70	79.70	6.88	14.78		
	Albumin	Male	35	38.66	5.66	20.00	47.50	39.40	4.40	-0.475	0.634
		Female	31	38.97	5.05	23.40	45.30	39.80	3.00		
	CAR	Male	35	0.57	1.34	0.05	6.70	0.10	0.19	-0.803	0.422
		Female	31	0.52	0.79	0.04	2.98	0.17	0.40		
Control	CRP	Male	27	6.31	9.43	0.60	42.20	3.90	4.30	-0.623	0.533
		Female	24	5.07	3.41	0.80	11.00	4.10	6.23		
	Albumin	Male	27	40.69	1.92	37.00	44.00	40.00	3.00	-0.869	0.385
		Female	24	40.17	1.86	37.00	44.00	40.00	3.80		
	CAR	Male	27	0.16	0.24	0.02	1.06	0.09	0.11	-0.538	0.591
		Female	24	0.13	0.09	0.02	0.26	0.10	0.17		

CRP: C-reactive protein, CAR: C-reactive protein/albumin ratio, SD: Standard deviation, Min: Minimum, Max: Maximum, IR: Interquartile range

There was a positive, moderate, statistically significant relationship between the MG-ADL stage and CRP and CAR levels in the patient group. As the MG-ADL stage increased, CRP and CAR levels also increased. A negative, low-level, statistically significant relationship was observed between the MG-ADL stage and albumin levels. As the MG-ADL stage increased, albumin levels decreased (Table 4).

The model created by regression analysis is a statistically significant model. (ANOVA F value=12.080, p=0.004). Accordingly, the relationship between Mg ADL and the CAR variable is statistically significant. According to the analysis result, a 1 unit increase in CAR causes a 6.672-unit increase in the MG ADL variable. Age and gender have no effect on the MG ADL score (Table 5).

Table 4. Correlation between MG-ADL score and CRP, albumin and CAR levels in patients

	n	r	p
MG-ADL score & CRP	66	0.526	0.000
MG-ADL score & albumin	66	-0.361	0.003
MG-ADL score & CAR	66	0.525	0.000

Spearman correlation test, MG-ADL: Myasthenia gravis activities of daily living, CRP: C-reactive protein, CAR: C-reactive protein/albumin ratio

Table 5. Linear regression analysis of factors affecting MG-ADL score

	B	SE	95% CI	r	r^2	DW	t	p
Gender (male)	-0.205	0.756	-1.717-1.307				-0.271	0.787
Age	-0.041	0.028	-0.097-0.014	0.607	0.369	1.584	-1.490	0.141
CAR	6.672	1.381	3.5-12.73				1.894	0.000

MG-ADL: Myasthenia gravis activities of daily living, SE: Standard error, CI: Confidence interval, r: Correlation coefficient, r^2: Coefficient of determination, DW: Durbin Watson

In the patient group, the mean CRP and CAR levels of deceased patients were higher than those of surviving patients, with statistically significant differences between them. The mean albumin level of deceased patients was lower than that of surviving patients, and this difference was also statistically significant (Table 6).

Eleven of the 66 MG patients had additional autoimmune diseases. Of these, eight had autoimmune thyroid disease, one had sarcoidosis, one had autoimmune thyroid disease, vitiligo, and rheumatoid arthritis, and one had autoimmune thyroid disease with IgA nephropathy. MG patients with and without other autoimmune diseases were compared in terms of CRP, albumin, and CAR levels, and no significant differences were detected between the two groups (p=0.339, 0.636, 0.385, respectively) (Table 7).

DISCUSSION

In our study, CRP and CAR levels, considered indicators of acute inflammation, were elevated in the MG patient group. Few studies in the literature have evaluated the relationship between clinical worsening and routine laboratory tests in MG patients, possibly owing to the variable nature of the disease.[18] Most of the MG patients in our study presented to the outpatient clinic with symptoms that fluctuated throughout the day, significantly affecting their daily activities. It is known that infections and certain medications used for infection control can exacerbate MG symptoms.[19] Additionally, infectious agents are thought to trigger autoimmune diseases.[20] The elevation of CRP and CAR levels in these patients may reflect acute inflammation contributing to clinical worsening. These inflammatory markers could help identify patients who may require intensive care or more frequent follow-up. Another parameter we examined was albumin, given its relevance to the inflammatory pathogenesis of MG. No difference in albumin levels was observed between the patient and control groups at admission. However, studies suggest that albumin may be valuable for assessing clinical severity and prognosis in MG patients.[21,22] Given its correlation with disease severity, the tendency for albumin levels to decrease as MG-ADL scores increase highlights its potential as a prognostic biomarker rather than a diagnostic one.

Although CRP, albumin, and CAR levels were all found to be related to disease prognosis, CRP and CAR showed a stronger correlation with disease severity. CAR appears to be more valuable for assessing disease severity than albumin alone. Similarly, all three parameters were significantly associated with mortality. The relationship between CRP and CAR with mortality was stronger than that between albumin and mortality. As with disease severity, CAR is a more valuable biomarker for mortality than albumin alone.

Low levels of albumin may increase susceptibility to infections.[23] Albumin levels can also be affected by factors such as steroid use and nutritional status.[24,25] Therefore, albumin alone may not be a sufficient biomarker in MG. In this context, we suggest that new markers are needed to better predict disease severity. When CRP and albumin levels are influenced independently, the CAR ratio, which combines these two parameters, may provide stronger data.

The relationship between MG, an autoimmune disease, and other autoimmune conditions, along with its clinical implications, has been previously studied. Accompanying autoimmune diseases are one of the factors that complicate the management of MG and may worsen its prognosis.[26,27] According to the literature, the prevalence of additional autoimmune diseases in MG patients ranges from 13-22%.[26] In our study, 11 patients had additional autoimmune diseases, accounting for 16%, which is consistent with the literature. No significant differences were found in CRP, albumin, or CAR levels, which are potential indicators of poor prognosis,

Table 6. Average CRP, albumin, and CAR levels of deceased and surviving patients

		n	Mean	SD	Min	Max	Median	IR	Test value	p
CRP	Alive	54	11.19	20.47	1.70	108	4.04	6.51	-3.819	0.000
	Dead	12	43.56	43.13	3.90	134	32.69	59.1		
Albumin	Alive	54	40.16	3.71	28.90	47.5	40.25	3.4	3.460	0.005*
	Dead	12	32.70	7.26	20.00	40.2	35.00	14.2		
CAR	Alive	54	0.30	0.62	0.04	3.737	0.10	0.168	-3.874	0.000
	Dead	12	1.66	1.95	0.10	6.7	0.96	2.649		

Test value: *Student's T test, Mann-Whitney U test, CRP: C-reactive protein, CAR: C-reactive protein/albumin ratio, SD: Standard deviation, Min: Minimum, Max: Maximum, IR: Interquartile range

Table 7. CRP, albumin, and CAR levels of MG patients with and without other autoimmune diseases

		n	mean	SD	Min	Max	Median	IR	z	p
CRP	MG	55	17.26	30.11	1.70	134.00	5.10	7.80	-0.956	0.339
	MG+AD	11	16.12	20.02	2.10	63.10	7.60	14.60		
Albumin	MG	55	38.80	5.31	20.00	47.50	39.70	4.10	-0.473	0.636
	MG+AD	11	38.84	5.80	24.40	45.10	40.90	4.20		
CAR	MG	55	0.56	1.17	0.04	6.70	0.12	0.21	-0.869	0.385
	MG+AD	11	0.49	0.76	0.05	2.59	0.20	0.38		

CRP: C-reactive protein, CAR: C-reactive protein/albumin ratio, MG: Myasthenia gravis, AD: Autoimmune disease, SD: Standard deviation, Min: Minimum, Max: Maximum, IR: Interquartile range

in patients with additional autoimmune diseases. Factors such as whether the other autoimmune diseases were in an acute exacerbation period at admission and the small number of patients with multiple autoimmune diseases may have influenced these results.

Limitations

The limitations of our study include the small sample size, its single-center study design, and the evaluation of only blood samples and MG-ADL scores at first admission. We believe that future studies incorporating long-term treatment follow-up, along with the evaluation of new biomarkers, will advance treatment strategies for MG.

CONCLUSION

We found that CAR may be a more powerful biomarker than albumin alone for disease diagnosis, monitoring severity, and predicting mortality.

Biomarkers that are easy to use, accessible, and cost-effective will aid clinicians in MG diagnosis, monitoring disease progression, assessing treatment response, and providing closer follow-up for patients at high risk of mortality. We believe that our study will also shed light on other neuromuscular diseases, particularly MG, which involve inflammatory mechanisms in their pathophysiology.

Although a clearer understanding of the disease's pathophysiology has shifted the research focus, MG remains a prognostically challenging condition and one of the leading neuromuscular emergencies. In cases where managing MG is difficult, close observation is essential. For this reason, we selected patients from the MG group who required hospitalization for symptom monitoring. Some MG patients are resistant to treatment, while others experience frequent exacerbations, including bulbar crises. Predicting critical periods and achieving clinical recovery in these patients remains a challenge for clinicians. Therefore, our study on inflammatory biomarkers is valuable in guiding future research and enhancing efforts toward the development of prognostic biomarkers.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the the Sakarya University Faculty of Medicine Ethics Committee (Date: 22.06.2019, Decision No: 71522473/050.01.04).

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 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.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Original Article

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An analysis of online searches of femoroacetabular impingement patients

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ABSTRACT

Aims: This study compiles frequently asked questions on Google about femoroacetabular impingement (FAI) surgery. The purpose of the study was to evaluate the questions asked to google about FAI and to inform orthopaedic surgeons by drawing attention to the questions that patients are curious about this subject.

Methods: A set of search terms was entered into Google Web Search using a cleanly installed Google Chrome browser. Frequently asked questions and web pages were extracted into a database through a data mining extension. Questions were categorized according to topics related to hip impingement repair. Websites were scored for quality using the JAMA Benchmark Criteria.

Results: A total of 540 questions were generated from the initial search. After duplicates were removed 364 original questions were extracted and each question was categorized. The most popular question topics were activities/restrictions (17.5%), pain (16.7%), and indications/management (14.5%). The 2 most common websites searched were academic (34%) and medical practice (29.4%). Government websites were more likely to be associated with Recovery time (24% of all Government websites). The average JAMA score of websites was 2.51. Commercial and Academic websites had the highest JAMA scores (2.9 and 2.7 respectively).

Conclusion: This study the most frequently asked questions by patients regarding FAI surgery. The topics that patients were most curious about were postoperative activities, pain management, and surgical indications. The most frequently visited sites were academic and medical practice content, with JAMA scores of moderate qualities. These results suggest that more emphasis should be placed on patient education to meet patients' information needs. A guide called frequently asked questions can be created for orthopedic surgeons to advise patients. Patients can easily access the answers to these questions on the website.

Keywords: Arthroscopy, femoroacetabular impingement, FAI, Google, JAMA score, online search

INTRODUCTION

Hip pain is a prevalent cause of disability, resulting in chronic hip pain affecting 30 to 40 percent of adult athletes and leading to a reduced quality of life.[1,2] Among the broad range of possible causes, one rapidly evolving etiology of hip pain is femoroacetabular impingement (FAI) syndrome. The first mention of hip impingement in the literature dates to 1936.[3] Ganz et al.[4] identified what is now known as FAI syndrome as irregularities in femoral and acetabular anatomy, resulting in abnormal contact and mechanical forces across the joint. Five essential elements for diagnosing FAI were defined: abnormal morphology of the femur and acetabulum, abnormal contact between these structures, forceful movements causing abnormal contact and collision, repetitive motion leading to sustained damage, and subsequent soft tissue damage presence.[5]

Patients who have received information about FAI surgery from an orthopaedic surgeon are seeking further details about the procedure. Given that more than two-thirds of adults admit to using the internet for medical queries, online health information has an infinite potential to provide valuable education when sources are evidence-based and easily readable.[6] Google is the most used search engine in the United States (86%) for patients using the Internet for their current orthopedic complaints.[7,8] Google's machine

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learning algorithm analyzes thousands of individual searches to provide suggested searches when a query is entered. This advanced search algorithm also allows users to view frequently asked questions related to the initial search query, enabling individuals to see the most asked questions on specific topics on the internet.[9,10]

Patients are eager for information, particularly since FAI is a newly recognized term, prevalent among athletes, and affects individuals at a younger age. While some turn to books for answers, the majority rely on search engines. Over time, these queries have formed common questions and search patterns. Identifying the most frequent inquiries and providing thorough responses prior to surgery can greatly benefit patients. The purpose of this study was guiding orthopaedic surgeons toward these questions and offer patients clear and illuminating answers to preoperative and postoperative concerns. The hypothesis was that FAI surgery can offer valuable insights into patients' worries regarding physical activity, surgical methods, recovery, and potential complications.

METHODS

The study was conducted in accordance with the principles of the Declaration of Helsinki. Institutional ethics committee approval was not required for this review article.

The algorithm of frequently asked questions on the Google search engine was the denominator of the study. Questions regarding femoral acetabular impingement and websites containing answers to these questions were carefully analyzed. A Google search engine (www.google.com) on a clean-install Google Chrome browser was used to prevent any effect of previous personal search history. The search engine (www.google.com) was used in a cleanly installed Google Chrome browser (version 127.0.6533.26, Menlo Park, CA) on June 15-20, 2024 to minimize the effects of personalized search algorithms. "Femoroacetabular impingement", "hip arthroscopy", and "hip impingement" terms were searched on Google web search. For each search term, frequently asked questions were refreshed until a total of 84 questions and sources of answers were collected. With the observational study, the questions were separated by Rothwell's Classification System. Data mining extension (Scraper, version 1.7) was used to extract each question and its associated webpage to a database. 2 reviewers classified questions according to Rothwell's classification system (MA, SS). This classification allows the questions to be categorized and divided into headings. Questions were categorized into three groups (fact, policy, value) based on Rothwell's classification system.[10] Each group was further detailed into specific subtitles; activities, restrictions, timeline of recovery, technical details, cost, anatomy/ function, diagnosis, indications/management, risk/complications, pain, longevity, evaluation of surgery, injury comparison, and others. Websites were classified as commercial, academic, medical practice, single surgeon, personal, government, social media, and others depending on the source. JAMA benchmark criteria were used to assess the quality of websites depending on authorship, attribution, currency, and disclosure, with a score out of 4 points.[11,12] After the initial classification, discrepancies between the 2 reviewers were resolved by a third party (MA).

Statistical Analysis

All statistical analyses were performed using Microsoft Excel (Microsoft, Redmond, USA). Cohen's kappa coefficients were calculated for interobserver reliability. The K value indicates agreement among observers. Landis and Koch previously categorized K values of 0.00 to 0.20 as slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; and 0.81 or greater, almost perfect agreement. The kappa value for the interobserver reliability was=0.90 (excellent agreement) for website classification. For question analysis, a Fischer exact test for proportions was performed to compare question categories and website classifications. Statistical significance was defined as a p-value less than 0.05.

RESULTS

A total of 540 questions were generated from the initial search. After duplicate questions were removed 364 original questions were extracted and each question was categorized. The top 10 most frequently asked questions for hip arthroscopy are presented in Table 1.

Table 1. Top 10 most frequently searched questions for hip arthroscopy

What is hip arthroscopy?
What sort of conditions can be treated?
What causes these conditions?
What does 'hip arthroscopy' entail?
What is the expected recovery?
What are the success rates of surgery?
I think I have a hip problem; how should I go about getting in contact with a qualified hip surgeon?
How long does recovering from hip impingement surgery take?
What does hip impingement feel like?
What are the types of hip impingement?

Most questions were in the Fact category according to Rothwell's classification (Figure 1). The most popular question topics were activities/restrictions (17.5%), pain (16.7%), and surgical detail (14.5%).

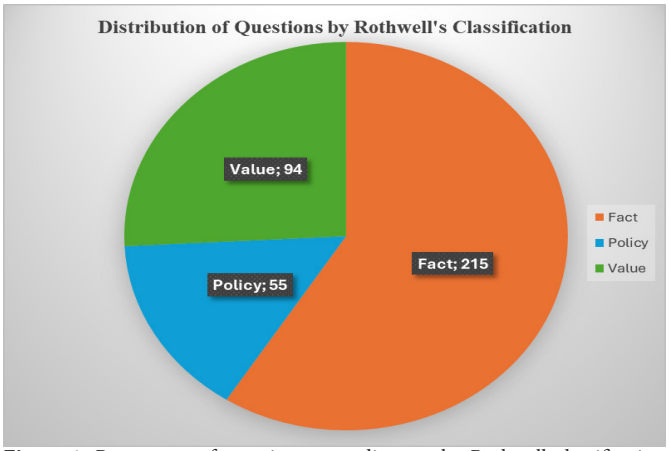

Figure 1. Percentage of questions according to the Rothwell classification under the fact, policy or value question headings in the diagram

Upon analysis of the searches, there was a notable curiosity regarding activity, pain, and surgical methods. The questions posed on various websites were classified using the Rothwell methods. Figure 2 categorizes these questions based on their content.

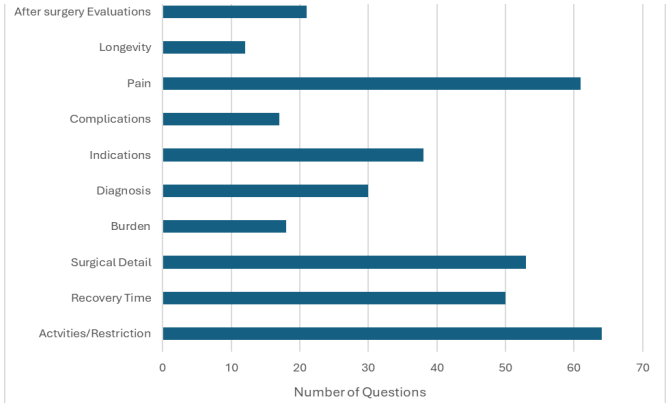

Figure 2. Relative distribution of questions by Rothwell's classification and by topic. The number of questions in each topic category

The questions are mostly in the fields of academics and medical practice. The questions were focussed primarily on academic and medical practices. Questions about physical activity, pain management, and surgical procedures were important components of the inquiries. The websites and question types were grouped in detail (Table 2).

The distribution by website source and topic showed that the two most frequently searched websites were academic (34%) and medical practice (29.4%). The distribution of website sourcesis summarized in Figure 3.

In the question topics of the website resources, the most searched topics were pain, activity, and surgical technique. These questions are detailed in Figure 4. Commercial websites were significantly more likely to be associated with questions about recovery time (21.1% of all commercial websites) and activities/restrictions (19.2% of all Commercial websites). Complications questions are more likely to be associated with Academic websites (47% of all questions). Academic websites are significantly more likely to be associated with surgical details of surgery (23.3%). Academic websites are more likely to be associated with surgical details of surgery detailed results are shown in Figure 4.

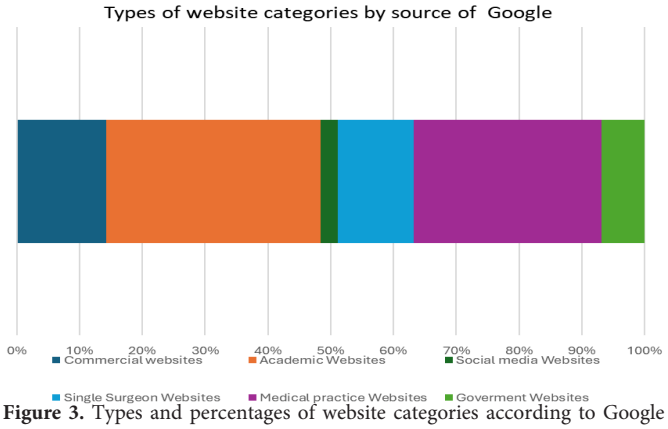

Figure 3. Types and percentages of website categories according to Google source

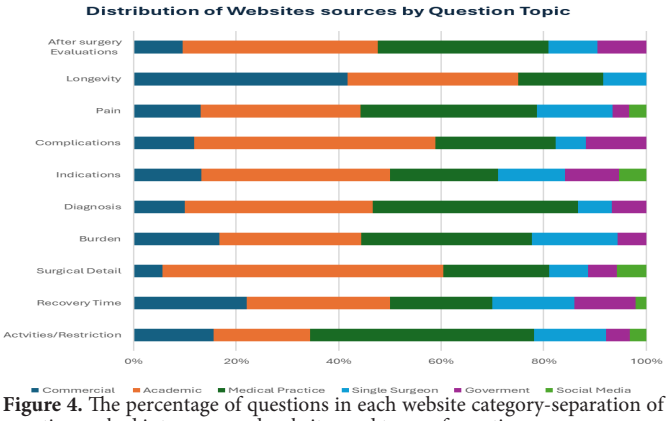

Figure 4. The percentage of questions in each website category-separation of questions asked into answered websites and types of questions

Table 2. Rothwell's classification system for frequently asked questions and sub-categorization of websites

	Commercial	Academic	Medical practice	Single surgeon	Government	Social media	Total	p-value
Fact	30	71	67	26	15	6	215	0.0214
Policy	7	22	12	6	6	2	55	0.6789
Value	15	31	30	12	4	2	94	0.1147
Total	52	124	109	44	25	10	364	-
p-value	0.3026	0.1061	0.0506	0.8755	0.8712	0.9458	-	
Activities/restriction	10	12	28	9	3	2	64	0.0412
Recovery time	11	14	10	8	6	1	50	0.0023
Surgical detail	3	29	11	4	3	3	53	0.3287
Burden	3	5	6	3	1	0	18	0.8912
Diagnosis	3	11	12	2	2	0	30	0.1576
Indications	5	14	8	5	4	2	38	0.7801
Complications	2	8	4	1	2	0	17	0.4456
Pain	8	19	21	9	2	2	61	0.0098
Longevity	5	4	2	1	0	0	12	0.6214
After surgery evaluations	2	8	7	2	2	0	21	0.0034
Total	52	124	109	44	25	10	64	-
p-value	0.0239	<.001	<.001	0.0127	N/A	N/A		

The average JAMA score for the different website categories was 2.516 (Table 3). Commercial and Academic websites had the highest JAMA scores (2.9 and 2.7 respectively). Websites were scored according to JAMA criteria. The commercial website received the highest score (2.9). Even though we think that it is the patient who asks the questions, some of these questions may have been asked by the assistant or specialist doctors to get quick information. However, websites associated with medical practice and single surgeons had the lowest JAMA scores (2.16 and 2.22 respectively).

Table 3. Distribution of website categories for hip arthroscopy with JAMA Benchmark Score

Website classification distributions	JAMA Score	n (%)
Academic websites	2.7	124 (34.06)
Medical practice websites	2.16	109 (29.94)
Commercial websites	2.9	52 (14.28)
Single surgeon websites	2.22	44 (12.08)
Government websites	2.42	25 (6.86)
Social media websites	2.68	10 (2.74)
Total websites	2.516	364 (100)

DISCUSSION

The important finding of this study is that hip impingement patients obtain information about their disease by asking questions such as activity and limitations, pain, surgical techniques, cost, and return to work on the search engine. Here, the surgeon informing the patient by considering these questions and providing postoperative education will ensure that the patient is safe. It was discovered to include going to the toilet, playing sports, driving, and starting to walk after undergoing hip impingement repair. Interestingly, the most frequently used sources for this information were medical practice websites and social media.

It is important in the treatment of hip impingement repair to know what questions patients ask. This knowledge enables doctors to have an idea of patients' concerns, allowing them to discuss the treatment stages and possible complications in detail. This approach facilitates patient-centered care, leading to better outcomes for patients. Patients follow various websites on the internet about hip impingement syndrome. Academic, commercial, surgeon's private website, websites of the Ministry of Health, etc. are followed.[13-15] Burrus colleagues found that most patients (82.3%) used Google to research their orthopedic conditions, followed by 49.9% using WebMD, and 33.7% the institution's orthopedic website.[16] Similarly, fraval and colleagues reported that 78.2% of patients found their best sources for information about their conditions, including facts, anatomy, techniques, and surgeries through search engines. The availability of online information is increasing patients' access to knowledge about their illnesses.[17] This study examines Google search engine analyses to identify the most frequently asked questions and sources used by hip impingement patients for obtaining information about their condition including facts, anatomy, techniques, and surgeries among others.

Rehabilitation programs after hip impingement repair have been extensively evaluated in the literature.[18-20] Although immobilization and protection with immobilization are important and repair prescriptions are still new, progressive and accelerative physical therapy programs have recently been developed that are thought to reduce pain and stiffness and improve outcomes.[21] However, it has become clearer that no single repair method can be applied to hip impingement repairs, as the morphology and extent of the repair have shown that it will lead to failure if not progressed with the appropriate rehabilitation protocol. Therefore, although social media is a quick and easily accessible platform with an abundance of information about activity after hip impingement repair, patients may not have the necessary knowledge to interpret this information in the context of their clinical picture. Since patients will be hospitalized for a certain period after hip impingement repair surgery, there is plenty of opportunity to ask questions during this time.[22] Misinterpretation and misapplication of this information by patients can lead to unwanted injuries and recurrent hip pain. It is therefore crucial that orthopaedic surgeons take ownership of the information that patients inevitably seek online and on social media, in an understandable format and at an appropriate literacy level. Patients also benefit if orthopaedic surgeons have informative and guiding qualities.

Physiotherapy and rehabilitation in the clinic after FAI surgery can accelerate recovery and alleviate hip pain for certain patients. Additionally, it can enhance the patient's overall well-being by fostering psychological stability.[23] Pain was the second most common question, accounting for 16.7% of all questions asked in this study. This is not surprising as pain is essential for patient satisfaction and is an integral part of postoperative rehabilitation. Musnch et al.[24] published a study in which opioid use reduced pain with sports procedures. Although the expectation of experiencing postoperative pain may cause anxiety about the procedure, orthopaedic surgeons should counsel patients about the pain management strategy they intend to use and its effectiveness. The success of regional nerve blocks, cryotherapy alternative nonopioid protocols, and multidisciplinary treatment have been shown to positively affect the patient's physical therapy and rehabilitation by providing postoperative pain control.[25,26] This study shows that patients search for pain management strategies on the internet, which comes from their desire to find what works best for them without being bound by protocols. There is also evidence that these protocols are inadequate. Pain may occur following FAI treatment. For optimal outcomes, it is advisable to seek guidance and counseling on pain management from an orthopedic surgeon.

Questions regarding the indications for hip impingement are in a common category. Causes of impingement include the abnormal structure of the femur or acetabulum, chronicity of impingement syndrome, athletics, age, strength, and function.[27,28] The decision to repair hip impingement requires an expert orthopaedic surgeon who can comprehensively evaluate the clinical picture including but not limited to patient age, activity level, social factors, comorbidities, degree of labrum tear, progression of the tear, the severity of pain,

location of the glass or pincer, and etiology of the injury.[29,30] This study highlights that, although patients can Google whether or not to undergo surgery, it requires a comprehensive approach that includes a shared decision-making model with the patient to give a patient an indication for FAI treatment and surgery.

Limitations

There are some limitations to this study. One of them is that an individual's search history may lead to different websites when searching for websites related to our research. Therefore, the data used was extracted using a cleanly loaded web browser. Another limitation is that in cases where scaffold and matrix biomaterials are developed for hip impingement, arthroscopic techniques such as muscle tissue, labrum, and capsule repair are developed, question topics will change on web pages. Additionally, there is the possibility of overlap when categorizing questions according to specific topics. Specific topics have been chosen to define the types of questions asked; however, this limitation is still an important aspect to be recognized.

CONCLUSION

This study has the most frequently asked questions by patients regarding FAI surgery. The topics that patients were most curious about were postoperative activities, pain management, and surgical indications. The most frequently visited sites were academic and medical practice content, with JAMA scores of moderate qualities. These results suggest that more emphasis should be placed on patient education to meet patients' information needs. A guide called frequently asked questions can be created for orthopedic surgeons to advise patients. Patients can easily access the answers to these questions on the website.

ETHICAL DECLARATIONS

Ethics Committee Approval

Institutional ethics committee approval was not required for this review article.

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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Evaluation of clinical outcomes with the modified nutritional risk score in critically ill patients

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ABSTRACT

Aims: Our aim in this study was to evaluate the effectiveness of the modified nutrition risk score (mNUTRIC) score in predicting clinical outcomes and mortality in patients admitted to intensive care units (ICUs).

Methods: This study was designed as a prospective observational cohort study. It was conducted in patients admitted to the Anesthesiology and Reanimation ICUs of Pamukkale University Hospital. The primary outcome measure of this study was the comparison of mNUTRIC scores at days 2, 7, and 12 between survivors and non-survivors. Secondary outcome measures included the effectiveness of predicting the necessity for invasive mechanical ventilation (IMV), hemodialysis, and vasopressor or inotropic support. Additionally, the study examined the impact of nutritional adequacy (categorized as hypocaloric or hypercaloric) and protein intake levels (classified as low, medium and high) on mortality among patients. Student's T test or Mann-Whitney U test was used for comparisons involving continuous variables, and the Chi-square test was used for categorical variables.

Results: The mNUTRIC scores of 176 patients who participated in the study were meticulously assessed. In this context, mNUTRIC scores were computed for the entirety of the patient cohort (n=176) on the second day for 91 patients on the seventh day, and for forty-six patients on the twelfth day on the second day the APACHE II, SOFA, and mNUTRIC scores exhibited significantly elevated values in patients who succumbed to their conditions (22.60±7.94, 6.81±3.03, and 5.00±2.03) in contrast to those who survived (16.99±5.05, 3.94±2.26, and 3.32±1.48, all $p<0.001$). On the seventh day these scores persisted at heightened levels in deceased patients (24.38±7.07, 6.82±3.52, and 5.00±1.61) relative to survivors (18.06±4.70, 3.85±2.10, and 3.50±1.58, all $p<0.001$). On the twelfth day the APACHE II, SOFA, and mNUTRIC scores recorded were 25.61±7.18, 7.00±3.57, and 5.52±1.81 for patients who did not survive, whereas survivors had scores of 18.70±5.88, 4.39±1.75, and 3.39±2.02 ($p=0.001$, $p=0.008$, $p<0.001$, respectively).

Conclusion: Statistically significant differences were observed in the APACHE II, SOFA, and mNUTRIC scores on days 2, 7, and 12 between surviving and deceased patients. However, it was observed that nutritional adequacy and protein intake were not determinants that directly affected the mortality risk in critically ill patients with high mNUTRIC scores.

Keywords: mNUTRIC, intensive care unit, mortality, morbidity, scoring system

INTRODUCTION

Nutritional deficiencies are common in critically ill patients in intensive care units (ICUs). Malnutrition rates range from 39% to 50%. This difference in the malnutrition rates of patients is influenced by patient demographics and screening methodologies used for evaluation.[1] Even patients with good nutritional status prior to intensive care unit (ICU) admission can experience significant declines in their nutrition during their stay in the intensive care unit. The acute phase response seen in critical illnesses triggers catabolism and a series of reactions, leading to a hypermetabolic state, which can initiate malnutrition or exacerbate an existing condition, thereby increasing mortality. This effect is particularly pronounced in elderly patients.[2] Research indicates that malnutrition is associated with accelerated protein loss, muscle mass reduction, sarcopenia, frailty, inadequate protein intake, and nutritional imbalances.[3] Research in the literature states that malnutrition increases health care costs and prolongs hospital stays. They also revealed that it also caused an increase in complication and mortality rates. Consequently, the prompt recognition and appropriate execution of nutritional risk management strategies among patients in the ICU is imperative for enhancing patient outcomes.[4]

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Critical care scoring systems are instrumental in assessing the severity of illness and in determining the risk of mortality. Such systems are routinely employed to facilitate clinical decision-making processes within the intensive care setting.[5,6] The acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scoring systems are frequently utilized in intensive care unit (ICU) populations to assess the severity of illness and to project potential mortality risk.[6,7] The APACHE II scoring system is a comprehensive evaluation tool that examines critical physiological indicators including but not limited to temperature, heart rate, respiratory rate, blood pressure, and arterial pH levels. In the computation of the aggregate score, it additionally considers the patient's age and pre-existing health conditions.[8,9] The SOFA score systematically assesses 6 organ systems, which include respiratory, coagulation, hepatic, cardiovascular, central nervous system, and renal functions. This evaluation is contingent upon distinct clinical and laboratory metrics. It is utilized to quantify the severity of organ dysfunction and to prognosticate disease outcomes, especially among individuals diagnosed with sepsis.[10,11] These evaluative frameworks, commonly employed within critical care settings, are integral in the determination of disease severity and the assessment of organ impairment. Nevertheless, these frameworks inadequately address the nutritional status of the patient population. Therefore, alternative methodologies are imperative to comprehensively assess nutritional vulnerabilities. In order to mitigate this constraint, Heyland and his research team developed the nutritional risk score (NUTRIC) specifically designed for patients in critical condition. NUTRIC integrates pre-hospitalization nutritional status, inflammation markers (such as interleukin-6 and the number of comorbidities), and disease severity scores. With this method, the assessment of nutritional risk in critically patients was provided.[12] The use of interleukin-6 (IL-6), which is not routinely measured in many ICU, is a disadvantage of the NUTRIC score. For this reason, Heyland and his team proposed that IL-6 should be excluded from the calculation when it is not present, and they called the calculation of this score the modified NUTRIC score (mNUTRIC). The metric score has been shown to be useful for clinical use in several studies.[13,14]

Our aim in this study was to evaluate the effectiveness of the mNUTRIC score in predicting clinical outcomes and mortality in patients admitted to intensive care. Our hypothesis, it is considered that the mNUTRIC measured will be as effective a tool for predicting clinical outcomes as the APACHE II and SOFA scores commonly used in the clinic.

METHODS

This study was planned as a prospective observational cohort study in patients admitted to the Anesthesiology and Reanimation ICU of Pamukkale University Hospital. Ethical approval was obtained from the Pamukkale University Non-interventional Clinical Researches Ethics Committee (Date: 29.09.2023, Decision No: 426637). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

All patients over 18 years of age who were admitted to critical care units and agreed to take part in the research were included. Exclusion criteria were as follows: patients who were discharged from the ICU within 48 hours or exitus, trauma patients, postoperative patients, patients admitted to the ICU due to intoxication or suicide, patients who were taken over after being followed up in other ICU, patients with recurrent ICU admissions, and patients who refused to take part in the study.

The patients were followed up for 28 days after being admitted to the ICU. During this period, vital parameters (mean arterial pressure, body temperature, heart rate, oxygenation status, respiratory rate) and biochemical values (arterial blood pH, PaO_2, venous blood bicarbonate, sodium, potassium, creatinine, leukocyte, hematocrit, platelet, bilirubin) were documented and APACHE II and SOFA scores were calculated. Albumin, total protein, CRP and PRC values were also recorded to assess nutritional status.

Body-mass index (BMI) was calculated by recording demographic information (age, gender), ICU hospitalization diagnosis, comorbidities, height and body weight of the patients. In addition, glasgow coma scores (GCS) were assessed at admission and patients were scored between 3-15 points according to eye opening, motor response and verbal response. In this score low values indicate high neurologic deficit; 15-14 points indicate mild, 13-9 points moderate and 8-3 points severe damage.[15]

When determining the acute physiology score in APACHE II scoring, the parameters measured within the first 24 hours after admission to the ICU are used. In subsequent measurements, the worst value in the last 24 hours is taken as basis. Chronic health status is scored between 0-5, taking into consideration the patient's health status in the last six months. Physiological variables include mean arterial pressure, body temperature, heart rate, partial arterial oxygen pressure (PaO_2), respiratory rate, arterial blood pH and bicarbonate, sodium, potassium, serum creatinine, leukocytes, hematocrit and blood glucose level. These variables are scored between 0-4. In addition, the patient's age is included in the assessment by scoring between 0-6. GCS is added to these variables and the total APACHE II score is calculated as a maximum of 71.[16]

Originally developed to assess sepsis-related organ dysfunction, the SOFA score has been validated over time for use in non-septic patient populations. The SOFA includes six variables assessing respiratory, coagulation, hepatic, cardiovascular, renal and neurologic systems. Each variable is scored between 0 and 4, with a maximum total score of 24.[17]

During the follow-up of the patients, their needs for intensive care support treatments were recorded. Treatments such as hemodialysis, vasopressor/inotrope support, invasive mechanical ventilation (IMV) support and the number of days these treatments were applied were tracked. In addition, the duration of the patients' stay in ICU and post- ICU outcomes (deceased/living) were documented.

The mNUTRIC scores of the patients were calculated based on age, comorbidities, length of hospital stay before ICU admission, APACHE II score, and SOFA score. A score of 0-2

was given for age (0 points for individuals under 50 years, 1 point for those between 50 and 75 years, and 2 points for those aged 75 and above). 0-1 for number of comorbidities, 0-1 for time spent in hospital before ICU admission, 0-3 for APACHE II score and 0-2 for SOFA score. The mNUTRIC score was obtained with the sum of these scores. mNUTRIC score was evaluated on the 2nd, 7th and 12th days of ICU hospitalization. Score between 0-4 points was considered as a low mNUTRIC score. Whereas a score between 5-9 points was considered as a high mNUTRIC score and indicated a high risk of malnutrition, worse clinical outcomes.[12]

Nutritional support to be administered to patients was calculated according to the intensive care clinical nutrition guideline updated by ESPEN in 2023.[18]

Every patient admitted to the intensive care unit was considered at risk of malnutrition. When the digestive system was functional, oral and enteral nutrition were initiated as the first options. For patients in whom enteral feeding was not possible, parenteral nutrition was started within the first 48 hours. Calorie requirement was determined as 25 kcal/kg/day based on actual body weight in patients with BMI <25 kg/m² and ideal body weight in patients with BMI >25 kg/m². Protein intake was planned as 1.3 g/kg/day. Nutritional support was applied unchanged by the study team. Nutritional adequacy was calculated as the ratio of total calories taken to total calories prescribed (nutritional adequacy = calories taken / calories prescribed). Accordingly, patients were classified as hypocaloric (<80% nutritional adequacy) and hypercaloric (>80% nutritional adequacy). Furthermore, protein intake was categorized as low (below 1.2 g/kg/day), median (between 1.2 and 1.5 g/kg/day), and high (above 1.5 g/kg/day).

The primary outcome measure of this study was the comparison of mNUTRIC scores at days 2, 7, and 12 between survivors and non-survivors. Secondary outcome measures included the effectiveness of the mNUTRIC score in predicting the necessity for IMV, hemodialysis, and vasopressor or inotropic support. Additionally, the study examined the impact of nutritional adequacy (categorized as hypocaloric or hypercaloric) and protein intake levels (classified as low or high) on mortality among patients with elevated mNUTRIC scores.

Statistical Analysis

The research data were analyzed using the SPSS version 21.0 statistical software. Descriptive statistics were reported using frequency (n), percentage (%), mean, standard deviation (SD), median, and the minimum and maximum values. The Chi-square test was employed to assess differences between categorical variables. In the comparison of continuous variables in independent groups, student's T test and Mann-Whitney U test were used if they did not comply with parametric assumptions. p values less than 0.05 were considered significant. Sensitivity and specificity analyses were performed to evaluate whether a variable had diagnostic or exclusionary properties.

RESULTS

The 616 patients were enrolled in the study; however, 440 patients were excluded based on predetermined exclusion criteria. The reasons for exclusion included: 281 patients who were undergoing postoperative follow-up, 79 patients admitted to the ICU as a result of traffic accidents, 10 patients treated for poisoning or suicide attempts, 52 patients who were either discharged or deceased within the first 48 hours of admission to the ICU, 8 patients transferred from other ICU and 10 patients who declined to provide informed consent.

The mNUTRIC scores of of 176 patients included in the study were evaluated. In this context, mNUTRIC scores were calculated for all patients (n=176) On the second day 91 patients, on the seventh day and 46 patients on the twelfth day (**Figure 1**).

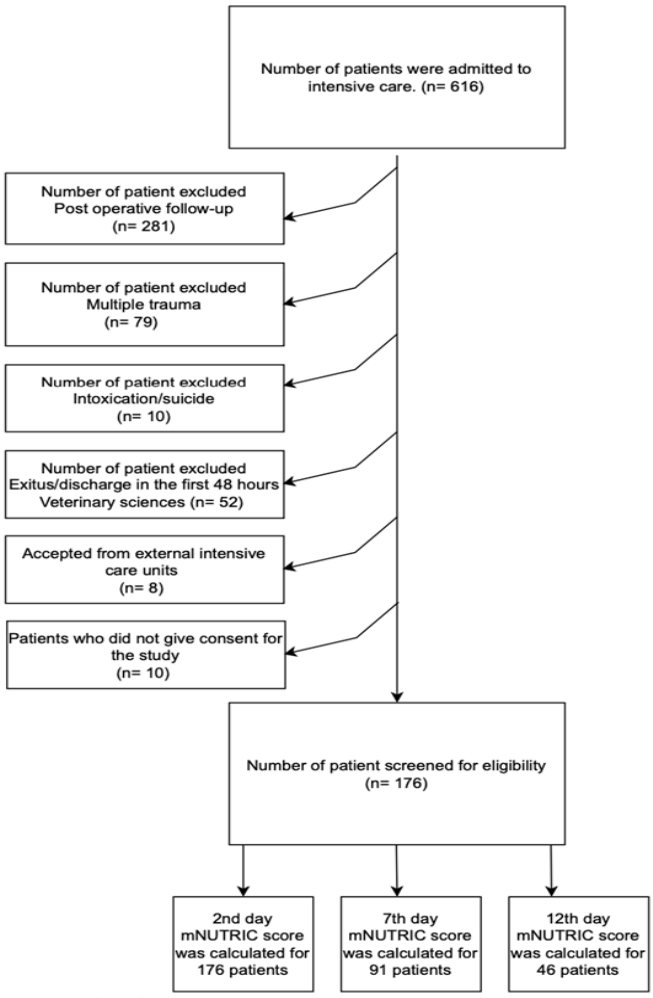

Figure 1. Flow chart

Demographic and hospitalization characteristics of patients in the ICU were evaluated (**Table 1**). A total of 176 patients participated in the study, comprising 95 males (54.0%) and 81 females (46.0%) (p=0.475). The age of the patients was mean 68.34±14.04 years, and the BMI was 27.38±7.57 kg/m². Among the patients, 3.4% (n=6) had no comorbidities, 29.5% (n=52) had one comorbidity, and 67.0% (n=118) had two or more comorbidities (p<0.001).

Table 1. Demographic data and intensive care unit hospitalization characteristics of patients		
Variables		**n (%)**
Gender	Male	95 (54.0)
	Female	81 (46.0)
Number of comorbidities	0	6 (3.4)
	1	52 (29.5)
	2 or more	118 (67.0)
ICU hospitalization	Respiratory	99 (56.3)
	Cardiovascular	10 (5.7)
	Gastrointestinal	8 (4.5)
	Urogenital	9 (5.1)
	Endocrine	3 (1.7)
	Neurological	9 (5.1)
	Malignancy	12 (6.8)
	Hematological	0 (.0)
	Sepsis	26 (14.8)
Hemodialysis	Treatment	51 (29.0)
	Not treatment	125 (71.0)
Vasopressor inotropes	Treatment	94(53,4)
	Not treatment	82(46,6)
ICU status	Died	77 (43.8)
	Living	99 (56.3)
		Median±SD
Age		68.34±14.04
Length (m)		1.66±.08
Body weight (kg)		75.26±20.62
BMI		27.38±7.57
Number of days ICU		10.46±8.13
Number of days IMV		3.89±7.93

ICU: Intensive care unit, BMI: Body-mass index, IMV: Invasive mechanical ventilation

The most prevalent diagnosis leading to ICU admission was respiratory system diseases, accounting for 56.3% (n=99) of cases, followed by sepsis (14.8%, n=26), malignancy (6.8%, n=12), and cardiovascular system diseases (5.7%, n=10) (p<0.001). Gastrointestinal (4.5%, n=8), urogenital (5.1%, n=9), endocrine (1.7%, n=3), and neurological diseases (5.1%, n=9) were less common reasons for admission, while no patients were admitted due to hematological conditions.

When the need for intensive care support therapies was analyzed, 29.0% (n=51) of the patients received hemodialysis treatment, while 71.0% (n=125) did not (p=0.002). Additionally, 53.4% (n=94) of the patients received vasopressor/inotrope support, whereas 46.6% (n=82) did not (p<0.001). The number of days spent under IMV support was 3.89±7.93 days (p=0.015).

When the status of the patients after intensive care was analyzed, it was observed that 43.8% (n=77) of the patients died, while 56.3% (n=99) survived (p=0.029). The total duration of ICU stay was 10.46±8.13 days.

The scores of the scoring systems were evaluated in living and deceased patients. On the second day, the APACHE II score was 22.60±7.94 in deceased patients and 16.99±5.05 in living patients (p<0.001), the SOFA score was 6.81±3.03 in deceased patients and 3.94±2.26 in living patients (p<0.001), and the mNUTRIC score was 5.00±2.03 in deceased patients and 3.32±1.48 in living patients (p<0.001). On the seventh day the APACHE II score was 24.38±7.07 in deceased patients and 18.06±4.70 in living patients (p<0.001), the SOFA score was 6.82±3.52 in deceased patients and 3.85±2.10 in living patients (p<0.001), and the mNUTRIC score was 5.00±1.61 in deceased patients and 3.50±1.58 in living patients (p<0.001). On the twelfth day the APACHE II score was 25.61±7.18 in deceased patients and 18.70±5.88 in living patients (p=0.001), the SOFA score was 7.00±3.57 in deceased patients and 4.39±1.75 in living patients (p=0.008) and the mNUTRIC score was 5.52±1.81 in deceased patients and 3.3 9±2.02 for living patients (p<0.001) (Table 2).

Table 2. Comparison of intensive care scoring scores of deceased and living patients			
	Died (n=77)	**Living (n=99)**	**p**
APACHE 2 2nd day	22.60±7.94	16.99±5.05	<0.001
SOFA 2nd day	6.81±3.03	3.94±2.26	<0.001
mNUTRIC 2nd day	5.00±2.03	3.32±1.48	<0.001
APACHE 2 7th day	24.38±7.07	18.06±4.70	<0.001*
SOFA 7th day	6.82±3.52	3.85±2.10	<0.001
mNUTRIC 7th day	5.00±1.61	3.50±1.58	<0.001
APACHE 2 12th day	25.61±7.18	18.70±5.88	0.001
SOFA 12th day	7.00±3.57	4.39±1.75	0.008
mNUTRIC 12th day	5.52±1.81	3.39±2.02	<0.001*

APACHE II: Acute physiology and chronic health evaluation II, SOFA: Sequential organ failure assessment, mNUTRIC: Modified nutrition risk score

ROC analysis was employed to assess the impact of mNUTRIC scores in forecasting mortality on days 2, 7, and 12 (Figure 2). Based on the analysis, the cut-off value was determined as 4.5 for the three time points. On the second day mNUTRIC score showed a predictive value for mortality with 60.9% sensitivity and 65.2% specificity (AUC=0.716; 95% CI: 0.564-0.867; p=0.012 On the seventh day the score showed 69.6% sensitivity and 60.9% specificity (AUC=0.673; 95% CI: 0.517-0.828; p=0.044). On the twelfth day the predictive power was found at 73.9% sensitivity and 60.9% specificity (AUC=0.770; 95% CI: 0.636-0.905; p=0.002).

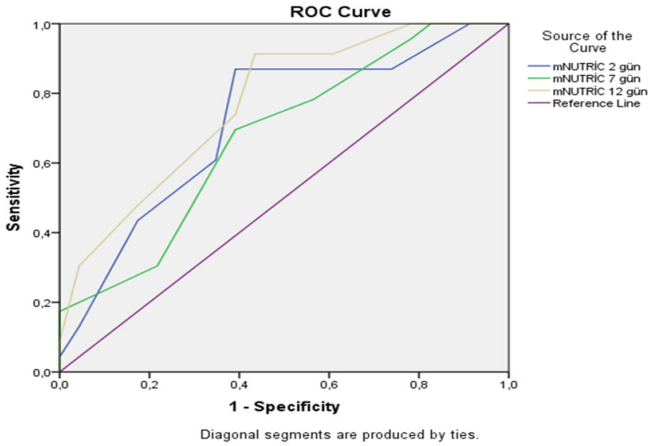

Figure 2. ROC analysis: power of mNUTRIC scores to predict mortality

ROC: Receiver operating characteristic, mNUTRIC: Modified nutrition risk score

The predictive values of mNUTRIC scores in predicting the need for hemodialysis, vasopressor/inotrope support and IMV support were compared (Table 3). In predicting the need for hemodialysis support, the mNUTRIC scores demonstrated the following performance metrics: the sensitivity of the mNUTRIC score On the second day was 66.7% with a specificity of 73.6% (p<0.001); On the seventh day the sensitivity was 69.0% and the specificity was 66.1% (p=0.002); and on the twelfth day the sensitivity increased to 77.8% while the specificity decreased to 57.1% (p=0.020).

Regarding the prediction of vasopressor or inotropic support, the mNUTRIC score exhibited a sensitivity of 52.1% and a specificity of 78.0% On the second day (p<0.001); On the seventh day the sensitivity was 59.3% with a specificity of 75.7% (p=0.001); and on the twelfth day the sensitivity rose to 67.7% while the specificity was reported at 66.7% (p=0.027).

In predicting the need for IMV support, the sensitivity of the mNUTRIC score on the second day was 55.3% with a specificity of 78.0% (p<0.001); On the seventh day the sensitivity increased to 64.4% with a specificity of 73.9% (p<0.001); and on the twelfth day the sensitivity was 67.7% while the specificity was 66.7% (p=0.027).

In our study, we evaluated the relationship between nutritional adequacy and mortality among patients with elevated mNUTRIC scores (Table 4). The analysis revealed no statistically significant association between nutritional adequacy and mortality in this patient population with high mNUTRIC scores. On the second day among patients with elevated mNUTRIC scores, 76.2% of those who received hypocaloric nutrition and 80.0% of those who received hypercaloric nutrition died (p=1.000). On the seventh day the mortality rate was 73.7% in patients with hypocaloric nutrition and 75.0% in those with hypercaloric nutrition (p=1.000). On the twelfth day the mortality rate was 63.6% in patients with hypocaloric nutrition and 62.5% in those with hypercaloric nutrition (p=1.000).

Table 4. The relationship between nutritional adequacy and mortality in patients with elevated mNUTRIC score

			ICU status				
			Died		Living		
			n	%	n	%	p
mNUTRIC 2nd day	Nutritional adequacy	Hypocaloric	16	76.2	5	23.8	1.000
		Hypercaloric	12	80.0	3	20.0	
mNUTRIC 7th day	Nutritional adequacy	Hypocaloric	14	73.7	5	26.3	1.000
		Hypercaloric	6	75.0	2	25.0	
mNUTRIC 12th day	Nutritional adequacy	Hypocaloric	7	63.6	4	36.4	1.000
		Hypercaloric	5	62.5	3	37.5	

mNUTRIC: Modified nutrition risk score, ICU: Intensive care unit

The relationship between protein intake and mortality among patients with elevated mNUTRIC scores was assessed (Table 5). The analysis indicated that there was no statistically significant association between protein intake and mortality in this cohort of patients with high mNUTRIC scores.

For mNUTRIC score of 2: Among patients with low protein intake, 24 (80.0%) died and 6 (20.0%) survived. In the

Table 3. Predictive values of mNUTRIC scores in predicting the need for hemodialysis, vasopressors/inotropes and IMV support

Hemodialysis		Received treatmentn (%)	Did not receive treatment n (%)	OR	Sensitivity (%)	Specificity (%)	p
mNUTRIC 2nd day	Low	17 (15.6)	92 (84.4)	5.576 (2.755-11.285)	66.7	73.6	<0.001
	High	34 (50.7)	33 (49.3)				
mNUTRIC 7th day	Low	9 (18.0)	41 (82.0)	4.339 (1.684-11.177)	69.0	66.1	0.002
	High	20 (48.8)	21 (51.2)				
mNUTRIC 12th day	Low	4 (20.0)	16 (80.0)	4.667 (1.222-17818)	77.8	57.1	0.020
	High	14 (53.8)	12 (46.2)				
Vasopressor inotrope				**OR**	**Sensitivity**	**OR**	**p**
mNUTRIC 2nd day	Low	45(41.3)	64(58.7)	3.872 (1.999-7.500)	52.1	78.0	<0.001
	High	49(73.1)	18(26.9)				
mNUTRIC 7th day	Low	22(44.0)	28(56.0)	4.525 (1.791-11.431)	59.3	75.7	0.001
	High	32(78.0)	9(22.0)				
mNUTRIC 12th day	Low	10 (50.0)	10(50.0)	4.200 (1.132-15.586)	67.7	66.7	0.027
	High	21(80.8)	5(19.2)				
IMV				**OR**	**Sensitivity**	**OR**	**p**
mNUTRIC 2nd day	Low	38 (34.9)	71(65.1)	4.391 (2.281-8.453)	55.3	78.0	<0.001
	High	47(70.1)	20(29.9)				
mNUTRIC 7th day	Low	16(32.0)	34(68.0)	5.135 (2.093-12.601)	64.4	73.9	<0.001
	High	29 (70.7)	12(29.3)				
mNUTRIC 12th day	Low	10(50.0)	10 (50.0)	4.200 (1.132-15.586)	67.7	66.7	0.027
	High	21 (80.8)	5(19.2)				

mNUTRIC: Modified nutrition risk score, IMV: Invasive mechanical ventilation

Table 5. The relationship between protein intake and mortality in patients with a high mNUTRIC score

			Post-ICU status				
			Died		Living		
			n	%	n	%	p
mNUTRIC 2	Amount of protein taken	Low	24	80.0	6	20.0	0.773
		Medium	2	66.7	1	33.3	
		High	2	66.7	1	33.3	
mNUTRIC 7	Amount of protein taken	Low	19	76	6	24	0.196
		Medium	0	0	1	100	
		High	1	100	0	0	
mNUTRIC 12	Amount of protein taken	Low	11	68.8	5	31.3	0.121
		Medium	0	0	2	100	
		High	12	63.2	7	36.8	

mNUTRIC: Modified nutrition risk score, ICU: Intensive care unit

medium protein intake group, 2 patients (66.7%) died and 1 (33.3%) survived. Similarly, in the high protein intake group, 2 patients (66.7%) died and 1 (33.3%) survived (p=0.773).

For mNUTRIC score of 7: In the low protein intake group, 19 patients (76.0%) died and 6 (24.0%) survived. The medium group saw 1 patient (100%) survive, while in the high group, 1 patient (100%) died (p=0.196).

For mNUTRIC score of 12: The low protein intake group had 11 patients (68.8%) who died and 5 (31.3%) who survived. In the medium group, all 2 patients (100%) survived. In the high protein intake group, 12 patients (63.2%) died and 7 (36.8%) survived (p=0.121).

These findings indicate varied mortality rates across different protein intake levels, with no statistically significant associations.

DISCUSSION

In this study, we evaluated clinical outcomes using the mNUTRIC score in critically ill patients. APACHE II, SOFA, and mNUTRIC mNUTRIC scores on days 2, 7, and 12 were significantly higher in deceased patients. ROC analysis results revealed that mNUTRIC scores had significant predictive value in predicting mortality, especially on the 12th day. Furthermore, this scoring system was effective in predicting the need for IMV, hemodialysis, and vasopressor or inotropic support. The mNUTRIC score has been validated as a reliable method for assessing the risk of mortality in critically ill patients and for predicting the requirement for intensive care support. However, it has been determined that nutritional adequacy and protein intake are not factors that directly determine the mortality risk in patients with a high mNUTRIC score.

When Kumar and others compared mNUTRIC, APACHE II, and SOFA scores, they found similar results in predicting mortality and intensive care prognosis. However, it has been stated that the NUTRIC score is superior to others due to its potential to improve nutritional competence and clinical outcomes.[19] Hai and colleagues noted that the mNUTRIC score shows similar results with other scores in sepsis patients and can be described as an independent predictor of sepsis.[20] In studies aimed at determining the optimal time to apply the metric score, Park et al.[1] 2. and 7. they compared the day's scores. 7. they found that the day mNUTRIC score performed better at predicting the 28-day mortality rate. In our study, patients 2., 7. and 12. according to the day data, mNUTRIC, APACHE II and SOFA scores were calculated, and all scores were found to be significant in predicting mortality. In addition, it was seen that these scores of deceased patients showed higher values. These results support that the mNUTRIC score is an important tool both in clinical evaluation and prognosis prediction.

In our study, the intensive care mortality rate was determined as 43.8% in patients. According to the results of the ROC analysis, the cut-off value of the NUTRIC score was calculated as 4.5 and rounded to 5 in accordance with the original study. In our study, the 12th day NUTRIC score was found to have the highest sensitivity in predicting mortality. However, all mNUTRIC scores were found to be significant in assessing mortality. In the literature, it is seen that the recommended cut-off values for the mNUTRIC score vary depending on patient outcome. For example, in one study with a mean age of 55.7, the cut-off value was determined as 4, while in another study with a mortality rate of 19%, the cut-off value was determined as 6.[19,21]

It is thought that these differences may be related to changes in patient average ages and mortality rates.

In our study, no statistically significant differences were observed between deceased and surviving patients concerning age, gender, height, body weight, BMI, number of comorbidities, and the diagnosis leading to ICU admission. Similarly, a study conducted by Mukhopadhyay et al.[22] in Singapore reported no significant differences in the mNUTRIC score relative to age, gender, BMI, and concomitant diseases. Although demographic characteristics and dietary habits may vary, both studies yielded comparable results.

Wang et al.'s[23] study on the mNUTRIC score has shown that patients at nutritional risk have a longer hospital stay, frequent use of mechanical ventilation, a high risk of acute renal failure, and a significant increase in 28-day mortality. Verma and colleagues found that the mNUTRIC score was associated with the stage of disease and the need for hemodialysis in patients with chronic renal failure.[24] In our study, it was observed that 51 out of 176 patients required hemodialysis and this requirement was higher in deceased patients. The predictive values of mNUTRIC scores in predicting the need for hemodialysis were determined to be the highest sensitivity in the 12th day score. Furthermore, it was determined that all mNUTRIC scores served as statistically significant indicators of the requirement for hemodialysis.

In a forward-looking investigation undertaken by Mahmoodpoor et al.[25] In Iran, the mNUTRIC score emerged as a robust indicator of mortality within the Intensive Care Unit (ICU) and the necessity for vasopressor intervention. Moreover, a heightened mNUTRIC score demonstrated a

statistically significant association with the utilization of vasopressors extending beyond a duration of three days. In the course of our investigation, it was noted that 94 individuals out of a cohort of 176 necessitated the administration of vasopressors or inotropes, with this requirement being markedly more prevalent among patients who succumbed. Upon conducting an analysis of the predictive values of mNUTRIC scores concerning the requisites for vasopressor and inotrope administration, it was determined that the greatest sensitivity corresponded with the score obtained on the 12th day. Furthermore, it was determined that all mNUTRIC scores served as substantial predictors of the necessity for vasopressor and inotrope administration.

The research conducted by Mendes et al.[26] in Portugal demonstrated that an elevated mNUTRIC score was associated with an extended duration of stay in the intensive care unit, a lengthened period of mechanical ventilation, and an increased incidence of mortality within a 28-day timeframe. In a comparative analysis executed by De Vries et al.,[27] the mNUTRIC scoring system demonstrated superior efficacy in forecasting 28-day mortality; nevertheless, a definitive correlation was not established between the mNUTRIC score and the length of mechanical ventilation. In our study, 85 out of 176 patients required IMV, and the duration of IMV was significantly greater among those who died. Additionally, it was determined that mNUTRIC scores provided sufficient predictive value for the need for IMV, with the highest sensitivity observed in the score recorded on the twelfth day. The fact that all patients in the study by de Vries et al.[27] were under IMV may have limited their ability to evaluate this relationship comprehensively.

In the literature, no significant relationship has been established between nutritional adequacy and mortality in patients with low mNUTRIC scores. However, Chourdakis et al.[28] reported that nutritional support may enhance clinical outcomes in patients with low mNUTRIC scores. In our study, patients were categorized based on calorie and protein intake into hypocaloric/hypercaloric and mNUTRIC 2 Amount of protein taken as low, medium, and high protein supplementation groups.

Nevertheless, no statistically significant differences were found between deceased and surviving patients regarding these parameters. Within our ICU, nutritional adequacy was calculated at 74.46%, with a mean protein intake of 0.77 g/kg/day. The absence of statistical differences may be attributed to the limited sample size.

Limitations

Our study has several limitations. Firstly, the fact that it was conducted at a single center may restrict the generalizability of the findings. In addition, the relatively small sample size may have led to the failure to detect some statistical differences between subgroups. In addition, patients' nutritional support was only monitored, but no intervention was performed. Finally, although the study used the mNUTRIC score for nutritional status and risk assessment, other potentially influential parameters were not analyzed in detail.

CONCLUSION

In this study, clinical outcomes were assessed using the mNUTRIC in critically ill patients. It was found that there were statistically significant differences in the mean APACHE II, SOFA, and mNUTRIC scores on days 2, 7, and 12 between deceased and surviving patients. ROC analysis results revealed that mNUTRIC scores have a significant predictive power in predicting mortality, while also being an effective tool in predicting the need for IMV hemodialysis and vasopressor/inotrope support. However, it was found that nutritional adequacy and protein intake were not factors that directly influenced the mortality risk in critically ill patients with high mNUTRIC scores. These findings elucidate that the mNUTRIC score serves as a reliable instrument for assessing both the mortality risk and the necessity for intensive care supportive interventions in patients with critical illness.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Pamukkale University Non-interventional Clinical Researches Ethics Committee (Date: 29.09.2023, Decision No: 426637).

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.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Review

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Assessment tools for evaluating body structure-function and activity in dyskinetic cerebral palsy: a systematic review of instrumented assessments according to ICF-CY

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ABSTRACT

Dyskinetic cerebral palsy (CP) is one of the most severe forms of CP, characterized by dystonia or choreoathetosis and can be classified into dystonic and choreoathetosis subgroups. The International Classification of Functioning, Disability, and Health-Child and Youth Version (ICF-CY) provides a framework for physical therapists to understand the health, functioning, activity, participation, and impact of dystonia and choreoathetosis. This review aimed to examine the clinical use of ICF-CY tools to assess body structure, function, and activity in children with dyskinetic CP. A systematic search was conducted in June 2024 using PubMed, Embase, Scopus, and Google Scholar databases. The search included terms related to cerebral palsy, dyskinesia, choreoathetosis, dystonia, body structure, function, and activity. After removing duplicates, 11,800 articles remained and 34 met the inclusion criteria. The review found that ICF-CY activity assessments focused primarily on fine-motor, communication, eating-drinking, bimanual fine motor, and speech functions following gross motor function. Some studies have evaluated ICF-CY body structure and function. Most studies used the Dyskinesia Impairment Scale. This review presents evaluations using instrumented assessments as objective outcome measures in patients with dyskinetic CP. Future studies should develop measurements that are applicable outside the laboratory by using new technologies.

Keywords: Dyskinetic cerebral palsy, assessment tools, ICF-CY, body structure and function, activity

INTRODUCTION

Dyskinetic cerebral palsy (CP) is one of the most severe forms of CP.[1] It is a motor disorder characterized by changes in muscle tone and posture, with a variable element of involuntary movement.[2,3] Dyskinetic CP is based on the predominance of dystonia or choreoathetosis; thus, it can be further classified into the dystonic and choreoathetosis subgroups. Dystonia and choreoathetosis often coexist in dyskinetic CP, and the term dyskinetic CP is used when the predominance of dystonia and choreoathetosis is difficult to define.[2-6]

In dystonic CP, involuntary movements and sustained/intermittent muscle contractions occur, causing abnormal twisted posture and repetitive movements in abnormal posture.[5] Dyskinetic CP is the most common definition of dystonia in children, which occurs as a result of hypoxic-ischemic damage to the basal ganglia, thalamus, brain stem, and cerebellum during the prenatal, perinatal, or infancy periods.[5]

In choreoathetoid CP, hyperkinesia and hypotonia co-occur and fluctuations in muscle tone are dominant.[5,7] Choreoathetoid movements are defined as rapid, involuntary, jumpy, and small-amplitude movements that usually involve the distal extremities. Athetosis is an involuntary, discrete, slow, ever-changing, complex, writhing, irregular movement. It is prominent on the distal extremities and face.[5,7] Choreoathetosis appears to be associated with pure thalamic and basal ganglia lesions.[4]

Currently, several scales are used to define the severity of dystonia in dyskinetic CP, such as the Barry-Albright Dystonia Scale (BADS), Dyskinesia Impairment Scale (DIS), Burke-Fahn-Marsden Dystonia Rating Scale Movement (BFM-M), hypertonia assessment tool (HAT), and Unified Dystonia Rating Scale (UDRS).[7-13] The DIS also assesses choreoathetosis and dystonia.[7] Clinical scales are often used in conjunction with questionnaires such as The pediatric evaluation of disability inventory (PEDI), Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD), and quality of upper extremity skills test (QUEST), which determine performance-based outcome measures.[14-16] In addition, individualized outcome measures such as the Goal Attainment Scaling (GAS) and the Canadian Occupational Performance Measure (COPM) are used to evaluate treatment outcomes in patients with dyskinetic CP.[17-23]

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Functional classification systems play an important role in the management of children and youth with CP and in distinguishing the characteristics of functional abilities, and can assist in setting goals and planning management. The most commonly used classification systems for CP are the gross motor function classification system (GMFCS), manual ability classification system (MACS), communication function classification system (CFCS), eating and drinking ability classification system (EDACS), Viking Speech Scale (VSS), and visual function classification system (VFCS).[24-31] Although dyskinetic CP is the second largest group of CP in the entire CP population, only a few studies have investigated the functional classification of dyskinetic CP. In addition, it is important to establish a comprehensive functional profile to develop targeted interventions for dyskinetic CP.

With increasing attention paid to limitations in function, activity, and participation in neurodevelopmental disability, function-based classification schemes have recently emerged.[32] The gross motor function classification system (GMFCS) addresses gross motor functional capacity and classifies children along a specific functional trait, particularly as it relates to the core functions of individual ambulation.[24] It is psychometrically appropriate in terms of reliability and validity, enables the identification of a child's skills and needs, and allows for clear and concise communication between healthcare professionals.[33] Unlike the traditional subtype classification scheme, it provides information about the correct prognosis and the need for eventual ambulation status when applied early in life.[34] The number of publications citing the GMFCS is increasing every year, and this classification system has become internationally accepted in research and clinical use for clear communication among health professionals about gross motor functioning in children.[35]

The International classification of functioning, disability, and health (ICF) is a classification system created by the World Health Organization (WHO) in 2001 to establish a standard language and common framework for describing health and health-related conditions.[36] After this classification system was established for adults by the WHO in 2001, the International classification of functioning, disability and health-child and youth version (ICF-CY), which deals with children and young people and considers growth and development, was published in 2007.[37] The ICF-CY provides a useful framework for physical therapists to better understand health, functioning, activity, participation, contextual factors, and the impact of dystonia and choreoathetosis. ICF contributes to a comprehensive understanding of dyskinetic CP and allows therapists to manage it effectively.[32] Moreover, evaluating the body functions, structures, and activity levels of children and adolescents with dystonia and choreoathetosis within the framework of the ICF-CY may provide more effective clinical management of dyskinetic CP.[7]

Currently, there is no consensus on most applicable, reliable, and valid tools used for the evaluation of choreoathetosis and dystonia in children with dyskinetic CP.[38] This systematic review aimed to describe and critically examine the rate of clinical use of tools reported to assess body structure function and activity under ICF-CY for clinical types of dystonia and choreoathetosis in children and adolescents with CP. Additionally, we aim to provide an overview of the parameters that can be derived from these measurement tools.

METHODS

Search Strategy

A systematic search was conducted in June 2024 using four electronic databases: PubMed, Embase, Scopus, and Google Scholar. The search strategy included the following blocks.

Diagnosis: terms related to cerebral palsy,

Movement disorder: Terms such as dyskinesia, choreoathetosis, and dystonia,

Body structure, function, and activity: Terms related to body structure function and activity.

The detailed search strategy for each database is provided in Supplementary **Table 1**.

Table 1. Inclusion and exclusion criteria defined in line with the PICOS design framework

	Definition	Inclusion/Exclusion criteria
Participants	Dyskinetic CP, patients aged 2-24 years	• The study sample or a significant number of subjects (50% minimum) are represented in the study population or in a sub-study population analyzed separately. • Because the definition of dyskinetic CP is not always clear, studies describing "dystonia and choreoathetosis ocurring with CP" were included.
Intervention	Instrumented Measurements to assess body structure-function and activity	• Studies in which body structure function and activity evaluations were performed and the results of these evaluations were specified were included. • In studies using video recordings, computerized analysis techniques that required observational video scores were also included.
Comparison	No control or comparison group was required	• Studies that compared the effect of the intervention assessed with a clinical test, control group, or methods were included. If there was no comparison, the method was presented in the review.
Outcome	ICF-CY categories	• Body structure function and activity categories were included in the ICF-CY categories. • Other ICF-CY categories (for example, mental function, sensory function, pain, or self-care) were excluded.
Study design	Original research studies and and participants and presenting sufficient knowledge of the methodology are included	• There are no restrictions on the type of studies: technical reports, case studies, case control studies, and intervention studies, etc. • Articles published in languages other than English were also excluded. • Only full-text articles were selected for both abstract and full-text articles published using the same data/methodology.

PICOS: Participants, intervention, comparison, outcome, study, CP: Cerebral palsy, ICF-CY: International classification of functioning, disability and health-child and youth version

Inclusion Criteria

The inclusion criteria were established using the PICOS framework.

Participants: Studies involving individuals diagnosed with cerebral palsy.

Intervention: Studies examining movement disorders (e.g., dyskinesia, choreoathetosis, dystonia).

Comparison: Studies that included a control group or comparative intervention.

Outcome: Studies reporting body structure function and activity outcomes.

Study design: Randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies.

Selection Process

The search results were imported into EndNote for reference. Duplicate records were removed prior to screening. The initial screening of the titles and abstracts was performed by a single reviewer (EB). The full texts of potentially eligible studies were retrieved and assessed in detail against the inclusion criteria by the same reviewer (EB).

Data Extraction

Data extraction was performed using a standardized form. The extracted data included the following.

- Study characteristics (author, year, country),
- Participant characteristics (sample size, age, gender, diagnosis),
- Intervention details,
- Outcomes measured,
- Main findings.

Quality Assessment

The quality of the included studies was assessed using the Cochrane Risk of Bias tool for randomized controlled trials and Newcastle-Ottawa Scale for observational studies. Risk of bias assessment was independently conducted by two reviewers (EB and MG). Discrepancies were resolved through discussion or by consulting with a third reviewer (CO).

Data Synthesis

Narrative synthesis of the findings was conducted because of the heterogeneity of the included studies. Where possible, a meta-analysis was performed using a random-effects model to account for the variability among studies. Statistical heterogeneity was assessed using the I^2 statistic.

Resolution of Disagreements

Any disagreements encountered during article selection, data extraction, or quality assessment processes were resolved by discussion between the primary reviewer (EB) and the second (MG) and third reviewers (CO).

RESULTS

Table 1 presents the inclusion and exclusion criteria created using the preferred reporting ıtems for systematic reviews and meta-analyses (PRISMA). After removing duplicate articles from the search results, 11,800 records remained. Forty-six articles meeting the inclusion and exclusion criteria were reviewed for further eligibility assessment, and the full texts were obtained.

In 34 of 46 articles, body structure function and activity evaluation of clinical types of dystonia and choreoathetosis in children and adolescents with CP, children, and young people with dyskinetic CP were included as the main participant group or as a separate subgroup, and the results have been reported accordingly. The descriptions of the included articles are shown in Table 2.

Function and Disability

Body functions and structures: Body structure function was evaluated in 32.3% of the 34 studies. The Dyskinesia Impairment Scale (DIS) was used in 14.71% of these studies; Barry-Albright Dystonia Scale (BADS) in 11.7%; Burke-Fahn-Marsden Dystonia Rating Scale-Movement (BFM-M) in 15.4%; as intellectual and executive function evaluation criteria, Raven's colored progressive matrices were used in 15.4%, the stop signal task in 15.4%, the Wisconsin card sorting test in 15.4%, the stockings of Cambridge test in 15.4%, magnetic resonance (MR) imaging in 20.5%, pattern/verbal recognition memory task in 7.6%, Benton's facial recognition test in 7.6%, Benton's judgment of line orientation test in 7.9%, The peabody picture vocabulary test in 7.6%, the computer-based instrument for low motor language testing (C-BilLLT) in 5.8%, IQ testing in 5.8%, Movement Disorder-Childhood Rating Scale (MD-CRS 4-18) in 2.9%, The neonatal neuroimaging classification system (NNICS) in 2.9%, spasticity test (SPAT) in 2.9%, Visual Analogue Scale (VAS) in 2.9%, pediatric evaluation of disability inventory (PEDI) in 2.9%.[4,21,39-54] Lexical Verbal Fluency tests in 15.4% Pena-Casanova et al.[55]

Activity

Activity was evaluated in 34 studies. The following classification systems were used in these articles: GMFCS, 94.1%; MACS, 70.5%, CFCS 32.3%; EDACS, 11.7%; bimanual fine motor function (BFMF) classification, 11.7%; and VSS, 8.8%. The gross motor function measure (GMFM) was used in 5.8% of patients.[4,21,39-43,45,47-65]

Gross Motor Function Classification System (GMFCS)

In the following studies, 27.9%-100% of the participants were classified as GMFCS V: Sun et al.[56] and Préel et al.[68] and Westbom et al.,[69] and Elze et al.[45] and Bonouvrié et al.,[51] Williams and Pountney,[66] Zouvelou et al.,[67] Bekteshi et al.[61] Vanmechelen et al.[39] and Monbaliu et al.[4] and Knights et al.,[11] and Eek et al.,[21] Carnahan et al.,[63] Monbaliu et al.,[41] Bonouvrie et al.,[42] Battini[54] and Unes et al.[53]

Of the participants, 42.8%-61% had GMFCS IV in the following studies: Shevell et al.,[70] Park et al.,[44] Andersen et al.[65] and Soleimani et al.[60]

In Gimeno et al.,[46] 85.7% of the participants had GMFCS IV or V (equal numbers of patients for each).

Table 2. Description of included articles

Study	Population/setting	Intervention/aim	Body structure and function scales	Activity scales	Results	Design
Sun et al.[56]	Twenty-six participants (28.0%) had dystonic CP, 26 (28.0%) had choreoathetotic CP, and 41 (44.1%) had mixed CP.	Clinical characteristics and functional status of children with different subtypes of dyskinetic cerebral palsy.		**GMFCS n (%)** I 13 (13.9), II 9 (9.6), III 22 (23.6), IV 23 (24.7), V 26 (27.9), **MACS** I 7 (7.5), II 29 (31.1), III 12 (12.9), IV 18 (19.3), V 25 (26.8) **CFCS** I 19 (20.4), II 34 (36.5), III 17 (18.2), IV 17 (18.2), V 6 (6.4)	Functional classification levels were distributed unequally among the 3 subgroups (p<.01). No significant difference between GMFCS and MACS was found among the 3 subgroups (p>.05). Different subtypes of dyskinetic CP have specific comorbidities, radiological characteristics, and functional attributes according to their etiological factors and brain lesions. Children with dystonic CP have more limited functional status than children with choreoathetotic CP.	Observational study
Shevell et al.[70]	Spastic quadriplegia 85 (35) Spastic hemiplegia 77 (31) Spastic diplegia 52 (21) Dyskinetic 16 (7) Ataxic-hypotonic 9 (4) Other 4 (2)	The relationship of cerebral palsy subtype and functional motor impairment: a population-based study.		**Dyskinetic GMFCS** I 1 (6.2), II 2 (12.5), III 1 (6.2), IV 7 (43.7), V 5 (31.2)	dSP subtype versus GMFCS levels I to III or IV to V was distributed pro-portionally as follows: spastic diplegic, 51/52 (98%) versus 1/52 (2%); spasticquadriparetic, 20/85 (24%) versus 65/85 (76%); spastic hemiplegic, 76/77 (99%)versus 1/77 (1%); dyskinetic, 4/16 (25%) versus 12/16 (75%); other (triplegic orataxic-hypotonic), 10/13 (77%) versus 3/13 (23%). These distributions (propor-tions) all yielded significant (p<0.001) pearson v2values	Observational study
Ballester-Plané et al.[57]	Fifty-two subjects with dyskinetic CP (28 males, mean age 24 y 10 mo, SD 13 y) and52 typically-developing controls (age- and gender-matched) completed a comprehensive neuropsychological assessment.	Cognitive functioning in dyskinetic cerebral palsy: Its relation to motor function, communication and epilepsy.		**GMFCS** I 15 (28.8), II 8 (15.3), III 6 (11.5), IV 11 (21.1), V 12 (23) **BFMF** I 7 (13.4), II 12 (23), III 16 (30.7), IV 12 (23), V 5 (9.6) **MACS** I 5 (9.6), II 10 (19.2), III 17 (32.6), IV 10 (19.2), V 10 (19.2) **CFCS** I 17 (32.6), II 23 (44.2), III 6 (11.5), IV 6 (11.5), V 0 (0)	Dyskinetic CP participants performed worse than controls on all cognitive func-tions except for verbal memory. Milder cases (GMFCS I) only showed impairment inattention, visuoperception and visual memory. Participants with GMFCS IIeIII also showedimpairment in language-related functions. Severe cases (GMFCS IVeV) showed impairmentin intelligence and all specific cognitive functions but verbal memory. CFCS was associated with performance in receptive language functions. Epilepsy was related to performance inintelligence, visuospatial abilities, visual memory, grammar comprehension and learning.	A case control study
Préel et al.[68]	The total number of CP cases was 1165 of which 92 had dyskinetic and 540bilateral spastic CP.	Children with dyskinetic cerebral palsy are severely affected as compared to bilateral spastic cerebral palsy.		**Dyskinetic GMFCS** I 119 6.7%, II 72 3.3%, III 50 5.6%, IV 158 22.2%, V 226 62.2%	Prevalence of dyskinetic CP was 0.16 per 1000 live births. Inparticipants with dyskinetic compared to bilateral spastic CP, there was more frequently an Apgar level less than five at five minutes (22.7% vs. 11.2%) and neonatal seizures (43.5% vs. 28.5%), but less respiratory deficiency, hyperbilirubinaemia and sepsis. Impairmentbased on gross motor function classification was more severe in dyskinetic CP (level III-V90.0% vs. 66.0%). In dyskinetic CP, there was a high rate of reduced development alquotient (68.1%), visual impairment (39.3%) and epilepsy (51.6%). Basal ganglia lesions were more prevalent in dyskinetic compared to bilateral spastic CP (27.7% vs. 12.8%)	Observational study (Cross-sectional)
Westbom et al.[69]	Total 343 Dyskinetic (50)	Cerebral palsy in a total population of 4-11 year olds in southern Sweden. Prevalence and distribution according to different CP classification systems.		**Dyskinetic: GMFCS** I 8 (16), II 4 (8), III 5 (10), IV 14 (28), V 19 (36)	The prevalence of CP was 2.4/1.000 (95% CI 2.1-2.6) in children 4-11 years of age born in Sweden, excluding post-neonatally acquired CP. Children born abroad had a higher prevalenceof CP with more severe functional limitations. In the total population, the prevalence of CP was 2.7/1.000 (95% CI 2.4-3.0) and 48% were GMFCS-level I (the mildest limitation of gross motor function). One third of the children with CP, who were born or had moved into the area after a previous study in 1998, were not in the CPUP database. The subtype classification in the CPUP database was adjusted in the case of every fifth child aged 4-7 years not previously reviewed.	Observational study (Cross-sectional)
Ballester-Plané et al.[58]	25 subjects with dyskinetic CP and 24 healthy controls	Whole-brain structural connectivity in dyskinetic cerebral palsy and its association with motor and cognitive function.		**Dyskinetic CP, GMFCS** I: 10 (40), II: 3 (12), III: 1 (4), IV: 4 (12), V: 7 (28) **MACS** I: 3 (12), II: 8 (32), III: 4 (16), IV: 3 (12), V: 7 (28)	Grossand fine motor functions correlated with FA in a pathway comprising the sensorimotor system, butgross motor also correlated with prefrontal, temporal and occipital connections. Intelligence correlatedwith FA in a network with fronto-striatal and parieto-frontal connections, and visuoperception was relatedto right occipital connections. These findings demonstrate a disruption in structural brain connectivity indyskinetic CP, revealing general involvement of posterior brain regions with relative preservation of pre-frontal areas. We identified pathways in which WM integrity is related to clinical features, including butnot limited to the sensorimotor system	Randomized controlled trial
Laporta-Hoyos et al.[47]	Thirty-nine participants (19 females, median age 21y) with DCP	Brain lesion scores obtained using a simple semi-quantitative scale from MR imaging are associated with motor function, communication and cognition in dyskinetic cerebral palsy.	1.Intellectual functioning Raven's coloured progressive matrices. 2. Four domains of executive functions were assessed: - Attentional control: the stop signal task (Cambridge Cognition, 1999) - Cognitive flexibility: Wisconsin card sorting test (Kongs et al., 2000). -Goal setting: Stockings of Cambridge test (Cambridge Cognition, 1999). - Information processing: Lexical verbal fluency test (Peña-Casanova et al., 2009). -Pattern/verbal recognition memory task (Cambridge Cognition, 1999). -Benton's facial recognition test (Benton, 1994) and Benton's judgment of line orientation test (Benton, 1994) -The Peabody picture vocabulary test third edition MRI	**Dyskinetic cerebral palsy GMFCS** I: 15 (38.4), II: 7 (17.9), III: 3 (7.6), IV: 5 (12.8), V: 9 (23) **MACS** I: 5 (12.8), II: 10 (25.6), III: 12 (30.7), IV: 3 (7.6) V: 9 (23) **CFCS** I: 15 (38.4), II: 16 (41), III: 4 (10.2), IV: 4 (10.2), V: 0	Brain lesions were most frequently located in the ventral posterior lateral thalamus and the frontal lobe. Gross (B=0.180, p<.001; B=0.658, p<.001) and fine (B=0.136, p=.003; B=0.540, p<.001) motor function were associated with global sqMRI score and parietal involvement. Communication functioning was associated with putamen involvement (B=0.747, p<.028). Intellectual functioning was associated with global sqMRI score and posterior thalamus involvement (B=-0.018, p<.001; B=-0.192, p<.001). Selective attention was associated with global sqMRI score (B=-0.035, p<.001), parietal (B=-0.063, p=.023), and corpus callosum involvement (B=-0.448, p<.001). Visuospatial and visuoperceptive abilities were associated with global sqMRI score (B=-0.078, p=.007) and medial dorsal thalamus involvement (B=-0.139, p<.012), respectively	Randomized controlled trial
Laporta-Hoyoset al.[59]	DCP [n ¼52; 24 females, median age 20.5 y: 5mo, interquartile range (IQR) ¼13.75 y: 7mo; GMFCS IeV]	Executive function and general intellectual functioning in dyskinetic cerebral palsy: comparison with spastic cerebral palsy and typically developing controls.		**Dyskinetic cerebral palsy GMFCS** I: 15 (80), II: 8 (15.3), III: 6 (11.5), IV: 11 (21.1), V: 12 (23) **MACS** I: 5 (9.6), II: 10 (19.2), III: 17 (32.6) IV: 10 (19.2),V: 10 (19.2) **CFCS** I: 17 (32.6), II: 23 (44.2), III: 6 (11.5), IV: 6 (11.5)	Both CP groups had lower intelligence than TDC and performed poorer in almost all EF tasks. Intelligence was higher in DCP than SCP (z ¼2.51, p ¼0.01). Participants with DCP also performed significantly better in goal-setting tasks (z ¼2.27, p ¼0.03) and in-formation processing (z¼2.54, p ¼0.01) than those with SCP.	Cross-sectional study
Elze et al.[45]	Children with HMDs, n=161; median age 10y 3mo, range 2y 6mo-21y	Burke-Fahn-Marsden dystonia severity, gross motor, manual ability, and communication function classification scales in childhood hyperkinetic movement disorders including cerebral palsy: a 'Rosetta stone'study.	BFM-M	**Dyskinetic cerebral palsy GMFCS** I: 22 (13.6), II: 20 (12.4), III: 9 (5.5), IV: 21 (13),V: 89 (55.2) **MACS** I: 7 (4.3), II: 21 (13), III: 20 (12.4), IV: 26 (16.1),V: 87 (54) **CFCS** I: 25 (15.5), II: 26 (16.1), III: 36 (22.3), IV: 49 (30.4),V: 22 (13.6)	All four scales were strongly associated (all Spearman's rank correlation coefficientrs >0.72, p<0.001), with worse dystonia severity implying worse function. Secondary dystoniashad worse dystonia and less function than primary dystonias (p<0.001). A longer proportionof life lived with dystonia is associated with more severe dystonia (rs=0.42, p<0.001)	Cross-sectional study

Table 2. Description of included articles (continues)

Study	Population/setting	Intervention/aim	Body structure and function scales	Activity scales	Results	Design
Bonouvrié et al.[31]	We conducted a multicenter, randomized, double-blind, placebo-controlled trial at the AUMC, located at Free University AUMC, Amsterdam, and the MUMC, Maastricht, the Netherlands.	The effect of intrathecal baclofen in dyskinetic cerebral palsy: the IDYS trial.	MRI the C-BiLLT	**Dyskinetic cerebral palsy GMFCS** IV: 8 (44.4), V: 10 (55.5) **MACS** III: 2 (11.1), IV: 4 (22.2), V: 12 (66.6)	Thirty-six patients were recruited from January 1, 2013, to March 31, 2018. Data for final analysis were availablefor 17 patients in the intrathecal baclofen group and 16 in the placebo group. Mean (standard deviation) GAS T score at3 months was 38.9 (13.2) for intrathecal baclofen and 21.0 (4.6) for placebo (regression coefficient=17.8, 95% confidenceinterval=10.4-25.0, p<0.001). Number and types of (serious) adverse events were similar between groups.	Sistematik review
Park et al.[44]	Twenty-three patients with dyskinetic CP (13 males, 10 females; mean age 34 years, range 16-50 years)	Neuroradiological and neurophysiological characteristics of patients with dyskinetic cerebral palsy.	BADS	**Dyskinetic cerebral palsy GMFCS** I: 1 (4.3), II: 9 (39.1), III: 1 (4.3), IV: 11 (47.8), V: 1 (4.3)	Mean BADS was 16.4±5.0 in ambulatory group (GMFCS levels I, II, and III; n=11) and 21.3±3.9 in nonambulatory group (GMFCS levels IV and V; n=12). Twelve patients showed normal MRI findings, and eleven patients showed abnormal MRI findings (grade I, n=5; grade II, n=2; grade III, n=4). About half of patients with dyskinetic CP showed putamen and thalamus lesions on MRI. Mean BADS was 20.3±5.7 in normal MRI group and 17.5±4.0 in abnormal MRI group. VBM showed reduced volume of the hippocampus and parahippocampal gyrus. In DTT, no abnormality was observed in CST, but not in SLF. In MEPs, most patients showed normal central motor conduction time.	Randomized controlled trial
Williams et al.[66]	Three participants had dyskinetic quadriplegia, seven had spastic quadriplegia, and one had spastic diplegia.	Effects of a static bicycling programme on the functional ability of young people with cerebral palsy who are non-ambulant.		**Dyskinetic cerebral palsy GMFCS** V: 3 (100) **GMFM**	Resultsshowed significant improvements in GMFM-66 (p=0.010)and in GMFM-88 dimensions D (Standing; p=0.012) and E (Walking, Running, and Jumping; p=0.011) over theintervention period, but not over the baseline or follow-upperiods. Significant improvements were found in 'cycling' ability for duration of pedalling (p<0.001), speed (p=0.01),and resistance (p=0.001).	Randomized controlled trial
Laporta-Hoyos et al.[68]	Thirty-three participants with dyskinetic CP (mean±SD age: 24.42±12.61, 15 female) were age and sex matched with 33 controls	White matter integrity in dyskinetic cerebral palsy: relationship with intelligence quotient and executive function.	1.Intellectual functioning Raven's coloured progressive matrices. 2. Four domains of executive functions were assessed: - Attentional control: the Stop signal task (Cambridge Cognition, 1999). Selective visual and - Cognitive flexibility: Wisconsin card sorting test (Kongs et al., 2000). -Goal setting: Stockings of Cambridge test (Cambridge Cognition, 1999). - Information processing: Lexical verbal fluency test (Peña-Casanova et al., 2009). MRI	**Dyskinetic CP GMFCS** I: 12 (36.3), II: 6 (18.1), III: 3 (9), IV: 5(15.1),V: 7 (21.2) **MACS** I: 5 (15.1), II: 8 (24.2), III: 11 (33.3), IV: 2 (6), V: 7 (21.2) **CFCS** I: 14 (42.4), II: 13 (39.3), III: 2 (6), IV: 4 (12.1),V: 0	White matter FA was significantly reduced in the CP group in all cerebral lobes, predominantly in regions connected with the parietal and to a lesser extent the temporal lobes. There was no significant correlation between IQ or any of the four executive function domains and WM microstructure in the control group. In participants with CP, lower IQ was associated with lower FA in all cerebral lobes, predominantly in locations that also showed reduced FA compared to controls. Attentional control, goal setting and information processing did not correlate with WM microstructure in the CP group. Cognitive flexibility was associated with FA in regions known to contain connections with the frontal lobe (such as the superior longitudinal fasciculus and cingulum) as well as regions not known to contain tracts directly connected with the frontal lobe (such as the posterior corona radiata, posterior thalamic radiation, retrolenticular part of internal capsule, tapetum, body and splenium of corpus callosum).	Randomized controlled trial
Soleimani et al.[60]	Unilateral Spastic 36 Bilateral Spastic 125 Ataxic 10 Dyskinetic 14 Unclassified(mixed) 15	Cerebral palsy: Motor types, gross motor function and associated disorders.		**Dyskinetic MACS** I: 0, II: 3 (21.4), III: 1 (7.1), IV: 5 (35.7), V: 5 (35.7) **GMFCS** I: 2 (14.2), II: 2 (14.2), III: 0, IV: 6 (42.8), V: 4 (28.5)	During the study period, 200 CP children (103 males, 97 females) aged 4-12 years were seen with an overall male: female ratio of 1.06, with a mean (SD) age of 7.7 (2.4) years. Level IV in MACS classification (23%) and also level IV in GMFCS classification (30.5%) were the more commons. The remaining cases were distributed rather equally to other levels, near to (19-20%) to the MACS classification and (11-24.5%) to the GMFCS classification per level.	Observational study (Cross-sectional)
Andersen et al.[65]	Of the 294 children, 96 had the spastic unilateral CP type, 143 the spastic bilateral, 19 the dyskinetic 15 the ataxic type. In 21, the subtype could not be classified by the referring centre.	Cerebral palsy in Norway: prevalence, subtypes and severity.		**Dyskinetic GMFM GMFCS** I- II: 0, III:2 (11), IV: 11 (61), V: 5 (28) **Bimanual fine motor function (BFMF)** I: 0, II: 0, III:1 (5), IV: 4 (21), V: 14 (74)	A total of 374 children with CP were identified with a prevalence of 2.1 per 1000 live births. Detailed information was obtained from 294 (79%) children. Median age at clinical assessment was 6.9 years (range: 1.9-10.2 years). Thirty-three percent of the children had spastic unilateral CP, 49% spastic bilateral, 6% dyskinetic, 5% ataxic CP and 7% were not classified. Severely impaired vision and hearing were present in 5% and 4% of the children, respectively. Active epilepsy was present in 28%, mental retardation in 31% and severely impaired or no speech in 28% children. The most severe impairments in gross motor function were observed in children with low Apgar scores, and the most severe impairments in fine motor function in children born at term, with normal birth weight and low Apgar scores.	Observational study (Cross-sectional)
Zouvelou et al.[67]	Fifteen patients manifested with features resembling dyski-netic CP (12 dystonic and 3 choreic), 9 resembled spastic CP, 5ataxic CP and 18 mixed CP.	The genetic etiology in cerebral palsy mimics: The results from a Greek tertiary care center.		**Dyskinetic GMFCS** I: 3 (20), II: 1 (6.6), III:3 (20), IV: 1 (6.6), V: 7 (46.6)	31.91% of patients manifested with features resembling dyskinetic CP, 19.14% spastic CP, 10.63% ataxic CP and 38.30% mixed CP. In 23 patients molecular diagnosis was reached and included 5 hereditary SPG in spastic CP mimics; HPRT1, TH, QDPR, DDC in dystonic CP mimics; ADCY5 and NIKX2-1 in choreic CP mimics; ANA1Ain ataxic CP mimics; andSPG, PDHA1, NIKX2-1, AT, SLC2A1 and SPRin mixed CPmimics. In 14 patients, the etiological diagnosis led to specific treatment.	Retrospective study
Bekteshi et al.[39]	53 participants with DCP	Clinical presentation of spasticity and passive range of motion deviations in dyskinetic cerebral palsy in relation to dystonia, choreoathetosis, and functional classification systems.		**Dyskinetic GMFCS** I: 10 (18.8), II: 5 (9.4), III:5 (9.4), IV: 7 (13.2), V: 26 (49) **MACS** I: 8 (15), II: 5 (9.4), III:6 (11.3) IV: 10 (18.8), V: 24 (45.2)	Spasticity and limited pROM were correlated with dystonia of the upper limbs (0.41<rs<p<.002) and lower limbs (0.31<rs<p<.025), and both functional systems of gross motor (0.32<rs<p<.018) and fine manual abilities (0.34<rs<p<.014). Hypermobility is correlated only with choreoathetosis of the lower limbs (0.44, p=.001).	Cross-sectional study
Vanmechelen et al.[39]	Fifty-two subjects with dyskinetic CP	Presence and severity of dystonia and choreoathetosis overflow movements in participants with dyskinetic cerebral palsy and their relation with functional classification scales.	Dyskinesia Impairment Scale	**Dyskinetic GMFCS** I: 9 (17.3), II: 4 (7.6), III:8 (15.3), IV: 9 (17.3), V: 22 (42.3) **MACS** I: 7 (13.4), II: 4 (7.6), III: 8 (15.3), IV: 13 (25), V: 20 (38.4) **CFCS** I: 6 (11.5), II: 18 (34.6), III:20 (38.4), IV: 7 (13.4), V: 1 (1.9) **EDACS** I: 8 (15.3), II: 19 (36.5), III:12 (23), IV: 10 (19.2), V: 3 (5.7) **VSS** I: 7 (13.4), II: 11 (21.1), III:13 (25), IV: 21 (40.3)	Dystonia and choreoathetosis overflow movements were simultaneously present. Median scores of dystonia overflow movements were significantly higher than choreoathetosis overflow movements. Dystonia and choreoathetosis overflow movements were significantly higher in extremities than in the central body. Correlations between dystonia and choreoathetosis overflow movements were fair. Moderate to good correlations were found between dystonia overflow score and gross motor function classification system, manual ability classification system, and eating and drinking ability classification system.	Cross-sectional study
Monbaliu et al.[4]	55 participants	Clinical patterns of dystonia and choreoathetosis in participants with dyskinetic cerebral palsy.	DIS, MRI	**Dyskinetic GMFCS** I: 10 (18.1), II: 5 (9), III:6 (10.9), IV: 7 (12.7), V: 27 (49) **MACS** I: 5 (9), II: 8 (14.5), III:7 (12.7), IV: 11 (20),V: 24 (43.6) **CFCS** I: 6 (10.9), II: 20 (36.3), III:18 (32.7), IV: 8 (14.5), V: 3 (5.4)	Dystonia and choreoathetosis are simultaneously present. Median levels of dystonia (70.2%) were significantly higher than levels of choreoathetosis (26.7%) and both were significantly higher during activity than at rest (both p<0.01). High correlations were found between dystonia levels and GMFCS level (Spearman's rank correlation coefficient, rs=0.70; 95% CI 0.53-0.81; p<0.01) and MACS (rs=0.65; 95% CI 0.47-0.81; p<0.01),and fair correlation with CFCS (rs=0.36; 95% CI=0.11-0.57; p<0.05). No significant correlation was found between choreoathetosis levels and motor classifications. Finally, higher choreoathetosis levels were found in participants with pure thalamus and basal ganglia lesions (p=0.03) than mixed lesions, but not for dystonia (p=0.41)	Cross-sectional study

Table 2. Description of included articles (continues)

Study	Population/setting	Intervention/aim	Body structure and function scales	Activity scales	Results	Design
Monbaliu et al.[40]	55 participants	Functional outcomes in children and young people with dyskinetic cerebral palsy.	DIS	**Dyskinetic GMFCS** I: 10 (18.1), II: 5 (9), III: 6 (10.9), IV: 7 (12.7), V: 27 (49) **MACS** I: 4 (7), II: 8 (15), III:7 (13), IV: 12 (22), V: 24 (44) **EDACS** I: 9 (16), II: 18 (33), III:10 (18), IV: 12 (22), V: 6 (11) **CFCS** I: 6 (10.9), II: 20 (36.3), III: 18 (32.7), IV: 8 (14.5),V: 3 (5.4) **VSS** I: 8 (14.5), II: 12 (21.8), III:11 (20), IV: 24 (43.6)	Over 50 per cent of the participants exhibited the highest limitation levels in GMFCS, MACS, and VSS. Better functional abilities were seen in EDACS and CFCS. Moderate to excellent interrelationship was found among the classification scales. All scales had significant correlation (rs=0.65-0.81) with dystonia severity except for CFCS in the young people group. Finally, only MACS (rs=0.40) and EDACS (rs=0.55) in the young people group demonstrated significant correlation with choreoathetosis severity	Cross-sectional study
Butler et al.[42]	7 Dyskinetic cerebral palsy	Temporal-spatial parameters of the upper limb during a reach & grasp cycle for children.		**MACS** I: 2 (28.5), II: 2 (28.5), III: 3 (42.8)	Heconsistent normative data and the substantial differences between children with CP and controls reflectutility of the reach & grasp cycle for quantitative evaluation of upper limb motor deficits.	Retrospective study
Gimeno et al.[46]	Secondary CP dystonia 14	Evaluation of functional goal outcomes using the COPM following DBS in childhood dystonia.	COPM, BFMDR	**GMFCS** I-III: 2 (14.2), IV-V: 12 (85.7) **MACS** I-III: 1 (7.1), IV-V: 13 (92.8)	DBS improved functional performance, independently of thedystonic phenotype. Improvements in individualized COPM functional goal areas wereseen in the absence of significant changes in BFMDRS scores, highlighting the relativeinsensitivity of impairment scales in this patient group.	Retrospective study
Eek et al.[21]	25 dyskinetic cerebral palsy	Intrathecal baclofen in dyskinetic cerebral palsy: effects on function and activity.	Barry-Albright Dystonia Scale Modified Ashworth Scale plastic goniometer	**Gross motor function measure 88-item version GMFCS** IV: 5 (20), V: 20 (80) **MACS** III: 1 (4), IV: 3 (12), V: 21 (84) **BFMF** III: 1 (4), IV: 6 (24), V: 18 (72)	After ITB in individuals with dyskinetic CP, improvements were found in sitting, communication, and fine motor skills. There was a reduction in dystonia and muscle tone, and pain and sleep improved.	A retrospective cohort study
Carnahan.[63]	51 dyskinetic	Association between GMFCS and MACS in children with cerebral palsy. A population-based study of 359 children.		**GMFCS** I: 4 (7.8), II: 2 (3.9), III:7 (13.7), IV: 17 (33.3),V: 21 (41.1) **MACS** I: 5 (9.8), II: 4 (7.8), III:5 (9.8) IV: 11 (21.5), V: 26 (50.9)	Gross motor function and manual ability are often discrepant in children with CP, and the patterns seem to vary across the different subgroups based on the predominant neurological findings. To give a complete clinical picture when evaluating these children, both aspects have to be described. The GMFCS and the MACS seem to work well in this context and seem very useful in population-based studies, in health care registers for children with CP, and in clinical practice.	Cross-sectional study
Eliasson.[26]	19 dyskinetic CP	The MACS for children with cerebral palsy: scale development and evidence of validity and reliability.		**MACS** III:3 (15.7), IV: 4 (21), V: 12 (23.5)	The results demonstrated that MACS has good validity and reliability. The intraclass correlation coefficient between therapists was 0.97 (95% confidence interval 0.96-0.98), and between parents and therapist was 0.96 (0.89-0.98), indicating excellent agreement.	
Monbaliu.[67]	55 Dyskinetic Palsy	The relationship of dystonia and choreoathetosis with activity, participation and quality of life in children and youth with dyskinetic cerebral palsy.	DIS	**GMFCS** I: 9 (17), II: 5 (9), III: 6 (11), IV: 7 (13), V: 27 (50) **MACS** I: 4 (7), II: 8 (15), III: 7 (13), IV: 11 (21),V: 24 (44) **GMFM the FMS the JTT the ABIL-K the LIFE-H**	This cross-sectional study is the first to examine the relationship of dystoniaand choreoathetosis in dyskinetic CP with the level of activity, participation and QOL. The results revealed dystonia has a higher impact on activity, participation and quality of lifethan choreoathetosis. These findings seem to suggest it is necessary to first focus ondystonia reducing intervention strategies and secondly on choreoathetosis.	
Dhondt et al.[52]	CP subtype classification was not possible for 26 children (2.3%). Among 1101 children included in subtype-stratified analyses: •Spastic CP: 948 children (86.1%) •Dyskinetic CP: 105 children (9.5%) (including dystonic dyskinesia in 59 and choreo-athetotic dyskinesia in 14 children) •Ataxic CP: 48 children (4.4%)	To report on the prevalence, neuroimaging patterns, and function of children with CP in Belgium for birth years 2007-2012, and identify distinctive risk indicators and differences in outcome between CP subtypes.	IQ testing MRICS the NNICS	**GMFCS** 20 (19.0), 25 (23.8), 11 (10.5), 23 (21.9), 24 (22.9), 2 (1.9) **MACS** 11 (10.5), 16 (15.2), 23 (21.9), 13 (12.4), 24 (22.8), 18 (17.1) **BFMF** 9 (8.6), 20 (19.0), 20 (19.0), 16 (15.2), 19 (18.1) **Missing** 21 (20.0) **VSS** 12 (11.4), 22 (21.0), 22 (21.0), 31 (29.5) **Missing** 18 (17.1)	In total, 1127 children with CP were identified in Belgium. The birth prevalence of overall CP was 1.48 per 1000 live births. The likelihood of dyskinetic CP increases if the child was born to a mother aged ≥35 years, mechanically ventilated, and had predominant grey matter injury, while an increased likelihood of ataxic CP is associated with ≥2 previous deliveries. Children with dyskinetic and ataxic CP are more likely to function with impairments in motor, speech, and intellectual abilities.	Observational study
Vanmechelen et al.[78]	Fifty-two subjects with dyskinetic CP were included.	This cross-sectional study aims to investigate the presence and severity of overflow move- ments of dystonia and choreoathetosis in dyskinetic CP and to assess the relationship of overflow movements with functional classification scales.	DIS	**GMFCS** 9 (17.3), 4 (7.6), 8 (15.3), 9 (17.3), 22 (42.3) **MACS** 7 (13.4), 4 (7.6), 8 (15.3), 13 (25), 20 (38.4) **CFCS** 6 (11.5), 18 (34.6), 20 (38.4), 7 (13.4), 1 (1.9) **EDACS** 8 (15.3), 19 (36.5), 12 (23), 10 (19.2), 3 (5.7) **VSS** 7 (13.4), 11 (21.1), 13 (25), 21 (40.3)	Dystonia and choreoathetosis overflow movements were simultaneously present. Median scores of dystonia overflow movements were significantly higher than choreoathetosis overflow movements. Dystonia and choreoathetosis overflow movements were significantly higher in extremities than in the central body. Correlations between dystonia and choreoathetosis overflow movements were fair. Moderate to good corre-lations were found between dystonia overflow score and gross motor function classification system, manual ability classification system, and eating and drinking ability classification system.	Cross-sectional study
Bonouvrié et al.[20]	A multi-center prospective cohort study was conducted including 34 non-walking individuals with severe dyskinetic CP	To assess attainment of individual treatment goals one year after ITB pump implantation in individuals with dyskinetic CP.	BADS DIS SPAT VAS PEDI C-BiLLT	**GMFCS IV** 13 (38.2%), V 21 (61.7%) **MACS** III 3 (8.8%), IV 9 (26.4%), V 22 (64.7%)	Seventy-one percent of individuals with dyskinetic CP fully achieved one or more treatment goals. One or more treatment goals were partially achieved in 97% of individuals. Two factors were found to be associated with attainment of goals: DIS score at baseline and the difference in pain score between baseline and follow-up. These two variables explain 30% of the variance in the outcome.	A multi-center prospective cohort study
33. Stewart et al.[43]	Fifty-seven children with dyskinetic CP	To outline the development and examine the content and construct validity of a new tool, the D-FİS, which measures the impact of dyskinesia on everyday activities in children with CP.	BADS D-FIS	**GMFCS** 8 (14), 6 (11), 7 (12), 23 (40), 13 (23) **MACS** 0, 19 (33), 12 (21), 12 (21), 14 (25), 0 **CFCS** 16 (28), 13 (23), 14 (25), 10 (17), 4 (7) **EDACS** 16 (28), 19 (33), 11 (19), 1 (2), 10 (17)	Fifty-seven parents of children [29 males, 28 females, mean [SD] age 11y 8mo (4y 4mo), range 2y 6mo-18y] completed the D-FIS. Correlation between D-FIS and GMFCS was r=0.86 (95% CI: 0.77–0.91, p<0.001); MACS r=0.84 (95% CI: 0.73-0.90, p<0.001); CFCS r=0.80 (95% CI: 0.67-0.88, p<0.001); and EDACS r=0.78 (95% CI: 0.66-0.87). Correlation between D-FIS and BADS was r=0.77 (95% CI: 0.64-0.86, p<0.001). Cronbach's alpha was 0.96.	Observational study
Battini et al.[24]	this measurement-focused study was carried out on a cohort of 57 participants with dcp	MD-CRS 4-18 is a tool aimed to evaluate movement disorders in developmental age, validated since 2008 and applied in the literature.	MD-CRS 4-18	**GMFCS** 8 (14), 1 (2), 3 (5), 12 (21), 33 (58), 8, 1, 3	This study supports the relevant contribution of MD-CRS 4-18 r to identify the severity of movement disorders in dyskinetic cerebral palsy, as indicated by the higher icc values on index ii compared to previous MD-CRS 4-18 results. SEM and Minimally detectable difference (Mdd) of MD-CRS 4-18 r in dcp were all very low, with sEMs ranging from 0.01 to 0.02 and Mdd from 0.03 to 0.06.	Observational study
Unes et al.[53]	The clinical types were spastic (n=159, 74 unilateral, 85 bilateral), dyskinetic (n=43, 34 dystonic, 9 choreoathetotic), ataxic (n=7) and unclassified (n=16) according to the SCPE classification	To investigate the relationships between four functional classification systems in children with CP and parent-interpredicted intelligence level, and the functional status in clinical types of CP.		**GMFCS** 5 (12), 4 (9), 5 (12), 12 (27), 17 (40) **MACS** 3 (7), 6 (14), 11 (26), 5 (11), 18 (42) **CFCS** **EDACS**	Correlations were found between all functional levels; the strongest were between GMFCS-MACS (r=0.784, p<.001), CFCS-EDACS (r=0.772, p<.001). Strong correlations were found for the IQ-CFCS (r=0.762, p<.001) and IQ-EDACS (r=0.634, p<.001). Correlations were stronger in children with bilateral CP and IQ level <70.	Observational study

CP: Cerebral palsy, CI: Confidence interval, MD-CRS 4-18: Movement disorders-childhood rating scale for age 4-18, HMDs: Hyperkinetic movement disorders, BFM-M: Burke-Fahn-Marsden Dystonia Rating Scale-movement, C-BiLLT: Computer-based instrument for low motor language testing, COPM: Canadian occupational performance measure, DBS: Deep brain stimulation, BFMDR: Burke-Fahn-Marsden Dystonia Rating Scale, MRICS: MRI classification system, AUMC: Amsterdam University Medical Center, MUMC: Maastricht University Medical Center, NNICS: Neonatal neuroimaging classification system, DIS: Dyskinesia Impairment Scale, SPAT: Spasticity test, VAS: Visual Analogue Scale, PEDI: Pediatric evaluation of disability inventory, ITB: Intrathecal baclofen, D-FIS: Dyskinetic Cerebral Palsy Functional Impact Scale, MACS: Manual ability classification system, GMFCS: Gross motor function, SPG: Spastic paraplegia genes, VSS: Viking Speech Scale, BADS: Barry-Albright Dystonia Scale, FMS: Functional Mobility Scale, JTT: Jebsen-Taylor hand function test, ABIL-K: ABILHAND-kids questionnaire, LIFE-H: LifeHabits kids, SEM: Standard error measurement

In the following studies, 35.9%-80% of the prticipants were GMFCS I: Ballester-Plané et al.[57] and Ballester-Plané et al.[58] and Laporta-Hoyos et al.,[47] and Laporta-Hoyos et al.,[48] Bonouvrie.[42]

Manual Ability Classification System (MACS)

In the following studies, 23.5%-84% of participants had MACS V: Elze et al.,[45] Bekteshi et al.,[61] Vanmechelen et al.,[39] Bonouvrié[51] and Monbaliu et al.,[4] Monbaliu et al.,[40] Butler et al.,[62] Eek et al.[21] Carnahan et al.,[63] Eliasson et al.,[26] and Monbaliu et al.,[41] Bonouvrie,[42] Stewart et al.[43] and Unes et al.[53]

Soleimani et al.[60] and Gimeno et al.,[46] 35.7% and 92.8% of the participants were MACS IV or MACS V, respectively, and they were equal in each study.

In subsequent studies, 17-33.3% of the participants were MACS III, and Laporta-Hoyos et al.,[47] Laporta-Hoyos et al.,[59] Laporta-Hoyos et al.,[48] Dhondt et al.,[52] Stewart et al.[43] and Unes et al.[53]

Sun et al.[56] and Ballester-Plané et al.,[58] and 31.1% and 32% of the participants were MACS II.

Communication Function Classification System (CFCS)

Elze et al.[45] found that 13.6% of the participants had CFCS IV.

In Vanmechelen et al.,[39] 38.4% of the participants were classified as CFCS III.

In these studies, 36.3%-44.2% of the participants had CFCS II. Sun et al.[56] Laporta-Hoyos et al.,[47] and Laporta-Hoyos et al.,[59] Monbaliu et al.[4] and Monbaliu et al.[40]

A study by Laporta-Hoyos et al.,[48] Stewart et al.[43] and Unes et al.,[53] 28% -44% of the participants were CFCS I.

Bimanual Fine Motor Function (BFMF) Classification

In Andersen et al.[65] and Eek et al.,[21] 72% and 74% of the participants had BMFM V, respectively.

In Ballester-Plané et al.,[57] Dhondt et al.,[52] 15.2% and 30.7% of participants had BMFM III.

Eating and Drinking Ability Classification System (EDACS)

Vanmechelen et al.,[39] Monbaliu et al.,[40] Stewart et al.,[43] 33% and 36.5% of the participants were EDACS II, respectively.

Viking Speech Scale (VSS)

In Vanmechelen et al.,[39] Monbaliu et al.[40] and Dhondt et al.,[52] 29.5% and 43.6% of the participants had CFCS IV, respectively.

Gross Motor Function Measure (GMFM)

Williams and Pountney,[66] Andersen et al.,[65] and Monbaliu et al.[40] used GMFM as an activity measure in their studies.

DISCUSSION

Our study provides an overview of instrumented measures used to assess body structure function and activity as part of ICF-CY in children and youth with CP and with clinical types of dystonia and choreoathetosis. The current study can guide researchers and clinicians in making informed decisions regarding evaluations for specific purposes in dyskinetic CP. In dyskinetic CP, there are a number of instrumented classification systems for assessing activity directly. Most body function assessment tools assess involuntary movements that are not directly related to the desired task, expressed as an excessive flow of muscle activation.

Body Structure and Function

This systematic review identified scales reported to measure dystonia and choreoathetosis in children with CP. All of these scales assess dystonia, but only the DIS assesses choreoathetosis in addition to dystonia. Two scales, the BADS and DIS, were designed primarily to measure secondary dystonia in people with CP. Other scales have been designed to assess primary dystonia or more than one type of movement disorder. Three articles evaluated dystonia and choreoathetosis at rest and during activities.[39,40,66] These assessments were performed using the DIS. This scale allows researchers to identify explosive movements found in dystonia and choreoathetosis and to map them in the body according to clinical patterns. In these articles, explosive movements of dystonia and choreoathetosis were evaluated simultaneously using this scale. Considering the reviewed articles, this scale has broadened our perspective on the structural and functional profiles of individuals with dyskinetic CP. Considering the reviewed articles, the DIS scale has expanded our perspective on the structural and functional profiles of individuals with dyskinetic CP. The DIS enables body structure and function assessment of dystonia and choreoathetosis in dyskinetic CP, together with functional classification systems that assess gross motor skills, upper extremity function, eating and drinking ability, communication, and speech.

In the articles included in our review, the clinical benefits of MRI imaging used in body structure-function assessment in children with dyskinetic CP have been shown to establish reasonable relationships between lesions in regions of the brain other than those that cause dyskinetic CP in general and add more value to clinical feedback.[45,46] However, a large proportion of individuals with dyskinetic CP have severe intellectual disabilities.[62,67] Tests assessing intellectual and executive function in the studies were carefully selected to allow most participants to respond autonomously. In the studies, the results of these tests were transferred to a computer environment and the use of assistive technology for communication was allowed. Participants were encouraged to use an assessment scale appropriate for their degree of disability and the communication devices that they normally use.

The impact of treatment options on different types and severity of dyskinetic CP also needs to be fully investigated. Therefore, the determination of dyskinetic CP and the dominant subclinical type requires clear evaluation and reporting criteria. One of the purposes of this review is to bridge this gap and identify and critically examine tools that assess body structure and function.

Activity

Most of the methods reviewed in the present study had this in common: they assess manual dexterity and/or ambulation activity during tasks that require some level of understanding

of the task instructions. The methods reviewed here provide the full functional profile of individuals with dyskinetic CP, including areas of speech, eating, and drinking, using current classification systems in addition to gross motor, dexterity, and communication classification. In most of the reviewed articles, individuals with dyskinetic CP had severe deficiencies in gross motor function, manual dexterity, and speech production. Therefore, a large number of children and adolescents with dyskinetic CP have been evaluated using only a few instrumentation methods.

The literature clearly demonstrates a high correlation between all CP subtypes that occur with significant frequency and the level of GMFCS (the low number of children with the ataxic-hypotonic variant precludes definitive analyses and statements regarding this subtype).[68] The GMFCS is a particularly valid method for assessing gross motor function, which ultimately reflects the ability to act independently. It is quite unusual and rare for a child with spastic diplegia or hemiplegia to be unable to ambulate independently. Ambulation is an important question asked by parents when their children are first diagnosed. Independent walking, however, is an important determinant of participation, leading to improved individual quality of life.[69,70] Independent ambulation occurs only in a small group of children with spastic quadriplegia or dyskinesia. Therefore, when the neurologic subtype is known, a strong prediction of ambulation-related functional status can be made, emphasizing that the GMFCS is a strong predictor. Conversely, the determined functional status can provide information about which neurological subtypes may occur.

Intervention outcomes for children with dystonia and other hyperkinetic movement disorders are often defined using a disorder-based dystonia rating scale such as the Burke–Fahn–Marsden Dystonia Rating Scale-Movement (BFM-M). However, without additional data, scores on such scales allow only limited inferences about an individual's functional status.[45] The use of functional classification scales such as the GMFCS, MACS, and CFCS provides a common language for describing motor affect severity and functional status of both patients and research participants. These scales require no formal clinician training, are fast, cost-effective, and easy to administer. They help contextualize BFM-M scores and facilitate the interpretation of research results by providing a clearer understanding of the functional abilities of the study participants. These classification systems, which reflect performance in daily life by focusing on function, provide meaningful information beyond etiology and disorder, as recommended by the ICF.[45]

Finer abilities in eating and drinking functions are a rare finding compared to gross motor and upper extremity functions, and this is consistent with the results of communication assessments in studies on dyskinetic CP.[4] However, speech production was not evaluated using the evaluation criteria of the EDACS and CFCS. This can be explained by one of the components evaluated at these scales. Communication function and eating and drinking abilities are supported by changes in the motor development processes. The focus of the EDACS and CFCS is to define an individual's ability to eat and drink safely and perform their daily communication function regardless of the communication method used. Speech production, respiratory control, phonation, and articulation were assessed using the VSS. The VSS, together with scales evaluating communication skills and eating and drinking abilities, provided complementarity to profile oral-motor function and upper/lower motor function in children with dyskinetic CP.

The GMFM, used as a measure of activity in the articles described in this systematic review, has been found to be successful in distinguishing various domains of motor dysfunction in children with CP and with spastic diplegia and athetosis. This criterion provides guidance for the development of children's participation in their functional activities, and therefore, in their activities in individual, family, and social circles.[71] In our literature review, we observed that the GMFM was used as an activity evaluation criterion for individuals with dyskinetic CP.

Body structure function and activity evaluations were performed at the ICF-CY level in the articles reviewed in this review. However, none of the articles evaluated the body structure function and activity in the daily environment of the participants. Therefore, it is controversial whether the results can be generalized to real-life situations. Many children and young people with dyskinetic CP depend on wheelchairs (manual or electric) in daily life. Therefore, it may be useful to evaluate the quality and duration of wheelchair use using instrumented methods in daily life. Evaluating wheelchair performance (or the performance of different controllers for motorized wheelchair mobility) in a virtual environment, as recently reported, is a very interesting option for this group.[72]

In recent years, wearable sensor technologies have been increasingly used to detect certain movements, such as neurological disorders, epilepsy, and stereotypical movement patterns including CP.[73-75] However, no study has specifically investigated dyskinetic CP. Wearable sensors allow the monitoring of dyskinetic movements in daily life outside the laboratory environment. Considering the severity of the disorder, movements may change over time and may be exacerbated by external stimuli such as stress, pain, and noise.[66] For this reason, an evaluation that can be performed for a longer period of time in the daily environment may provide more reliable evaluation results in children and adolescents with dyskinetic CP.[76-79]

CONCLUSION

This review presents the instrumented measures used as objective outcome measures in patients with dyskinetic CP. Future studies should aim to develop instrumented measurements that can be applied outside the laboratory with new technological developments. This is especially important for severely disabled young adults and children with dyskinetic CP.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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

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