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The impact of the COVID-19 pandemic on internet usage profiles in individuals: the mediating role of ADHD symptoms

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ABSTRACT

Aims: Attention deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by attention deficit, impulsivity, and hyperactivity. This disorder may have had an impact on individuals' internet usage profiles, particularly due to the pandemic measures. The aim of the study was to determine the prevalence of ADHD and to examine the factors affecting internet addiction in this disorder.

Methods: This clinical study was designed as a cross-sectional and descriptive study and was conducted on 250 participants living in the city center of Sakarya and selected by random sampling method. The sociodemographic data form, Addiction Profile Index internet (APIINT) form, Adult ADHD Self-Report Scale (ASRS), Epidemic Anxiety Assessment Scale (EAAS) were applied to the participants online via e-mail via Google forms.

Results: Of the participants, 14 (5.6%) stated that they were diagnosed with ADHD in childhood and 20 (8%) in adulthood. The number of patients who reported that they were diagnosed with any psychiatric disorder in adulthood (other than ADHD) was 50 (20%). With the APIINT scale score, the APIINT total score mean values were found to be significantly higher in the groups diagnosed with ADHD in childhood, diagnosed with ADHD in adulthood and suspected ADHD with ASRS compared to the group without ADHD diagnosis (p=0.001).

Conclusion: Internet use has intensified during the pandemic, and it has been observed that this situation may be related to the level of anxiety about the pandemic. Internet addiction was found to be higher in those with ADHD than in the non-ADHD group. The study is valuable in that it examines the changes in people's media and technology usage habits during the pandemic, but studies with larger samples, face-to-face interviews, and follow-up data are needed to better understand the subject.

Keywords: ADHD, internet addiction, COVID-19, media, technology

INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by a persistent pattern of inattention, hyperactivity, and impulsivity.[1] It affects approximately 5-10% of school-aged children and usually begins in childhood and continues into adulthood in approximately 60% of individuals.[2] The disorder can impair individuals' performance in social, educational, and work environments.[3] ADHD typically begins before age 7.[4] Genetics play an important role in ADHD, with studies pointing to multiple susceptibility genes across different populations.[5] It is considered one of the most common neurodevelopmental disorders of childhood.[2]

Internet addiction has attracted significant attention in recent years, with an increase in research focusing on its epidemiology, behavioral aspects, and impact on individuals' daily lives.[6] Although it is difficult to give a standard definition of internet addiction, it is generally characterized by symptoms such as inability to control desire for internet activities, extreme irritability when away from the internet, and weakening of relationships in the work environment, social relationships and family relationships.[7] There are studies showing a direct relationship between internet addiction and psychological problems.[8] Additionally, internet addiction has been linked to various factors such as temperament, urbanization, social anxiety, and parenting styles.[9-11]

The COVID-19 pandemic has led to a significant increase in anxiety symptoms, depression, addictions, and internet usage worldwide due to global stay-at-home mandates

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and quarantines.[12,13] This increase in online activities has particularly manifested itself in areas such as telehealth, distance education and e-commerce.[14,15] The shift to online platforms has become essential to maintaining productivity during the pandemic.[16] In terms of social interactions, the pandemic has also accelerated the digitalization of face-to-face communities, with religious gatherings, social events and community activities shifting to online platforms.[17]

Studies have found that internet addiction has increased during the COVID-19 pandemic. A positive relationship has been demonstrated between internet addiction and intolerance of uncertainty regarding COVID-19, depression, and perceived risk. This suggests that the uncertainty and risks brought by the pandemic may contribute to an increase in internet use and addiction.[18] It has been determined that the pandemic has led to an increase in internet-based addictive behaviors, including internet addiction, gaming disorder and social media addiction, and that the feeling of isolation and loneliness experienced during the pandemic may have led individuals to excessive internet use as a coping mechanism.[19]

Additionally, individuals with pre-existing conditions such as ADHD have been found to be more prone to internet addiction during the COVID-19 pandemic. Studies have shown that children with ADHD tend to overuse the internet during the pandemic, leading to worsening ADHD symptoms, emotional dysregulation, and angry outbursts.[20-23] The pandemic is also causing an increase in addictive internet and substance use behaviors, further complicating mental health issues.[24]

This study aimed to examine the prevalence of ADHD and the characteristics of internet use accompanying this disorder. It also evaluates the psychological media and technology usage habits of individuals during the COVID-19 pandemic and aims to reveal the specific difficulties experienced by individuals diagnosed with ADHD during this process. This aspect of the research can make significant contributions to the development of strategies for the management of ADHD and to better understand the needs of individuals in extraordinary situations such as pandemics.

METHODS

Ethical Approval

Ethics committee approval was obtained from Sakarya University Faculty of Medicine Non-interventional Ethics Committee (Date 29.05.2020, Decision No: 2020/309). The research was conducted in accordance with the 1964 Helsinki Declaration.

Research Design and Sample Selection

This clinical research was designed as a cross-sectional and descriptive study and was conducted between 20/06/2020 and 20/10/2020 on 250 volunteer participants living in the city center of Sakarya and selected by random sampling method. Individuals between the ages of 18-65, who are literate and able to understand the scales used and select the appropriate answer were included in the study.

Consent to Participate

Informed consent was obtained from all study participants

Study Procedure

The sociodemographic data form applied to the participants, BAPI internet (APIINT) Form, ASRS, EAAS surveys were compiled by the researchers in the form of consecutive questions using Google Forms. The prepared forms were sent to the participants online via e-mail and they were asked to answer them.

Data Collection Tools

Sociodemographic Data Form: It was created by the researchers to include questions such as the participants' gender, age, marital status, education level, place of residence, employment status, monthly income level, and whether a curfew was imposed due to COVID-19 in their place of residence.

APIINT Addiction Form: It was developed by Ögel[25] and his colleagues to determine the level of internet addiction in accordance with the concept of addiction and the literature. It is a self-report scale consisting of 18 items. The first item includes the frequency of internet use, which includes a six-item answer. Other questions are scored between 0 (never) and 4 (almost always). The Cronbach alpha value of the scale is .88. The sub-dimensions of the scale were determined as frequency of internet use, addiction diagnosis criteria, the effect of internet use on life, intense desire to use, and motivation to reduce internet use. The cut-off score of the scale is two.

Epidemic Anxiety Assessment Scale (EAAS): It was developed by Yazıcı et al.[26] to assess the level of anxiety related to epidemics. It is a Likert-type scale consisting of 15 items, with each question being scored between 0 (almost never) and 4 (almost always). The Cronbach's alpha value of the scale is .94.

Adult ADHD Self-Report Scale (ASRS): The Adult ADHD Self-Report Scale (ASRS) is a comprehensive scale developed by the Adult ADHD Working Group in collaboration with the World Health Organization (WHO) to assess symptoms of ADHD in adults.[27] This 18-item scale allows individuals to self-assess their ADHD symptoms according to DSM-IV criteria.[27] The ASRS serves as a valuable screening tool for ADHD and provides a dimensional self-assessment consistent with diagnostic criteria.[28] The Turkish validity and reliability was carried out by Doğan et al.[29]

Statistical Analysis

The study data were entered into the SPSS (statistical package for the social sciences) 22.00 program on a computer with Windows 10.0 package program installed and evaluated with this program. First, descriptive and frequency analyses were performed, then the groups were compared. Normality tests were performed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. When comparing the groups diagnosed with ADHD and those not diagnosed with ADHD, the groups were evaluated with the Mann-Whitney U test because they did not show a normal distribution. The relationship between the APIINT, ASRS and EAAS scales was determined with Spearman correlation analysis. The significance level was determined as 0.05 for two sides.

RESULTS

Our study included 250 individuals between the ages of 18-65. Of the participants, 163 (65.2%) were female and 87 (34.8%) were male, with an average age of 33.5±11.5 years. The sociodemographic characteristics of the patients and their COVID-19 positivity status are presented in Table 1.

Table 1. Sociodemographic characteristics of participants

	n	%
Gender		
Woman	163	65.2
Man	87	34.8
Marital status		
Married	109	43.6
Single	132	52.8
Divorced	6	2.4
Living separately	3	1.2
Education level		
Primary school	5	2
Middle school	3	1.2
High school	33	13.2
University	163	65.2
Master's degree and above	46	18.4
Place of living		
Rural	15	6
Urban	235	94
Active working status		
Working regularly	141	56.4
Works irregularly	17	6.8
Doesn't work	92	36.8
Monthly income level		
0-2000 TL	75	30
2001-5000 TL	83	33.2
5001-10.000 TL	76	30.4
10.001 TL and above	16	6.4
Living area		
There is a curfew on weekends and similar occasions	218	87.2
No curfew	27	10.8
There is a curfew every day	**5**	**2**
COVID suspicion or positivity	15	6
Total	250	100

Of the participants, 14 (5.6%) stated that they were diagnosed with ADHD in childhood and 20 (8%) in adulthood. The number of patients who reported that they were diagnosed with any psychiatric disorder (other than ADHD) in adulthood was 50 (20%).

While the number of patients reporting that there was at least one family member diagnosed with ADHD was 32 (12.8%), the number of patients reporting that there was no family member diagnosed with ADHD was 218 (87.2%).

While the number of patients who reported receiving psychiatric treatment for any reason was 69 (27.6%), the number of patients who reported not receiving psychiatric treatment was 181 (72.4%).

The number of patients who used at least one of tobacco, alcohol or any psychoactive substance was 122 (48.8%); 87 people (50.9%) reported using tobacco, 80 people (48.5%) reported using alcohol and 1 person (0.6%) reported using substances (n=171).

The patients' levels of internet addiction, the severity of anxiety related to the pandemic, and ADHD symptoms were assessed using the APIINT, ASRS, and EAAS scales, and the results are presented in Table 2.

Table 2. Numerical data regarding APIINT, EAAS and ASRS scales

Scales	Lowest score (n=250)	Highest score (n=250)	Avg±SD (n=250)
APIINT	0.10	3.60	1.65±0.75
ASRS	0	22	8.09±4.51
EAAS	1	54	14.36±10.65

APIINT: Addiction Profile Index internet, EAAS: Epidemic Anxiety Assessment Scale, ASRS: Adult Self-Report Scale

The APIINT cut-off score was 2, and the number of patients with a score above 2 was 81 (32.4%).

The correlation levels between the APIINT, ASRS, and EAAS scales were examined. When all scales were compared in pairs through correlation analyses, a significant positive correlation was found between them (Table 3).

Table 3. Evaluation of the correlation relationship of APIINT, ASRS and EAAS scales

		ASRS total score	APIINT total score	EAAS total score
ASRS	r	1000	.474**	.261**
	p		.001	.001
	n	250	250	250
APIINT	r	.474**	1000	.400**
	p	.001		.001
	n	250	250	250
EAAS	r	.261**	.400**	1000
	p	.001	.001	
	n	250	250	250

**Correlation level 0.001, Spearman correlation analysis was applied, APIINT: Addiction Profile Index internet, ASRS: Adult Self-Report Scale, EAAS: Epidemic Anxiety Assessment Scale

According to ASRS scores, no individual with a high probability of ADHD (24 points and above) was identified in our study; the number of individuals considered to have probable ADHD (17-23 points) was determined to be 16 (6.4%). It was determined that 234 patients (93.6%) scored 16 points and below.

Evaluations Regarding Participants' Television, Telephone and Internet Usage Profiles

The participants' usage durations of television, phone, and internet were analyzed in hours and summarized in Table 4. It was found that a quarter of the participants used the internet for more than 6 hours, while approximately one-fifth used their phones for more than 6 hours. The reasons for patients' use of phones and the internet are summarized in Figure.

Table 4. Numerical data on television, telephone and internet usage times

	Television (n=250)		Telephone (n=250)		Internet (n=250)		
Duration (hour)	**n**	**%**	**n**	**%**	**Duration (hour)**	**n**	**%**
I never watch	69	27.6	-	-	I never use	1	0.4
1-2 hour	103	41.2	64	25.6	1-2 hour	55	22
3-4 hour	58	23.2	93	37.2	3-4 hour	83	33.2
5-6 hour	15	6	46	18.4	5-6 hour	48	19.2
6 hour and above	5	2	47	18.8	6 hour and above	63	25.2

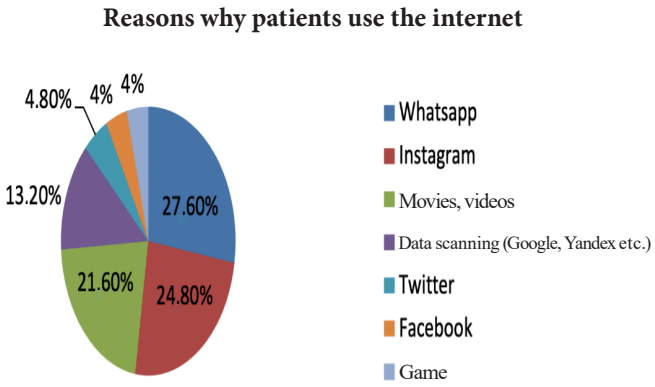

Figure. Numerical data on patients' reasons for internet use

In the sociodemographic data form, patients were asked questions about the duration of phone, tablet/PC and internet/social media use during the pandemic and options were presented. During the pandemic, it was determined that 68.4% of the participants experienced an increase in tablet usage, and 76.8% reported an increase in the time spent watching television. Data on patients' opinions on the subject are shown in Table 5.

Table 5. Evaluations regarding tablet/PC, phone and TV/radio usage time

	Tablet /PC		TV		TV/radio	
Question-1 (n=250)	**n**	**%**	**n**	**%**	**n**	**%**
Has there been an increase in your usage time during the pandemic?						
Yes	171	68.4	192	76.8	125	50
No	66	26.4	58	23.2	102	40.8
I don't use	13	5.2	-	-	23	9.2

PC: Personal computer, TV: Television

The mean APIINT total score values in the patient group diagnosed with ADHD in childhood were higher than in the group without the diagnosis (p: 0.001).

The mean APIINT total score values in the patient group diagnosed with ADHD in adulthood were higher than in the group without the diagnosis (p: 0.001).

The mean APIINT total score values in the group thought to have ADHD diagnosis with ASRS are higher than the group thought to not have ADHD (p: 0.001).

The analysis results of the relationship between the presence of ADHD diagnosis and APIINT total scores are presented in Table 6.

Table 6. Evaluation of the relationship between ADHD and APIINT total score

		n	u	z	p*
APIINT total score	**Childhood ADHD**				
	There is a diagnosis	14			
	No diagnosis	236	611.000	-3.960	0.001
	Total	250			
	Adult ADHD				
	There is a diagnosis	20			
	No diagnosis	230	1231.500	-3.445	0.001
	Total	250			
	ADHD detected by ASRS				
	Possibly ADHD	16			
	Not ADHD	234	663.000	-4.320	0.001
	Total	250			

*Mann-Whitney U test was used, ADHD: Attention deficit/hyperactivity disorder, APIINT: Addiction Profile Index internet, ASRS: Adult Self-Report Scale

DISCUSSION

This article presents the findings of a study conducted on 250 individuals between the ages of 18 and 65. Participants were assessed in terms of various sociodemographic characteristics, including gender, marital status, level of education, place of residence, active employment status, monthly income level, region of residence, curfew status during the COVID-19 pandemic, and psychological health status. The study also examined the participants' television, phone, and internet usage habits and how these habits changed during the pandemic. In particular, the focus was on the participants' psychological health status, including the proportion of individuals diagnosed with ADHD, psychiatric disorders, and tobacco, alcohol, and other psychoactive substance use.

The COVID-19 pandemic has caused a significant increase in internet usage globally. Studies have shown a significant increase in online activities during the pandemic, with internet services experiencing significant growth ranging from 40% to 100% compared to pre-pandemic levels.[30] This increase in internet usage has been observed across a range of age groups, suggesting that the pandemic has had a widespread impact on a variety of online behaviors.[31] Notably, in 2020, the first year of the pandemic, the number of internet users globally increased by 10.2%, marking the most significant growth in the last decade.[32] In our study, after the COVID-19 pandemic, 68.4% of the participants had an increase in tablet and computer usage, and 76.8% had an increase in phone usage. These results are consistent with previous literature and indicate a significant increase in internet usage during the COVID-19 period.

The relationship between COVID-19 and internet addiction has been investigated in terms of perceived risk and emotion regulation. Recent studies have shown a significant positive relationship between perceived risk of COVID-19 and internet addiction, and difficulties in emotion regulation further strengthen this link.[33] This suggests that fear and uncertainty surrounding the pandemic may drive individuals to seek solace or distraction through increased internet use, potentially leading to addictive behaviours. Childhood traumatic experiences, poor physical health, depression,

and anxiety have been identified as key risk factors in the progression of pandemic-induced addictive internet use, highlighting the complex interaction of psychological and environmental factors that trigger internet addiction during COVID-19.[34] In our study, a moderately significant correlation was found between the epidemic anxiety assessment scale and the internet addiction scale (APIINT). This situation, in line with the literature, shows that disease anxiety during the pandemic period may be related to screen addiction.

When studies examining the relationship between internet addiction and ADHD are examined, it has been shown that there is a strong relationship between ADHD and internet addiction in various age groups, including adolescents and adults. Chou and colleagues found that adolescents diagnosed with ADHD have a higher risk of developing internet addiction than those without ADHD.[35] This is further supported by the finding that adolescents with ADHD are more vulnerable to internet addiction symptoms, which may increase the risk of depression and anxiety among parents.[36] Additionally, Rupesh and colleagues observed that children with ADHD showed a higher tendency towards internet addiction compared to their non-ADHD peers.[37]

When we look at the studies examining the screen time of ADHD patients during the COVID-19 period, it was found that the total internet usage time in ADHD patients increased by 46% compared to the pre-COVID-19 period.[21] Another study has shown that the COVID-19 period leads to worsening ADHD symptoms, emotional dysregulation and angry outbursts.[20-23] In our study, participants were examined in 3 different categories in terms of ADHD (those diagnosed with ADHD in childhood, those diagnosed with ADHD in adulthood and those diagnosed with ASRS) and compared with the other group in terms of APIINT scores, and it was determined that the APIINT scores of the ADHD group were statistically significantly higher than the non-ADHD group. These results are consistent with previous literature. The fact that this comparison was made on 3 different categories allowed the differences between the subcategories to be evaluated.

Limitations

If we talk about the limitations of this study, first of all, the selection of participants and demographic diversity come to the fore. The sample size and socioeconomic diversity of 250 individuals included in the study may not reflect all the characteristics of the general population, which may limit the generalizability of the findings. In addition, relying on data reported by the participants themselves may lead to response biases and subjective assessments. Collecting data on psychological states and behaviors using the self-report method has some limitations due to the lack of objective measurement techniques. The accuracy of data on the diagnosis and treatment of ADHD and other psychiatric disorders may also be limited due to the lack of access to participants past medical records. Finally, the impact of dynamic factors such as the social and psychological effects of the COVID-19 pandemic on the study results may not have been fully controlled, which is a factor that should be taken into account when interpreting the findings of the study. Despite these limitations, the study presents important findings and provides valuable insights into psychological health, sociodemographic characteristics, and media use during the pandemic.

CONCLUSION

The frequency of ADHD in children and adults, its correlation with sociodemographic traits, and the necessity of psychiatric therapy were all investigated in this study. Increased internet use during the pandemic may be linked to anxiety levels, and people with ADHD are more likely to develop an internet addiction. In addition to developing support services, it is advised that people with ADHD be monitored for behavioral addictions like substance and internet addiction. The study offers crucial information for comprehending how media and technology usage patterns changed during the epidemic and how sociodemographic characteristics affected mental health.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Sakarya University Faculty of Medicine Non-interventional Ethics Committee (Date 29.05.2020, Decision No: 2020/309).

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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Outcomes of COVID-19 restrictions on patients with type 2 diabetes in Turkiye

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ABSTRACT

Aims: This study aimed to assess the impact of the national COVID-19 lockdown in Turkiye, initiated in March 2020, on glycemic and lipid parameters in patients with type 2 diabetes mellitus (T2DM).

Methods: We included T2DM patients who visited Akdeniz University Hospital between 11.03.2019 and 10.03.2021. Clinical and laboratory data (age, gender, blood glucose, serum creatinine, LDL, triglyceride, HDL, hemoglobin, HbA1c) were retrieved from the hospital database for analysis.

Results: A total of 1,715 T2DM patients were included, with 828 males (48.2%) and 887 females (51.8%). The number of patients seen before and during the pandemic was 930 and 785, respectively. The mean glucose levels before and during the pandemic were 153 mg/dl (149.25-157.47) and 165 mg/dl (160.14-170.62), respectively ($p<0.001$). HbA1c levels increased from 8.11% (7.99-8.23) to 8.30% (8.16-8.43) ($p=0.046$). Triglyceride levels rose from 189.17 mg/dl (181.13-197.21) to 215.12 mg/dl (202.80-227.45) ($p=0.001$). Significant deterioration in glucose ($p<0.000$), triglycerides ($p<0.001$), and HbA1c ($p=0.046$) levels was observed during the pandemic.

Conclusion: The COVID-19 lockdown negatively impacted the glycemic control and lipid profiles of patients with type 2 diabetes, indicating a potential worsening of metabolic parameters during this period.

Keywords: Diabetes mellitus, COVID-19, diabetes complications

INTRODUCTION

Coronaviruses are significant pathogens capable of causing infections in both humans and animals. COVID-19, caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China, in late 2019 and rapidly spread across the globe. The World Health Organization (WHO) declared it a pandemic in March 2020.[1] The COVID-19 pandemic has become one of the foremost health challenges of the last century.

Similarly, diabetes mellitus (DM) has also been declared a pandemic by WHO. It is a chronic metabolic disorder characterized by hyperglycemia, necessitating ongoing medical care.[2] Type 2 DM, a common chronic illness, is increasingly prevalent worldwide. The incidence of diabetes has risen significantly in recent years. For instance, the global number of individuals with DM was estimated at 285 million in 2009, 366 million in 2011, 415 million in 2015, and 425 million in 2017. Projections indicate there will be 578 million cases by 2030 and 700 million by 2045.[3] In our country, data reveal that the number of diabetes patients has doubled over the past decade. Moreover, the prevalence of diabetes among adults exceeded 13.4% in 2010.[4] The coexistence of these two pandemics-the COVID-19 pandemic and the diabetes pandemic has led to a significant number of individuals affected by both conditions, resulting in poorer health outcomes for these patients.[5]

The presence of diabetes negatively impacts clinical outcomes in various disease states. It is frequently associated with metabolic disorders involving proteins, fats, and electrolytes, as well as acid-base imbalances. Diabetic patients face a heightened risk of vascular diseases affecting the brain, heart, or kidneys compared to non-diabetic individuals.

In Turkiye, schools and universities were closed on March 16, 2020, following the first official case reported on March 11, 2020. Throughout March, the government imposed a series of restrictions, closing public facilities such as cinemas, theaters, cafes, sports arenas, and entertainment venues. Domestic and international travel restrictions were enacted, and lockdown measures were put in place for individuals under 18 and over 65. These restrictions began to be gradually lifted starting June 1, 2020. Consequently, outpatient clinical services were disrupted, adversely affecting the follow-up care of diabetes patients. A study from China indicated a deterioration in

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glycemic control and elevated fasting blood sugar levels among individuals with diabetes during the COVID-19 pandemic.[6]

During the pandemic, the management of diabetic patients, along with many other health issues, faced significant disruptions. These included barriers to accessing healthcare services and inconsistencies in the supply of necessary medications. The experiences recorded during previous crises suggest a likelihood of increased rates of diabetes and associated complications both during and after the pandemic. Additionally, the lack of opportunities for physical exercise, challenges in adhering to dietary regimens, and psychological stress related to illness anxiety further complicate blood sugar regulation in diabetic patients during this period.

In this context, we aim to investigate the impact of the COVID-19 pandemic on the management and blood sugar levels of patients with diabetes mellitus.

METHODS

Ethics

Ethical approval was obtained from the Akdeniz University Faculty of Medicine Clinical Researches Ethics Committee (Date: 18.08.2021, Decision No: KAEK-559-560). Furthermore, the study was approved by the Ministry of Health of the Republic of Turkiye (2021-06-24T22_43_30) for the research. All procedures comply with the provisions of the Declaration of Helsinki.

Study Design

Type 2 DM patients who applied to Akdeniz University Medical Faculty Hospital Internal Diseases Polyclinic between 11.03.2019-10.03.2021 were included in the study. Patients under 18 and patients who followed up for type 1 DM were not included in the study. The patient's clinical and laboratory data (age, gender, glucose, creatinine, LDL, triglyceride, HDL, hemoglobin, HbA1c) in the hospital database were collected.

Statistical Analysis

Data were analyzed using SPSS version 20.0 software (IBM Corp., USA). Quantitative data were reported as means with standard deviations (SD) for parametric distributions and as medians with minimum and maximum values for non-parametric distributions. The Kolmogorov-Smirnov test was employed to assess the distribution of variables. A one-way ANOVA was conducted for parametric data, while the Welch ANOVA test was utilized to compare means between groups when homogeneity of variance assumptions were violated. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patients Demographics

The study included a total of 1,715 patients diagnosed with diabetes mellitus (DM). Of these, 828 (48.2%) were male, and 887 (51.8%) were female. The participants' mean age was 58.49 years, ranging from 19 to 93 years.

Before the pandemic, 930 patients were admitted to the internal medicine outpatient clinic, compared to 785 patients during the pandemic. Among individuals with type 2 DM, the mean age prior to the pandemic was 59.01 years (range: 58.26-59.76), while during the pandemic, it was slightly lower at 57.90 years (range: 57.06-58.73).

A subgroup analysis was conducted based on age groups. Among 1,178 patients under 65 years old, the mean age was 53.13 years (range: 52.43-53.83) before the pandemic and 52.02 years (range: 51.29-52.74) during the pandemic. For the 537 patients aged 65 years and older, the mean age was 71.32 years (range: 70.69-71.94) prior to the pandemic and 71.49 years (range: 70.79-72.19) during the pandemic (Table 1).

Table 1. Demographic characteristics of the patients

		Groups		
Variables	**Total patients**	**Group 1 (before pandemic)**	**Group 2 (through pandemic)**	**p-value**
Number (%)	1715	930	785	
Mean age±SD		59.01±0.75	57.90±0.83)	0.052
65>	1178	53.13±0.7	52.02±0.72	0.030
<65	537	71.32±0.62	71.49±0.7	0.714
Gender (%)	1715			
Male	828	448	380	
Female	887	482	405	
Glucose (mg/dl, mean±SD)	158.69±3.28	153±4.47	165±5.62	0.000<
Serum creatinine (mg/dl, mean±SD)	0.92(0.81-1.03)	0.95±0.2	0.87±0.3	0.797
LDL (mg/dl, mean±SD)	123.31±1.7	122.56±2.24	124.33±2.62	0.314
HDL (mg/dl, mean±SD)	43.82±0.46	43.88±0.62	43.75±0.7	0.781
Triglyceride (mg/dl, mean±SD)	200.64±7.15	189.17±8.04	215.12±12.32	0.001
25-OH vitamin D3 (ng/ml, mean±SD)	18.93±0.33	18.94±0.36	19.27±0.6	0.350
HbA1c (%)	8.20±0.9	8.11±0.12	8.30±0.14	0.046
Vitamin B12 (pg/ml, mean±SD)	400.58±9.78	398.28±11.32	407.4±16.65	0.374
Hemoglobin (g/L, mean±SD)	13.33±0.8	13.33±0.11	13.34±0.13	0.918
Ferritin (ng/ml, mean±SD)	82.56±6.06	83.12±8.96	81.03±7.91	0.731
TSH (mU/L, mean±SD)	2.38±0.23	2.49±0.38	2.24±0.23	0.279
FT4 (ng/dl, mean±SD)	1.20±0.1	1.20±0.1	1.20±0.1	0.665

SD: Standard deviation, LDL: Low density lipoprotein, HDL: High density lipoprotein, TSH: Thyroid stimulating hormone, FT4: Free thyroxine

Lockdown May Lead to Poorer Blood Glucose Control Among Individuals with DM

The study revealed notable changes in key metabolic parameters among patients with diabetes mellitus before and during the pandemic. The mean glucose level increased significantly from 153 mg/dl (range: 149.25-157.47) before the pandemic to 165 mg/dl (range: 160.14-170.62) during the pandemic (p<0.001). Similarly, the average HbA1c level rose from 8.11% (range: 7.99-8.23) before the pandemic to 8.30% (range: 8.16-8.43) during the pandemic, a statistically significant difference (p=0.046).

In addition, the mean triglyceride level showed a marked increase, rising from 189.17 mg/dl (range: 181.13-197.21) before the pandemic to 215.12 mg/dl (range: 202.80-227.45) during the pandemic (p=0.001). These findings indicate a significant worsening in glucose (p<0.001), triglyceride (p<0.001), and HbA1c (p=0.046) levels during the pandemic, reflecting an overall decline in glycemic and lipid control among patients with diabetes.

The Lockdown can Worsen Metabolic Syndrome in Both Men and Women

The analysis of gender differences revealed that women experienced a significant increase in triglyceride levels during the pandemic. Before the pandemic, the mean triglyceride level in women was 177.33 mg/dl (range: 168.04-186.62), which rose to 201.38 mg/dl (range: 187.77-214.99) during the pandemic (p=0.004). In contrast, no significant gender-based differences were observed for glucose levels (p=0.078) or HbA1c levels (p=0.706) (Table 2).

When comparing the biochemical parameters of male and female individuals before and during the pandemic, significant changes were observed. The average glucose level increased from 158.60 mg/dl (range: 152.82-164.38) before the pandemic to 174.33 mg/dl (range: 166.69-181.97) during the pandemic (p<0.001). Similarly, the average triglyceride level rose from 201.60 mg/dl (range: 188.27-214.94) before the pandemic to 229.80 mg/dl (range: 208.89-250.70) during the pandemic (p=0.026). Additionally, the average HbA1c increased from 8.23% (range: 8.06-8.41) before the pandemic to 8.57% (range: 8.35-8.78) during the pandemic, reflecting a statistically significant difference (p=0.018) (Table 3).

DISCUSSION

This study examined the impact of the national lockdown in Turkiye on patients with type 2 diabetes mellitus (T2DM) during the global COVID-19 pandemic. Overall, the findings indicate that the lockdown had a detrimental effect on the health status of T2DM patients across both genders. Significant deteriorations in key biochemical parameters were observed, reflecting poorer glycemic control and worsening metabolic syndrome. These results underscore how lifestyle changes induced by the lockdown negatively influenced the disease trajectory and metabolic control in individuals with diabetes.[7]

Key factors contributing to these adverse outcomes included reduced physical activity, disruptions to dietary routines, and limited access to healthcare services. The inability to visit hospitals or pharmacies, treatment discontinuation due to infection fears, lack of physician oversight for critical interventions, and heightened anxiety and stress-especially in a population already prone to depression-further exacerbated these challenges.[8] A study conducted in Spain on dietary habits among T2DM patients during the lockdown revealed efforts to improve nutrition, such as increased vegetable consumption and reduced intake of fast food. However, it also noted an increased consumption of carbohydrate-rich foods, likely driven by boredom and stress. This shift, combined

Table 2. Biochemical parameters of female individuals before and during the pandemic

		Groups		
Variables	**Total patients**	**Group 1 (before pandemic)**	**Group 2 (through pandemic)**	**p-value**
Number (%)	887	482	405	
Age, mean±SD		59.80±1.1	58.20±1.01	0.046
65>	590	310	280	
65<	297	172	125	
Glucose (mg/dl, mean±SD)	887	148.74±5.9	157±6.1	0.078
Serum creatinine (mg/dl, mean±SD)	887	0.97±0.39	0.76±0.30	0.304
LDL (mg/dl, mean±SD)	887	125.99±3.8	128.10±3.4	0.376
HDL (mg/dl, mean±SD)	887	47.75±1.1	47.56±1.1	0.791
Triglyceride (mg/dl, mean±SD)	887	177.33±10.9	201.38±12.1	0.004
25-OH vitamin D3 (ng/ml, mean±SD)	887	18.11±0.5	19.07±0.85	0.078
HbA1c (%)	887	8.02±0.19	8.04±0.27	0.706
Vitamin B12 (pg/ml, mean±SD)	887	398.91±15.9	422.19±24.5	0.128
Hemoglobin (g/L, mean±SD)	887	12.51±0.13	12.67±0.11	0.107
Ferritin (ng/ml, mean±SD)	887	59.79±7.1	57.96±11.9	0.787
TSH (mU/L, mean±SD)	887	2.64±0.4	2.24±0.23	0.78
FT4 (ng/dl, mean±SD)	887	1.19±0.02	1.19±0.02	0.686

SD: Standard deviation, LDL: Low density lipoprotein, HDL: High density lipoprotein, TSH: Thyroid stimulating hormone, FT4: Free thyroxine

Table 3. Biochemical parameters of male individuals before and during the pandemic

		Groups		
Variables	**Total patients**	**Group 1 (before pandemic)**	**Group 2 (through pandemic)**	**p-value**
Number (%)	828	448	380	
Age, mean±SD		58.16±1.07	57.57±1.19	0.470
Number		448	380	
65>	588	318	270	
65<	240	130	110	
Glucose (mg/dl, mean±SD)	828	158.60±5.78	174.33±7.64	0.001
Serum creatinine (mg/dl, mean±SD)	828	0.94±0.29	0.98±0.3	0.101
LDL (mg/dl, mean±SD)	828	118.95±8.31	120.23±3.91	0.619
HDL (mg/dl, mean±SD)	828	39.68±0.74	39.46±0.8	0.685
Triglyceride (mg/dl, mean±SD)	828	201.60±13.33	229.80±2.91	0.026
25-OH vitamin D3 (ng/ml, mean±SD)	828	19.99±0.43	19.60±0.75	0.378
HbA1c (%)	828	8.23±0.17	8.57±0.22	0.018
Vitamin B12 (pg/ml, mean±SD)	828	396.50±15.79	390.89±21.39	0.678
Hemoglobin (g/L, mean±SD)	828	14.25±0.14	14.05±0.19	0.104
Ferritin (ng/ml, mean±SD)	828	116.53±16.80	111.51±10.80	0.622
TSH (mU/L, mean±SD)	828	2.32±0.67	2.24±0.44	0.843
FT4 (ng/dl, mean±SD)	828	1.21±0.01	1.21±0.02	0.887

SD: Standard deviation, LDL: Low density lipoprotein, HDL: High density lipoprotein, TSH: Thyroid stimulating hormone, FT4: Free thyroxine

with reduced physical activity, contributed to elevated blood glucose, HbA1c, and triglyceride levels.[9]

A simulation model using multivariate regression analysis compared the effects of previous natural disasters with those of the COVID-19 lockdown on patients with diabetes. The analysis identified a linear relationship between the duration of isolation and the worsening of diabetes-related complications.[10] For example, during the Gulf War, which involved a 60-day lockdown, patients with type 1 and type 2 diabetes experienced worsened glycemic control and weight gain, although these changes were not statistically significant.[11] 1999 Marmara earthquake removed from discussion

In the present study, a significant increase in HbA1c levels was observed in both male and female patients following the lockdown, aligning with findings from previous research.[12-15] These results emphasize the profound impact of pandemic-induced restrictions on the metabolic health of T2DM patients, highlighting the need for proactive strategies to mitigate such effects during future public health emergencies.

Our findings revealed that the worsening of HbA1c levels was more pronounced in men compared to women. This disparity may be attributed to the lower number of female patients presenting to outpatient clinics during the pandemic compared to pre-pandemic levels (**Table 2**). Despite this gender-based difference, our results align with previous studies showing an overall exacerbation of HbA1c levels in patients, regardless of gender. This deterioration is likely associated with prolonged periods of lockdown, weight gain, and impaired glycemic control.[14-17]

A similar trend was observed in patients with type 1 diabetes mellitus (T1DM) in India, where glycemic control worsened following the lockdown.[17] Conversely, studies from Europe reported an improvement in glycemic control among T1DM patients during the lockdown period.[18,19] The authors of these studies hypothesized that the increased availability of time for self-management during lockdowns may have allowed patients to better regulate their condition.

The adverse effects of various disasters on chronic disease management and quality of life are well-documented. Our findings emphasize the critical importance of closely monitoring vulnerable populations, such as individuals with diabetes, during public health crises and other disruptive events to mitigate the potential worsening of disease outcomes.[20]

Limitations

Although this article compared two different time points, it was challenging to establish a precise causal relationship between the data and the constraint. Furthermore, our study did not include a detailed assessment of factors that may affect patients' glycemic values, such as lifestyle changes, dietary compliance, stress factor, and access to medications during restriction. Third, anthropometric assessments such as body-mass index could not be evaluated.

CONCLUSION

The mandatory quarantines imposed during the COVID-19 pandemic have caused significant changes in lifestyle, dietary habits, and social isolation, leading to a rapid and substantial deterioration in cardiometabolic health among our patients. In other words, the SARS-CoV-2 outbreak has triggered a swift rise in metabolic syndrome cases and worsened diabetes in individuals already living with the condition. Prolonged and persistent stress, coupled with social isolation, has had harmful effects on cardiometabolic health. The impact of COVID-19 restrictions, isolation, and loneliness on health and mortality highlights the worsening of diabetes management, treatment, and complications. Our results demonstrated that lockdown has been lead to worsening metabolic syndrome

both in males and females. Future research will shed light on the long-term cardiometabolic consequences and burdens resulting from the COVID-19 pandemic.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the the Akdeniz University Faculty of Medicine Clinical Researches Ethics Committee (Date: 18.08.2021, Decision No: KAEK-559-560).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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The impacts of comorbid diseases on surgical and clinical outcomes in spondylolisthesis surgery

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ABSTRACT

Aims: Management of comorbidities has a significant bearing on clinical outcomes from surgery, especially in the context of wound healing and pain management. This study aims to compare surgical patients with comorbidity (case group) and without (control group) based on recovery outcomes.

Methods: Surgical patients n=150 were enrolled patients in the case group (n=75), and control group (n=75). We collected and compared baseline demographic data, preoperative and postoperative pain levels based on the Visual Analogue Scale, discharge outcomes and assessment of wound healing. Factors affecting wound healing were evaluated using multivariate logistic regression, and predictors of postoperative pain were examined with multivariate linear regression.

Results: Demographic data revealed that the groups were comparable regarding age (p=0.122) and gender (p=0.758). The case group did have a higher mean body-mass index (BMI) of 28.9±3.4 than the control group mean BMI, which was 25.7±2.9; (p<0.001). Preoperative 7.5±1.2 vs 6.8±1.1, (p=0.001) and postoperative 4.8±1.5 vs 3.2±10, (p<0.001), pain scores were significantly greater in the case group. This is especially true for the case group, as only 40% were discharged in less than or equal to 24 hours compared with 73.3% of control (p<0.001). Cure of all wounds occurred in 90.7% of controls compared with 66.7% of cases (p<0.001), and delayed healing was significantly greater in cases (33.3% vs 9.3%, p=0.002). The case group had an odds ratio of 0.25 (p<0.001) for complete wound healing on multivariate analysis whereas group status, age, BMI and diabetes mellitus were significant postoperative pain predictors.

Conclusion: These findings highlight the need to direct resources towards preoperative evaluations before spondylolisthesis surgery and strategies in recovery after surgery for patients with diseases/disorders relevant to common problems seen.

Keywords: Spondylolisthesis, comorbid diseases, wound healing, spine surgery

INTRODUCTION

Spondylolisthesis is a spinal disorder with the anterior slipping of one vertebra relative to another, giving rise to varying degrees of instability and neurological impairment. This can occur at any level of the lumbar spine, but happens more commonly in L4-L5 and L5-S1 segments. Spondylolisthesis comes in multiple types (isthmic, degenerative, traumatic or pathological) each with a different etiology and clinical significance.[1] The prevalence of spondylolisthesis differs widely between age groups or populations.[2] Studies have shown that it is isthmic spondylolisthesis is incredibly common in young people, especially sports, this has been estimated at owners 5-7%. Some studies say degenerative spondylolisthesis more frequent in older people, approximately 20% of individuals over the age of 50 will develop this condition is less typical.[3]

Moreover, although the disorder is more prevalent in women as compared to men, especially among degenerative types (suggesting hormonal factors such as changes after menopause affecting bone density and spinal fortitude). Additionally, geographical and ethnic disparities exist as some hereditary groups with a tendency towards spinal disorders have shown higher prevalence.[4] Clinically relevant, spondylolisthesis symptom severity ranges from mild discomfort to extreme pain and disability. In rare cases, nerve root compression may result in neurological deficits; patients often present with low back pain radiating to the lower extremities and muscle spasms.[5]

If the slippage compresses the spinal cord or nerve roots, it can cause pain, numbness, or weakness of the legs.[6] Radiculopathy is when nerve roots are compressed, leading to pain or sensory changes radiating down the lower extremities which often feels like shooting pain and can be debilitating. Spondylolisthesis is related with chronic pain syndromes that

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have enormous impact in the quality of life of the patient. This disease affects the physical mobility of an individual, leading to less participation in daily activities making mental health problems worse such as depression and anxiety.[7] Management is generally medical for chronic pain syndromes, and has a significant effect on the patient's quality of life.[8] The disease can significantly limit the physical activity of people with limiting their ability to move and participate in day-to-day activities contributing to mental health issues like depression and anxiety. Obesity, for example, can impede rehabilitation efforts and is linked to an increased risk of surgical complications. Diabetes can also worsen wound healing and make a person more prone to infections. To maximize surgical outcomes for patients with spondylolisthesis, a comprehensive evaluation and management of comorbidities are essential. This ensures that interventions are customized to each patient's particular health profile to produce the greatest outcomes.[9]

There are many studies relating comorbidity to adverse surgical outcomes regardless of procedure, illustrates the universal impact of comorbidities on the surgical outcomes.[10] These studies indicate that greater challenges in managing pain, slower wound healing, prolonged recovery time, and higher complication rates are common occurrences in patients who also have comorbidity factors such as obesity, diabetes, and cardiovascular disease. In fact, researches have shown that diabetes can impair the healing of surgical wounds leading to a greater risk of surgical site infections and longer hospital stays whereas obesity may cause increased postoperative pain and analgesic requirements.[11]

Comorbidities can impact surgical outcomes via different pathways, ranging from biological mechanisms such as reduced immune response to porous tissue perfusion which may contribute to delayed recovery. Likewise, comorbidities often require more complex perioperative management, as well as surgical techniques or anesthesia choice. Although comorbidities and surgical outcomes have been well described in the literature, there is limited information on these details specific to spondylolisthesis.[12] Most of the contemporary literature on spondylolisthesis surgery fails to take into account how comorbid disorders interact to affect the individual processes underlying both long-term recovery from disability and functional improvement. A comprehensive knowledge of the drug–drug interactions that exist for each clinical situation we may encounter in this setting is, however, critical for appropriate risk stratification and management planning as it allows clinicians to identify high-risk patients who will benefit from more aggressive postoperative care or further optimization preoperatively.[13] Focusing on outcomes such as pain, wound healing rates, recovery curves over time and complications measured by frequencies, our study was analysing the impact of different comorbidities on surgical results in spondylolisthesis patients. This study is designed to provide information that could translate into clinical practice, effective management of patients in cardiothoracic surgery, and most importantly lead to improved surgical outcomes.

Our study aims to compare surgical patients with comorbidity (case group) and without (control group) based on recovery outcomes.

METHODS

The study was carried out with the permission of the Hitit University Faculty of Medicine Clinical Researches Ethics Committee (Date: 17.12.2022, Decision No: 2022-14). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This cross-sectional study was conducted in a cohort of 150 patients who were diagnosed with spondylolisthesis requiring surgery. The study duration was six months from Feb 2023 to Jul 2023 at Çorum Erol Olçok Training and Research Hospital, Department of Neurosurgery. Patients were classified into two groups at baseline in equal number of patients. Diabetes mellitus, hypertension, and aspirin intake were history in 75 cases of patients paralleled with the case group. It compared each case subject to 75 age- and sex-matched controls without any of these disorders.

Inclusion criteria: Confirmed diagnosis of spondylolisthesis, age range 18-60 years and the willingness to follow the study's guidelines and finish all necessary tests is a must.

Exclusion criteria: As we were analyse patients with bleeding disorders, those who also had other underlying diseases (for example: haemophilia) or difficulties for blood clotting medications that affected blood clotting were excluded from our study.

Total patient number was 150 followed through the hospital registration system. Background data including age, sex, body-mass index (BMI) and surgery duration were taken from the patient's files. Our study examined the following outcomes. Measures: Visual Analogue Scale (VAS) for the severity of, (Q1) preoperative radicular pain and (Q2) postoperative radicular pain (grade 0-10: grade 0=no pain; grade 10=as severe as I could imagine). Discharge status from Surgical Site: The status of discharge was collected. Wound healing: The patient was interviewed, and the surgical field inspected through at physical examination by a neurosurgeon.

Statistical Analysis

The data was analysed by SPSS 21. Quantitative variables are presented as mean±standard deviation (SD) and categorical variables are summarized using frequency (percentage). Continuous variables were compared using a T test or Mann-Whitney test, depending on data distribution and the reaction of equal variances between study groups. Statistical analysis p values ≤0.05 were deemed statistically significant.

RESULTS

Table 1 displays the baseline characteristics of subjects who were segregated into two categories, the control group (normal patients without underlying comorbidities) and the case group (patients with comorbids).

Table 1. Baseline characteristics of patients

Characteristic	Case group (n=75)	Control group (n=75)	p-value
Age (years)	39.0±12.4	39.8±11.5	0.122
Gender (M/F)	40/35	42/33	0.758
BMI (kg/m^2)	28.9±3.4	25.7±2.9	<0.001
Duration of surgery (min)	120.3±15.2	110.1±10.8	0.004

M/F: Male/female, BMI: Body-mass index, min: Minute

The average age of the control group is 39.8 years. The average age of the case group was 39.0 years. The p-value for age is 0.122, which indicates that the two groups are equal concerning this covariate and therefore do not differ statistically from each other in terms of this variable. Likewise there is no significant difference in the gender distribution; 40 males and 35 females in case group while 42 males and 33 females in control group (p=0.758). The mean BMI of the case group is 28.9 (±3.4), which is significantly higher than that of the control group, whose mean BMI equals 25.7 (±2.9). A significant difference was found between case and control groups where the average weight for cases is heavier (p-value in BMI <0.001). Regarding the duration of the surgery the average time for the case group was 120.3 minutes (±15.2), and the control group 110.1 minutes (±10.8). The p-value, here, 0.004, shows its statistically significant difference which means the procedure in the case group takes longer. All data were entered into Statistical Package for the Social Sciences software (version 23). Differences in continuous variables such as age, BMI and length of operation of continuous variables were analyzed using the independent samples T test whereas.

Table 2 and Figure 1 reveals that both groups (case and control group) were assessed for radicular pain preoperatively and six weeks after surgery using the VAS. Preoperative VAS, the case group's score=7.5 (±1.2), demonstrates considerable pain levels before surgery. However, the control group's preoperative VAS score is much lower at 6.8 (±1.1). Statistical comparison of preoperative pain between two groups showed statistically significant differences between two groups, p value=0.001 indicating that a case group is more deluged by the pain as compared to the control group. Postoperatively, VAS is 4.8 (±1.5) for the case group and significantly lower at 3.2 (±1.0) for the control group, respectively. The postoperative pain for patients in the case group remains more severe postoperatively (p<0.001) suggesting a highly significant difference. Continuous variables: differences were analyzed using an independent samples T test.

Table 2. The severity of preoperative and postoperative radicular pain measured by the VAS

Pain measurement	Case group (n=75)	Control group (n=75)	p-value
Preoperative VAS score	7.5±1.2	6.8±1.1	0.001
Postoperative VAS score	4.8±1.5	3.2±1.0	<0.001

VAS: Visual Analogue Scale

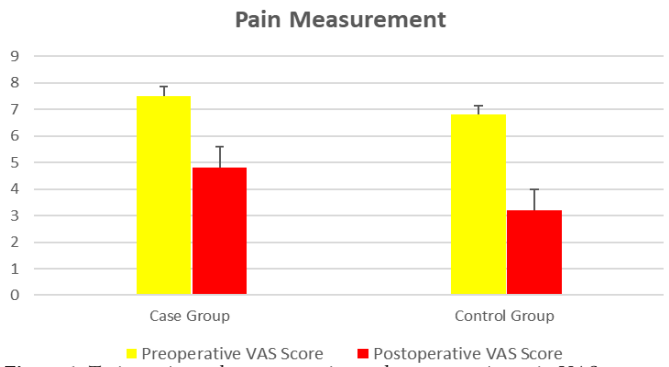

Figure 1. To investigate the preoperative and postoperative pain VAS score
VAS: Visual Analogue Scale

Table 3 and Figure 2 reveal the discharge outcomes. However, in the control group, hospital discharges occurred within 24 hours after surgery for 55 patients (73.3%) of the total. In contrast, only 30 of patients from the case group (40% of the total) were discharged from hospital. Statistically significant difference in discharge outcomes between both groups, with case group being discharged later (p<0.001). On the contrary, only 20 patients (26.7%) in control group left the ward after 24 h and 45 patients (60%) in case group with significant difference on discharge time (p=0.001). A chi-square test was performed for these categorical variables.

Table 3. Discharge from surgical site

Discharge outcome	Case group (n=75)	Control group (n=75)	p-value
Discharged within 24 hours	30 (40%)	55 (73.3%)	<0.001
Discharged after 24 hours	45 (60%)	20 (26.7%)	<0.001

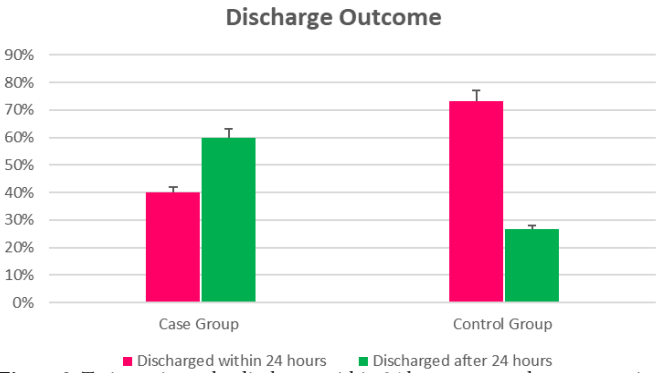

Figure 2. To investigate the discharge within 24 hours pre- and post-operative

Results of wound healing were shown in Table 4 and Figure 3. Total healing was attained in 68 patients (90.7%) of control group and 50 patients (66.7%) of case group (p<0.001). The p-value 0.002 indicates a statistically significant difference in the healing state between both experimental groups, to the favor of the control group. Moreover, delayed recovery occurred in only 25 patients (33.3%) from the case group and 7 patients (9.3%) from the control group. This difference is also statistically significant, as denoted by the identical p-value of 0.002. A chi-square test was performed to compare the wound healing status among groups.

Table 4. Wound healing assessment evaluated during follow-up visits

Wound healing status	Case group (n=75)	Control group (n=75)	p-value
Complete healing	50 (66.7%)	68 (90.7%)	0.002
Delayed healing	25 (33.3%)	7 (9.3%)	0.002

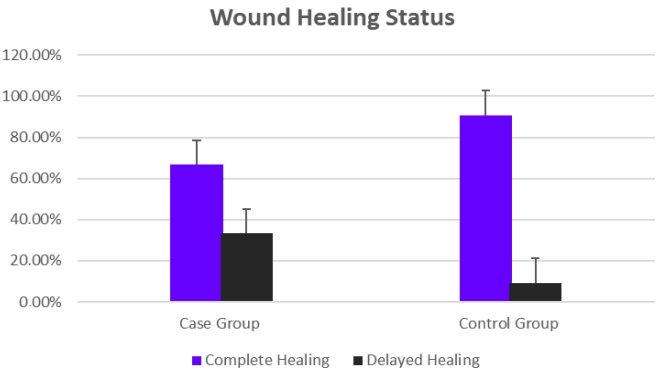

Figure 3. Wound healing was evaluated during follow-up visits

Table 5 presents the results of a multivariate logistic regression assessment of potential factors influencing postoperative wound healing status in patients.[8] Odds ratio (OR) (case vs control), 0.25; p<0.001; 95% confidence interval (CI), 0.12 to 0.53. That is to say, compared with the control group, full wound healing in patients of case group was very unlikely. Age shows an OR of 1.05 having a significant p-value (0.002) which means that with every more year of age the chances of full healing increase. There was no difference in healing status by gender with an OR of 0.80 (p=0.556), suggesting that the distinction between females and males may be negligible. Every increase in BMI is associated with a significant 12% increased odds of delayed healing [OR 1.12 (95% CI, 1.06-1.20), p=0.002]. Diabetes mellitus is associated with an OR of 0.40 (p=0.014) meaning that patients with the disease are less likely to be fully recovered. Hypertension, with an OR of 0.55 (p=0.140) showed a trend towards significantly decreased likelihood of recovery. Use of aspirin did not demonstrate a strong association with healing (OR=0.60, p=0.175). Finally, for surgery duration, the OR is 1.02 (p=0.021), indicating that increased surgical times suggest an increase in delayed wound healing risk. Overall, the study highlights key factors affecting wound healing with respect to age, BMI and diabetes status of case group.

Table 5. Multivariate logistic regression analysis of wound healing status

Variable	OR	95% CI	p-value
Group (case/control)	0.25	0.12-0.53	<0.001
Age (per year)	1.05	1.02-1.09	0.002
Gender (female/male)	0.80	0.39-1.63	0.556
BMI (per unit increase)	1.12	1.04-1.20	0.002
Diabetes mellitus	0.40	0.19-0.83	0.014
Hypertension	0.55	0.25-1.20	0.140
Aspirin use	0.60	0.29-1.24	0.175
Surgery duration (per min)	1.02	1.01-1.04	0.021

OR: Odds ratio, CI: Confidence interval, BMI: Body-mass index

Table 6 summarizes the findings from a multivariate linear regression analysis of postoperative pain in relation to various predictors. The average difference in CI value is: 1.80 (case group compared to control) with t-value of 4.00, standard error (SE): 0.45, p-value <0.001 highly significant. The implication here is that postoperative pain scores are significantly higher for case group patients than control group groups.

Table 6. Multivariate linear regression analysis of postoperative pain scores

Variable	Coefficient (β)	SE	t-value	p-value
Group (case/control)	1.80	0.45	4.00	<0.001
Age (per year)	0.05	0.02	2.50	0.013
Gender (female/male)	-0.20	0.30	-0.67	0.507
BMI (per unit increase)	0.10	0.05	2.00	0.046
Diabetes mellitus	0.90	0.40	2.25	0.027
Hypertension	0.50	0.38	1.32	0.189
Aspirin use	0.40	0.35	1.14	0.256
Surgery duration (per min)	0.02	0.01	2.00	0.047

SE: Standard error, BMI: Body-mass index

Age has a coefficient of 0.05 (p=0.013), which implies that there is an increase in postoperative pain scthes with patient age amounting to a small but statistically significant difference the p-value of the coefficient for gender is 0.507 (coefficient -0.20) indicating, respectively, that there is no difference in pain scores between males and females. The BMI coefficient of 0.10 (p=0.046) indicates that higher BMI is significantly associated with increased postoperative pain; every unit increase in the BMI scale results in a 0.1-point increase on the 10-point verbal numeric rating scale for postoperative pain, indicating moderate effect size. Diabetes mellitus is associated with coefficient (p=0.027) of 0.90, indicating that patients who are diabetic have more pain than expected after surgery. Pain scores were also influenced neither by use of aspirin nor hypertension, with respective coefficients 0.40 (p=0.256) and 0.50 (p=0.189). Finally, the length of surgery showed a coefficient of 0.02 (p=0.047) and indicating that longer surgical times are related to higher levels of postoperative pain. This analysis illustrates the effect of age, BMI, diabetes and group to predict outcomes in post-operative pain.

DISCUSSION

Spondylolisthesis a relatively common spine condition is caused by high energy traumas, degenerative changes or developmental abnormalities.[14] Surgical treatment usually involves decompression and stabilization to alleviation pain and restore function. Conversely, patient outcomes may be impacted by underlying comorbidities and surgery may additionally be complicated.[15]

The investigation of the baseline features displayed vital insights into the demographic and clinical attributes of individuals enrolled in this study. Many important characteristics were compared between the control group, which included healthy individuals without any underlying medical issues, and the case group, consisting of patients with comorbidities.[16]

No statistically significant difference was found between the two groups (p=0.122). Mean age was 39.0 years (±12.4) for case and 39.8 years (±11.5) for controls, respectively.[17] This means that the study doesn't suffer from an age-related complication and allows us to have a clearer comparison of surgery outcomes. The p-value of the gender distribution was 0.758, suggesting no apparent differences in the gender composition and limiting gender-related biases.[18]

BMI was a notable finding with a mean of 28.9 (±3.4) in the case group against a mean of 25.7 (±2.9) in controls.[19] Mean BMI was significantly lower in the control than the case group (p<0.001, and still remarkable being that this higher mean value for the case is difference in terms of percentage). Elevated BMI is commonly associated with comorbid conditions, such as diabetes, hypertension and cardiovascular disorders that can impact surgical outcomes, recovery and complications. This underscores the need for closer surveillance and tailored surgical treatment strategies in patients with elevated body mass indices.[20]

The duration of the operation was also significantly longer in the case group with a p-value of 0.004 at 120.3 minutes (±15.2) versus 110.1 minutes (±10.8) in the control group.[21] This

means that the procedures performed in the case group were more complex with longer times to intervene. This extended duration might be associated with significantly protracted convalescence and an increased peril of postoperative complications, affirming that patients harboring comorbidities are best managed with targeted postoperative treatment strategies.[10]

In our study findings that preoperative postoperative pain levels had results largely similar to our studies, which adds credibility to the hypothesis of a relationship between comorbidities and pain perception. Laratta et al.,[22] conducted an exploration of pain ratings with surgical patients of different comorbidities and identified similar patterns. In their study, patients with multiple comorbidities had a mean score of 7.4 for preoperative VAS, which value is very comparable to the crusader VAS value of 7.5 in our case group. This similarity bolsters the hypothesis that baseline pain levels lit related to surgery can be dramatically raised by preoperatively malady.

In our study, it was found that the patients with comorbidities presented higher pain than healthy patients after surgery (4.6 vs. 3.1 in mean VAS score respectively). The persistence of these findings underscores the need for better pain management strategies in that population and the chronic nature of the pain faced by patients with comorbid illnesses.[23]

Additionally, Schneider et al.[24] studied the impact of other chronic diseases on early recovery outcomes and postoperative pain. The researchers found, moreover, that those with comorbidities not only reported significantly higher pain scores but also used opioids for particularly longer durations and had slower functional recovery than those without comorbidities. These findings are similar to our results, where we observed significantly higher pain scores (4.8±1.5) in the case group a week postoperatively, the rationale being that patients with higher levels of postoperative pain may become quite dependent on analgesics thereby prolonging hospital stay.[25] When taken together with earlier studies, our results show the importance of adjusting pain management protocols for surgical patients with comorbidities. Based on prior research, the unique challenges presented by these patients warrant an individualized plan for pain management aimed at optimizing recovery while minimizing complications associated with inadequate treatment of pain. Taken together, our study adds further evidence for the relationship between comorbidities and pain while also providing a rationale for precautionary measures to ensure optimal pain management in surgical cohorts at risk. Closer monitoring and longer-term care are required due to these problems, including infections, delayed mobilization, and generally poor physiological responses.[26]

Additionally, our evaluation of wound healing showed that only 66.7% of the case group experienced full healing, compared to 90.7% of the control group ($p<0.001$). The case group's noticeably greater rate of delayed healing (33.3% vs. 9.3%, $p=0.002$) supports earlier research showing how comorbidities, especially diabetes and obesity, negatively impact wound healing. For instance, compared to patients without diabetes, diabetic patients had a 40% increased risk of developing wound-healing issues, according to Farmer et al.[27] study. This is probably caused by elements linked to various disorders, such as decreased blood flow, neuropathy, and weakened immune response.

The multivariate analyses of wound healing and postoperative discomfort yield a comprehensive understanding of the key factors influencing recovery outcomes in our study. The multivariate logistic regression analysis indicated that the odds ratio of complete wound healing in the case group was substantially lower than that in the control group (0.25, $p<0.001$). As shown in this figure, comorbidities significantly impacted recovery, consistent with the literature indicating that several variables including age, BMI and diabetes are strong predictors of clinical wound healing outcomes.[28]

This research backs up earlier studies particularly when it came to the role of diabetes. In a landmark work by Rabah et al.[29] if patients are suffering from diabetes the chances of patient's wound healing poorly were significant during this period mainly due to decreased perfusion and immunity. As in our results, wherein case group patients had more diabetes and increased BMIs with impaired wound healing, their findings showed that diabetic patients had three times higher incidence of poor wound healing compared to non-diabetic patients. Many studies have repeatedly identified age as a predictor for impaired wound healing. They explained that older adults healed slower than younger persons due to physiological changes with aging and reduced collagen synthesis. Our inclusion of age as a strong predictor, which suggests that patients may be vulnerable to factors preventing proper healing in greater numbers the older they get, supports these results.[30]

The multivariate linear regression analysis of postoperative pain sheds further light on the factors affecting our cohort's perception of pain. These included diabetes mellitus ($p=0.027$), age ($p=0.013$), BMI ($p=0.046$) and group status (case v control, $p<0.001$). Consistent with other investigations that identified comorbid diseases as significant factors for postoperative pain, the case group had higher scores for discomfort. For example, Ge et al.[31] found that patients with higher BMIs often reported increased pain levels post-surgery due to increased tissue trauma and inflammatory responses.

In addition, diabetes has been shown to lead to high levels of pain after surgery. The people with diabetes not only feel the pain more strongly but they also likely to have a very different pathway which is altered in such as way that their suffering state may be worse as they have added pathways for pain which are further intensified due to changes occurring inside and outside of them as well. These findings are in alignment with our results demonstrating that high VAS scores were significantly associated with diabetes among the case group, suggesting that tailored pain management strategies may be especially important for this population.[32]

By demonstrating clear associations between these variables and patient recovery, our study underscores the importance of comprehensive preoperative assessments and individualized postoperative care plans. This may help enhance surgical outcomes and recovery rates, possibly in patients with comorbidity burdened health disparities. By building on

earlier studies, we can better address the challenges posed by comorbidities in surgical populations. These lessons will assist us in improving our patient care and management processes.

CONCLUSION

Patients with comorbidities have blunted surgical outcomes, characterised by a higher intensity postoperative pain and slower ticks of the wound. Our findings underscore the need for risk stratification of patients undergoing surgical procedures in advance to implement targeted pre-operative assessments and postoperative rehabilitation strategies after surgery in at-risk populations. More studies are still needed to determine how to safely provide pain management and wound care safely in patients across all combinations of these health characteristics.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Hitit University Faculty of Medicine Clinical Researches Ethics Committee (Date: 17.12.2022, Decision No: 2022-14).

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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Evaluation of the physical and emotional effects of the earthquake in fibromyalgia patients

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ABSTRACT

Aims: Fibromyalgia (FMS) is a soft tissue disease characterized by widespread pain and tenderness. Poor living conditions and stress can cause the symptoms of the disease to aggravate. Natural disasters such as earthquakes can also increase the severity of symptoms such as pain and sleep disturbance in fibromyalgia patients by creating physical and psychological stress. In this study, we aimed to show the physical and psychological effects of the earthquake on fibromyalgia patients.

Methods: Our study is of prospective type and was conducted between 01.09.2023 and 01.11.2023. 59 earthquake victims and 50 non-earthquake victims FMS patients diagnosed with FMS according to the ACR2016 diagnostic criteria were included. All patients filled out four forms: Perceived Stress Scale (PSS) showing psychological states, Fibromyalgia Impact Questionnaire (FIQ) showing physical states, EuroQol Group (EQ5D3L) general quality of life scale showing quality of life, EQ5D3L-VAS scale showing pain conditions and Pittsburgh Sleep Quality Index showing sleep quality.

Results: ASD, FIQ, EQ5D3L, EQ5D3L-VAS and Pittsburg scores of fibromyalgia patients who were earthquake victims were statistically significantly higher than FMS patients who were non earthquake victims (respectively $p=0.008$, $p<0.001$, $p=0.008$, $p=0.008$, $p=0.008$).

Conclusion: It is known that the risk of developing chronic pain syndromes and psychological distress increases after unexpected natural disasters such as earthquakes. In this study, we showed that the earthquake negatively affected pain, fatigue, sleep and quality of life in fibromyalgia patients. Thus, we tried to draw attention to the importance of appropriate screening, management, emotional support and mental health services for post-earthquake fibromyalgia patients.

Keywords: Fibromyalgia, pain, natural disaster, earthquake

INTRODUCTION

Natural disasters such as earthquakes negatively affect people physically and psychologically. In addition, it causes economic and social difficulties. Two major earthquakes of magnitude 7.7 and 7.6, with the epicenter in Kahramanmaraş, occurring in Turkiye on February 6, 2023, and approximately 17,000 aftershocks that occurred subsequently, caused serious losses to a large part of the society. According to the latest reports of the World Health Organization (WHO), more than 50 thousand deaths occurred in the earthquake, which affected approximately 15 million people in 10 provinces, and more than 3 million people had to change their place of residence.[1] In addition, individuals suffered serious social and economic damage due to the destruction of historical places, destruction of business centers that provide employment, damage to schools, hospitals becoming unusable and lack of resources that will arise in the future

Fibromyalgia (FMS) is a soft tissue disease that is characterized by widespread pain and tenderness and occurs through central sensitization.[3] In addition to symptoms such as widespread pain, sleep disturbance, fatigue, and cognitive dysfunction, anxiety and depression are also frequently observed in these patients.[4] There is evidence of a relationship between traumatic experiences and the prevalence of fibromyalgia.[5] Poor living conditions and stress can cause the symptoms of the disease to aggravate. Natural disasters such as earthquakes, floods and fires can increase the severity of symptoms in fibromyalgia patients because they are stress factors.[6] Evaluation of these patients is very important in terms of patient management and possible worsening of the disease course. Considering the deteriorations in the climate, various geological factors and the damage caused to nature by humans, the expected increase in natural disasters in the future shows the importance of

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this issue. In this study, we aimed to show the effect of the earthquake on the physical and mental states of fibromyalgia patients.

METHODS

Study Design

Our prospective study was approved by the Harran University Clinical Researches Ethics Committee (Date: 21.08.2023, Decision No: HRÜ/23.15.30). The study protocol was prepared in accordance with the Declaration of Helsinki. Informed written consent was obtained from the participants in the study.

Participants

A total of 109 patients, 59 patients from Şanlıurfa, the earthquake region, and 50 patients from Istanbul, the region not affected by the earthquake, over the age of 18 years diagnosed with fibromyalgia according to American College of Rheumatology 2016 diagnostic criteria was included in the study. Patients with major depression, history of chronic disease, heart disease, diabetes mellitus, rheumatic disease and malignancy were not included.

Collection of Data

59 patients with fibromyalgia who applied to the Physical Medicine and Rehabilitation outpatient clinic of Şanlıurfa Training and Research Hospital between 01.09.2023 and 01.11.2023, and 50 patients with fibromyalgia who applied to the Physical Medicine and Rehabilitation outpatient clinic of İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital on the same dates, were included in the study.

Demographic characteristics of the patients, including age, gender, marital status, educational status and body-mass index (BMI), were recorded. A total of four forms were filled out: the Perceived Stress Scale (PSS), which shows their psychological state, the Fibromyalgia Impact Questionnaire (FIQ), which shows their physical condition, the EuroQol5D3L General Quality of Life Scale, which shows their quality of life, and the Pittsburgh Sleep Quality Index, which shows their sleep quality.

Perceived Stress Scale (PSS): The PSS developed by Cohen et al.[7] is a self-reported measure of perceived stress, feelings, and thoughts in the past month. The PSS consists of 14 items scored on a 5-point Likert-Type Scale ("1=never" to "5=very Often"). The total score ranges from 14 to 70, with higher scores indicating higher stress levels. The PSS was adapted to Turkish by Eskin et al.[8]

Fibromyalgia Impact Questionnaire (FIQ): The FIQ developed by Burchardt et al.[9] is used to assess the health status and physical functionality of individuals diagnosed with fibromyalgia. It is a 10-item scale that evaluates work status, productivity level, depression, anxiety, sleep, pain, stiffness, fatigue, and overall well-being. Patients are asked to indicate the most appropriate level for themselves over the past week. The total score achievable on the test is 100, with higher scores indicating lower levels of functionality. The Turkish validity of the questionnaire was established by Ediz et al.[10]

EuroQol5D3L: The EuroQol 5-dimension 3-level (EQ-5D-3L) instrument is a standardized, generic measure developed by the EuroQol Group to assess health-related quality of life. It encompasses five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels of severity: no problems, some problems, and extreme problems. Additionally, the EQ-5D-3L includes a Visual Analogue Scale (EQ VAS) ranging from 0 to 100, allowing individuals to rate their overall health status. The instrument is widely utilized in clinical and economic evaluations due to its simplicity, reliability, and validity.[11]

Pittsburgh Sleep Quality Index (PSQI): It is developed by Buysse et al.[12] in 1989, is a 24-item instrument used to evaluate sleep quality over the past month. Of these, 19 questions are self-assessment items, while the remaining 5 are answered by the individual's roommate or partner, if applicable. The calculation of the total PSQI score and component scores is based solely on the responses provided by the participant. These questions provide information on seven components: subjective sleep quality (component 1), sleep latency (component 2), sleep duration (component 3), habitual sleep efficiency (component 4), sleep disturbances (component 5), use of sleep medication (component 6), and daytime dysfunction (component 7). Each component is scored on a scale of 0 to 3. The sum of the seven component scores constitutes the total PSQI score, which ranges from 0 to 21. Individuals with a total score of 5 or less are considered to have "good" sleep quality, whereas those with a score above 5 are categorized as having "poor" sleep quality.[12] The validity and reliability of the PSQI in Turkiye were established by Ağargün et al.[13]

Statistical Analysis

The data analyses were performed with SPSS version 25.0 program. The suitability of the data for normal distribution was examined using the Shapiro Wilk test and histogram graphics. According to the normality test results, continuous variables were presented as median (minimum: maximum) values and categorical variables as number (n) and percentage (%). Categorical variables between the two groups were compared with the Pearson chi-square test. Mann Whitney U test was used for variables that were not normally distributed, and Spearman correlation analysis was used for correlation analysis. A value of $p<0.05$ was considered statistically significant.

RESULTS

There was no statistically significant difference in the comparisons made between fibromyalgia patients who were earthquake victims and patients who did not experience an earthquake in terms of gender, age, BMI, education level and marital status (**Table 1**).

The median PSS score of fibromyalgia patients who were earthquake victims was 31, and it was statistically significantly higher than the median ASD score of non-earthquake FMS patients ($p=0.008$) (**Table 2**).

The median FIQ score of fibromyalgia patients who were earthquake victims is 74, which is statistically significantly higher than the median FIQ score of non-earthquake FMS patients ($p<0.001$).

Table 1. Demographic data

	Earthquake victim FMS (n=59)	Non-earthquake victim FMS (n=50)	p
Gender[a]			
Woman	46 (78%)	30 (60%)	0.068[2]
Male	13(22%)	20 (40%)	
Age[b]	39.8±10.1	43.2±8.8	0.100[1]
BMI[b]	26.9±4.8	26.1±3.8	0.061[1]
Education[a]			
Primary school	43 (72.9%)	31 (62%)	0.121[2]
Middle school	12 (20.3%)	9 (18%)	
High school/university	4 (6.8%)	10 (20%)	
Marital status[a]			
Married	56 (94%)	42 (84%)	0.117[2]
Single/divorced	3 (5%)	6 (5.1%)	

FMS: Fibromyalgia, a: n (%) b: mean±standart deviation 1: Mann-Whitney U, 2: Pearson chi-square

Table 2. Clinical data

	Earthquake victim FMS (n=59)	Non-earthquake victim FMS	p
PSS[a]	31 (16-49)	28 (11-40)	0.008[1]
FIQ[a]	74 (16-90)	57.6 (11.3-88.5)	<0.001[1]
EQ5D3L[a]	0.56 (0.1-1)	0.35 (0.08-1)	0.008[1]
EQ5D3L-VAS[a]	40 (0-100)	60 (10-80)	<0.001[1]
Pittsburg[a]	12 (4-21)	9 (3-16)	<0.001[1]

FMS: Fibromyalgia, PSS: Perceived Stress Scale, FIQ: Fibromyalgia Impact Questionnaire, EQ5D3L: EuroQol5D3L, [a]: median (min-max), [1]: Mann Whitney U

The median EQ5D3L score of fibromyalgia patients who were earthquake victims is 0.56, which is statistically significantly higher than the median EQ5D3L score of non-earthquake FMS patients (p=0.008) (Table 2).

The median EQ5D3L-VAS score of fibromyalgia patients who were earthquake victims is 40, which is statistically significantly higher than the median EQ5D3L-VAS score of non-earthquake FMS patients (p=0.008) (Table 2).

The median Pittsburg score of fibromyalgia patients who were earthquake victims is 12, which is statistically significantly higher than the median Pittsburg score of non-earthquake FMS patients (p=0.008) (Table 2).

There is a moderate positive correlation between PSS and FIQ (rho=0.495 p<0.01) (Figure).

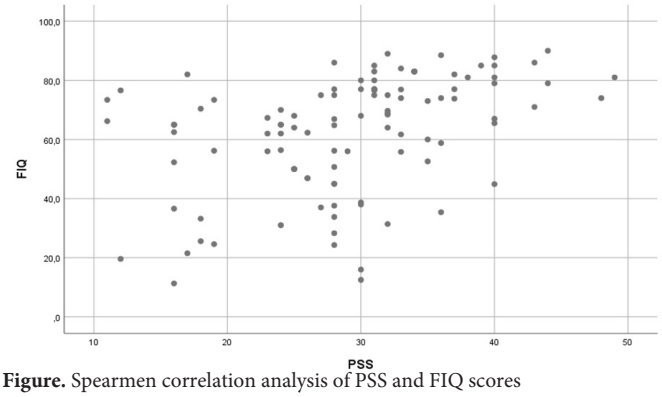

Figure. Spearmen correlation analysis of PSS and FIQ scores

PSS: Perceived Stress Scale, FIQ: Fibromyalgia Impact Questionnaire

In our study, 59.3% of earthquake victim fibromyalgia patients reported that their general health status was affected by the earthquake. 21.7% of patients rated their general health as worse and 37.3% of patients rated their general health as much worse after the earthquake. Additionally, 64.4% of the patients reported that their pain levels were affected by the earthquake. 15.3% of patients rated their pain levels as worse and 49.1% of patients rated their pain levels as much worse after the earthquake (Table 3).

Table 3. Earthquake-related pain and general health condition

Did the earthquake affect your general health?	n	%
Yes	35	59.3
No	24	40.7
How did the earthquake affect your general health?		
Much worse	22	37.3
Worse	13	21.7
Matter	0	
Much matter	0	
Did the earthquake affect your pain level?		
Yes	38	64.4
No	21	35.6
How did the earthquake affect your pain level?		
Much worse	29	49.1
Worse	9	15.3
Matter	0	
Much matter	0	

DISCUSSION

In our study, we showed that earthquake, one of the natural disasters, negatively affects pain, fatigue, sleep and quality of life in fibromyalgia patients. Destruction of living spaces after an earthquake, death of close friends and relatives, uncertainty about the future and many other earthquake-related factors lead to acute and chronic stress. Acute and chronic stress are known to trigger fibromyalgia symptoms.[14]

It has been shown in many studies that people's physical and mental health conditions are worse after the earthquake.[15-18] In addition to the devastating consequences of the initial impact of the earthquake, the difficult living conditions experienced in the post-earthquake period negatively affect people's general health status and pain levels. Cammack et al.[19] reported that two Christchurch earthquake survivors developed allodynia, chronic pain, and mood disorders requiring antidepressants and opioid analgesics after their general health stabilized. Similarly, Angeletti and colleagues examined the triage documents of nearly 1000 patients who applied to the emergency department with complaints of pain after the earthquake and found that 34.6% of the patients reported pain for various reasons. 58.8% of patients were affected by severe pain and 3% had widespread joint/muscle pain.[20] In our study, 59.3% of earthquake victims evaluated their general health condition as much worse after the earthquake. Additionally, 64.4% of patients rated their pain levels as much worse after the earthquake.

Natural disasters such as earthquakes are significant sources of stress for various reasons. It is well-established that stress is closely associated with sleep disturbances.[21] Several studies have demonstrated that sleep disorders are highly prevalent following earthquakes.[22,23] In a study conducted after the Great East Japan earthquake, the prevalence of insomnia was recorded at 9.7% in November 2009 (prior to the earthquake, with 1,224 participants), whereas in July 2011 (four months after the earthquake, with 1,259 participants), this rate had increased to 25.7%, which is 2.7 times higher than before the disaster.[22] In another study conducted in Athens, it was found that while sleep problems were reported in approximately 20-30% of adults in the general population, this rate increased to 60% in individuals from the disaster-stricken areas several months after the earthquake.[24] Moreover, the study identified difficulties in adapting to new living conditions as a predictor of sleep disturbances. In a study by Akbaş et al.,[25] thirty patients affected by the February 6, 2023 earthquake in Turkiye, were evaluated along with a control group of individuals not exposed to the earthquake. The results revealed a significant deterioration in sleep quality among the earthquake survivors compared to those not affected by the disaster. Similarly, in our own study, sleep disorders were found to be significantly more prevalent among earthquake survivors with fibromyalgia syndrome (FMS) compared to those who had not experienced the earthquake.

Numerous studies have been conducted on the health issues faced by disaster victims, with mental health problems such as depression and anxiety being the most commonly reported following disasters.[26] In a study by Guimaro and colleagues, psychological stress following the 7.0 magnitude earthquake in Haiti in 2010 was assessed. Survivors were monitored for two months, and it was found that 55% of the individuals exhibited symptoms of depression, and 40% displayed symptoms of anxiety.[27] In a study conducted in Turkiye with 100 elementary school teachers directly exposed to the February 6, 2023 earthquake, high levels of anxiety were reported post-disaster, and it was recommended that support interventions for disaster survivors be systematic.[28] Similarly, another study conducted after the same disaster identified that the traumatic responses exhibited by the disaster victims included emotions such as pain, fear, anger, guilt, tension, meaninglessness, uncertainty, withdrawal, and hopelessness.[29] Likewise, after the 7.4 magnitude Marmara earthquake in Turkiye in 1999, high levels of depression, post-traumatic stress, and anxiety were reported.[30] In a study conducted by Marthoenis et al.,[31] the predictors of depression and anxiety following an earthquake were investigated. Injury to a first-degree family member, hospitalization, and experiencing post-earthquake stress were identified as predictors of depression, while personal injury, the destruction of one's home, and fear of staying in buildings were found to be predictors of anxiety. A systematic review identified the primary risk factors for the development of mental health disorders following earthquakes as sociodemographic characteristics such as gender, age, and education, the level of exposure to the earthquake, peritraumatic distress, low social support, a history of personal or family mental health disorders, and exposure to other forms of trauma.[32]

There is a well-established relationship between stress and fibromyalgia. A study by Gupta and colleagues demonstrated that the activity of certain endocrine pathways and neurotransmitters changes in parallel in both fibromyalgia and stress. Furthermore, it was concluded that chronic stress induces changes in various hormones and neurotransmitters, which may contribute to the pain and fatigue symptoms observed in fibromyalgia.[33] Similarly, Malt et al.[34] found an exaggerated response to stressors in 42 women diagnosed with fibromyalgia. Another study by Salaffi at al.[35] found that, in fibromyalgia patients, perceived stress levels were significantly higher after the earthquake, along with increased levels of pain and fatigue. In our own study, a correlation was found between perceived stress and fibromyalgia activity in fibromyalgia patients.

After the Great East Japan disaster, Usui et al.[6] evaluated sensitivity to traumatic stress in fibromyalgia patients and showed that fibromyalgia patients were more sensitive to chronic rather than acute stress. In a study conducted in Italy with a 6-month follow-up after the earthquake, 55 fibromyalgia patients and 49 control groups were included, and although there was no significant difference in total FIQ, FAS score and SAPS (Self-Assessment Pain Scale) between the groups at the beginning, a significant difference was found in these scores at the end of 6 months. Higher results were obtained in fibromyalgia patients who experienced an earthquake compared to those who did not experience an earthquake.[35] Our study was conducted 6 months after the earthquake with a similar number of patients, and the FIQ, PSS and EQ5D3L scores of fibromyalgia patients who were earthquake victims were found to be higher than those who were not earthquake victims. These results show that although the disease activities of fibromyalgia patients may not change after acute stress, they may worsen with chronic stress, and therefore it is important to follow up these patients.

Cognitive and behavioral coping strategies in stress management; It plays an important role in preventing psychological trauma and mental disorders.[36] It has been found that people with higher levels of optimism are more resilient to stress and have better coping methods. It is also thought that education level and social support protect mental health and help mitigate stressful situations.[37] Tang et al.[38] They examined 349 earthquake victims after the 6.5 magnitude Ludian earthquake and found that physical and mental status varied by education and age. Earthquake victims with higher education levels had better methods of coping with stress. Similarly, Khachadourian et al.[39] In a cohort study they conducted after the Spitak earthquake, they measured the quality of life of 725 earthquake victims 23 years after the earthquake using the EQ5D5L Quality of Life Scale. This study showed that people who experienced the loss of close relatives and friends and received less socioeconomic support had worse quality of life. The authors also showed that the female gender has a poorer ability to cope with stress.[28,38] In a study conducted by Oztekin et al.[40] following the February 6th earthquake in Turkiye, 418 volunteers were assessed to examine the effects of demographic characteristics on post-earthquake stress, anxiety, and depression. The findings

revealed that women experienced significantly higher levels of stress and depression compared to men following the earthquake. Considering that fibromyalgia is more common in female gender, we can say that these patients will be worse affected by traumatic events such as earthquakes.

Limitations

The limitations of our study are that PTSD was not evaluated, the number of patients was small, and other accompanying stress factors such as loss of loved ones were not questioned. Studies with improved methodology and longer follow-up periods are needed on this subject.

CONCLUSION

Although many studies investigating the effects of unexpected natural disasters such as earthquakes on the daily lives of survivors have shown an increased risk of developing chronic pain syndromes and psychological distress after natural disasters, published data on fibromyalgia patients is quite limited. In this study, we showed that the earthquake negatively affected pain, fatigue, sleep and quality of life in fibromyalgia patients. Thus, we tried to draw attention to the importance of appropriate screening, management, emotional support and mental health services for post-earthquake fibromyalgia patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Harran University Clinical Researches Ethics Committee (Date: 21.08.2023, Decision No: HRÜ/23.15.30).

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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The role of Geriatric Nutritional Risk Index in sepsis-related mortality in intensive care

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ABSTRACT

Aims: This study explores the link between nutritional status and sepsis outcomes, focusing on Geriatric Nutritional Risk Index (GNRI) scores and clinical endpoints such as mortality, intensive care unit (ICU) stay duration, and functional recovery.

Methods: The study was a retrospective, observational investigation of 250 older patients with sepsis in the intensive care unit. GNRI was calculated based on admission albumin level and ratio of actual body weight to ideal body weight. Groups were defined as major risk (GNRI <82), moderate risk (GNRI 82 to <92), low risk (GNRI 92 to ≤98), and no risk (GNRI >98). The primary outcome measured was 28-day hospital mortality. Additionally, the relationship between the GNRI score and the SOFA and APACHE II scores was assessed.

Results: In the univariate analysis comparing median values between survivor and non-survivor groups, significant differences were found in body-mass index, albumin levels, C-reactive protein levels, SOFA score, APACHE II score, and GNRI score. The 28-day hospital mortality rates for each GNRI group were: 5.7% in the very low risk group (GNRI >98), 9.8% in the low risk group (GNRI 92-98), 8.5% in the moderate risk group (GNRI 82-92), and 35.8% in the very high risk group (GNRI <82). The optimal cutoff for predicting outcomes was identified as GNRI <85. In a comparison of area under the curve (AUC) values, GNRI demonstrated superior predictive ability compared to APACHE II and SOFA scores, with AUC values of 0.629 (95% CI 0.543-0.715) for GNRI, 0.579 (95% CI 0.493-0.664) for SOFA, and 0.550 (95% CI 0.455-0.646) for APACHE II.

Conclusion: This study demonstrates that GNRI is a significant predictor of mortality and prolonged length of stay in patients with sepsis in the ICU. These findings underscore the importance of assessing and improving nutritional status in the management of sepsis.

Keywords: Geriatric Nutritional Risk Index, sepsis, malnutrition, mortality

INTRODUCTION

Sepsis is a critical condition that arises from the body's overactive response to an infection, resulting in widespread inflammation, organ failure, and potentially fatal outcomes. This condition predominantly affects older adults and remains one of the leading causes of mortality in influencing sepsis outcomes in the elderly, and understanding this risk factor is crucial for improving patient prognoses.[1,2]

In older adults, sepsis can exacerbate or initiate nutritional deficiencies due to increased catabolic processes and insufficient oral intake. These patients face a higher risk of sepsis attributable to weakened immune function, multiple chronic diseases, and existing nutritional deficiencies. The progression of sepsis in this population can rapidly worsen, resulting in higher mortality rates compared to younger individuals. Therefore, it is crucial to assess the nutritional status of the elderly using comprehensive nutritional screening tools. Implementing early nutritional interventions based on reliable assessments can help mitigate the severity of illness and expedite recovery.[3] Among the available tools, the Geriatric Nutritional Risk Index (GNRI) has proven to be an essential predictor of sepsis-related mortality. The GNRI is a straightforward yet effective metric that incorporates body weight, height, and serum albumin levels. Lower GNRI scores are indicative of a higher risk of malnutrition and are associated with poorer clinical outcomes.[4]

One critical advantage of the GNRI is its ability to identify patients at risk of malnutrition before overt clinical symptoms manifest. Timely detection of at-risk patients can significantly inform clinical decision-making. The GNRI serves as a practical and swift screening tool, enabling healthcare providers to stratify patients based on nutritional risk and allocate resources effectively.[5] The nutritional risk screening 2002 (NRS-2002), another malnutrition screening tool, demands a more comprehensive assessment. In contrast, the

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malnutrition universal screening tool (MUST) primarily addresses the general population, rather than specifically targeting older intensive care unit (ICU) patients. This specificity makes the GNRI more practical and relevant for assessing nutritional risk in the elderly ICU demographic.[6]

While the GNRI is a valuable tool for identifying malnutrition, it has limitations, particularly its reliance on serum albumin levels. Albumin levels can be influenced by factors unrelated to nutritional status, such as inflammation, infection (e.g., sepsis), fluid imbalances (e.g., hypervolemia or dehydration), liver function abnormalities, and renal insufficiency. These conditions can significantly alter serum albumin concentrations, leading to potential misinterpretations of a patient's nutritional status. Consequently, the GNRI may not always accurately reflect the true nutritional health of individuals, especially in populations with high rates of comorbid conditions.[3]

To address these limitations, it is essential to use the GNRI alongside other clinical and nutritional assessments. Integrating comprehensive clinical evaluations, dietary intake records, anthropometric measurements, and other biochemical markers can provide a more holistic and accurate assessment of a patient's nutritional status. This multifaceted approach ensures that clinicians can identify and address malnutrition more effectively, thereby improving patient care and outcomes in vulnerable populations.

Few studies have examined the relationship between the GNRI and short-term mortality in acutely hospitalized older patients. This study aims to evaluate the predictive value of GNRI for outcomes in older ICU patients with sepsis. By analyzing the association between GNRI scores and various clinical endpoints, including mortality, length of ICU stay, and functional recovery, we aim to gain a deeper understanding of the impact of nutritional status on sepsis outcomes in this frail group.

METHODS

Ethics

The study protocol was approved by the KTO Karatay University Faculty of Medicine Non-drug and Medical Device Researches Ethics Committee (Date: 31.10.2024, Decision No: 2024/024) (Document Date and Number: 01.11.2024-96819). The study was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013.

Study Setting and Patients

This retrospective, descriptive, observational study focuses on patients with sepsis in ICUs. Conducted between January 1, 2022, and September 30, 2024, the study included 250 patients over the age of 65 who were followed for sepsis in the third step ICU (internal medicine 1-2-3) of Konya City Hospital, which has a total of 45 beds. Demographic, physiological, and laboratory data were collected. The GNRI score was classified into four categories according to Bouillanne et al.'s[4] study: major risk (GNRI <82), moderate risk (GNRI 82 to <92), low risk (GNRI 92 to ≤98), and no risk (GNRI >98).

Definition

Sepsis was diagnosed based on confirmed ICU admission for sepsis or infection, with accompanying organ dysfunction. This was identified using a Sequential Organ Failure Assessment (SOFA) score of 2 or above, in line with the third International consensus definitions for sepsis and septic shock (sepsis-3).[7] Severe sepsis is defined as sepsis in conjunction with one of the following conditions: cardiovascular organ dysfunction, acute respiratory distress syndrome, or dysfunction in two or more other organs. Septic shock is characterized by severe sepsis with persistent hypotension, necessitating vasopressor therapy despite adequate fluid resuscitation (20-30 ml of crystalloid per kilogram of body weight).[7]

Data Collection

We retrospectively gathered clinical and laboratory data from the hospital information system. For each patient, age, sex, height, body mass index, co-morbidities, sites of infection, vital signs, APACHE II score, Glasgow Coma Scale, and SOFA score were recorded. Both SOFA and APACHE II scores were utilized as mortality risk factors.

The GNRI score was calculated using the equation described by Bouillanne et al.[4] Ideal body weight (IBW) was determined according to the Lorentz formula, and the GNRI score was derived from the ratio of the admission albumin level and actual body weight to the IBW.

The Lorentz formula was used to calculate the IBW;

- For men: IBW=(height-100)-[(height-150)/4]
- For women: IBW=(height-100)-[(height-150)/2]

The GNRI score was calculated using the following formula:

- GNRI=[1.489×albumin (g/L)]+[41.7×(weight/IBW)]

Risk categories based on GNRI were defined as follows: very low risk (GNRI >98), low risk (GNRI 92-98), moderate risk (GNRI 82-92), and very high risk (GNRI <82).

Outcome Measures

The primary outcome measured was 28-day hospital mortality. Additionally, the relationship between the GNRI score and the SOFA and APACHE II scores was assessed.

Statistical Analysis

The data analyses were conducted using SPSS statistical software (version 21.0; SPSS, Chicago, IL, USA). Continuous variables were expressed as means with standard deviation (SD) for parametric data, or medians with interquartile range (IQR) for non-parametric data. Categorical variables were presented as numbers and percentages. Univariate analyses were performed using student's T test or the Mann-Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables.

For multivariate analysis, a logistic regression model with a stepwise variable selection method was employed. Variables that remained significant ($p<0.05$) in the multivariate model were considered independent predictors for 28-day hospital mortality. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each predictor.

To compare the discriminative ability of the GNRI, APACHE II, and SOFA scores, receiver operating characteristic (ROC) curve analysis with area under the curve (AUC) calculations was utilized. The cutoff points for mortality risk for each score were determined from the highest sensitivity and (1-specificity) values on the ROC curve.

RESULTS

Between January 1, 2022, and September 30, 2024, a total of 3,456 patients were admitted to the 45-bed internal medicine intensive care unit. Among these, 1,876 patients received intensive care for infection-related reasons. During this period, 876 patients were diagnosed with sepsis, and from this group, 250 patients aged 65 and older were included in our study. The overall 28-day hospital mortality rate was 28.9% (95% CI, 22.8%-33.0%). The characteristics of survivors and non-survivors are detailed in Table 1.

Table 1. General characteristics of the patients

Variable[a]	Total (n: 250)	Survivors (n: 178)	Non-survivors (n: 72)	p-value[b]
Age (years-mean±SD)	77±10.1	76±9.6	79±9.5	0.156
Male sex, n (%)	116 (46.4)	90 (50.5)	35 (48.6)	0.265
BMI, kg/m²-median (IQR)	23.4 (22.4-25.2)	22.7 (21.5-23.6)	20.9 (19.8-22.3)	<0.003
Sepsis severity, n (%)				
Severe sepsis	61 (24.4)	33 (19)	28 (38.8)	<0.012
Septic shock	27 (10.8)	17 (9.6)	10 (13.8)	<0.011
Co-morbidity, n (%)				
Hypertension	197 (78.8)	142(80)	55(79)	0.242
Diabetes mellitus	161 (64.4)	115(65)	46(64)	0.453
Cerebrovascular disease	73 (29.2)	53(30.1)	20(29.8)	0.324
Cancer	22 (8.8)	5 (2.80)	8 (11.1)	0.001
COPD	141 (56.4)	101(56.7)	40 (55.2)	0.165
Chronic kidney disease	17 (6.8)	12(6.7)	5 (6.1)	0.231
Congestive heart failure	116 (46.4)	82 (46)	34 (47)	0.435
Dementia	49 (19.6)	34 (19.1)	15 (20.1)	0.276
Site of infection, n (%)				
Lower respiratory	163 (65.2)	102 (57.3)	61 (84.7)	<0.001
Genitourinary	102 (40.8)	73 (41)	29 (40.1)	0.158
Hepatobiliary	35 (14)	24 (13.4)	11 (15.1)	0.276
Gastrointestinal	40 (16)	28 (15.7)	12 (16.2)	0.119
Laboratory parameter-median (IQR)				
Hemoglobin, g/dl	12 (10.6-13.4)	11.9 (10.8-13.2)	12.2 (9.6-12.4)	0.082
Platelet count, x1000 cells/mm³	225 (165-342)	221 (166-365)	217 (163-348)	0.584
Albumin, g/dl	3.8 (3.3-4.0)	3.6 (3.2-3.8)	2.9 (2.6-3.6)	<0.001
C-reactive protein, g/dl	101 (67-221)	106 (72-198)	110 (78-278)	<0.002
Mortality prediction model				
SOFA score-median (IQR)	2 (2-5)	2 (1-4)	4 (2-7)	<0.001
APACHE II-median (IQR)	19 (14-25)	18 (13-21)	27 (18-32)	<0.001
GNRI score-median(IQR)	94.3 (86.3-98.8)	95.1 (85.3-99.1)	84.3 (77.1-93.2)	<0.001
LOS in ICU (day)	12 (5-18)	13 (6-19)	18 (12-27)	<0.001

[a]Data are reported as mean±SD or percentages n (%) or the median IQR (inter quartile range), [b]Continuous and categorical variables were compared between groups with Mann-Whitney U test or the Fisher's exact test, respectively, p<0.05 was considered statistically significant in all analyses, SOFA: Sepsis-related organ failure assessment, APACHE II: Acute physiology and chronic health evaluation II, GNRI: Geriatric Nutritional Risk Index, COPD: Chronic obstructive pulmonary disease, LOS in ICU: Lenght of stay in intensive care unit, BMI: Body-mass index, N: Number, SD: Standard deviation, IQR: Inter-quartile range

In the univariate analysis comparing median values between survivor and non-survivor groups, significant differences were observed in body-mass index, albumin, C-reactive protein, SOFA score, APACHE II score, and GNRI score. Similarly, sepsis, septic shock, cancer, lower respiratory infection, and ICU length of stay also showed significant differences between survivors and non-survivors (Table 1).

The 28-day hospital mortality rates for each GNRI group were as follows: 5.7% in the very low-risk group (GNRI >98) (OR, 2.378; 95% CI, 0.981-7.527), 9.8% in the low-risk group (GNRI 92-98) (OR, 2.874; 95% CI, 1.023-7.872), 8.5% in the moderate-risk group (GNRI 82-92) (OR, 3.125; 95% CI, 1.745-8.683), and 35.8% in the very high-risk group (GNRI <82) (OR, 16.341; 95% CI, 7.215-32.143).

The optimal cutoffs for the indicators were GNRI <85, with a sensitivity of 61.9%, specificity of 78.8%, positive predictive value (PPV) of 32.3%, and negative predictive value (NPV) of 91.2%.

The ROC curves for GNRI, APACHE II, and SOFA are presented in Figure. When comparing the AUCs, GNRI demonstrated superior predictive ability over both APACHE II and SOFA scores. The AUC values were as follows: GNRI 0.629 (95% CI, 0.543-0.715); SOFA 0.579 (95% CI, 0.493-0.664); APACHE II 0.550 (95% CI, 0.455-0.646).

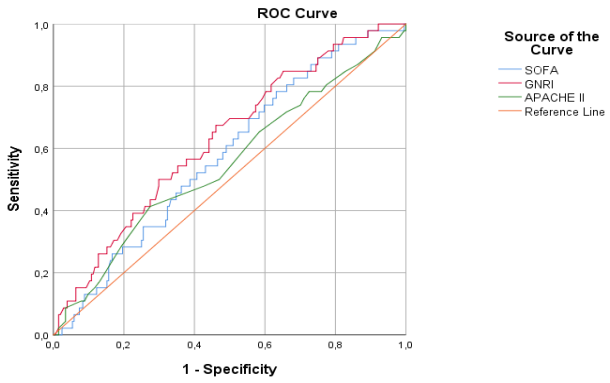

Figure. Receiver operating characteristic curves of the Geriatric Nutritional Risk Index, APACHE II, and the sepsis-related organ failure assessment for in-ICU mortality. Area under the ROC curve (AUC) (95% CI) values are also given: GNRI 0.629 (0.543-0.715), SOFA 0.579 (0.493-0.664), APACHE II 0.550 (0.455-0.646)

APACHE II: Acute physiology and chronic health evaluation II, ICU: Intensive care unit, ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval, GNRI: Geriatric Nutritional Risk Index

There was no statistically significant difference in CRP levels between the GNRI groups. CRP levels for each GNRI group were as follows: 88±12 in the very low-risk group (GNRI >98), 92±14 in the low-risk group (GNRI 92-98), 87±16 in the moderate-risk group (GNRI 82-92), and 98±21 in the very high-risk group (GNRI <82) (p=0.119).

The results of the multivariate logistic regression analysis are shown in Table 2. Specifically, lower albumin levels (OR=0.89, 95% CI: 0.77-1.03, p<0.001) were significantly associated with an increased risk of short-term mortality. The presence of septic shock (OR=1.53, 95% CI: 1.41-1.65, p<0.001) also markedly increased the risk. Additionally, older age (OR=1.06, 95% CI: 1.01-1.12, p=0.028) was associated with greater short-term mortality. Lower GNRI scores (OR=0.94, 95% CI: 0.83-1.05, p<0.001) and higher SOFA scores (OR=0.91, 95% CI: 0.82-1.10, p<0.001) were also significant predictors. Lastly,

elevated APACHE II scores (OR=0.88, 95% CI: 0.79-0.99, p<0.001) indicated a higher risk of short-term mortality.

Table 2. Multivariate logistic regression analysis predicting short-term mortality

Variables	OR	95% CI	p-value
Albumin level	0.89	0.77-1.03	<0.001
Septic shock	1.53	1.41-1.65	<0.001
Weight	1.03	0.88-1.18	<0.001
Age	1.06	1.01-1.12	0.028
GNRI scores	0.94	0.83-1.05	<0.001
SOFA scores	0.91	0.82-1.10	<0.001
APACHE II scores	0.88	0.79-0.99	<0.001

GNRI: Geriatric Nutritional Risk Index, SOFA: Sequential organ failure assessment, APACHE II: Acute physiologic assessment and chronic health evaluation, OR: Odds ratio, CI: Confidence interval, p-value less than 0.05 was considered statistically signifcant

DISCUSSION

This study explored the role of the GNRI in sepsis-related mortality and ICU length of stay, demonstrating that low GNRI values were linked to a higher risk of malnutrition, increased mortality rates, and prolonged ICU stays. Additionally, significant correlations were identified between low GNRI values and advanced age, elevated CRP levels, as well as higher SOFA and APACHE II scores. These results support the hypothesis that a low GNRI not only heightens susceptibility to sepsis but also adversely impacts the clinical trajectory. We propose that a GNRI score below 85 serves as an independent predictor of mortality, particularly in older sepsis patients admitted to the ICU.

The observation that low GNRI values correlate with malnutrition aligns with existing literature, which underscores the adverse effects of malnutrition on the development of sepsis and mortality among older patients.[7]

While energy and protein requirements escalate in sepsis, inadequate fulfillment of these needs in the elderly can compromise the immune system, heightening infection susceptibility. Additionally, malnutrition has been linked to organ dysfunction in sepsis patients, leading to elevated SOFA and APACHE II scores. Nutritional assessment is very important in intensive care patients. As stated in the surviving sepsis campaign guidelines, nutritional support supports the healing process of patients.[2] Appropriate and adequate protein and carbohydrate support, having scores to define malnutrition in the early period, reduces complications that may develop during the intensive care period without muscle loss in patients. The GNRI seems to be a simple scoring system and a good marker for nutritional support at intensive care admission. Consequently, this study proposes that a low GNRI may serve as an indicator of malnutrition and a predictor of sepsis prognosis.

The findings of our study are consistent with the existing literature. For example, Durán Alert, et al.[8] have identified GNRI as a significant prognostic marker in critically ill patients, with lower GNRI values being associated with higher mortality rates. Similarly, Bouillanne, et al.[4] indicated that GNRI is an effective measure for assessing malnutrition risk in the elderly, noting that lower GNRI scores correlate with poorer clinical outcomes. These studies affirm the potential of GNRI as a valuable tool for predicting prognosis in older sepsis patients.

In this study, there was no statistically significant difference in CRP levels between the GNRI groups (p=0.119). The similar CRP levels across categories in our study demonstrate that the GNRI is a reliable nutritional assessment tool that is not influenced by the severity of inflammation. This finding suggests that the GNRI can independently evaluate nutritional status without the confounding effects of inflammation, making it a trustworthy tool for clinical practice. Consequently, these features of the GNRI can be highlighted as one of the strengths of our study and underscore its significant role in assessing the nutritional status of critically ill patients.

Furthermore, recent research has investigated the relevance of GNRI to mortality and length of hospital stay across various disease groups, particularly those with nutritional impairments and frequent malnutrition comorbidities. Markus Haas et al.[9] identified GNRI as an independent survival risk factor in patients with metastatic head and neck cancers. In addition, Xie et al.[10] demonstrated a correlation between GNRI and overall survival in a meta-analysis of patients with gastrointestinal malignancies.

GNRI has also been evaluated as a prognostic factor in older patients with cardiac and renal conditions. A comprehensive meta-analysis by Hengdon, et al.[11] involving 10,589 patients revealed that a one-unit decrease in GNRI was associated with a 6% increase in all-cause mortality. In the context of hemodialysis patients, GNRI frequently correlates with the creatinine index, which is used to monitor nutritional status.[12] Additionally, a retrospective study involving 12,058 intensive care patients with acute kidney injury underscored the GNRI's utility as a critical nutritional assessment tool in this population.[13]

Collectively, these studies, along with our findings, underscore the crucial role of nutritional monitoring and its significant association with overall mortality rates, especially among vulnerable and critically ill patients.

However, there are also conflicting findings regarding the prognostic value of GNRI. Some studies suggest that GNRI may not be robust enough as an independent marker, particularly in critically ill patients. Plauth et al.[14] highlighted the importance of using more objective measurements to assess malnutrition and its clinical impacts, particularly in vulnerable groups such as critically ill patients. In addition, in our study, although the AUC value of GNRI was better than the other scoring systems, it was not sufficiently strong in all three. This may be explained by the retrospective nature of the study and the inadequacy of the study population. This indicates that GNRI can be used as a complementary tool in certain situations, but it may not be a powerful diagnostic tool alone.

The influence of GNRI on nutritional status and sepsis prognosis can be affected by various factors, including underlying comorbidities, the severity of the disease, and

the patient's overall clinical condition. Therefore, it may be more beneficial to use GNRI in conjunction with other clinical scores and biomarkers rather than relying on it alone. Combining GNRI with other nutritional assessment tools such as the mini nutritional assessment (MNA), subjective global assessment (SGA), or nutritional risk screening 2002 (NRS-2002) may provide a more comprehensive evaluation of nutritional status.[15]

The development of the GNRI within the older population brings into question its applicability to younger sepsis patients. This highlights the need to investigate the validity and reliability of the GNRI across different age groups.

This study demonstrates that the GNRI is a significant predictor of mortality and prolonged ICU stays in sepsis patients. Lower GNRI scores are linked to advanced age and higher disease severity scores. These findings underscore the critical importance of assessing and improving nutritional status in the management of sepsis.

Incorporating the GNRI into routine clinical practice may aid in the early identification of high-risk patients and the development of appropriate nutritional interventions. Future research should focus on comparing the GNRI with other nutritional assessment tools, validating it across different age groups, and assessing the impact of nutritional interventions on sepsis outcomes.

Randomized controlled trials could be designed to evaluate the effect of early and intensive nutritional support on clinical outcomes in high-risk patients identified using the GNRI.

The findings of this study highlight the critical importance of early nutritional assessment and intervention in the management of sepsis patients in the ICU. Regular use of nutritional risk assessment tools, such as the GNRI, can aid in the early identification and management of malnutrition in sepsis patients, thereby contributing to reduced mortality rates and shorter hospital stays. In conclusion, it is recommended to adopt a holistic approach to sepsis treatment, incorporating the optimization of nutritional status as an integral component of treatment protocols.

Limitations

Our study has certain limitations, including its single-center design and relatively small sample size. These factors may restrict the generalizability of the findings and highlight the need for larger, multicenter studies. Future research conducted in different geographical regions and diverse patient populations could offer a better understanding of the GNRI's impact on sepsis prognosis. Additionally, our study did not track the dynamic changes in GNRI, limiting our ability to assess how shifts in nutritional status affect prognosis. In acute and rapidly progressing conditions like sepsis, temporal changes in nutritional status may be crucial.

Future studies should consider measuring GNRI at regular intervals and exploring the relationship between these changes and clinical outcomes to better evaluate the effectiveness of nutritional interventions.

CONCLUSION

Low GNRI values are linked to an increased risk of malnutrition, higher mortality, and extended ICU stays in older sepsis patients. Additionally, significant correlations exist between GNRI and factors such as age, CRP levels, SOFA, and APACHE II scores. GNRI shows promise as a tool for assessing prognosis in older sepsis patients in clinical practice. However, its prognostic value should be evaluated in conjunction with other clinical parameters and validated through further research.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted in the KTO Karatay University Faculty of Medicine Non-drug and Medical Device Researches Ethics Committee (Date: 31.10.2024, Decision No: 2024/024).

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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Intrauterine fetal death and stillbirth: evaluations in a tertiary center

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ABSTRACT

Aims: Despite routine prenatal care, intrauterine fetal death (IUFD) is unpredictable. With early diagnosis and prompt treatment of maternal and obstetric problems, IUFD may become less common. The aim of this study was to determine the prevalence of IUFD in pregnant patients in a tertiary care center.

Methods: A descriptive cross-sectional study was conducted at a tertiary center from January 2020 to August 2024 and was approved by the Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Research Ethics Committee (Date: 08.11.2024, Decision No: 2024/318). Demographic characteristics of pregnant women, medical and obstetric complication rates, and histopathological findings of the placenta were recorded.

Results: IUFD was diagnosed in 137 of 20,356 deliveries (0.67%). Of these, 104 cases were included in the study. The period with the highest stillbirth rate was 28-33 weeks (36.3%), 46.2% of pregnant women gave birth for the first time and 77.9% were between the ages of 20-24. The most common maternal problems were maternal anemia (n=39, 37.5%). The most common perinatal outcomes were preeclampsia/eclampsia (n=12, 11.5%) and the rate of pregnant women without any perinatal problems was 57.7% (n=60). The caesarean section rate was 37.5% (n=39). In addition, the most common placental histopathological examinations were placental infarction (n=26, 25%).

Conclusion: A significant amount of IUFD can be prevented with routine prenatal care of patients and society, close monitoring of risk groups, and educating pregnant women.

Keywords: Fetal demise, intrauterine fetal death, perinatal deaths, stillbirth

INTRODUCTION

The death of a fetus after the twentieth week of pregnancy is known as intrauterine fetal death (IUFD). Intrauterine death before the 24th week is called early intrauterine fetal death, and intrauterine fetal death after the 28th week of pregnancy is called late intrauterine fetal death.[1] Over two million pregnancies globally are affected by IUFD each year, making it one of the most prevalent unfavorable pregnancy outcomes.[2] Most of these IUFDs occur in low- and middle-income countries, and fetal deaths have remained roughly the same since 2019, despite most being preventable, making them a major public health concern.[3,4] IUFD rates are considered a clear reflection of the standards of prenatal care in that community.[5]

Classifying the causes of IUFD has long been a controversial issue.[6] Chromosome anomalies, infections, fetal anemias including alpha thalassemia, cord injuries, gastroschisis, extended preterm premature rupture of membranes, and abnormalities in the fetal structure are among the causes of intrauterine fetal death.[7] Hypertension, diabetes mellitus, renal disease, autoimmune disorders, placental abruption, fetal growth restriction, rhesus isoimmunization, multiple gestation, post-term pregnancy, antiphospholipid syndromes, infections (particularly malaria and syphilis), a history of stillbirths, thrombophilias, systemic lupus erythematosus, advanced age, alcoholism, obesity, low socioeconomic status, illiteracy, smoking, and illnesses of the heart and blood systems are among the maternal associations.[8] Additionally, a number of problems continue after the birth of a stillborn fetus, with postpartum depression and other issues causing the cost of a stillbirth to be 10-70% more than the cost of a live birth.[9] It is the duty of service providers to support families, look into the reason for death, and act quickly to reduce the stillbirth rate. The global health community considers care during pregnancy and childbirth to lower the rate of stillbirth to be a key indicator of a health system's quality.[10]

The aim of our study was to find the incidence of IUFD to find the frequency of various risk factors associated with fetal death in a tertiary care center and to evaluate the consequences.

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METHODS

This study was conducted at a tertiary center between January 2020 and August 2024 and was approved by the Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Researches Ethics Committee (Date: 08.11.2024, Decision No: 2024/318). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Pregnant women with a gestational age of 22 weeks or more who were diagnosed with intrauterine dead fetus before the onset of labor were included in the study. All cases of IUFD referred to our clinic are routinely confirmed by fetal doppler and ultrasonography. A detailed history including the current pregnancy and past obstetric history was obtained from the hospital record system. Previously diagnosed pregnancy complications and perinatal outcomes were recorded from these examinations. The decision regarding the mode of delivery was based on clinical assessment of the progress of labor and the mother's condition. The fetus was weighed grossly. Histopathology findings of the examined placenta were included in the data. No photographs or X-Rays of the fetuses were taken after delivery. In the postpartum wards, mothers were monitored daily for maternal postpartum complications such as sepsis and length of hospital stay. Pregnant women with a gestational age of less than 22 weeks, pregnant women diagnosed with COVID-19 by polymerase chain reaction method (PCR), and those with missing examination data and histopathological data were not included in the study. Additionally, anomalous fetuses and medical termination of pregnancy were excluded from the study.

Statistical Analysis

Data analysis was performed using SPSS version 20 software. The findings were then presented in tables using Microsoft Excel 2016. The software used for data calculation and tabulation was SPSS version 20. Using descriptive statistics. The results were discussed, and conclusions were drawn.

RESULTS

A total of 20356 women who gave birth were retrospectively reviewed from the hospital record system. 137 (0.67%) patients diagnosed with intrauterine dead fetus were reached, 21 patients were not included in the study because placental histopathological examination was not performed, and 12 patients were not included in the study because of missing data in their files. The mean age of these pregnant women was 28.3±5.7, and the mean gestational week was 34.2±4.0. The mean birth weight was calculated as 2236.5±919.9. Among the age groups, IUFD was most frequently seen between the ages of 20-34. IUFD was most common in primiparous pregnancies and between the 28th and 33rd weeks of gestation. Regarding clinical features, the rate of maternal anemia was found to be 37.5% (n=39). Additionally, when hospital files were scanned, it was seen that more than half of the pregnant women (52.9%) (n=55) did not have prenatal care. Other demographic and clinical features are summarized in Table 1. Preeclampsia was the most common perinatal outcome (11.5%) (n=12), 4 of these cases were complicated by eclampsia. The rarest is polyhydramnios at 1.9% (n=2). The cause of intrauterine fetal death could not be explained in 60 (57.7%) of the pregnant women. In addition, 9 (8.5%) of the patients had two or more perinatal outcomes. 1 (0.1%) of the cases had four conditions: oligohydramnios, preeclampsia, abruptio placentae, fetal growth restriction. One (0.1%) of the cases had three conditions: GHT, oligohydramnios, and preeclampsia. Seven (6.7%) of the cases had two perinatal conditions, 31 (29.8%) had only one perinatal condition, and 60 (57.7%) had no perinatal conditions. More details about the distribution of obstetric complications are provided in Table 2. When the placentas were examined histopathologically, although placental infarction and hematoma were found to be close in number (n=26, 25%; n=22, 21.1%, respectively), placental infarction was the most common placental pathology (n=26, 25%). Other placental histopathological findings are detailed in Table 3.

Table 1. Demographic and clinical characteristics of pregnant mothers with IUFD

Parametres		Frequency (n=104)	Percentage
Age (years)	<20	5	4.8%
	20-34	81	77.9%
	35-39	15	14.4%
	≥40	3	2.9%
Parity	Nulliparous	26	25%
	Primiparous	48	46.2%
	Multiparous	30	28.8%
Delivery mode	Vaginal delivery	65	62.5%
	Caesarean section	39	37.5%
Gestational age (week)	22-27	6	5.8%
	28-33	38	36.3%
	34-36	22	21.2%
	37-42	37	35.6%
	>42	1	0.9%
Previous stillbirth		3	2.9%
Prenatal care visit frequency	0	55	52.9%
	0-4	33	31.7%
	>4	16	15.4%
Fetal gender	Female	56	53.8%
	Male	48	46.2%
Maternal anemia		39	37.5%
Associated medical illness (e.g., asthma, hypothyroidism, allergic rhinitis, chronic hypertension, type 1-2 diabetes mellitus etc.)		7	6.7%

IUFD: Intrauterine fetal death

Table 2. Medical and obstetric complications in pregnant mothers with IUFD

Associated complications	Frequency (n=104)	Percentage
Unexplained[a]	60	57.7%
Preeclampsia	8	7.7%
Eclampsia	4	3.8%
Oligohydramnios	10	9.6%
Polihydramnios	2	1.9%
Macrosomia	4	3.8%
Abruptio Placentae	8	7.7%
Gestational diabetes mellitus	4	3.8%
Gestational hypertension	7	6.7%
Fetal growth restriction	6	5.8%
Total	113[b]	108.5%[b]

[a]Cases without any perinatal problems, [b]The percentages are calculated based on the total number of patients (n=104), but the cumulative percentage exceeds 100% due to multiple conditions occurring in the same individuals. This table is meant to show the overall prevalence of each condition. IUFD: Intrauterine fetal death

Table 3. Histopathological findings of the placenta		
Histopathological findings	**Frequency (n=104)**	**Percentage (%)**
Normal histopathology	17	16.3%
Placental infarct	26	25%
Placental hematoma	22	21.1%
Placental inflammation/infection	19	18.3%
Placental calcification	6	5.8%
Placental abruption	14	13.5%

DISCUSSION

The frequency of stillbirths varies considerably depending on the country of observation, with a global rate of 18.9 per 1,000 live births. The incidence ranges from 2 per 1,000 live births in highly developed countries, such as Finland, to 7 per 1000 live births in the United States. In comparison, in less developed countries, such as Pakistan, the incidence can be as high as 47 per 1000 live births.[11] The decline in IUFD rates worldwide has been slower than expected, particularly due to difficulties and inequalities in access to health care in less socioeconomically developed countries.[11] In our study, the IUFD rate in the last four years was calculated as 0.67%. The studies have identified IUFD as a risk factor, especially in pregnant women over 40 years of age, regardless of gestational age, including term pregnancies.[8] Considering that chronic diseases such as diabetes and hypertension are known risk factors, it is expected that these conditions are seen at a higher rate in pregnant women over the age of 40. On the other hand, a different study concluded that intrauterine fetal death is more common in the 18-35 age group with a rate of 78.33%.[12] Similarly, in our study, the most common IUFD occurred in the 20-34 age group with a rate of 77.9%. We believe that the reason for this is that the majority of pregnant women (77.9%) are between the ages of 20-34, which is consistent with the profile of pregnant women in our country. There are also studies showing that IUFD rates are not high in adolescent pregnancies.[13,14] Similarly, there were 5 adolescent pregnant women in our study and the in IUFD rate in our population was 4.8%. This rate was lower than in other age groups.

Patient parity is one of the risk factors for intrauterine fetal death, but there is no full consensus on this issue.[1] Some sources indicate that primiparous women are at higher risk,[1] while some studies indicate that the risk increases after the second or even fifth birth.[1] In our population, more than half of the IUFD cases (46.2%) occurred in primiparous pregnant women.

Some studies did not observe post-term intrauterine fetal death.[12] Similarly, in our study, only 0.9% were over 42 weeks and 36.5% were term gestation, and the majority of intrauterine fetal deaths occurred earlier than 37 weeks of gestation in 63.5%. However, in the same study, the mean gestational week of intrauterine fetal deaths was 38.5±1.14, while in our study, the mean gestational week was 34.2±4.0. We believe this is because the rate of preeclampsia in our study was 11.5%. In other studies, it was found that intrauterine fetal deaths due to preeclampsia were most common at 34 weeks.[15]

There are studies in the literature that conclude that male fetuses have a 10% higher risk of intrauterine fetal death than female fetuses.[16] In our analysis, on the contrary, female fetuses were slightly more common than male fetuses.

Even if IUFD occurs, the mother should be evaluated thoroughly when choosing the method of delivery. The American College of Obstetricians and Gynecologists recommends vaginal delivery for pregnancies resulting in intrauterine fetal death. A trial of labor is recommended even if a previous cesarean delivery has occurred; however, in cases where the risk of uterine rupture is higher, a repeat cesarean procedure is justified.[1] It is also important to remember that induction of labor in these cases carries a much higher risk of uterine rupture than in cases where labor is initiated after a previous cesarean delivery with a viable fetus.[12] In our study, vaginal delivery was 62.5%, while the cesarean section rate was 37.5%. Cesarean section procedures were needed due to reasons such as placental abruption and bleeding, fetal malpresentation, fetal macrosomia, and unsuccessful vaginal delivery induction.

In the literature, a number of maternal diseases have been associated with an increased risk of intrauterine fetal death. A higher incidence of this occurrence has been consistently associated with diabetes and hypertensive diseases.[1] They were also the most common among the patients in our study. Chronic or gestational hypertension during pregnancy is known to increase the risk of placental abruption and uteroplacental circulation problems.[17] It has long been known that diabetes during pregnancy increases the risk of fetal death.[17,18] The pathophysiological mechanism by which inadequate glycemic control leads to fetal death is mostly represented by metabolic problems that increase oxidative stress, cardiac disorders and placental vascular pathology.[17,18] Studies have shown that fetal death occurs most frequently in full-term pregnancies in these patients, regardless of whether the diabetes is present before or during pregnancy, with the highest risk in patients with pregestational diabetes and in all patients with poor glycemic control during pregnancy, especially in the third trimester.[18,19] It is of great importance to note that the conditions mentioned are preventable. Pre-pregnancy counseling, appropriate therapy, lifestyle changes and regular monitoring can prevent the complications of diabetes and hypertension or even prevent the development of the diseases in some cases.

Histopathological findings of the placenta are increasingly discussed in studies on intrauterine fetal death.[20] Various studies show that pathological changes found in the placenta are considered to be the cause or at least a contributing factor in fetal death in up to 60% of cases.[20] In our study, this percentage was even higher-up to 83.7% of placentas had some pathological findings. This may occur due to parenchymal thrombosis and placental infarction, infections or vascular occlusions.[21] In our study, evidence of placental infarction was found in 25% of cases, which is similar to the 27% rate reported in the literature.[21] In the literature, data on the frequency of chorioamnionitis in cases of intrauterine fetal death in term pregnancies vary greatly, from 10-15% to almost 30%.[1,21,22] In our study, evidence of infection was found in

18.3% of cases. We believe that the susceptibility to infections in some conditions, such as diabetes and anemia, contributes to this rate.

Approximately 1% of pregnancies are complicated by placental abruption, and it is reported to cause fetal death in 10-20% of cases.[1,23] Due to the subclinical presentation of the condition, placental abruption is primarily diagnosed clinically, but in some cases, diagnosis can only be made by histological examination of the placenta.[23] In our study, 7.7% of the pregnant women clinically presented with placental abruption, while this rate was found to be 13.5% in histopathological examination. This shows that the number of subclinical placental abruption cases is remarkable.

Limitations

It should be noted that in order to draw valid conclusions about the quality of prenatal care in our region, a comprehensive review of intrauterine fetal death data in pregnancies, including fetal autopsies, is necessary. Furthermore, a limitation of this study is that it is primarily descriptive and includes data from a four-year period, which makes our study population quite small and makes it difficult to draw definitive conclusions. Another limitation is that information on the body mass index, socioeconomic level and education level of pregnant women is unavailable in the hospital data. We believe that future studies on this subject should be prospective and include standard fetal autopsy and examination of the placenta and umbilical cord by pathologists who specialize in obstetrics.

CONCLUSION

We believe that in order to prevent IUFD and its negative effects, public awareness should be raised about IUFD risk factors, the quality of prenatal care should be improved, education on the birth and pregnancy process should be increased, and participation in these trainings should be encouraged to reduce treatment delays.

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 Scientific Research Ethics Committee (Date: 08.11.2024, Decision No: 2024/318).

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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Osajin is a promising candidate for sepsis-induced brain damage via suppression of the 8-OHdG/Bax/caspase-3 pathway in a rat model of sepsis

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ABSTRACT

Aims: We examined the protective effect of the natural product osajin against sepsis-induced brain damage by targeting the 8-hydroxydeoxyguanosine (8-OHdG)/Bcl-2-associated×protein (Bax)/caspase-3 pathway in the brain tissue of septic rats.

Methods: Osajin was isolated from *Maclura pomifera* fruit, the structure was confirmed, and a rat model of brain damage was established by the cecal ligation and puncture (CLP) method. Osajin was administered to the animals with sepsis-associated brain damage at 150 and 300 mg/kg. Following euthanasia, histopathological examination, detection of 8-OHdG by immunohistochemistry, and the estimation of Bax and caspase-3 expression using an immunofluorescent technique in the brain tissue were performed.

Results: Histopathological examination revealed the presence of severe inflammation, marked degeneration, and necrosis in the brains of rats with sepsis. The results of immunohistochemical and immunofluorescent assays revealed that the CLP technique induced marked 8-OHdG, Bax, and caspase-3 expression in the brain tissues of septic rats compared with those in healthy rats. Osajin administration at a dose of 150 mg/kg ($p<0.05$) and 300 mg/kg ($p=0.0022$) reversed the histopathological changes and significantly ameliorated the increased 8-OHdG, Bax, and caspase-3 expression compared with that in septic rats.

Conclusion: The histopathological, immunohistochemical, and immunofluorescent evidence indicates that osajin can reverse brain damage caused by sepsis by inhibiting the 8-OHdG/Bax/caspase-3 pathway. Accordingly, this natural product represents a promising candidate for the management of brain damage in septic patients.

Keywords: Bax, caspase-3, osajin, sepsis, brain damage, 8-OHdGs

INTRODUCTION

Sepsis is a major problem for intensive care units and results in a high mortality rate worldwide. More than 30 million cases of sepsis and 5 million deaths occur annually.[1] Its management also represents a significant financial burden to the health sector worldwide. Sepsis causes damage to many organs, including the brain, as a result of an exaggerated immune response.[2] Although the molecular mechanisms underlying brain damage associated with sepsis are complex and have been inadequately described, neuronal apoptosis is an important pathophysiological mechanism that drives sepsis-associated brain damage through the activation of inflammation, oxidative stress, and mitochondrial damage mechanisms.[3] Sepsis-associated brain damage results in many complications, such as blood-brain barrier dysfunction and sepsis-associated encephalopathy, which alters the mental status of septic patients admitted to intensive care units.[4,5] Greater than 70% of sepsis patients develop sepsis-associated encephalopathy (SEA).[6] Currently, there are no specific treatments for sepsis-induced brain dysfunction, although the use of antibiotics and fluid support ameliorates the symptoms.[7] We hypothesize that targeting oxidative stress, mitochondrial damage, and apoptosis mechanisms may be an important strategy for managing brain damage during sepsis and its various complications that lead to consciousness disorders, seizures, and coma. Accordingly, the use of agents that possess antioxidant and antiapoptotic

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properties shows beneficial results. Osajin is an isoflavone isolated from the *Maclura pomifera* (rafinesque) Schneider fruits that has many therapeutic properties,[8-11] including a protective effect against sepsis-induced multiple organ injury. Our previous studies showed that osajin could reverse liver[12] and kidney[13] damage in a rat model of sepsis induced by cecal ligation and puncture (CLP) by suppressing oxidative stress, inflammation, and apoptosis in various tissues. To date, we have not found any studies of the effects of osajin on sepsis-induced brain damage in rats. Based on our previous data, we aimed to examine the neuroprotective effects of osajin against brain damage resulting from sepsis in a rat model by targeting the 8-hydroxydeoxyguanosine (8-OHdG)/Bcl-2-associated×protein (Bax)/caspase-3 pathway, which promotes oxidative DNA damage, mitochondrial damage, and apoptosis. The results were corroborated by a histopathological study of the rat brain tissue.

METHODS

Isolation and Characterization of Osajin

The verification of the *Maclura pomifera* species was done using international diagnostic methods. The extraction, isolation, and purification of osajin were carried out by chromatographic methods and confirmation of the chemical structure was done using spectroscopic methods (**Figure 1**). These steps are explained in detail in previous studies.[12,13]

Animals, Experimental Groups, and Sepsis Model

The experiment was conducted using 30 adult male Sprague-Dawley rats (weighing 200-250 g). Ethical approval was obtained from the Atatürk University Rectorate Animal Experiments Local Ethics Committee (Date: 01.09.2015, Decision No: 133). All procedures were carried out in accordance with the ethical rules and the principles. The rats were divided equally into five experimental groups as shown in **Table** and allowed to acclimate for seven days. Polymicrobial sepsis was induced using the CLP method as described in previous studies.[12,13] Briefly, after administering general anesthesia consisting of thiopental sodium, the cecum was withdrawn, tied, and two punctures were made to allow the contents of the cecum to spread into the peritoneal cavity. It was then restored and the abdomen was closed. Complete details regarding the study groups are listed in **Table**.

The doses of osajin were determined based on previous studies.[11,14] After applying the CLP technique for 24 h, the animals were euthanized under general anesthesia. The brains were immediately collected and placed in a suitable fixative solution for subsequent examination.

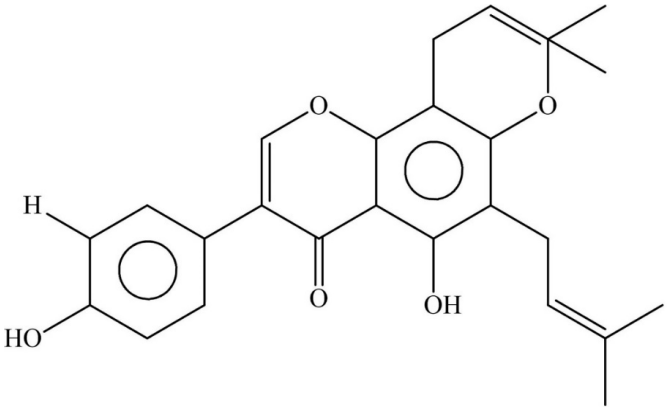

Figure 1. Chemical structure of osajin

Histopathological Examination of the Brain Tissue

After fixing the brain tissues in 10% neutral formalin solution for 48 h, they were subjected to a consecutive routine series of alcohol and xylol washes. The samples were embedded in paraffin and 4-µm thick tissue sections were prepared. The tissue sections were examined using a light microscope (Olympus BX 51, Japan) following hematoxylin-eosin (H&E) staining.

Immunohistochemical Evaluation of the Brain Tissue

Based on the procedures described previously[13] for immunoperoxidase evaluation, the primary antibody (8-OHdG, no: sc66036) was applied to the tissues and incubated accordingly. The 3-3' diaminobenzidine (DAB) chromogen was used for color development. The stained sections were examined by light microscopy (Zeiss AXIO, Germany).

Double Immunofluorescence Evaluation of the Brain Tissue

The sample preparation procedures were done as previously described.[13] For immunoperoxidase examination, the primary antibody (Bax, no: sc7480) was applied to the tissues. A secondary antibody was used as a secondary marker (FITC, no: ab6785) and the samples were incubated in the dark for 45 min. The same previous steps were applied to the tissue sections using caspase 3 (no: sc56053) as a second primary antibody and texas red (no: ab6719) as an immunofluorescence secondary antibody. The samples were incubated in the dark for 45 min. DAPI with mounting medium (no: D1306 D) was applied to the sections and incubated for 5 min in the dark before examination of the stained sections under a fluorescence microscope (Zeiss AXIO, Germany).

Table. Details of the experimental groups

Group name	Number of rats	Description	Administration method of osajin or ceftriaxone/time	Brain tissue collection time
Sham	6 rats	Laparotomy without CLP	-	24 hours after the operation
Sepsis	6 rats	CLP	-	24 hours after the CLP technique
Osajin150	6 rats	150 mg/kg (BW) osajin+CLP	Oral gavage/15 minutes before the CLP technique	24 hours after the CLP technique
Osajin300	6 rats	300 mg/kg (BW) osajin+CLP	Oral gavage/15 minutes before the CLP technique	24 hours after the CLP technique
Ceftriaxone	6 rats	50 mg/kg (BW) ceftriaxone+CLP	Intraperitoneal injection/15 minutes before the CLP technique	24 hours after the CLP technique

CLP: Cecal ligation and puncture, BW: Body weight

Statistical Analysis

GraphPad prism (version 8.0.2) software was used for statistical analysis of the histopathological assays. $p<0.05$ was considered statistically significant. The non-parametric Kruskal-Wallis test was used to detect group interactions and the Mann-Whitney U test was used to determine differences between groups. To determine the intensity of the positive staining from the images obtained by immunohistochemical and immunofluorescence staining, five random areas were selected from each image and evaluated by the ZEISS Zen Imaging Software program. A one-way ANOVA followed by Tukey's test was performed to compare positive immunoreactive cells and immunopositive stained areas with those of healthy controls. $p<0.05$ was considered statistically significant and the data are presented as the mean±SD.

RESULTS

Histopathological Examination

The brain tissues were examined histopathologically in all experimental groups and the results are summarized as follows:

Sham group: Normal histological structures in the brains were observed (Figure 2).

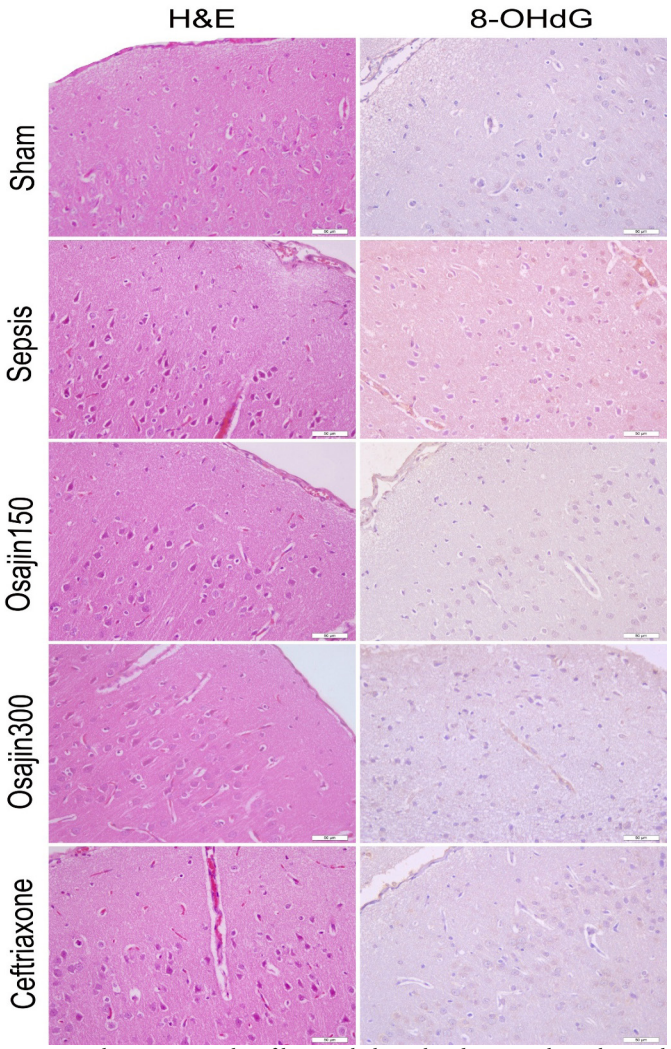

Figure 2. Photomicrography of histopathological and immunohistochemical assessment of brain tissues

H&E: Hematoxylin and eosin, 8-OHdG: 8-hydroxydeoxyguanosine, IHC-P, Bar: 50µm

Sepsis group: Hyperemia and inflammation were observed in the meningeal and interstitial vessels, whereas severe degeneration and necrosis were observed in the neurons (Figure 2).

Osajin150 group: Moderate degeneration and mild necrosis were observed in the neurons and moderate hyperemia was detected in the vessels.

Osajin300 group: Mild degeneration of the neurons and hyperemia of the vessels were observed in the brain tissues (Figure 2). In addition, the results were supported by statistical analysis, in which osajin administration at a dose of 300 mg/kg resulted in a significant decrease in necrosis ($p<0.001$) and degeneration ($p=0.0022$) compared with the sepsis group (Figure 3).

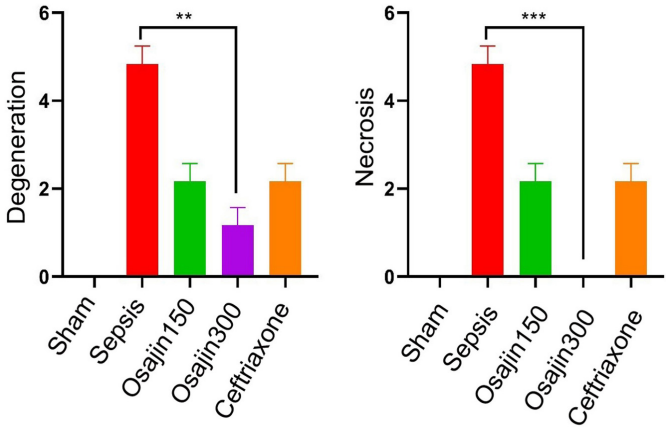

Figure 3. Statistical analysis results of histopathological findings in brains of septic rats

The results are presented as mean±standard deviation, degeneration (**p=0.0022), necrosis (***p<0.001)

Ceftriaxone group: Moderate degeneration, mild necrosis of the neurons, and moderate hyperemia of the vessels were observed in the brain tissues (Figure 2).

Statistical results of the histopathological findings are presented in Figure 3 after conducting the appropriate analyses.

Immunohistochemical Evaluation

The histopathological findings were supported by the immunohistochemical evaluation of 8-OHdG expression in histological sections of the rat brains. The results for the different groups are as follows:

Sham group: 8-OHdG expression was negative in the brain tissues (Figure 2).

Sepsis group: High levels of 8-OHdG expression were detected in the cytoplasm of the neurons (Figure 2).

Osajin150 group: Moderate expression of cytoplasmic 8-OHdG was evident in the neurons (Figure 2).

Osajin300 group: Mild expression of cytoplasmic 8-OHdG was detected in the neurons (Figure 2). Statistical analysis indicated that osajin administration resulted in a significant decrease in 8-OHdG levels (28.12±3.05) ($p=0.0022$) for this group compared with the sepsis group (90.14±3.75) (Figure 4).

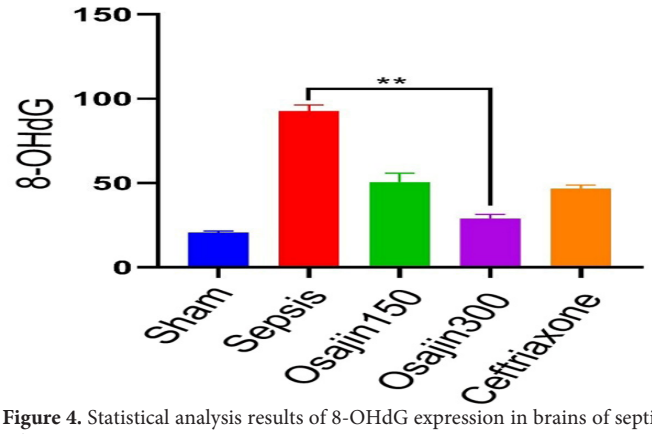

Figure 4. Statistical analysis results of 8-OHdG expression in brains of septic rats

The results are presented as mean±standard deviation, **p=0.0028. 8-OHdG: 8-hydroxydeoxyguanosine

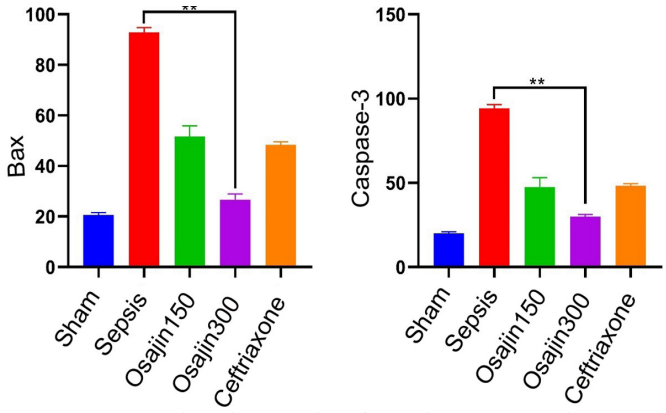

Figure 6. Statistical analysis results of cytoplasmic Bax and caspase-3 expressions in brains of septic rats

The results are presented as mean±standard deviation, Bax (**p=0.0028) and caspase-3 (**p=0.0022). Bax: Bcl-2-associated×protein

Ceftriaxone group: Moderate expression of cytoplasmic 8-OHdG was detected in the neurons (Figure 2).

Statistical results of immunohistochemical evaluation are presented in Figure 4 after conducting the appropriate analysis.

Double Immunofluorescence Evaluation

The immunofluorescence evaluation of Bax and caspase-3 expression in the brain tissues was performed to strengthen the conclusions of this study. The results of the different groups are as follows:

Sham group: Bax and caspase-3 expression was negative in the brain tissues of this group (Figure 5).

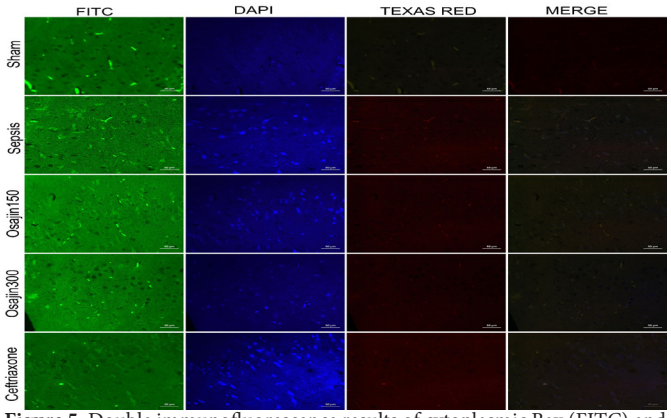

Figure 5. Double immunofluorescence results of cytoplasmic Bax (FITC) and caspase-3 (TEXAS RED) in neurons

Bax: Bcl-2-associated×protein. IF, Bar: 50µm

Sepsis group: Strong expression of Bax and caspase-3 was detected in the cytoplasm of the neurons (Figure 5).

Osajin150 group: Moderate cytoplasmic Bax and caspase-3 expression were observed in the neurons of the brain tissues for this group (Figure 5).

Osajin300 group: When the brain tissues for this group were examined by immunofluorescence, mild cytoplasmic Bax and caspase-3 expression were detected in the neurons (Figure 5). A significant reduction in Bax (25.55±2.50) and caspase-3 (29.78±2.57) (p=0.0022) levels was reported for this group compared with the sepsis group (90.54±3.08, 94.83±3.84 respectively) (Figure 6).

Ceftriaxone group: Ceftriaxone administration caused moderate expression of cytoplasmic Bax and caspase-3 in the neurons (Figure 5).

Figure 6 shows the statistical analysis of the double immunofluorescence evaluation for all groups.

DISCUSSION

The present study is the first to evaluate the neuroprotective effects of the natural product osajin, an isoflavone isolated from the fruit of *Maclura pomifera*, against sepsis-induced brain damage. The results provide insight into its therapeutic potential for reducing the burden of brain damage on septic patients. The immunohistochemical and immunofluorescence results highlight the role of the 8-OHdG/Bax/caspase-3 pathway in the promotion of brain injury and reveal the ability of osajin to suppress the components of this pathway in brain tissues.

Of the four nucleotides comprising DNA, guanine is the most susceptible to hydroxylation by hydroxyl radicals because it is the lowest nucleobase in terms of redox capacity.[15] 8-OHdG, which is the first component of the targeted pathway in the present study, is formed following an attack by a hydroxyl radical at the C8 position.[13] Elevated levels of 8-OHdG are an indicator of oxidative damage to DNA or oxidative stress,[16] which occurs from increased levels of reactive oxygen species (ROS) during sepsis.[17] Increased 8-OHdG levels in brain tissues are clear evidence that DNA in the neurons is exposed to damage resulting from excessive ROS production and the collapse of the antioxidant system. Increased expression of 8-OHdG in the serum and brain tissues of LPS-induced septic rats has been reported.[18] Lorente et al.[17] found an association between oxidative DNA damage and mortality and lipid peroxidation in septic patients and suggested serum 8-OHdG as a biomarker for predicting mortality and as a potential target for treating sepsis patients with antioxidant agents. The antioxidant activity of osajin prompted us to investigate its effects in the present study. Osajin reversed the negative effects of the CLP procedure on 8-OHdG expression in brain tissue. Thus, it represents a promising therapeutic agent that can protect genetic material from brain cell damage during sepsis and prevent SEA. Although there are few studies on the

effect of osajin on 8-OHdG expression in brain tissue during sepsis, a study conducted by Alhilal et al.[13] in renal tissue during sepsis supports our findings.

The second component of the pathway targeted in the present study was Bax, which is a pro-apoptotic mediator. It was assessed in brain tissue to evaluate mitochondrial damage and the progression of apoptosis. During cellular homeostasis, Bax is present in the cytosol in an inactive state.[19] It is activated by various cellular signals, such as p53-mediated stimulation following DNA damage.[20] In this context, the importance of assessing 8-OHdG levels is an important component of the pathway targeted in the present study. Activated Bax enters the mitochondrial membrane and becomes an integral membrane protein that forms channels and causes gaps in the mitochondrial membrane to permit the release of cytochrome c, which weakens the membrane and activates pro-apoptotic caspases.[19-21] Therefore, targeting Bax represents an important strategy for reversing apoptosis and disrupting the execution phase of apoptosis. Osajin suppressed this pro-apoptotic mediator and maintained the integrity of the mitochondrial membrane, thus inhibiting apoptosis.

The third component of the pathway is caspase-3. The execution of apoptosis during sepsis is achieved by the activity of the caspases.[22] The most important caspase is caspase-3, which is activated by DNA damage[16,23] or another pathway in the cytosol that leads to an irreversible step in apoptosis by inducing DNA degradation in the nucleus. CLP augmented Bax and apoptosis in the brain tissue of septic rats.[3,24] We examined the role of osajin in suppressing caspase-3. It suppresses caspase-3 through its antioxidant activity by inhibiting DNA damage, which stimulates caspase-3 as the primary executor of apoptosis in neurons. In previous studies, osajin prevented apoptosis during sepsis by inhibiting caspase-3 in hepatic tissue[12] and 8-OHdG and caspase-3 expression in renal tissue.[13] Pomiferin, an isoflavone isolated from *Maclura pomifera* fruits that has a chemical structure similar to osajin, also exerted hepatoprotective effects against apoptosis by reducing caspase-3 and 8-OHdG levels during hepatic injury induced by nickel.[25]

When brain tissues were examined histopathologically, the necrosis of neurons was the predominant histopathological change. This necrosis may be the result of hypoxia in neurons as well as the lethality of ROS to the cellular membranes in the brain resulting from the breakdown of the antioxidant defense system in septic rats. Osajin administration improved the structure of the brain tissues through antioxidant and anti-apoptotic activity.

In summary, brain injury leading to SEA during sepsis occurs as a result of neuronal apoptosis, which develops through the activation of the following sequential pathological mechanisms: 1) Increased ROS levels, particularly hydroxyl radical; 2) Hydroxyl radical-induced DNA lesions; 3) Formation of 8-OHdG as a marker of oxidative DNA damage; 4) 8-OHdG-mediated p53 activation; 5) p53-mediated Bax activation; 6) Mitochondrial damage induced by Bax; 7) Release of cytochrome c from the damaged mitochondrial membrane; 8) Cytochrome c-mediated caspase-3 activation; 9) Apoptosis of neurons; and 10) Brain injury leading to SEA. This pathological chain was disrupted by targeting its most important cornerstones, 8-OHdG, Bax, and caspase-3, through osajin administration. Figure 7 shows the proposed pathophysiology of brain injury development in a rat model of sepsis and the pathways targeted by osajin.

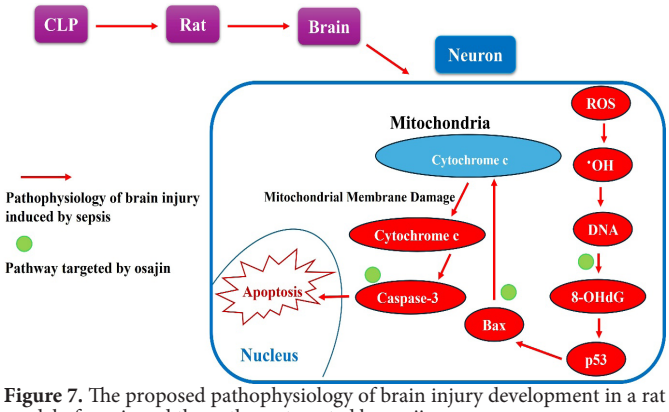

Figure 7. The proposed pathophysiology of brain injury development in a rat model of sepsis and the pathway targeted by osajin

Limitations

Undoubtedly, examining p53 and cytochrome c expression in brain tissue would have strengthened the conclusions of this study. These limitations of the present study will be addressed in future studies.

CONCLUSION

Osajin exhibited protective effects against sepsis-induced brain damage by inhibiting the 8-OHdG/Bax/caspase-3 pathway. These effects were observed at a dose of 300 mg/kg. Accordingly, osajin represents a promising candidate for the treatment of brain tissue damage in septic patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Atatürk University Rectorate Animal Experiments Local Ethics Committee (Date: 01.09.2015, Decision No: 133).

Informed Consent

Since experimental animals were used in this study, informed consent was not required.

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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Evaluation of hematologic inflammation parameters and cranial magnetic resonance imaging findings in patients with trigeminal neuralgia

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ABSTRACT

Aims: This study aimed to evaluate the relationship between trigeminal neuralgia (TN) and hematological parameters, including leukocyte-based inflammatory indices, and to explore their association with cranial magnetic resonance imaging (MRI) findings.

Methods: A retrospective analysis was conducted on 114 patients with newly diagnosed TN and 114 healthy control groups with comparable demographic characteristics. Clinical, laboratory, and cranial MRI data were collected from hospital records. White matter abnormalities were identified via cranial MRI, and inflammatory indices were calculated as follows: neutrophil-to-lymphocyte ratio (NLR)=Neutrophil count/lymphocyte count, platelet-to-lymphocyte ratio (PLR)=Platelet count/lymphocyte count, Systemic Immune-Inflammation Index (SII)=Platelet count×neutrophil count/lymphocyte count, and Systemic Inflammatory Response Index (SIRI)=Neutrophil count×monocyte count/lymphocyte count.

Results: TN patients showed significantly higher leukocyte counts (7.4±1.8 vs. 6.0±1.9 $\times 10^3$/µl, $p<0.001$), neutrophil counts (4.2±1.1 vs. 2.8±0.8$\times 10^3$/µl, $p<0.001$), CRP levels (median: 2.6 vs. 0.8 mg/dl, $p<0.001$), and inflammatory indices (NLR, PLR, SII, and SIRI; $p<0.001$ for all) compared to control group. White matter abnormalities were detected in 16.7% of TN patients, predominantly in the frontal (11.4%) and parieto-occipital (7.0%) regions. Patients with white matter abnormalities exhibited significantly higher inflammatory indices than those without. Compared to other inflammatory parameters, SIRI demonstrated the highest diagnostic performance for TN (threshold: 0.7; sensitivity: 84.2%, specificity: 82.5%) and white matter abnormalities (threshold: 1.3; sensitivity: 78.9%, specificity: 82.1%).

Conclusion: Inflammatory markers, particularly SIRI, are significantly elevated in TN patients and are associated with white matter abnormalities. These markers may serve as useful non-invasive tools for predicting TN and related MRI findings.

Keywords: Trigeminal neuralgia, inflammation markers, white matter lesions, cranial MRI, Inflammation Index

INTRODUCTION

Trigeminal neuralgia (TN) is described as sudden, intense, brief, stabbing pain attacks, typically affecting one side of the face and localized to the distribution of one or more branches of the trigeminal nerve.[1] It typically occurs in middle and older age and is more common in women than in men.[2,3] However, the etiology and underlying mechanisms of TN remain insufficiently understood.[4]

Compression of the trigeminal nerve is linked to significant myelin erosion and disintegration due to inflammation, especially at the site of nerve indentation.[5,6] Structural changes related to this compression may impact the functionality of voltage-gated sodium (Nav) channels, which play a significant role in the onset of TN symptoms.[7] It has also been shown that changes in Nav expression play a role in the development of neuropathic and inflammatory pain.[8,9] Moreover, the cerebrospinal fluid of TN patients demonstrates significant increases in inflammatory mediators such as chemokines, pro-inflammatory cytokines, growth factors, and tumor necrosis factor superfamily, suggesting a pathophysiologic role for neuroinflammation.[10,11] Furthermore, neuroimaging studies conducted on TN patients indicate that neuroinflammation could be associated with brain structure and function such as white and gray matter volume changes.[12,13]

Previous rare studies have reported conflicting results regarding the association between systemic inflammatory indices, such as the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), measured using a low-cost, more practical, and simpler method, and TN.[14-16] However, the relationship between systemic inflammatory markers and cranial magnetic resonance imaging (MRI) findings in these patients has not yet been investigated. This study aimed to assess the relationship between TN and hematological

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parameters, including leukocyte-based inflammation indices, and to examine their connection to cranial MRI findings.

METHODS

Ethics

Following the principles set forth in the Declaration of Helsinki, this single center retrospective study was conducted at the Atlas University Medicine Hospital Neurology Clinical from January 2021 to November 2023. The study received approval from the Üsküdar University Non-interventional Researches Ethics Committee (Date: 27.11.2023, Decision No: 2023-61). The local ethics committee did not require informed consent because the study was retrospective.

Study Population

A total of 144 patients diagnosed with TN were retrospectively examined. The diagnosis of TN was determined according to the criteria of International Classification of Headache Disorders (ICHD3).[1] Patients with chronic conditions (cerebrovascular disease, central nervous system vasculitis, rheumatologic disease, hypertension, diabetes mellitus, chronic any diseases, hematologic disorders, acute inflammatory diseases), those with a history of TN, those with cranial MRI findings of pathologies such as masses or trauma sequelae, those who had undergone surgery in the past month prior to diagnosis, those using steroids, antibiotics, antivirals, antiplatelet, anticoagulant, or immunosuppressant drugs, those who were pregnant, and those with missing data were excluded from the study. After this exclusion process, 114 patients with newly diagnosed with TN were enrolled in this study. The control group, consisting of 114 healthy individuals who underwent check-up programs, had no comorbidities, had normal brain imaging results, and were matched with TN patients by age and sex, was also included in the study.

Study Protocol

Demographic, clinical, and imaging data were obtained from the hospital's electronic information system and patient records. Blood samples and cranial MRI data for all patients were collected at the time of their initial hospital admission. Prior to starting any treatment, complete blood count and biochemical parameters were measured using venous blood samples taken after a 12-hour fasting period during outpatient evaluations. All samples were analyzed in a single laboratory following the same methodology outlined below. Pain severity was assessed by the patients using the Visual Analogue Scale (VAS), with scores ranging from 1 to 10.

Biochemical Analysis

Venous blood samples were analyzed using a Cell-Dyn 3700 SL device (Abbott Diagnostics, Chicago, USA). Hemoglobin levels were measured photometrically, platelet count via the impedance method, and CRP levels using the immunoturbidimetric method. The inflammatory indices were respectively calculated as follows: NLR=Neutrophil count/lymphocyte count, PLR=Platelet count/lymphocyte count, Systemic Immune-Inflammation Index (SII)=Platelet count×neutrophil count/lymphocyte count, and Systemic Inflammatory Response Index (SIRI)=Neutrophil count× monocyte count/lymphocyte count.

Cranial MRI Evaluation

The patients' cranial MRI images were retrospectively evaluated. All imaging were performed with a 1.5 Tesla MRI machine (Achieva, Philips Medical Systems, Best, The Netherlands). The MRI protocol consisted of various sequences: T1-weighted imaging (T1WI) in axial and sagittal planes, T2-weighted imaging (T2WI) in axial, coronal, and sagittal planes, along with axial and coronal fluid-attenuated inversion recovery (FLAIR). White matter and basal ganglia lesions were assessed using the age-related white matter changes (ARWMC) scale, which evaluates white matter lesions based on their size and location.[17] The brain was divided into five regions for assessment in both hemispheres: (1) frontal region: the anterior portion of the brain, located in front of the central sulcus; (2) parieto-occipital region: the parietal and occipital lobes combined; (3) temporal region: the lateral section of the brain, extending from the posterior part of the Sylvian fissure to the lateral ventricles; (4) infratentorial region: including the brainstem and cerebellum; and (5) basal ganglia and insula: covering the striatum, globus pallidus, thalamus, internal and external capsules, and insula. Lesions were graded as follows: grade 0: no lesions; grade 1: focal lesions; grade 2: lesions with a tendency to merge; grade 3: diffuse involvement of the entire region, with or without U-fiber involvement.

Hyperintense lesions measuring less than 5 mm and numbering between 4 and 12 in the periventricular white matter on cranial MRI were included in the study. Patients were categorized into those with and those without white matter lesions.

Statistical Analysis

Data analysis was conducted using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Numerical variables with a normal distribution, as verified by Kolmogorov-Smirnov tests, are presented as mean±standard deviation (SD), while non-normally distributed variables are expressed as median values with interquartile ranges (25^{th}-75^{th} percentile). For group comparisons, the student's T test was used for normally distributed data, and the Mann-Whitney U test was applied for data not meeting normality assumptions. Categorical variables are shown as frequencies and percentages, with comparisons between groups performed using the chi-square or Fisher's exact tests. To identify independent predictors of TN, a multivariable logistic regression analysis was carried out using the backward Wald method. The receiver operating characteristic (ROC) curve analysis was employed to evaluate diagnostic performance, reporting the area under the curve (AUC), standard error (SE), sensitivity, and specificity. The Youden index method was used to determine the optimal cutoff values of hematological parameters or indices for predicting TN and the presence of white matter abnormalities. Comparisons of AUCs were made using a nonparametric approach based on the generalized U-statistics framework, with the covariance matrix estimation method described by DeLong et al.[18] Statistical significance was set at $p<0.05$ (*) for all tests.

RESULTS

The study included 114 control participants (mean age: 49.7±11.9 years) and 114 patients with TN (mean age: 49.5±13.7 years). The two groups had comparable age and gender distributions. The majority of patients with TN had right side dominance (66.7%). In the TN group compared to the control group, the mean leukocyte counts (7.4±1.8 vs. 6.0±1.9×10^3 µl, p<0.001), mean red blood cells (RBC) (4.6±0.5 vs. 4.4±0.5×10^6 µl, p=0.011), mean neutrophil counts (4.2±1.1 vs. 2.8±0.8×10^3 µl, p<0.001), mean monocytes count (0.4±0.1 vs. 0.5±0.1×10^3 µl, p<0.001), and median CRP level (2.6 vs. 0.8 mg/dl, p<0.001) were higher, while the median lymphocyte counts was found to be lower (2.1±0.6 vs. 2.3±0.6×10^3 µl, p<0.001). Also, in the TN group, inflammation indices (NLR, PLR, SII, and SIRI) were found to be higher (Table 1).

The effects of hematological parameters and inflammation indices on TN were analyzed using multivariable regression models. Model I multivariable regression analysis included only hematological parameters. Model II multivariable regression analysis included leukocytes, RBC, CRP, NLR, and PLR, while lymphocyte subtypes were excluded due to high collinearity with NLR and PLR. Model III multivariable regression analysis included leukocytes, RBC, CRP, SII, and SIRI, while lymphocyte subtypes, NLR, and PLR were excluded due to high collinearity with SII and SIRI. Among these, Model III demonstrated superior performance in explaining the variance associated with TN compared to other models. Accordingly, increased CRP (OR=2.85, p<0.001) and SIRI (OR=13.48, p<0.001) levels were identified as independent predictors of TN (Table 2).

Cranial MRI revealed that 16.7% of TN patients exhibited white matter abnormalities. These lesions were predominantly located in the frontal region (11.4%), with fewer cases involving the parieto-occipital (7.0%) and temporal regions (0.9%). In patients with white matter abnormalities compared to those without, the median NLR (2.8 vs. 1.8, p<0.001), median PLR (138.8 vs. 125.3, p=0.016), median SII (751.6 vs. 454.4, p<0.001), and median SIRI (2.1 vs. 1.0, p<0.001) levels were higher. There was no significant difference in VAS scores between the groups (Table 3).

Table 1. Demographic and laboratory findings

Variables	Control group n=114	Trigeminal neuralgia group n=114	p
Age, years	49.7±11.9	49.5±13.7	0.873
Gender, n (%)			
Female	85 (74.6)	85 (74.6)	0.999
Male	29 (25.4)	29 (25.4)	
Side, n (%)			
Left	-	38 (33.3)	-
Right	-	76 (66.7)	
Laboratory findings			
Leukocytes, ×10^3 µl	6.0±1.9	7.4±1.8	<0.001*
RBC, ×10^6 µl	4.4±0.5	4.6±0.5	0.011*
Hemoglobin, g/dl	13.4±1.2	13.2±1.5	0.568
Hematocrit, %	39.9±2.8	39.6±4.0	0.505
Platelets, ×10^3 µl	252.5±50.6	256.6±55.7	0.563
Lymphocytes, ×10^3 µl	2.3±0.6	2.1±0.6	<0.001*
Neutrophils, ×10^3 µl	2.8±0.8	4.2±1.1	<0.001*
Monocytes, ×10^3 µl	0.4±0.1	0.5±0.1	<0.001*
CRP, mg/dl	0.8 (0.1-2.3)	2.6 (2.1-3.3)	<0.001*
NLR	1.0 (0.9-1.6)	1.8 (1.6-2.6)	<0.001*
PLR	107.7 (90.2-120.9)	125.4 (106.6-148.7)	<0.001*
SII	260.8 (228.3-392.6)	480.8 (370.0-668.5)	<0.001*
SIRI	0.5 (0.4-0.7)	1.0 (0.7-1.4)	<0.001*
VAS	-	9.0 (7.0-9.0)	-
Cranial MRI findings, n (%)			
White matter hyperintensity			
No	-	95 (83.3)	-
Yes	-	19 (16.7)	-
Side			
Frontal region	-	13 (11.4)	-
Parieto-occipital region	-	8 (7.0)	-
Temporal region	-	1 (0.9)	-

Data are mean±standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Abbreviations: RBC: Red blood cells, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammatory Response Index, VAS: Visual Analogue Scale, MRI: Magnetic resonance imaging

Table 2. Independent predictor of trigeminal neuralgia

Variables	Univariable regression		Model I regression		Model II regression		Model III regression	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Leukocytes	1.55 (1.31-1.84)	<0.001*	-	-	-	-	-	-
RBC	2.01 (2.15-2.50)	0.015*	-	-	-	-	-	-
Lymphocytes	0.43 (0.26-0.69)	<0.001*	0.34 (0.15-0.78)	0.011*	Not including		Not including	
Neutrophils	4.72 (4.14-4.10)	<0.001*	2.73 (1.69-4.40)	<0.001*	Not including		Not including	
Monocytes	1.05 (1.03-1.08)	<0.001*	1.05 (1.01-1.09)	0.006*	Not including		Not including	
CRP	3.25 (3.29-3.61)	<0.001*	2.68 (1.79-4.00)	<0.001*	3.08 (2.08-4.56)	<0.001*	2.85 (1.96-4.13)	<0.001*
NLR	6.59 (6.63-6.97)	<0.001*	Not including		7.03 (3.01-16.42)	<0.001*	Not including	
PLR	1.02 (1.01-1.04)	0.001*	Not including		-	-	Not including	
SII	1.03 (1.01-1.05)	<0.001*	Not including		Not including		-	-
SIRI	20.66 (20.18-20.16)	<0.001*	Not including		Not including		13.48 (4.43-40.95)	<0.001*
			Nagelkerke R^2=0.325		Nagelkerke R^2=0.354		Nagelkerke R^2=0.489	

The effects of age and gender were adjusted in the regression analysis. *p<0.05 indicates statistical significance. Abbreviations: OR: Odds ratio, CI: Confidence interval, RBC: Red blood cells, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammatory Response Index

Table 3. Findings associated with white matter in trigeminal neuralgia

	White matter hyperintensity		
Variables	**No (n=95)**	**Yes (n=19)**	**p**
Age, years	48.7±13.8	53.2±12.7	0.200
Gender, n (%)			
Female	71 (74.7)	14 (73.7)	0.923
Male	24 (25.3)	5 (26.3)	
Laboratory findings			
Leukocytes, ×10³ µl	7.1±1.5	8.9±2.2	<0.001*
RBC, ×10⁶ µl	4.6±0.5	4.6±0.4	0.920
Platelets, ×10³ µl	256.4±56.7	257.7±52.0	0.923
Lymphocytes, ×10³ µl	2.1 (1.8-2.5)	1.9 (0.8-2.2)	0.012*
Neutrophils, ×10³ µl	4.0±1.0	4.8±1.1	0.004*
Monocytes, ×10³ µl	0.5±0.1	0.5±0.2	0.406
CRP, mg/dl	2.1 (1.9-2.8)	2.6 (2.4-3.4)	0.036*
NLR	1.8 (1.6-2.3)	2.8 (2.4-5.5)	<0.001*
PLR	125.3 (102.1-144.2)	138.8 (112.1-335.1)	0.016*
SII	454.4 (356.0-640.5)	751.6 (522.8-1476.6)	<0.001*
SIRI	1.0 (0.7-1.2)	2.1 (1.4-2.4)	<0.001*
VAS	8.4±1.4	8.2±1.3	0.489
Moderate	17 (17.9)	4 (21.1)	0.746
Severe	78 (82.1)	15 (78.9)	

Data are mean±standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Abbreviations: CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, RBC: Red blood cells, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammatory Response Index, VAS: Visual Analogue Scale

Table 4. Findings associated with VAS score in trigeminal neuralgia

	VAS score		
Variables	**Moderate (n=21)**	**Severe (n=93)**	**p**
Age, years	49.0 (36.0-62.0)	51.0 (41.0-60.0)	0.994
Gender, n (%)			
Female	14 (66.7)	71 (76.3)	0.358
Male	7 (33.3)	22 (23.7)	
Laboratory findings			
Leukocytes, ×10³ µl	7.1±1.5	7.5±1.8	0.313
RBC, ×10⁶ µl	4.6±0.3	4.6±0.5	0.935
Platelets, ×10³ µl	274.7±48.6	252.5±56.7	0.100
Lymphocytes, ×10³ µl	2.1±0.4	2.0±0.6	0.817
Neutrophils, ×10³ µl	4.0±1.2	4.2±1.0	0.559
Monocytes, ×10³ µl	0.5±0.1	0.5±0.1	0.572
CRP, mg/dl	2.6 (2.2-3.0)	2.5 (2.0-3.4)	0.405
NLR	1.8 (1.6-2.4)	1.8 (1.6-2.7)	0.324
PLR	135.3 (110.1-177.2)	124.0 (104.4-148.7)	0.236
SII	529.8 (369.8-629.6)	460.0 (370.7-669.5)	0.759
SIRI	0.9 (0.6-1.3)	1.0 (0.7-1.4)	0.236
White matter hyperintensity			
No	17 (81.0)	78 (83.9)	0.746
Yes	4 (19.0)	15 (16.1)	

Data are mean±standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Abbreviations: CRP: C-reactive protein, MRI: Magnetic resonance imaging, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, RBC: Red blood cells, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammatory Response Index, VAS: Visual Analogue Scale

Demographic and clinical parameters showed no significant differences in patients with moderate and severe pain (Table 4).

Table 5 presents the diagnostic performance of inflammatory markers in predicting TN and white matter abnormalities.

Table 5. Diagnostic performance of inflammation parameters in predicting trigeminal neuralgia and white matter

Variable	AUC±SE	95% CI	Sens. (%)	Spec. (%)	Threshold values
Trigeminal neuralgia (vs. control)					
Leukocytes	0.723±0.03	0.658-0.789	57.0	81.6	≥7×10³ µl
RBC	0.617±0.04	0.545-0.690	43.9	84.2	≥4.7×10⁶ µl
Platelets	0.512±0.04	0.437-0.587	28.9	90.4	≥278×10³ µl
Neutrophils	0.759±0.03	0.710-0.808	70.7	72.5	≥3.2×10³ µl
Lymphocytes	0.625±0.04	0.553-0.698	70.2	21.1	≤1.85×10³ µl
Monocytes	0.566±0.04	0.492-0.641	77.2	42.1	≥0.4×10³ µl
NLR	0.741±0.03	0.689-0.793	69.3	79.5	≥1.7
PLR	0.638±0.04	0.566-0.709	56.1	80.7	≥122.8
SII	0.811±0.03	0.767-0.875	80.6	61.4	≥268.5
SIRI	0.832±0.03	0.776-0.886	84.2	82.5	≥0.7
CRP	0.782±0.03	0.721-0.831	74.3	78.3	>2.4 mg/dl
White matter hyperintensity (vs. normal MRI)					
Leukocytes	0.744±0.07	0.609-0.879	63.2	82.1	8.7×10³ µl
Neutrophils	0.683±0.06	0.589-0.767	71.2	47.8	>3.50×10³ µl
Lymphocytes	0.675±0.07	0.581-0.759	42,1	85.8	≤1.23×10³ µl
NLR	0.799±0.06	0.674-0.924	78.9	80.0	≥2.3
PLR	0.675±0.07	0.533-0.817	42.1	95.8	≥187.8
SII	0.789±0.06	0.661-0.916	89.5	55.8	≥476.7
SIRI	0.831±0.06	0.717-0.945	78.9	82.1	≥1.3
CRP	0.618±0.03	0.546-0.691	70.2	57.9	>2.8 mg/dl

*p<0.05 indicates statistical significance. Abbreviations: AUC: Area under the curve, SE: Standard error, CI: Confidence interval, Sens: Sensitivity, Spec: Specificity, RBC: Red blood cells, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammatory Response Index, CRP: C-reactive protein, MRI: Magnetic resonance imaging

Among the markers, SIRI showed the highest performance. For TN, a SIRI threshold of 0.7 provided 84.2% sensitivity and 82.5% specificity. For white matter abnormalities, a threshold of 1.3 yielded 78.9% sensitivity and 82.1% specificity.

DISCUSSION

To the best of our knowledge, this study is one of the few to investigate the relationship between TN, hematological inflammation parameters, and cranial MRI findings. Additionally, this study is the first to assess the association between SII, SIRI and TN. TN patients had higher leukocyte-based inflammatory indices, and SIRI was found to be an independent predictor. In the TN cohort, inflammatory indices were elevated in patients with white matter abnormalities. Furthermore, SIRI demonstrated superior diagnostic performance compared to other inflammatory markers in predicting both TN and white matter abnormalities.

Previous research has indicated that the progression of TN is induced by inflammatory factors such as tumor necrosis factor, C-C motif chemokine ligand 2 (CCL2), interleukin (IL)-6, and transient receptor potential ankyrin 1 (TRPA1).[19-22] In an experimental model of trigeminal neuropathic pain caused by infraorbital nerve constriction, it was proposed that pain-like behaviors are facilitated by the TRPA1 channel. This is linked to oxidative stress byproducts secreted by monocytes and macrophages concentrated around the site of the nerve injury.[23] Following tissue damage, pro-inflammatory cytokines are expressed by neutrophils, lymphocytes, monocytes and macrophages.[24] This highlights the role of immune cells in the heightened pro-inflammatory cytokine levels observed in TN patients after neurological injury.[10,20] In line with these findings, lymphocyte levels and their subtypes were elevated in TN patients relative to the control group.[14] This finding aligns with the elevated CRP levels in TN patients, which serve as a recognized marker of immune-inflammatory status.[25,26]

Blood parameters are routinely accessible laboratory tests during the initial phase of hospital admission, and they are universally obtained within the first hour.[27] In clinical practice, an easily assessable biomarker could be a crucial predictor for diagnosing central nervous system diseases, assessing prognosis, or identifying high-risk patients. A recent study investigated the role of preoperative inflammatory markers in patients with newly diagnosed glioma, schwannoma, meningioma, pituitary adenoma, or trigeminal neuralgia. The study demonstrated that meningioma and glioma patients had elevated NLR and PLR levels, while TN patients showed levels comparable to the healthy control group.[28] In the existing literature, there are contradictory findings concerning NLR and PLR levels when comparing TN patients with healthy control groups. In a retrospective study conducted in China, newly diagnosed TN patients were reported to have higher NLR and PLR levels than healthy controls.[14] Studies conducted in Turkey have indicated that TN patients show no significant differences in NLR or PLR levels compared to the healthy control group.[15,16] In these studies, the disease duration was either unspecified or focused on patients with chronic disease. Thus, variations among the studies may stem from differences in patient selection.

The current study revealed that newly diagnosed TN patients displayed significantly higher NLR and PLR levels when compared to healthy controls. Furthermore, NLR levels provided superior diagnostic performance over PLR levels in the prediction of TN. These results align with the role of neutrophils and lymphocytes in driving elevated pro-inflammatory cytokine production in TN patients.[24] However, in this cohort, more comprehensive inflammatory indices could better represent the innate immune reaction to nerve damage. SIRI, incorporating monocytes, was identified as an independent predictor of TN and outperformed other inflammatory indices in diagnostic performance. Moreover, the regression model that incorporated SIRI provided a better explanation of the variance in TN than models that including NLR, PLR, or their components. The superior diagnostic performance of SIRI can likely be explained by the involvement of its components in the neuroinflammatory processes triggered by the cytokine-chemokine network, which plays a key role in the pathogenesis of TN.[29,30] Moreover, platelets and platelet-related indices, such as PLR, appear to play a less significant role in the pathogenesis of TN compared to neutrophils or monocytes. This observation aligns with findings from previous studies, which reported no significant differences in platelet levels between TN patients and healthy controls.[14,15] While platelets contribute to the inflammatory milieu by releasing pro-inflammatory mediators like platelet-derived growth factor, their involvement may be less pronounced in the neuroinflammatory processes central to TN.[31] In contrast, neutrophils and monocytes, through their direct roles in cytokine-chemokine signaling and innate immune activation, are likely the primary drivers of inflammation and nerve damage in TN.[31] Consequently, platelet-related indices such as PLR may have limited utility in capturing the complex inflammatory mechanisms underlying TN when compared to indices like NLR or SIRI, which incorporate more dominant immune cell types in the neuroinflammatory response.

Previous research has revealed the presence of white matter abnormalities in TN patients, likely resulting from the effects of chronic pain and peripheral nerve damage.[32-34] Previous studies on TN patients have demonstrated white matter integrity disruption in the right anterior limb and left genu of the internal capsule, the bilateral superior corona radiata, the splenium and body of the corpus callosum, the bilateral posterior corona radiate, and the left posterior thalamic radiation.[35,36] Consistent with these studies, white matter hyperintensities were predominantly located in the frontal and parieto-occipital regions, indicating potential cognitive-emotional or motor function impairment. The exact mechanism underlying the impact of TN on brain white matter integrity has yet to be determined. A previous study found reduced fractional anisotropy in TN patients, linked to increased radial diffusivity, suggesting that demyelination and neuroinflammation might disrupt white matter integrity in these patients.[37] This may explain the higher inflammatory indices observed in TN patients with white matter abnormalities. Studies conducted on other neurological diseases also support the current findings. A study on Parkinson's patients showed that they had lower

fractional anisotropy and higher radial and mean diffusivity compared to healthy control group. The observed reductions in fractional anisotropy and elevations in radial and mean diffusivity were linked to elevated systemic inflammatory markers, including lymphocyte and granulocyte apoptosis.[38] In autopsied brains of monkeys induced with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, an increased infiltration of lymphocyte function-associated antigen 1-positive leukocytes was observed in the substantia nigra.[39] The activation of microglia, facilitated by leukocytes and cytokines, may lead to demyelination and the development of neuritis, ultimately affecting the structural integrity of white matter.[38] On the other hand, pain severity did not correlate with either white matter lesions or inflammatory indices. This finding suggests that in newly diagnosed TN patients, the connection between white matter lesions and neuroinflammatory processes is independent of the mechanisms driving pain intensity.

Limitations

This study has several limitations, including its retrospective design, single-center nature, and relatively small sample size, which may limit the generalizability of the findings. Additionally, the absence of advanced immunological analyses such as cytokine profiling or flow cytometry prevents a more detailed exploration of systemic and neuroinflammatory mechanisms. Furthermore, cranial MRI assessments did not include evaluations of gray matter lesions or cortical thickness, which could provide deeper insights into structural brain changes associated with TN. Future studies with larger, multicenter cohorts and the integration of advanced imaging and immunological techniques are needed to overcome these limitations and better understand the pathophysiology of TN.

CONCLUSION

This study revealed that inflammatory indices were significantly higher in TN patients compared to healthy controls. Furthermore, white matter lesions were associated with elevated inflammation indices, pointing to a potential connection between neuroinflammation and structural alterations in the brain. SIRI demonstrated the highest diagnostic accuracy among inflammatory markers in predicting TN and white matter abnormalities, highlighting its potential utility as both a diagnostic and prognostic screening non-invasive tool for TN.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Üsküdar University Non-interventional Researches Ethics Committee (Date: 27.11.2023, Decision No: 2023-61).

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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Bibliometric analysis of urinary tract infections: trends, collaborations, and knowledge gaps (2004-2023)

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ABSTRACT

Aims: Infections of the urinary tract, or UTIs, are a major public health issue that affects patient prospects especially in cases of nosocomial infections. Albeit quite a bit of research has been conducted there are still information gaps especially with respect to strategies for its prevention as well as the impact of environmental and social determinants. In this paper, we target to conduct a review of bibliometrics of UTI researches from 2004 to 2023, including number and types of publications, prominent scholars, journals, organizations, and specific areas of interest for publication purposes.

Methods: Data for this bibliometric analysis were retrieved from the Web of Science Core Collection, covering articles published between January 1, 2004, and December 31, 2023. The analyses and visualizations were performed using VOSviewer software. Key metrics included annual publication trends, leading journals, citation analyses, keyword clusters, and collaboration networks among authors and institutions.

Results: A total of 3,145 articles were analyzed. Publication volumes demonstrated a steady increase from 2004 to 2022, followed by a slight decline in 2023. The most prolific journals were Antibiotics Basel and the Journal of Antimicrobial Chemotherapy. Major themes included antimicrobial resistance, Escherichia coli, and infection control. The centers for disease control and prevention (CDC) and Johns Hopkins University were the leading contributors in this field. Collaboration networks highlighted strong international ties, particularly among institutions in the United States and Europe.

Conclusion: Bibliometric trends underscore the increasing academic focus on UTIs, particularly regarding antibiotic stewardship and resistance. However, significant knowledge gaps persist in the prevention and management of UTIs, especially in hospital settings. Future research should prioritize multidisciplinary approaches and strengthen international collaborations to address these gaps effectively.

Keywords: Urinary tract infections, bibliometric analysis, antimicrobial resistance, infection control

INTRODUCTION

Urinary tract infections (UTIs) refer to infections occurring in any part of the urinary system and are commonly caused by microorganisms that disrupt the normal flow of urine. UTIs are a prevalent issue among hospital-acquired infections,[1] holding a significant position among nosocomial infections and having a considerable impact on patient health outcomes.[2,3]

Despite the extensive body of research on urinary tract infections (UTIs), critical information gaps and contentious issues persist. Existing studies predominantly focus on the etiology, clinical management, and treatment approaches of UTIs.[4-6] However, the relationship between UTIs and societal or environmental factors, as well as strategies for risk mitigation and prevention, necessitates further research. These gaps, particularly regarding the practical solutions for managing UTIs in hospital settings, reveal significant shortcomings in the literature.

The primary aim of this study is to conduct a bibliometric analysis of research on UTIs over the past 20 years to evaluate scientific advancements, central research themes, and knowledge gaps in the field. Alongside the increasing prevalence of UTIs, driven by factors such as inappropriate antibiotic use, hospital-acquired infections, and demographic changes, their management has become increasingly critical.[7] Although there have been advancements in diagnostic and treatment methods, further development is needed in prevention strategies and antibiotic management.

The purpose analysing UTI research is supposed to enable them to prevent, treat, and manage UTI in a much more effective manner in the future. By accommodating the

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geographic and institutional analysis of UTI related research, this research intends to be of assistance, to the future researchers and policies about UTI. The researchers want to be helpful in filling the knowledge gaps so as to help improve UTI policies and also help improve the systems so that it is easier to handle UTIs.

METHODS

Ethics

Since this research is a bibliometric study, it did not require ethics committee approval. It is conducted with the institution's permission. All procedures were carried out in accordance with the ethical rules and the principles.

Data Sources

For the purposes of this bibliometric analysis data was collected from WoS Core Collection. WoS is an important source pouring high quality, peer-reviewed journal articles from various parts of the world which is essential in the organized compilation of scientific related information.[8] The article aimed to study "urinary tract infections" and thus searched any published studies done between January 1, 2004, and December 31, 2023.

Study Selection Process

From a first search, the result was about 3,640 articles focusing on "UTI". There were limits set as the articles fetched were searched based on their titles, abstracts, and keywords. The repetition of records was sorted out, post which the focus shifted to peer-reviewed correspondence. In the end, 3,145 scholarly articles were available for the purpose of analysis.

The chosen articles contained information that was classified in the category of the infectious diseases on the Web of Science Categories section. The first 6 articles were independently reviewed by 2 reviewers, and conflicts were solved by discussion among the reviewers.

Data Collection Process

The process of collecting the data went on from January to March 2024. For every selected article, the following information was obtained: titles of articles, names of authors, year of publication, name of the journal, journal impact factor, number of citations, country of the institution, name of the institution, and phrases. The reliability of the data was checked by two other independent reviewers and any discrepancies were discussed so as to arrive at one solution. This procedure enabled thorough assessment of the studies collected and formed the basis of the bibliometric assessment conducted.

Data Synthesis and Analysis

The specific software used was VOSviewer (Leiden University, Netherlands; version 1.6.11) which was used to assist in the visualization of the research trends and collaboration networks. In particular, the focus of the analysis was on:

- Annual publication trends
- Journal-specific publication trends
- Citation analyses, including authors, article titles, journals, publication years, and citation counts
- Keyword analysis
- Institutional affiliations of authors
- Inter-institutional publications analysis
- Author collaboration analysis
- Citation distributions by countries

Statistical Analysis

Descriptive statistics, frequencies, and percentages were used to summarize publication numbers, citation counts, and the distribution of articles across journals and institutions. Temporal trends in publication output were evaluated by examining changes in annual article counts. Co-occurrence networks were built and analyzed with University Research Informatics VOSviewer for evidence of relationships between keywords and among the 200 most common keywords, their clusters and connections. Cluster coefficients and linkage density of keywords were used to measure intra-relationships in the dataset. Inter-institutional and country-level collaboration networks were visualized using bibliometric mapping techniques. The intensity and frequency of collaborations were measured through the thickness of connecting lines, revealing shared research focuses among institutions and countries.

RESULTS

Examination of Articles by Year

The number of articles published on "urinary tract infections" (UTIs) in the Web of Science database by year is illustrated in Figure 1. Figure 1 shows the number of articles published annually between 2004 and 2023. In 2004, the number of articles was relatively low at 66, but it rose to 97 by 2006, marking a notable increase. Between 2007 and 2010, the number of publications remained stable, followed by a gradual increase from 2011 to 2015. A significant acceleration occurred in 2014-2015. Between 2016 and 2019, the number of articles steadily increased, reaching 249 in 2019. The peak was observed in 2021 and 2022, with 265 and 278 articles, respectively. However, a slight decline occurred in 2023, with the number of publications falling to 254.

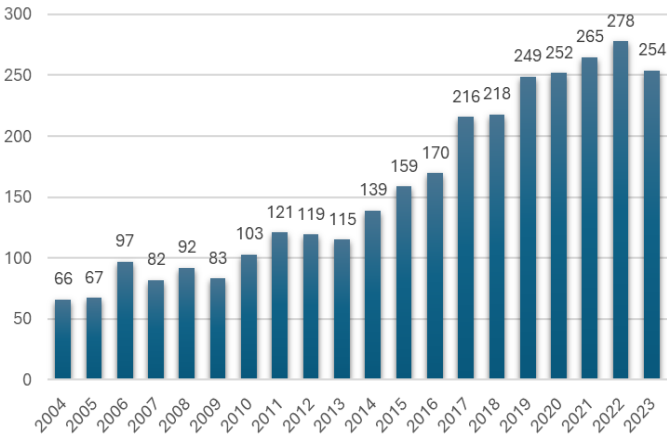

Figure 1. Number of articles published by year on the topic of "urinary tract infections"

Overall, there has been a consistent upward trend in publications from 2004 to 2022, despite a slight decrease in 2023, indicating that the field continues to attract academic interest.

Examination of Articles by Journals

The distribution of articles on UTIs across journals in the Web of Science database is presented in Table 1. The journal with the highest number of articles is Antibiotics Basel, contributing 229 articles and accounting for 7.28% of the total. This is followed by the Journal of Antimicrobial Chemotherapy, which reflects its prestige in the field of antimicrobial therapy, contributing 6.68% of articles. The American Journal of Infection Control and the International Journal of Antimicrobial Agents each published 161 articles, together constituting 10.24% of the total.

Table 1. Journal name, number of articles, and article percentage related to the publications

Row	Journal name	Number of articles	%
1	Antibiotics Basel	229	7.28
2	Journal of Antimicrobial Chemotherapy	210	6.68
3	American Journal of Infection Control	161	5.12
4	International Journal of Antimicrobial Agents	161	5.12
5	BMC Infectious Diseases	126	4.00
6	Infection and Immunity	122	3.88
7	Infection Control and Hospital Epidemiology	112	3.56
8	Clinical Infectious Diseases	111	3.53
9	European Journal of Clinical Microbiology Infectious	101	3.21
10	Infection and Drug Resistance	97	3.08
11	Other	1715	54.54

Other notable journals include BMC infectious diseases (4.00%) and infection and immunity (3.88%), which focus on infectious diseases and immunological aspects. Journals such as infection control and hospital epidemiology and clinical infectious diseases provide platforms for studies on infection control and hospital-acquired infections. Additionally, the Infection and Drug Resistance Journal has made significant contributions to research on antimicrobial resistance.

A substantial proportion of the articles (54.54%) falls under the "others" category, indicating a wide distribution of research across diverse journals.

Most-Cited Articles: Authors, Article Titles, Journals, Publication Years, and Citation Counts

The citation counts of articles on UTIs, along with author names, article titles, journal names, and publication years, are provided in Table 2. The most-cited study, published in 2016 in Clinical Infectious Diseases, is titled "implementing an antibiotic stewardship program" and has received 2,026 citations. the second most-cited study, also from 2016, is titled "clinical practice guideline for the management of candidiasis," with 1,952 citations.

The third most-cited article, published in 2008 in infection control and hospital epidemiology, is titled "antimicrobial-resistant pathogens associated with healthcare-associated infections" and has 1,568 citations.

These papers that are drawn on frequently emphasize drug resistance, treatment of infections and the adherence to the guidelines in practice. All in all, clinical infectious diseases and infection control and hospital epidemiology publish among the top articles in this segment of publications.

Table 2. Most-cited articles: authors, article titles, journal names, publication years, and citation counts related to the publications

Row	Authors	Article titles	Journal names	Publication years	Citation counts
1	Barlam TF, et al.	Implementing an antibiotic stewardship program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America	Clinical Infectious Diseases	2016	2026
2	Pappas PG, et al.	Clinical practice guideline for the management of candidiasis: 2016 Update by the Infectious Diseases Society of America	Clinical Infectious Diseases	2016	1952
3	Hidron AI, et al.	Antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the centers for disease control and prevention, 2006-2007	Infection Control and Hospital Epidemiology	2008	1568
4	Falagas ME, Kasiakou SKi	Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections	Clinical Infectious Diseases	2005	1320
5	Sievert DM	Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for disease control and prevention, 2009-2010	Infection Control and Hospital Epidemiology	2013	1196
6	Weiner LM	Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for disease control and prevention, 2011-2014	Infection Control and Hospital Epidemiology	2016	889
7	Umscheid CA	Estimating the proportion of healthcare-associated infections that are reasonably preventable and the related mortality and costs	Infection Control and Hospital Epidemiology	2011	757
8	Muller LMAJ	Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus	Clinical Infectious Diseases	2005	691
9	Pitout JDD	Emergence of *Enterobacteriaceae* producing extended-spectrum β-lactamases (ESBLs) in the community	Journal of Antimicrobial Chemotherapy	2005	604
10	Loveday HP	Epic 3: national evidence-based guidelines for preventing healthcare-associated infections in NHS Hospitals in England	Journal of Hospital Infection	2014	536

Keyword Analysis

This citation analysis looked at the keyword deployment in the UTI literature. A cut-off point of five was established which resulted in 361 keywords included in the analysis from 4,041 keywords used (Figure 2).

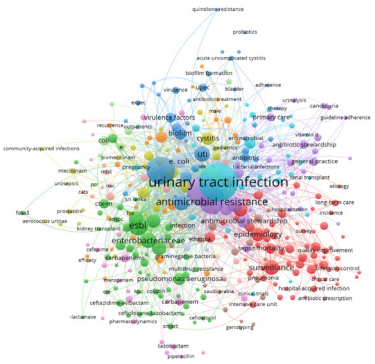

Figure 2. Co-occurring keywords and their frequency of use

The relationships among these keywords were visualized with 5,180 interconnections and were classified into 13 categories. Commonly used keywords are "urinary tract infection," "*Escherichia coli*," "antimicrobial resistance," and "antibiotic resistance." This literature provides compelling evidence of strong interest on microbiological, clinical and drug resistance issues (Figure 2).

The strong connections between keywords like "antimicrobial resistance" and "epidemiology" suffice to portray UTI as an area of great significance for research with regards to treatment as well as public health. This analysis assists in determining the areas which require more research and those that are likely to be researched in the future within this field.

Most-Cited Institutions with Number of Publication Output

A list of institutions to address procedure author's addresses contained in the articles covering issues concerned with UTIs together with the publication count and quotation count is given in Table 3. The centers for disease control and prevention (CDC) ranks number one with a total of 31 publications and a citation score of 8227, owing to their notable input in the area of concern. Second and third places are John Hopkins university and university of Michigan, with a citation count of 6194 and 4934 respectively.

Table 3. Institutions with the most citations and publication counts in the Web of Science

Row	Institution name	Publication count	Citation count
1	Centers for Disease Control and Prevention	31	8227
2	Johns Hopkins University	30	6194
3	University of Michigan	61	4708
4	University of Washington	46	4255
5	University of Pittsburgh	28	4.00
6	University of Pennsylvania	31	3750
7	Case Western Reserve University	20	3167
8	Wayne State University	26	3106
9	The University of Utah	20	3041
10	University of California, San Francisco	20	3012

Among other institutions one should mention the University of Washington, University of Pittsburgh, and the University of Pennsylvania. In terms of the number of publications, Case Western Reserve University and Wayne State University are on the lower edge but they are impressive in terms of the number of citations.

Overall these findings are useful to scholars who desire to forge ahead in the competitive UTI research field.

Analysis of Inter-Institutional Collaboration

The inter-institutional collaboration analysis of UTI-related articles is visualized in Figure 3. The collaboration map created with VOSviewer shows the positions and densities of institutions based on their publication counts and collaboration networks. The University of Michigan leads with 59 connections, demonstrating its leadership in research and its extensive collaboration network.

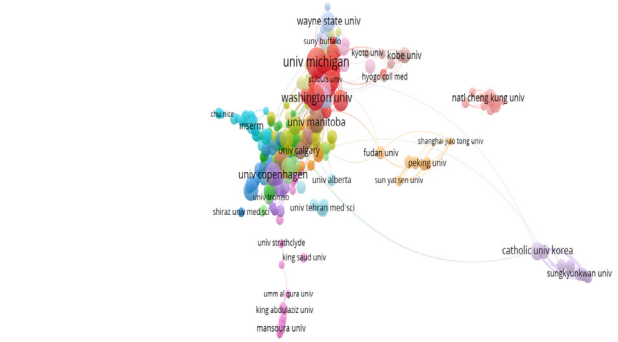

Figure 3. Bibliometric network visualization of inter-institutional collaboration

Other institutions with strong collaboration networks include the University of Manitoba (56 connections) and the University of Washington (43 connections). European institutions like the University of Copenhagen also demonstrate robust international connections.

Asian institutions, such as The Catholic University of Korea, show strong regional collaborations. These findings offer insights into collaboration intensities and geographical distributions in UTI research.

Collaboration Among Authors

Bibliographic coupling analysis reveals scientific links and thematic relationships among authors and their works. This analysis shows that authors working with shared sources often focus on similar research questions.

The analysis examined 16,508 authors, narrowing it to 190 authors with more than five publications. Figure 4 visualizes these authors' scientific connections, grouped into 14 clusters.

Key clusters include the following;

Blue cluster: Features authors with extensive collaboration networks, such as Wagenlehner Florian and Naber Kurt G.

Red cluster: Represents tightly connected authors, including Barbara W. Trautner and Jennifer Meddings.

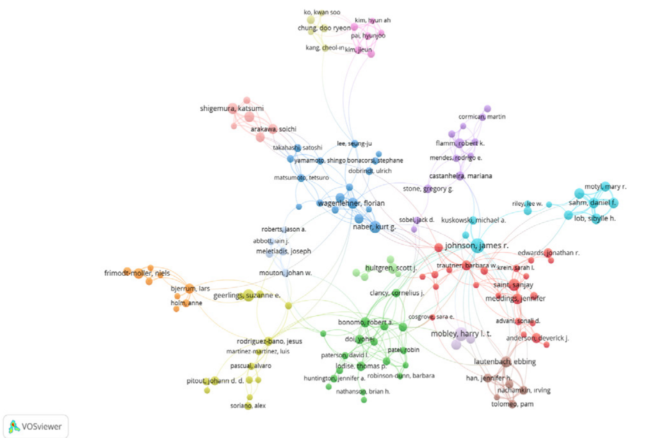

Figure 3. Bibliometric network visualization of author collaboration (the size of the circles represents the focal authors, and the lines between circles indicate collaborations)

Turquoise cluster: Includes authors frequently cited, such as Johnson James R.

The clusters and scientific links help identify potential areas of collaboration and future research themes in the UTI field.

Distribution of Citations by Country

The distribution of citations and collaboration networks among countries is visualized in Figure 5.

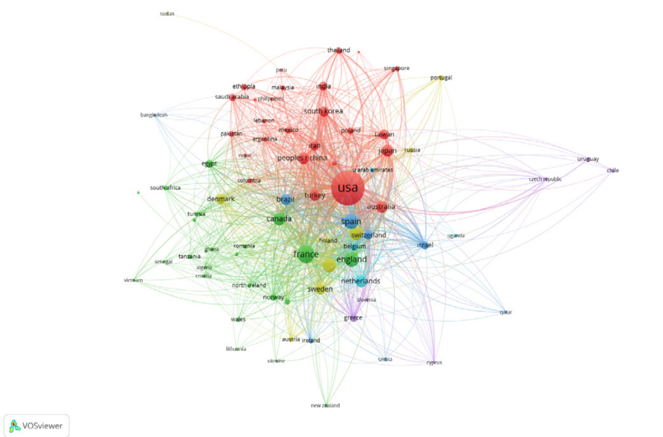

Figure 5. Distribution of citations by country

The analysis, which included 79 countries with at least five publications, revealed six clusters:

USA: The largest node, reflecting its dominant role in UTI research and strong global collaborations.

European Countries: Countries like the UK, France, and Germany demonstrate robust intra-European and international collaborations.

Asian Countries: Nations like China, India, and Japan exhibit strong regional and intercontinental ties.

Turkiye: Acts as a bridge between Europe and Asia, contributing to regional and international collaborations.

These findings underscore the central roles of the USA and Europe in UTI research while highlighting the growing influence of Asian countries.

DISCUSSION

The findings of this bibliometric analysis comprehensively reveal the growth of academic research on urinary tract infections (UTIs), the journals publishing these studies, the most-cited articles, collaboration among authors, and country-level contributions. These results can be discussed in light of relevant literature to highlight trends and identify gaps.

The analysis of the Web of Science data reveals a general increase in the interest and volume of articles published on UTIs between the periods of 2004 and 2023 with a marked increase occurring between 2014 and 2015 and the preceding and other days. The number of publications peaked in 2021 and 2022. Such increase is indicative of the growing importance of UTIs in both practice and in research. Mostafaei et al.[9] identified some of the factors that contributed to this development as advances in microbiome and therapeutic research. The marginal decrease registered almost in the month of August 2023 may be explained in terms of changes in research focuses in the postcovid era or the area of research having become too mature in some domains.

Amidst such pronouncements, the reports of a more focused anti-microbial resistance literature highlights just how trying times on issues surrounding therapeutic intervention abound, especially in the UTI literature, with the most cited journals, Antibiotics Basel and Journal of Antimicrobial Chemotherapy, making the emphasis needed Indeed, Kumar et al.[10] have acknowledged this also becoming evident with increasing corpus of literature on treatment and prevention in pediatric UTI research. As well as journals such as BMC infectious diseases and clinical infectious diseases reinforcing how important infection control and immunological aspects of such work are.

There is an evident trend in several studies that correlate antibiotic stewardship with clinical practice guidelines and antimicrobial resistance. While other examples might be sought depending on the specific focus of the study, the most-cited article, "implementing an antibiotic stewardship program", will be often referenced. Many authors also have a similar focus and see it necessary, for example, Shaikh et al.,[11] Morris & Wiswell,[12] to conduct meta-analyses on child UTIs with this knowledge base in mind.

The keyword analysis turned out that *Escherichia coli*, antimicrobial resistance and antibiotic resistance were the hot topics. For instance, Beerepoot et al.[13] highlighted the possibilities of prophylaxis in reducing the infective episodes among predisposed individuals. These findings call attention to the strong clinical and microbiological orientation of UTI research, while also supplementing the directions of the inquiries into with inter-disciplinary approaches.

However, collaboration analysis demonstrates that UTI research development can be facilitated by authors Wagenlehner and Naber Florian and the Johns Hopkins University.[14] On the other hand, bibliographic coupling analysis reveals certain structural geographic organization, representing cooperative relations and common interests

in the research work of the scholars. It is these networks, especially those that include powerful authors, which will assist in the collaboration in the future.

Country-level analysis indicates that the USA leads in research output and collaboration intensity, followed by European countries. The emerging contributions of Asian countries and Turkiye's role as a regional bridge highlight a growing diversification in global research contributions. Strengthening international collaborations could further enhance knowledge sharing and innovation in this field.

Limitations

This study has several limitations. First, the analysis was confined to articles indexed in the Web of Science database, potentially excluding significant studies indexed in other databases such as PubMed, Scopus, or Google Scholar. Second, the timeframe of the analysis, spanning 2004-2023, excludes earlier studies that might provide historical context to the trends observed. Third, only English-language articles were included, introducing a language bias that might have excluded valuable contributions in other languages.

These limitations underscore the need for broader bibliometric analyses that include multiple databases and multilingual publications to provide a more comprehensive understanding of UTI research trends.

CONCLUSION

This study provides a detailed bibliometric analysis of UTI research conducted between 2004 and 2023, highlighting academic efforts, trends, and knowledge gaps in the field. The findings reveal a consistent increase in publication volumes, with antimicrobial resistance, infection control, and *Escherichia coli* as the most frequently studied themes. Key contributors, including high-impact journals, authors, and institutions, have played a significant role in advancing UTI research. The central roles of the USA and European countries in fostering international collaborations were evident, alongside the growing influence of Asian nations and Turkey's unique position as a bridge between continents. Despite advancements in diagnostic and therapeutic approaches, significant knowledge gaps remain, particularly in the prevention and management of hospital-acquired UTIs. Addressing these gaps requires a multidisciplinary approach and enhanced international collaborations. Future studies should focus on innovative, integrated strategies to improve UTI prevention, management, and treatment, especially in resource-limited settings. Efforts to address these gaps could contribute significantly to improving global healthcare outcomes and policies, ultimately reducing the burden of UTIs on public health systems worldwide.

ETHICAL DECLARATIONS

Ethics Committee Approval

Since this research is a bibliometric study, it did not require ethics committee approval. It is conducted with the institution's permission.

Informed Consent

Since this research is a bibliometric study, it did not require informed consent.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

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Analysis of static pelvic tilt variations in transfemoral prosthesis users: comparison of different socket designs with healthy controls

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ABSTRACT

Aims: The aim of this study was to investigate pelvic tilt angles in patients with transfemoral prosthesis, considering different socket designs, and to compare them with healthy controls.

Methods: In this cross-sectional study, 28 male participants were enrolled, including 14 unilateral transfemoral prosthesis users (prosthesis group) and 14 demographically similar healthy subjects (control group). Pelvic tilt angles in both sagittal and frontal planes were measured using a digital inclinometer mounted on a two-arm caliper.

Results: All participants had anterior pelvic tilt. Within the prosthesis group, there was no significant difference in anterior pelvic tilt and lateral pelvic tilt angles between the prosthetic side and the contralateral side (p=0.106, effect size (ES)=0.464; p=0.055, ES=-0.564, respectively). There was no significant difference in anterior pelvic tilt and lateral pelvic tilt angles between the prosthetic side and the contralateral side of the participants using both quadrilateral socket design and ischial containment socket designs (p=0.499, ES=-0.256; p=0.128, ES=-0.575; p=0.063, ES=-0.703; p=0.612, ES=-0.192, respectively). However, a significant difference was found in both the right and left anterior pelvic tilt angles and the lateral pelvic tilt angles between the prosthesis group and the control group (p=0.001, ES=-0.582; p<0.001, ES=-0.635; p<0.001, ES=-0.797, respectively).

Conclusion: The findings reveal that while anterior pelvic tilt is present in all participants, significant differences exist between prosthesis users and healthy individuals in both anterior and lateral pelvic tilt angles. These results underscore the importance of considering pelvic alignment in the design and fitting of prostheses, potentially in forming clinical practices to enhance the comfort and functionality for transfemoral prosthesis users.

Keywords: Transfemoral prostheses, pelvic tilt angle, anterior pelvic tilt, lateral pelvic tilt

INTRODUCTION

Pelvic tilt (PT) is defined as the position of the pelvis in the sagittal plane in a static posture. PT typically refers to the angle in the sagittal plane where the line joining the anterior superior iliac spine (ASIS) and posterior superior iliac spine (PSIS) intersects a horizontal line.[1] Anterior pelvic tilt (APT) is characterized by the ASIS positioning lower than the PSIS in the sagittal plane or undergoing a downward rotation relative to the PSIS. Posterior pelvic tilt (PPT) is defined by the elevation of the ASIS above the PSIS in the sagittal plane or its rotational movement exhibiting an upward inclination relative to the PSIS.[2] APT angles in asymptomatic individuals have been reported to be in the average range of 6-7° for both sexes.[3] Changes in PT have been associated with many musculoskeletal conditions, including knee osteoarthritis,[4] low back pain[5] and lumbar spinal stenosis.[6] In addition, these changes are likely to affect lower limb alignment, balance and posture.

Unilateral lower limb amputation can lead to significant changes, including altered gait, imbalance, and compensatory movements. It often causes increased strain on the remaining limb, potential joint pain, and muscle imbalances. There may also be changes in posture, pelvic tilt, and mobility, as well as a need for prosthetics and rehabilitation to restore function and stability.[7] In addition, quality of life and body image perception of patients with amputation may be impaired.[8]

The prosthetic socket component assumes a pivotal role in exerting influence over the strength of the residual limb.[9] The shape of the socket interacting with the stump has undergone various changes over time. The development of ischial containment socket (ICS) designs in the early 1980s,[10] in contrast to the previously prevalent quadrilateral sockets, aimed to place the femur in an adducted position. This positioning enhances gait efficiency through gluteus medius

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muscle movement.[11] Studies have demonstrated that ICS designs that are found to position the femur more medially[12] reduce energy consumption while walking compared to a quadrilateral socket[13] and improve the metabolic cost of walking, along with a reduction in lateral compensatory movements of the trunk.[14] Contemporary socket designs surrounding the ischio pubic ramus have emerged as alternatives to ICS designs.[15]

Several investigations have explored pelvic kinematics in both the sagittal and frontal planes during walking among individuals with TFA. In the sagittal plane, it was noted that TFA individuals exhibited increased APT angles in comparison to healthy controls.[16,17] Regarding the frontal plane, it was determined that pelvic obliquity was heightened in individuals with TFA compared to their healthy counterparts.[16] However, to our knowledge, although dynamic pelvic kinematics have been subject to inquiry in existing literature, there remains a scarcity of studies examining static pelvic tilts. Static PT is important for posture and posture assessments and, together with dynamic PT, provides crucial information in clinical practice and rehabilitation processes. In addition, static PT significantly impacts the fit and use of prostheses in TFP users. Accurate assessment of a patient's pelvic alignment allows for the creation of a more effective and targeted rehabilitation program. However, potential changes in pelvic slopes attributable to differences in socket designs remain unclear.

Post-surgery muscle imbalance, different socket designs, and gait and balance issues may potentially induce changes in pelvic mechanics. There is a lack of studies in the literature that examine alterations in static pelvic tilts resulting from prosthesis utilization. This study aims to investigate PT angles in patients with transfemoral prostheses, considering different socket designs, and to compare these angles with those of healthy controls. The hypothesis suggests that pelvic tilt angles will differ among patients with transfemoral prostheses, regardless of socket type, and will also differ from those observed in healthy subjects. This study, focusing on static PT, aims to fill the gap in the literature regarding this relatively underexplored area compared to dynamic pelvic kinematics. Additionally, it will contribute to a better understanding of the role of pelvic alignment in the process of prosthesis fitting and alignment, particularly in terms of posture assessments and rehabilitation. By providing further insight into how socket design influences static PT and prosthesis use, it will offer practical implications for clinical applications and rehabilitation strategies.

METHODS

Study Design and Participants

This cross-sectional investigation transpired from January 2022 to December 2023. Ethical approval was obtained from the KTO Karatay University Faculty of Medicine Non-medicine and Medical Device Researches Ethics Committee (Date: 20.12.2021, Decision No: 2021/006). Adherence to ethical principles was ensured throughout the study, following the guidelines stipulated by the Declaration of Helsinki. Study participants received comprehensive information about the research, and their participation was contingent upon the acquisition of written informed consent. A total of 28 male volunteers, consisting of TFP users (prosthesis group, n=14) and healthy subjects of similar age and body-mass index (BMI) (control group, n=14), participated in the study.

Participants were aged 18 years or older, had no history of surgeries affecting pelvic mechanics (e.g., lower back, pelvis, or hip), and volunteered willingly. The prosthesis group consisted of individuals with at least one year of unilateral transfemoral prosthesis use. Exclusion criteria included inability to cooperate, history of surgeries, fractures, or musculoskeletal conditions impacting pelvic mechanics, high BMI (BMI ≥35) hindering anatomical landmark identification, and, for the prosthesis group, prosthesis use at any level other than transfemoral.

Pelvic Tilt Measurement

In the sagittal plane, PT was measured using a digital inclinometer (baseline evaluation instruments, white plains, NY, USA) attached to a two-arm caliper. Participants stood with feet shoulder-width apart (approximately 30 cm), with arms either crossed over the chest or extended sideways to prevent interference. Weight was distributed evenly, and potential hip rotations were controlled. The evaluator palpated the PSIS and ASIS, positioning the caliper arms on these landmarks with assistance from a physiotherapist or orthotic-prosthetic technician. Inclinometer readings were recorded and repeated for the opposite side.[18] Lateral pelvic tilt (LPT) in the frontal plane was measured with the caliper arms over the ASISs, and inclinometer values recorded (**Figure 1A, B**). APT is defined as PSIS higher than ASIS, while PPT is the reverse; LPT is identified when one ASIS is higher than the other. This reliable, valid, and cost-effective method is commonly used for assessing pelvic asymmetry.[19] All measurements were conducted by a single, experienced musculoskeletal clinician and researcher.

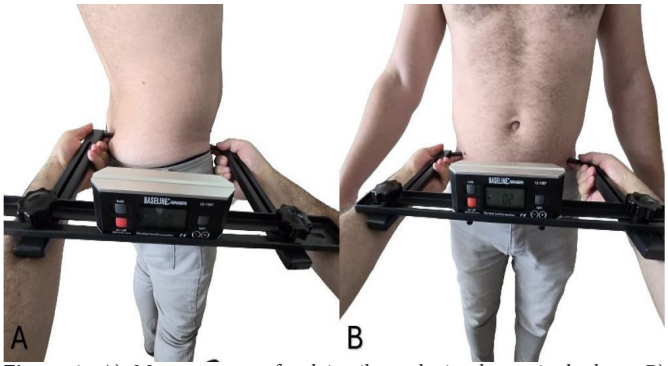

Figure 1. A) Measurement of pelvic tilt angle in the sagittal plane, B) Measurement of pelvic tilt angle in the frontal plane

Statistical Analysis

Data analysis was conducted using SPSS 25 (IBM Inc., Armonk, NY, USA), and sample size was determined with G* Power software. A pilot test with 10 volunteers (5 prosthesis group, 5 control group) was performed to estimate the required sample size. A power analysis based on the pilot

study indicated an α level of 0.05, power of 0.95, and ES of 1.46, suggesting a minimum of 14 participants per group.

Descriptive statistics, including mean, standard deviation, median, and quartiles, were presented for both categorical and continuous variables. Variance homogeneity was assessed with the Levene test, and normality was verified using the Shapiro-Wilk test. Since APT and LPT values among all prosthesis users followed a normal distribution, within-group differences were analyzed via paired samples T test. For quadrilateral and ICS socket groups, due to small sample sizes, the Wilcoxon test was used. ESs were calculated using Cohen's d for parametric cases and $r=Z/\sqrt{N}$ otherwise. For independent group comparisons, the independent T test or Mann-Whitney U test was applied as appropriate, with $p<0.05$ considered statistically significant.

RESULTS

Participants

The study included 14 patients with unilateral TFP (mean age: 41.64±14.15 years) and 14 healthy subjects of similar age and BMI (mean age: 42.79±10.30 years). Seven of the patients using TFP were using a quadrilateral socket design, while the other seven were using an ICS design. The duration of prosthesis use was similar between these patients (p=0.949). Two females using TFP were excluded from the study because the pelvic structure in women is different from that in male and there was no possibility of numerical comparison. Additionally, two patients with knee disarticulation were excluded due to potential biomechanical factors that could impact the study outcomes. Participant demographics, including mean age, BMI, and comparisons based on groups and prosthesis usage duration in the TFP group, are detailed in Table 1.

Table 1. Demographic characteristics of the participants

	Total (n=28)	Prosthetic group (n=14)	Control group (n=14)	p
	Mean±SD	Mean±SD	Mean±SD	
Age (years)	42.21±12.16	41.64±14.15	42.79±10.30	0.809[a]
BMI (kg/m²)	26.45±3.91	26.44±4.13	26.46±3.82	0.989[a]
Prosthesis usage time (months)	-	176.57±141.84	-	-

SD: Standard deviation, BMI: Body-mass index, [a]Independent two group T test, p<0.05 bold statistically significant differences

Among the TFP users, 8 (57.1%) and 6 (42.9%) employed prostheses on the right and left extremities, respectively. Detailed information about the prostheses utilized by patients in the prosthesis group and the underlying reasons for amputation are provided in Table 2.

Comparison of PT Angles in the Prosthesis Group

All participants had APT and there was no significant difference in APT and LPT angles between the prosthetic side and the contralateral side in the prosthesis group (p=0.106, effect size (ES)=0.464; p=0.055, ES=-0.564, respectively).

There was no significant difference in APT and LPT angles between the prosthetic side and the contralateral side of the participants using both quadrilateral socket designs and ICS designs (p=0.499, ES=-0.256; p=0.128, ES=-0.575; p=0.063, ES=-0.703; p=0.612, ES=-0.192, respectively) (Figure 2).

Comparison of PT angles between groups

The right APT, left APT, and LPT angles were observed to be higher in the prosthesis group compared to the control group (p=0.001, ES=-0.582; p<0.001, ES=-0.635; p<0.001, ES=-0.797, respectively) (Table 3).

Table 2. Information about the prostheses used by the patients

Prosthetic side	Cause of amputation	Type of socket	Type of suspension	Type of knee	Type of foot	Walking aid	Prosthesis usage time (months)
Left	Firearm injury	Quadrilateral	Pin lock system	Mechanical knee	Single axis foot	No	72
Left	Firearm injury	ICS	Passive vacuum	Pneumatic knee	Carbon foot	No	144
Right	Vascular diseases	Quadrilateral	Pin lock system	Mechanical knee	Single axis foot	No	42
Left	Traffic accident	ICS	Pin lock system	Microprocessor knee	Carbon foot	No	120
Right	Vascular diseases	Quadrilateral	Pin lock system	Mechanical knee	SACH foot	No	24
Right	Traffic accident	Quadrilateral	Suction	Microprocessor knee	Carbon foot	No	384
Left	Firearm injury	ICS	Passive vacuum	Microprocessor knee	Carbon foot	No	180
Left	Firearm injury	ICS	Pin lock system	Microprocessor knee	Hydraulic prosthetic foot	No	324
Right	Firearm injury	Quadrilateral	Active vacuum	Microprocessor knee	Hydraulic prosthetic foot	Yes	468
Right	Osteosarcoma	ICS	Pin lock system	Pneumatic knee	Carbon foot	No	18
Right	Burn	Quadrilateral	Suction	Mechanical knee	Single axis foot	Yes	72
Right	Traffic accident	Quadrilateral	Suction	Microprocessor knee	Carbon foot	No	300
Right	Firearm injury	ICS	Suction	Microprocessor knee	Carbon foot	No	204
Left	Traffic accident	ICS	Passive vacuum	Microprocessor knee	Carbon foot	No	120

ICS: Ischial containment socket

Figure 2. Anterior and lateral pelvic tilt angles on the prosthetic side and contralateral side

Table 3. Comparison of APT and LPT values between groups

	Prosthetic group (n=14)	Control group (n=14)			
	Mean±SD M (IQR 25-75)	Mean±SD M (IQR 25-75)	z	p	Effect size
Right APT (°)	12.79±4.31 13.8 (7.975-16.225)	7.42±1.74 7.20 (6.275-9.325)	-3.079	0.001[a]	-0.582
Left APT (°)	14.29±6.76 13.9 (8.825-17.850)	7.27±1.78 7 (6.100-9.400)	-3.360	<0.001[a]	-0.635
LPT (°)	3.14±2.23 2.75 (1.400-4.625)	0.21±0.15 0.20 (0.100-0.325)	-4.218	<0.001[a]	-0.797

APT: Anterior pelvic tilt, LPT: Lateral pelvic tilt, SD: Standard deviation, M: median, IQR: Interquartile range, p<0.05 bold, statistically significant differences, [a]Mann-Whitney U test, Effect sizes were calculated using the r=Z/√N formula

DISCUSSION

This study examined PT angles in transfemoral prosthesis (TFP) users with different socket designs, comparing them to healthy controls. No significant differences were observed between the prosthetic and contralateral sides or between quadrilateral and ICS socket designs. However, the prosthesis group showed significantly higher right APT, left APT, and LPT angles than controls. Although the APT angle on the prosthetic side was 2.63° higher and LPT was 1.92° lower, these differences did not reach statistical significance. Herrington[3] identified the smallest detectable difference (SDD) in pelvic tilt as 2.5° in asymptomatic individuals, suggesting that our findings may reflect clinically relevant differences despite the lack of statistical significance. Clinically, elevated APT in prosthesis users may lead to back pain, balance and posture issues, and may impact prosthesis fit and duration of use.

Significant differences between the TFP and control groups in right APT (5.37°), left APT (7.02°), and LPT (2.93°) angles suggest that pelvic asymmetry may stem from muscle imbalances due to amputation. Muscle loss, particularly in the hamstrings, quadriceps femoris, and adductor magnus, affects lower extremity control.[20] Post-surgery, residual stumps often move into abduction, altering PT angles on the prosthetic side.[21] Other factors influencing asymmetry include prosthesis lengths,[22] alignment, and soft tissue condition proximal to the stump. Furthermore, it has been reported that stump length is among the factors influencing pelvic asymmetry.[23] The adductor magnus, crucial for thigh stabilization, loses substantial function post-amputation, potentially leading to femoral abduction, whereas knee disarticulation that preserves this muscle can maintain femoral alignment.[20]

Limited studies address static pelvic asymmetry in TFP users, despite extensive research on dynamic pelvic kinematics. Gaunaurd et al.[22] identified asymmetry in the pelvic innominate slope in TFP users, but their study included more male participants, knee disarticulation cases, and had a larger sample. Our smaller sample, excluding females and knee disarticulation cases, may explain the lack of significant findings. Increased sample size might yield significant results.

Socket designs can affect the contraction strength and function of the muscles within the socket. Socket designs that keep the femur in an adducted position help the hip abductors to stabilize the pelvis and reduce compensatory movements associated with the pelvis and trunk.[21] Prior research suggested quadrilateral sockets might limit frontal-plane pelvic movement, but the small sample size limited interpretation.[24] In our study, socket type did not significantly affect pelvic asymmetry, though larger sample sizes may clarify these findings. An alternative to traditional socket-based systems is osseointegration prostheses, which eliminate the need for a socket entirely. These prostheses may influence pelvic mechanics differently by enabling more natural muscle activation and direct load transfer through the femur. They have been associated with improvements in comfort and functional mobility, potentially reducing compensatory movements and asymmetries. Studies have shown that osseointegration prostheses for transfemoral amputees can significantly improve walking parameters, quality of life, and prosthesis use compared to socket prostheses.[25,26] Additionally, these prostheses offer better stability, reduced pain, and fewer skin problems at the stump/socket interface. However, complications such as infections and the need for additional surgeries are notable challenges.[25] Further research comparing osseointegration systems with conventional socket designs could provide valuable insights into their distinct effects on pelvic mechanics.

Our hypothesis that PT angles would be different in patients using TFP regardless of socket type was not realized. This discrepancy may be attributed to the limited number of TFP users and heterogeneity in the duration of prosthesis use. Nonetheless, our second hypothesis, positing different PT angles in TFP users and healthy individuals, was affirmed.

Limitations

Several limitations were identified in the study. Firstly, the stump length in prosthesis patients was not measured, and its potential impact on prosthetic control and pelvic stability was not investigated. Stump length is considered a critical parameter and may play a role in these aspects. Secondly, the prosthesis use durations were not homogeneous. The duration of prosthesis use may influence changes in PT angles. Over

time, muscle atrophy, hypertrophy, and habitual walking patterns may contribute to changes in PT. Furthermore, although a pilot study was conducted to guide participant recruitment, a larger cohort would have allowed for a more robust interpretation of the results. Finally, the insufficient representation of females in the prosthesis group (only 2 out of 16 patients were female) limited the opportunity for gender-specific comparisons.

CONCLUSION

Among patients with TFP, no statistically significant differences in PT angles were observed between the prosthetic side and the contralateral side in both the sagittal and frontal planes. However, a significant difference in these angles was found when comparing prosthetic patients to healthy controls. Differences in pelvic tilt angles are likely to lead to orthopedic dysfunctions such as low back pain, muscle imbalance and socket alignment problems over time. Further studies should focus on the presence of these problems in TFP users.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval was obtained from the the KTO Karatay University Faculty of Medicine Non-medicine and Medical Device Researches Ethics Committee (Date: 20.12.2021, Decision No: 2021/006).

Informed Consent

Informed consent was obtained from all patients for being included in the study.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The author has no conflict of interest to declare in relation to this article.

Financial Disclosure

The author declares 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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Breastfeeding practices and influencing factors among mothers: a survey study

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ABSTRACT

Aims: Breastfeeding practices vary across communities, and the continuation of breastfeeding for the recommended duration remains suboptimal. This study aims to evaluate the breastfeeding practices of mothers with children older than 12 months and the factors influencing these practices.

Methods: This survey study was conducted at the Child Clinic of Konya Beyhekim Training and Research Hospital from November 15 to December 30, 2024. A total of 218 mothers were selected through simple random sampling. Data were collected using a structured questionnaire that assessed sociodemographic information, health status, breastfeeding practices, and related experiences. The questionnaire was administered face-to-face during hospital visits.

Results: The study found that 63% of mothers exclusively breastfed their infants for the first six months postpartum. Among those who did not provide breast milk immediately, the primary reason cited was that 73% felt they had insufficient milk, while the second most common reason was that the baby was ill or required incubator care. 65% of mothers continued breastfeeding for over 12 months. Comparing the characteristics of mothers who exclusively breastfed their babies for the first 6 months and those who did not, significant differences were found in age groups, mode of delivery, number of living children, multiple pregnancies, prematurity, birth weight, infant illness, hospitalization, pacifier use, and bottle feeding.

Conclusion: Study findings emphasize that more than half of mothers feed their babies exclusively with breast milk for the first 6 months, and a significant portion of them continue breastfeeding after the first year. It has been shown that some baby and maternal factors may be effective in feeding babies only breast milk for the first 6 months.

Keywords: Breastfeeding, survey study, infant, postpartum period

INTRODUCTION

Breast milk is the most natural source of nutrition that can meet all of an infant's needs during the first six months of life. For healthy growth and development, it is recommended that infants be exclusively breastfed for the first six months and continue to receive breast milk alongside complementary foods for at least two years afterward. Breastfeeding offers numerous benefits for both infants and maternal health.[1] It is estimated that exclusive breastfeeding for six months and continuing breastfeeding throughout the first year of life could prevent a significant proportion of deaths in children under five years of age.[2]

The timing of breastfeeding initiation, exclusive breastfeeding for the first six months, and the duration of breastfeeding can vary significantly between communities. However, despite the numerous advantages of breast milk, the continuation of breastfeeding for the recommended duration remains suboptimal.[1] For instance, data indicates that only 25% of infants in Europe and 43% in the Southeast Asia region are exclusively breastfed at six months of age. In many countries, although initiation rates of breastfeeding are high at birth, there is a noticeable decline in the rates of exclusive breastfeeding over time. This is particularly evident in Europe, where the prevalence of exclusive breastfeeding at six months is markedly low.[3] Globally, the rate of exclusive breastfeeding for the first six months is 44%, while in Turkiye, this rate is reported to be 41%. Furthermore, among newborns aged 0-1 month, 59% are exclusively breastfed, whereas this figure drops to 45% for infants aged 2-3 months and 14% for those aged 4-5 months.[4]

Previous studies have shown that the proportion of mothers who breastfeed for a year or longer is significantly higher in developing countries. This rate was reported to be 91.8% in Africa, 87.5% in Asia, approximately 85% in Kenya, and 59.9% in Latin America and the Caribbean.[5,6] In a study conducted in our country, the proportion of mothers who breastfed for more than one year was found to be 12.3%.[7] The variations in these rates may be attributed to cultural differences and socioeconomic factors among countries.[8] In poorer countries,

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the initiation of breastfeeding tends to be delayed, and the rate of exclusive breastfeeding for the first six months remains below 40%.[9]

Various factors influence breastfeeding practices, including education level, employment status, family structure, income level, pregnancy desirability, health issues, parity, prior breastfeeding experience, breastfeeding education, and mode of delivery.[10] The study results examining factors affecting breast milk and breastfeeding vary across different countries and regions within the same country.[8] Promoting early initiation of breastfeeding after birth is essential for increasing mothers' awareness and knowledge of proper breastfeeding practices.[11] In this context, identifying community practices and experiences regarding breast milk and breastfeeding is crucial for increasing exclusive breastfeeding rates during the first six months. Therefore, this study aims to evaluate the breastfeeding practices of mothers with children older than 12 months and the various factors influencing these practices.

METHODS

Ethics

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the KTO Karatay University Faculty of Medicine Non-Drug and Non-Medical Device Researches Ethics Committee (Date: 31.10.2024, Decision No: 2024/005) and an informed consent form was obtained from the participants.

Study Design and Participants

The research employed survey design. It was conducted at the Child Clinic of the Konya Beyhekim Training and Research Hospital of the University of Health Sciences between November 15, 2024, and December 30, 2024. The inclusion criteria for participants were mothers with children over 12 months old who presented to the Child Clinic at Konya Beyhekim Training and Research Hospital.

Inclusion criteria: Participants were mothers with children over 12 months old who presented to the Child Clinic during the study period.

Exclusion criteria: Mothers who chose not to participate in the study were excluded. Additionally, mothers whose questionnaire forms were not fully completed were also excluded from the analysis. Specifically, mothers with children under 12 months old were not included in the study.

Sample Size

The study population was determined based on the total number of births at our hospital in 2024, which was 1075. Using a known population sampling method with a 5% margin of error and an expected prevalence of 25%,[12] the required sample size was calculated to be 211. However, to better represent the population, the study was completed with 218 participants. A simple random sampling method was employed, where eligible mothers were randomly selected from the hospital's patient list to ensure randomness. During the study period, mothers who visited the Child Clinic during working hours were invited to participate in the study. Each day, 7 or 8 mothers were randomly selected from all eligible mothers present at the clinic, ensuring a random selection process to reach a total of 218 participants.

Questionnaire

The questionnaire was designed to assess breastfeeding experiences and knowledge about breast milk. It included sections on sociodemographic information, health status, breastfeeding practices, the transition to complementary foods, and questions regarding the mothers' experiences with breastfeeding.

Data Collection Process

Data collection involved mothers filling out questionnaires upon their visit to the hospital. The distribution of the questionnaires was conducted face-to-face with those who consented to participate in the study. The questionnaire was administered in a private setting to ensure that participants could answer independently. The duration for completing the questionnaire was approximately 15-20 minutes. The survey form was prepared and revised according to the previous studies.[12-17] The questionnaire included the following components:

Sociodemographic information: Place of residence, mother's age, education level, employment status, family income, and family structure.

Health and pregnancy information: Frequency of antenatal visits, training received on breastfeeding and breast milk during pregnancy, the source of breastfeeding education, duration of training, planned pregnancy status, mode of delivery, and number of living children.

Child-related information: Child's gender, multiple pregnancies, preterm birth status, age at delivery, illnesses during the neonatal period, whether hospitalization was required at birth and duration of stay, and birth weight.

Breastfeeding experience: Timing of the initiation of breastfeeding, reasons for any delays beyond the first half hour, first food given after birth, whether colostrum was administered, exclusive breastfeeding status, timing of the introduction of complementary foods, reasons for providing less than six months of breastfeeding, duration of breastfeeding for the last child, frequency of breastfeeding, first complementary food introduced, provision of water while breastfeeding, use of pacifiers or bottles, and the presence of formula or other foods equivalent in value to breast milk.

Statistical Analysis

Categorical variables were reported as counts and percentages. The Shapiro-Wilk test was utilized to evaluate the distribution of the data. Since the data did not follow a normal distribution, results were expressed as medians with interquartile ranges (IQR). Comparisons of categorical variables among different groups were performed using the chi-square test or Fisher's exact test as appropriate. To assess the reliability of the questionnaire, Cronbach's alpha was calculated. Factor analysis was conducted to evaluate the construct validity of the questionnaire, with the assessment of Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's

test of Sphericity. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS software for Windows, version 21.0.

RESULTS

A total of 218 volunteer mothers participated in the study. The sociodemographic characteristics of the participants included a median age of 34 years (IQR: 9), with the most common age range being 25-34 years (Table 1). Most mothers were college graduates and predominantly lived in nuclear family structures. About one-third were employed, and roughly one-third reported earning the minimum wage. Most participants had antenatal follow-up at least four times, and approximately half received breastfeeding education, primarily from midwives/nurses.

The experiences of mothers regarding breast milk and breastfeeding are summarized in Table 2. Regarding breastfeeding practices, around 65% of mothers-initiated breastfeeding within the first half hour after birth. Among those who did not, 73% cited insufficient milk as the primary reason. About 79% reported that breast milk was the first food given to their newborns, and 92% provided colostrum. Approximately 63% exclusively breastfed for the first six months, with insufficient breast milk being the most common reason for those who did not (69%).

Comparative analysis revealed no significant differences between mothers who exclusively breastfed for the first six months and those who did not in terms of residence, education, family structure, employment, income, antenatal follow-up frequency, or breastfeeding education received ($p>0.05$). However, significant differences were noted in age groups, mode of delivery, number of living children, multiple pregnancies, prematurity, birth weight, infant illness, hospitalization, pacifier use, and bottle feeding ($p<0.05$, Table 3).

To assess the reliability of the questionnaire, Cronbach's alpha was calculated. The overall Cronbach's alpha value for the questionnaire was found to be low, with the highest Alpha value of 0.416 observed when the item "Reason for breastfeeding for less than 6 months?" was excluded from the analysis. Additionally, the other items exhibited low Cronbach's alpha values, indicating potential issues with internal consistency. Factor analysis was conducted to evaluate the construct validity of the questionnaire. The KMO measure of sampling adequacy was found to be 0.604, which is considered adequate for conducting factor analysis. The Bartlett's test of Sphericity yielded a significant result (chi-square=4188.951, df=595, $p<0.001$), indicating that the correlations between items were sufficient for factor analysis.

DISCUSSION

This study is a survey examining mothers' experiences with breastfeeding. Current findings indicate an exclusive breastfeeding rate of 63% during the first six months postpartum. Among those who did not exclusively breastfeed, insufficient breast milk was the most commonly cited reason. Furthermore, 65% of mothers reported breastfeeding for over 12 months.

Table 1. Sociodemographic and obstetric characteristics of all mothers

Where do you reside?	
Rural, n (%)	38 (17.4)
City, n (%)	180 (82.6)
Mother's age, year, median (IQR) (min-max)	34 (9) (21-48)
Mothers' age groups	
19-24 years	20 (9.2)
25-34 years	112 (51.4)
35 years and above	86 (39.4)
Mother's educational background	
Primary school, n (%)	28 (12.8)
Middle school, n (%)	32 (14.7)
High school, n (%)	64 (29.4)
Faculty, n (%)	94 (43.1)
Family structure	
Nuclear family, n (%)	198 (90.8)
Extended family, n (%)	20 (9.2)
Working status	
Not working, n (%)	156 (71.6)
Working, n (%)	62 (28.4)
Income status	
Minimum wage and below, n (%)	70 (32.1)
Above minimum wage, n (%)	148 (67.9)
Antenatal monitoring frequency	
Less than 4 times, n (%)	30 (13.8)
4 times or more, n (%)	188 (86.2)
Have you received training on breast milk and breastfeeding during pregnancy?	
No, n (%)	110 (50.5)
Yes, n (%)	108 (49.5)
Who provided you with training on breast milk and breastfeeding?	
Physician, n (%)	14 (11.1)
Midwife/nurse, n (%)	94 (87)
Family elder, n (%)	0 (0)
Written visual media, n (%)	2 (1.9)
How long did you receive training on breast milk and breastfeeding?	
Short term (1-2 hours), n (%)	74 (68.5)
Long term (1 day or more), n (%)	34 (31.5)
Was it a planned pregnancy?	
No, n (%)	42 (19.3)
Yes, n (%)	176 (80.7)
What was your last birth method?	
By normal vaginal route, n (%)	86 (39.4)
Cesarean section, n (%)	132 (60.6)
How many living children do you have?	
0, n (%)	4 (1.8)
1, n (%)	70 (32.1)
2, n (%)	84 (38.5)
3 or more, n (%)	60 (27.5)
Baby's gender	
Male	124 (53.9)
Female	106 (46.1)
Was it a multiple pregnancy? n (%)	
No, n (%)	206 (94.5)
Yes, n (%)	12 (5.5)
Is your child premature?	
No, n (%)	172 (78.9)
Yes, n (%)	46 (21.1)
Pregnancy age, week, median (IQR), min-max	38 (1) (33-42)
Birth weight, grams, median (IQR), min-max	3100 (563) (1300-4500)
Babies' clasification according to birth weight	
Less than 2500 grams, n (%)	28 (12.8)
Between 2500-4000 grams, n (%)	182 (83.5)
More than 4000 grams, n (%)	8 (3.7)
Did your baby get sick as a newborn?	
No, n (%)	168 (77.1)
Yes, n (%)	50 (22.9)
Was your baby hospitalized as a newborn?	
No, n (%)	166 (76.1)
Yes, n (%)	52 (23.9)
How long was the hospital stay? Days, median (IQR), min-max	2 (6) (1-27)

Table 2. Results of mothers' breastfeeding experiences and breast milk

When did you first give breast milk to your baby after birth?	
In the first half hour, n (%)	142 (65.1)
At 1 hour, n (%)	34 (15.6)
In the 2nd hour, n (%)	18 (8.3)
At the 3rd hour or later, n (%)	24 (11)
Why couldn't you give your baby breast milk within the first half hour after birth?	
My milk did not come, n (%)	54 (72.97)
I was in pain, n (%)	2 (2.71)
My baby was sick or in an incubator, n (%)	12 (16.21)
The baby did not suck, n (%)	6 (8.12)
What was the first food given to your baby after birth?	
Breast milk, n (%)	172 (78.9)
Formula, n (%)	44 (20.2)
Water, n (%)	2 (0.9)
Has your baby been given colostrum?	
No, n (%)	18 (8.3)
Yes, n (%)	200 (91.7)
How often did you breastfeed your baby?	
Whenever the baby wants	190 (87.2)
Every 1 hour	6 (2.8)
Every 2 hours	20 (9.2)
Every 3 hours	2 (0.9)
How long did you give your baby exclusive breast milk?	
0-1 month, n (%)	38 (17.4)
2-3 months, n (%)	14 (6.4)
4-5 months, n (%)	28 (12.8)
6 months, n (%)	138 (63.3)
What was the reason for breastfeeding your baby for less than 6 months?	
Stopped sucking, n (%)	14 (17.9)
Breast milk was not enough, n (%)	54 (69.2)
I started work, n (%)	2 (2.6)
The baby was sick, n (%)	6 (7.7)
Because I'm sick myself, n (%)	2 (2.6)
How long did you breastfeed your last child? (n:214)	
Less than 1 month, n (%)	10 (4.7)
1-3 months, n (%)	20 (9.3)
4-6 months, n (%)	10 (4.7)
7-12 months, n (%)	34 (15.9)
12 months and above, n (%)	140 (65.4)
When did you start supplementary foods?	
0-2 months, n (%)	24 (11)
3-4 months, n (%)	18 (8.3)
5-6 months, n (%)	92 (42.2)
7 months and above, n (%)	84 (38.5)
What was the first complementary food you started giving your baby?	
Formula	52 (23.9)
Fruit juice or puree	28 (12.8)
Yogurt	128 (58.7)
Cooking water	10 (4.6)
Did you give your baby water while breastfeeding?	
No, n (%)	124 (56.9)
Yes, n (%)	94 (43.1)
Did your baby suck on a pacifier?	
No, n (%)	106 (48.6)
Yes, n (%)	112 (51.4)
Have you used a bottle while feeding your baby?	
No, n (%)	82 (37.6)
Yes, n (%)	136 (62.4)
Do you think there is any formula or other food that has the same value as breast milk?	
No	200 (91.7)
Yes	18 (8.3)

Table 3. Comparison of sociodemographic and obstetric characteristics of mothers according to exclusive breastfeeding status for the first six months

	Exclusive breastfeeding status for the first six Months					
	No		Yes		95% CI	p-value
Where do you reside?	**n**	**%**	**n**	**%**		
Rural	18	22.5	20	14.5	0.845-3.474	0.133
City	62	77.5	118	85.5		
Mothers' age groups						
19-24 years	12	15	8	5.8		
25-34 years	44	55	68	49.3		0.020
35 years and above	24	30	62	44.9		
Mother's educational background						
Primary school, n (%)	14	17.5	14	10.1		0.379
Middle school, n (%)	12	15	20	14.5		
High school, n (%)	24	30	40	29		
Faculty, n (%)	30	37.5	64	46.40		
Family structure						
Nuclear family, n (%)	26	32.5	44	31.9	0.571-1.854	0.925
Extended family, n (%)	54	67.5	94	68.1		
Working status						
Not working, n (%)	52	65.0	104	75.40	0.333-1.107	0.102
Working, n (%)	28	35.00	34	24.60		
Income status						
Minimum wage and below, n (%)	26	32.5	44	31.9	0.571-1.854	0.925
Above minimum wage, n (%)	54	67.5	94	68.1		
Antenatal monitoring frequency						
Less than 4 times, n (%)	10	12.50	20	14.50	0.373-1.903	0.681
4 times or more, n (%)	70	87.50	118	85.50		
Have you received breastfeeding training during pregnancy?						
No, n (%)	44	55.00	66	47.80	0.767-2.317	0.307
Yes, n (%)	36	45.00	72	52.20		
Who is the person you received training on breast milk and breastfeeding?						
Physician, n (%)	42	52.50	66	47.80		
Midwife/nurse, n (%)	4	5.00	10	7.20		0.617
Family elder, n (%)	34	42.50	60	43.50		
Written visual media, n (%)	0	0.00	2	1.40		
Was it a planned pregnancy?						
No, n (%)	12	15.00	30	21.7	0.305-1.325	0.224
Yes, n (%)	68	85.00	108	78.30		
What was your last birth?						
By normal vaginal route, n (%)	22	27.50	64	46.40	0.242-0.794	0.006
Cesarean section, n (%)	58	72.50	74	53.60		
How many living children do you have?						
0, n (%)	0	0.00	4	2.90		
1, n (%)	34	42.50	36	26.10		0.013
2, n (%)	22	27.50	62	44.90		
3 or more, n (%)	24	30.00	36	26.10		
Multiple pregnancy, n (%)						
No	70	87.50	136	98.60	0.022-0.483	0.001
Yes	10	12.50	2	1.40		
Is your child premature?						
No, n (%)	56	70.00	116	84.10	0.229-0.857	0.014
Yes, n (%)	24	30.00	22	15.90		
Babies' clasification according to birth weight						
Less than 2500 grams, n (%)	20	25.00	8	5.80		
Between 2500-4000 grams, n (%)	58	72.50	124	89.90	-	<0.0001
More than 4000 grams, n (%)	2	2.50	6	4.30		
Did your baby get sick as a newborn?						
No, n (%)	50	62.50	118	85.50		<0.0001
Yes, n (%)	30	37.50	20	14.50		
Was your baby hospitalized as a newborn?						
No, n (%)	50	62.50	116	84.10	-	<0.0001
Yes, n (%)	30	37.50	22	15.90		
Did your baby suck on a pacifier?						
No, n (%)	26	32.50	80	58.00	0.196-0.622	<0.0001
Yes, n (%)	54	67.50	58	42.00		
Have you used a bottle while feeding your baby?						
No, n (%)	18	22.50	64	46.40	0.180-0.625	<0.0001
Yes, n (%)	62	77.50	74	53.60		

The systematic review conducted by Wu et al.[18] identified several factors influencing exclusive breastfeeding, including maternal employment status, breastfeeding knowledge, mode of delivery, number of births, perceived insufficient milk supply, maternal feeding attitudes, breastfeeding self-efficacy, and intentions. The relationship between exclusive breastfeeding and maternal sociodemographic characteristics is intricate. While some studies indicate a significant association with maternal residence[19], current findings align with those of Göktepe et al.,[20] showing no significant relationship. The correlation between maternal age and exclusive breastfeeding rates also varies across research. Some studies suggest that older maternal age is linked to higher breastfeeding rates,[12,21] while others report no significant association.[22] Importantly, current findings reveal that mothers aged 19-24 exhibited lower exclusive breastfeeding rates compared to older mothers, suggesting that younger maternal age may negatively affect breastfeeding duration.

To effectively support breastfeeding, it is crucial to educate mothers during both prenatal and postnatal periods. Research indicates that a significant proportion of mothers receive information about infant feeding during pregnancy, primarily from healthcare professionals.[23,24] Increased emphasis on breastfeeding education during pregnancy is necessary to enhance maternal knowledge and practices.

In examining factors influencing exclusive breastfeeding, significant relationships have been noted regarding maternal characteristics, including age, education level, and frequency of antenatal visits.[12] However, other studies have shown no significant links with factors like gestational age or maternal residence.[20] While some research suggests a connection between maternal education and breastfeeding duration,[19] current findings align with those of Göktepe et al.,[20] showing no significant associations with exclusive breastfeeding rates. Nonetheless, a relationship was identified between the number of living children and breastfeeding practices.

The relationship between delivery methods and exclusive breastfeeding varies across studies. While some research shows no significant differences in breastfeeding initiation based on delivery method,[25] others report significant delays in breastfeeding for cesarean deliveries.[22,26] Present study reflects this trend, highlighting the need for healthcare professionals to implement strategies that promote timely breastfeeding initiation, particularly for mothers who experience cesarean sections.

Previous studies have shown that longer breastfeeding durations are associated with increased gestational age and normal birth weight.[26] The current study identified significant differences among those exclusively breastfeeding for the first six months based on factors such as multiple pregnancies, prematurity, birth weight, infant health status, and hospitalization. These findings suggest that premature infants or those requiring hospitalization may not receive breast milk or may receive it later due to their medical conditions.

A comprehensive study conducted in Japan in 2021 involving 80,491 mothers found that 37.4% of mothers exclusively breastfed their infants for the first six months.[27] According to the 2018 Turkiye Demographic and Health Survey (TDHS), the rate of exclusive breastfeeding for the first six months was reported at 41%.[4] The World Health Organization aims to increase this rate to at least 50% by 2025.[28] In contrast, Göktepe et al.[20] found this rate to be 55% in their study, while the current study reports an exclusive breastfeeding rate of 63% during the first six months. Additionally, the breastfeeding initiation rate within the first hour of birth was found to be 71% in the 2018 TDHS data and approximately 77% in Göktepe et al.'s[20] study, whereas the present study found this rate to be 80.7%. This exceeds UNICEF's target of 80% for early breastfeeding initiation set in 2016.[28] These results highlight the positive trends in breastfeeding practices and indicate significant progress toward global breastfeeding goals.

Çalık et al.[12] indicated that a notable proportion of mothers-initiated breastfeeding within the first half-hour postpartum, with many providing breast milk as the first food. In the current study, about 65% of mothers reported breastfeeding within the first 30 minutes after birth, with around 79% indicating that breast milk was their infant's first food. Aligning with Çalık et al., who noted that many mothers breastfed their infants on demand, the present study found that a significant majority of mothers breastfed their infants whenever they wished. Furthermore, a notable proportion of mothers reported exclusively breastfeeding for the first six months. Çalık et al. identified key reasons for not breastfeeding for less than six months, including the infant ceasing to suck and insufficient breast milk.[12] A 2023 study conducted in Australia revealed that the most common reasons for discontinuing breastfeeding were breastfeeding challenges and low milk supply. This study also emphasized the importance of providing breastfeeding support based on women's age and education during the early postpartum period.[29] In the current study, among those unable to breastfeed within the first half-hour, many attributed this to the absence of breast milk, while the second most common reason was the infant's illness or need for incubator care.

In Çalık et al.'s[12] study, a significant number of mothers began introducing complementary foods at 4-5 months, with many offerings' formula and water as complementary foods. In contrast, the current study found that a considerable proportion of mothers breastfed their infants for over 12 months. The most common age for introducing solid foods was reported to be between 5-6 months, with yogurt being frequently mentioned as the first complementary food. Additionally, many mothers indicated that they provided water while breastfeeding, used pacifiers, and fed their infants using bottles. These findings underscore the importance of ongoing education and support for mothers regarding breastfeeding practices, particularly in addressing the barriers faced by those unable to initiate breastfeeding early or maintain exclusive breastfeeding for the recommended duration. Enhancing awareness and resources can play a significant role in achieving global breastfeeding targets and promoting infant health.

Limitations

This study is a survey based on the opinions of mothers who are presented at the hospital, which limits the ability to establish causative relationships. Additionally, the sample

may not be representative of the entire population, and, therefore, the findings cannot be generalized to all women. Consequently, the results of this study should be interpreted with caution. The results of the reliability analysis indicate a need for further refinement of the questionnaire. The low Cronbach's alpha values across multiple items suggest that the items may not effectively measure a cohesive construction. Although the KMO value indicates that the sample size is adequate for factor analysis, the significant Bartlett's test of Sphericity confirms the need for modifications to enhance the reliability and validity of the questionnaire. Despite these limitations, the study has yielded some significant findings within the present study population.

CONCLUSION

Research findings emphasize that more than half of mothers feed their babies exclusively with breast milk for the first 6 months, and a significant portion of them continue breastfeeding after the first year. It has been shown that some baby and maternal factors may be effective in feeding babies only breast milk for the first 6 months. More comprehensive studies are needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the KTO Karatay University Faculty of Medicine Non-Drug and Non-Medical Device Researches Ethics Committee (Date: 31.10.2024, Decision No: 2024/005).

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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Evaluation of dentoalveolar and temporomandibular joint injuries during endotracheal intubation: a survey study

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ABSTRACT

Aims: Endotracheal intubation is a widely utilised technique in the fields of anesthesia and resuscitation. However, dentoalveolar and temporomandibular joint (TMJ) injuries may occur frequently during this procedure. Such injuries can result in patient morbidity and, in some cases, may also give rise to medico-legal issues. It is therefore essential to develop a comprehensive understanding of the prevalence of such injuries, the risk factors that contribute to their occurrence, and effective management strategies to minimize the likelihood of these complications arising.

Methods: A cross-sectional study was conducted to evaluate the knowledge and attitudes of 227 anesthesiologists across Turkiye regarding dentoalveolar and TMJ injuries occurring during endotracheal intubation. A previously validated online questionnaire consisting of 20 questions was administered. Data were analyzed with IBM SPSS v23 software, and the significance level was evaluated as $p<0.05$ using Fisher's exact test with Monte Carlo correction between categorical data.

Results: The survey revealed that 67.4% of the participants reported cases of dental trauma in adult patients, with a smaller percentage (28.2%) reporting cases in pediatric patients. The survey also revealed that the use of protective devices was minimal, with only 5.3% of participants reporting their use. However, a significant proportion (93%) of the participants stated that education should be provided on the prevention and management of dental trauma. The most common site of injury was the anterior teeth of the maxilla (82.8%), and the most common type of trauma was tooth fracture (56.6%). Furthermore, temporomandibular joint dislocation was reported in 26.4% of participants during the intubation process.

Conclusion: Dentoalveolar and TMJ injuries during endotracheal intubation are a prevalent yet under-researched problem. This study underscores the necessity for training programmes to formulate preventive measures and emergency intervention methods. Preoperative dental assessments and the utilization of protective devices can markedly reduce the incidence of such injuries.

Keywords: Dentoalveolar injuries, temporomandibular joint injuries, endotracheal intubation, survey

INTRODUCTION

Endotracheal intubation is a widely utilized technique in the fields of anaesthesia and resuscitation, particularly in emergency settings. This procedure entails the insertion of a probe through the oral and nasal cavities, extending into the trachea, with the objective of maintaining an open airway and facilitating artificial respiration. However, the teeth, which are located in the anterior part of the face and act as a functional natural barrier, are at risk of damage during this procedure and may be among the most frequently affected structures in endotracheal intubation.[1] Preoperative dental injuries are among the most common anaesthesia-related medico-legal complaints and account for approximately one third of all medico-legal cases.[2] Dental trauma or other intraoral damage during general anaesthesia contributes to the overall morbidity of the patient and constitutes a significant problem that may result in legal proceedings.[3] It is important to note that such injuries occur during surgical interventions not directly related to dental trauma. In particular, complications such as unexpected pain, aesthetic problems, and functional impairments may have a detrimental effect on the patient's quality of life and normal functioning, and thereby threaten overall well-being.[4] Furthermore, the financial burden of

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prosthetic replacement for lost or damaged teeth can prove to be a considerable strain on the patient.[5,6] In rare cases, life-threatening complications such as oesophageal perforation and mediastinitis have been reported in association with the aspiration of dentures or teeth. The majority of dental injuries occurring in the preoperative period (50-75%) take place during tracheal intubation.[1] Although the incidence of dental injuries in general has been reported to range between 0.06% and 12%, the actual prevalence of these rates may be underestimated.[7] During intubation, anaesthetists may use the upper teeth as a fulcrum if they do not have a clear view of the glottic orifice. Supporting the upper jaw and thus the upper anterior teeth during laryngoscopy may improve the line of sight and facilitate placement of the endotracheal tube. This use of the laryngoscope explains the frequency of dental injury during difficult intubation.[8]

A number of factors have been identified that can lead to accidents during endotracheal intubation. These factors are either directly related to the intubation process (e.g., inadequate alignment of the pharyngeal, laryngeal and buccal axes, inadequate compression of the base of the tongue, or the presence of airway obstructions and laryngeal stenosis) or to skeletal and dental abnormalities. Skeletal predisposing factors include, in particular, the presence of skeletal class II malocclusion, restricted mouth opening, reduced mandibular mobility, temporomandibular joint diseases and osseo-articular problems. Dental predisposing factors include carious lesions, extensive restorations, endodontically treated teeth, periodontal lesions, fixed prostheses, rhizalised deciduous teeth, dental malpositions and the presence of isolated teeth. These factors may increase the risk of complications during intubation, potentially leading to damage to the teeth.[9,10]

Major dental injuries reported during anaesthetic procedures include subluxation, crown fracture and tooth avulsion. Effective management of these common complications is of paramount importance for both patient safety and the success of the treatment process.[11] The maxillary anterior region, and more specifically the maxillary incisors, are the most commonly affected. This is due to the direct contact of the maxillary left central incisor with the laryngoscope blade, which is used as a fulcrum for positioning the laryngoscope.[12]

Tooth loss can have a direct impact on the patient's quality of life, potentially resulting in aesthetic, functional or psychological concerns. For the clinician, it is critical to prevent life-threatening complications such as tooth aspiration. Consequently, reducing the risk of dental injury during anaesthetic procedures and addressing emerging issues promptly are crucial for patient health and clinical success.[13]

The present study was conducted for the purpose of evaluating the knowledge and attitudes of anaesthesiologists with regard to the management of dentoalveolar and temporomandibular joint injuries. The study aims to reveal the physicians' approaches to such injuries, their level of awareness, and their strategies in the prevention or treatment of possible complications.

METHODS

This cross-sectional study was conducted online with 227 general anesthesia and reanimation physicians in Turkiye in order to evaluate their knowledge and attitudes about dentoalveolar and temporomandibular joint injuries during endotracheal intubation. Ethics Committee approval of our study was obtained from Mersin University Clinical Researches Ethics Committee (Date: 10.07.2024, Decision No: 2024-644). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study utilized a questionnaire comprising 20 questions, which had been developed by adapting existing, validated questionnaires.[11,14,15] The administration of the questionnaires was conducted in Turkish, the official language of the Turkish Republic. The survey started with a reminder that participation was voluntary, and all participation was entirely based on free will. The target sample size was determined to be 207 individuals, with a confidence level of 95% (1-α), a power level of 80% (1-β), and an effect size of g=0.064.[16]

Statistical Analysis

The data were analyzed using IBM SPSS V23. The Fisher's exact test with Monte Carlo correction was used to analyze the relationship between the categorical data. Frequency and percentage were used to represent categorical data. The significance level was taken as $p<0.05$.

RESULTS

Demographic Characteristics

Of the 227 anesthesiologists who participated in the study, 43.6% were female and 56.4% were male, and the age distribution was concentrated in the 25-30 (34.8%) and 31-35 (27.8%) age groups.

Prevalence of Dental Traumas

The rate of individuals reporting dental trauma in adult patients was 67.4%, while this rate was 28.2% in pediatric patients. The most common site of injury was the anterior maxillary teeth (82.8%), and the most common type of trauma was tooth fracture (56.6%) (**Table 1**). The approach adopted by anesthetists in cases of trauma to teeth or oral tissues was found to vary:

- 34.4% of them stated 'I solve it myself',
- 30.8% of them responded 'I refer the patient to the relevant department in dentistry',
- 30.8% of them answered 'I call the consulting physician' (**Table 1**).

Protective Measures and Awareness

The rate of protective device use was low (5.3%) and 93% of the participants stated that training on the prevention and management of dental trauma was necessary (**Table 1**).

Trauma Management and Awareness

In the management of serious injuries such as tooth avulsion, the majority of the participants (79.7%) stated that they referred the case to dentistry. However, only 13.7% stated that they preserved the avulsed tooth in a suitable solution, while

Table 1. Descriptive statistics of variables

	Frequency	Percentage
Gender		
Woman	99	43.6
Male	128	56.4
Age		
25-30 age group	79	34.8
31-35 age group	63	27.8
36-40 age group	26	11.5
41-50 age group	43	18.9
Over 51 age group	16	7
How many years have you been working in this field as an expert? (as of the beginning of your residency training)		
1-5 years group	126	55.5
6-10 years group	39	17.2
11-15 years group	19	8.4
16-20 years group	18	7.9
Over 21 years group	25	11
Are you aware that you could potentially cause trauma to the teeth, jaw, or oral tissues during endotracheal intubation?		
Yes	223	98.2
No	4	1.8
Have you ever caused trauma to the teeth, jaw, or oral tissues during endotracheal intubation in any pediatric patient?		
Yes	64	28.2
No	163	71.8
Have you ever caused trauma to the teeth, jaw, or oral tissues during endotracheal intubation in any adult patient?		
Yes	153	67.4
No	74	32.6
If your answer to question 5 or 6 is "yes", did you notice this situation yourself?		
Yes	153	90
No	17	10
What do you do if you cause trauma to the teeth, jaw, or oral tissues?		
I may not notice the situation	9	4
I solve it myself	78	34.4
I refer the patient to the relevant department in dentistry	70	30.8
I call the consulting physician	70	30.8
Do you use dental protectors to prevent any dental trauma during endotracheal intubation?		
Yes	12	5.3
No	215	94.7
Which area of teeth is most traumatized during endotracheal intubation?		
Maxilla anterior	188	82.8
Mandibula anterior	34	15
Mandibula posterior	4	1.8
Maxilla posterior	1	0.4
What type of trauma have you most frequently encountered during endotracheal intubation?		
Dental damage	111	50.2
Temporomandibular joint damage	8	3.6
Palatal soft tissue damage	57	25.8
Gingival soft tissue damage	45	20.4
In which age group have you mostly encountered dental trauma?		
0-6 age group	17	7.9
7-15 age group	14	6.5
16-25 age group	3	1.4
26-65 age group	64	29.9
66 years and older group	116	54.2
Which is the most common type of dental trauma you encounter during endotracheal intubation?		
Fracture of the visible part of the tooth in the mouth	116	56.6
Tooth avulsion	73	35.6
Fracture of the tooth filling	16	7.8

Table 1. Descriptive statistics of variables (continues)

	Frequency	Percentage
Have you ever caused dental avulsion during endotracheal intubation?		
Yes	95	41.9
No	132	58.2
What do you do with an avulsed tooth?		
I would discard the tooth	23	10.1
I would immediately replant and stabilize it	10	4.4
I would replant it after completing my current operation	9	4
I would replant and stabilize it after completing my current operation	4	1.8
I would refer the patient to the relevant department in dentistry	181	79.7
How do you preserve the avulsed tooth when referring your patient to the dentist?		
I wrap it in a moist sponge/tissue	68	30
I wrap it in a dry sponge/tissue	53	23.4
I send it in saliva	1	0.4
I send it in a solution specifically developed for this purpose	31	13.7
I send it in distilled water	8	3.5
I send it in milk	6	2.6
I have no information about this	60	26.4
Have you experienced temporomandibular joint dislocation during endotracheal intubation?		
Yes	60	26.4
No	167	73.6
What do you do in case of a temporomandibular joint dislocation?		
I am often not aware of it	18	7.9
I reposition it	145	63.9
I refer the patient to a dentist	58	25.6
I do nothing	6	2.6
Have you received training on what to do after dental trauma?		
Yes	20	8.8
No	207	91.2
Do you think training should be provided on preventing dental trauma or its emergency management during endotracheal intubation?		
Yes	211	93
No	16	7

26.4% stated that they did not have any information on this subject.

Temporomandibular Joint Injuries

Among the participants, 26.4% reported experiencing temporomandibular joint dislocation during intubation. In this case, 63.9% replaced the dislocation themselves, while 25.6% referred the patient to the dentist. The rate of those who did not recognize the dislocation was 7.9%.

Education and Requirements

The majority of the participants (91.2%) stated that they had not received any training on the management of dental trauma, whereas 93% stated that such training was necessary.

Methods of Preservation of Avulsed Tooth and Distribution According to Years of Professional Experience

An analysis of the methods of preservation of avulsed teeth was conducted according to years of professional experience, revealing significant differences between different groups. While 27.8% of novice (1-5 years) anesthetists stated that they wrapped the avulsed tooth in a damp sponge or tissue, 30.2% stated that they had no information on this subject. In the

group with 6-10 years of experience, the proportion of those who preferred wrapping the avulsed tooth in a dry sponge or tissue increased to 30.8%. However, the rate of using 'solution specifically developed for this purpose' in this group was 10.3% (Table 2).

In the more experienced group (11-15 years), the proportion of wrapping in damp sponge/tissue increased to 42.1%, while the proportion of wrapping in dry sponge/tissue decreased to 15.8%. In this group, the use of developed solutions was recorded as 21.1%. Amongst participants with 16-20 years of experience, the use of moistened sponges was 38.9%, and 11.1% of those kept avulsed tooth in milk. In the group with 21 years of experience and above, 40% wrapped in moist sponge/tissue, and 20% wrapped in dry sponge/tissue. In this group, the use of distilled water reached 12%, and the rate of those who said 'I have no information' was recorded as 16% (Table 2).

As shown in Table 2, the relationship between professional experience and avulsed tooth preservation method was found to be statistically significant (p=0.048). Significant differences were observed between the 1-5 year and 6-10-year groups, as well as between the 1-5 year and 16-20-year groups.

Temporomandibular Joint Dislocation Management

Significant differences were found between participants who experienced temporomandibular joint dislocation and those who did not in terms of their attitudes towards this condition.

Among the participants who experienced dislocation, 78.3% stated that they repositioned the dislocation themselves, 13.3% referred the patient to a dentist, and 6.7% stated that they were not aware of the dislocation. The proportion of those who did not perform any intervention was 1.7%.

Among the participants who did not experience dislocation, the rate of those who said 'I reposition it' decreased to 58.7%, while the rate of those referring to a dentist increased to 29.9%. The proportion of those who were not aware of the dislocation was 8.4%, and the proportion of those who did not perform any intervention was 3%.

The differences in management between those who experienced temporomandibular joint (TMJ) dislocation during endotracheal intubation and those who did not were statistically significant (p=0.043) (Table 3). This finding suggests that the experience of dislocation may have a bearing on the management approach.

A statistically significant correlation was identified between the approaches applied after causing trauma to the teeth, jaw or oral tissues and the status of causing trauma in pediatric patients (p=0.004) (Table 4). In adult patients, no statistically significant correlation was found between causing trauma to teeth, jaw or oral tissues during endotracheal intubation and the approaches applied after trauma (p=0.353) (Table 4).

Table 2. Examination of the relationship between year of specialisation and avulsed tooth preservation status

	1-5	6-10	11-15	16-20	Over 21	Total	Test statistics	p
How do you preserve an avulsed tooth?								
I wrap it in a moist sponge/tissue	35 (27.8)	8 (20.5)	8 (42.1)	7 (38.9)	10 (40)	68 (30)		
I wrap it in a dry sponge/tissue	29 (23)	12 (30.8)	3 (15.8)	4 (22.2)	5 (20)	53 (23.4)		
I send it in saliva	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	1 (0.4)		
I send it in a solution specifically developed for this purpose	20 (15.9)	4 (10.3)	4 (21.1)	1 (5.6)	2 (8)	31 (13.7)	33.177	0.048*
I send it in distilled water	4 (3.2)	1 (2.6)	0 (0)	0 (0)	3 (12)	8 (3.5)		
I send it in milk	0 (0)[a]	3 (7.7)[b]	1 (5.3)[ab]	2 (11.1)[b]	0 (0)[ab]	6 (2.6)		
I have no information about this	38 (30.2)	11 (28.2)	3 (15.8)	4 (22.2)	4 (16)	60 (26.4)		

*Fisher's exact test with Monte Carlo correction, [a,b]No difference between proportions with the same letter, n (%)

Table 3. Perspectives on TMJ dislocation among anesthetists who have and have not encountered TMJ

	Yes	No	Total	Test statistics	p
What do you do in case of a temporomandibular joint dislocation?					
I am often not aware of it	4 (6.7)	14 (8.4)	18 (7.9)		
I reposition it	47 (78.3)[a]	98 (58.7)[b]	145 (63.9)	7.904	0.043*
I refer the patient to a dentist	8 (13.3)[a]	50 (29.9)[b]	58 (25.6)		
I do nothing	1 (1.7)	5 (3)	6 (2.6)		

*Fisher's exact test with Monte Carlo correction, [a,b]No difference between proportions with the same letter, n (%), TMJ: Temporomandibular joint

Table 4. Evaluation of the post-traumatic attitude of physicians who encountered dental trauma during endotracheal intubation in pediatric and adult patients

Pediatric	Yes	No	Total	Test statistics	p
What do you do if you cause trauma to the teeth, jaw, or oral tissues?					
I may not notice the situation	5 (7.8)	4 (2.5)	9 (4)		
I solved it myself	31 (48.4)[a]	47 (28.8)[b]	78 (34.4)	12.879	0.004*
I refer to the patient to the relevant department in dentistry	15 (23.4)	55 (33.7)	70 (30.8)		
I called the consulting physician	13 (20.3)[a]	57 (35)[b]	70 (30.8)		
Adult					
What do you do if you cause trauma to the teeth, jaw, or oral tissues?					
I may not notice the situation	7 (4.6)	2 (2.7)	9 (4)		
I solved it myself	57 (37.3)	21 (28.4)	78 (34.4)	3.196	0.353*
I refer to the patient to the relevant department in dentistry	47 (30.7)	23 (31.1)	70 (30.8)		
I called the consulting physician	42 (27.5)	28 (37.8)	70 (30.8)		

*Fisher's exact test with Monte Carlo correction, [a,b]No difference between proportions with the same letter, n (%)

DISCUSSION

Although anesthetists are among the occupational groups that frequently encounter preoperative dental damage, knowledge about the procedures they perform when they encounter such situations is quite limited. In the literature, there are few studies evaluating the level of knowledge about dental trauma among anaesthetists.[14] In the context of our study, a questionnaire-based investigation was conducted to evaluate the knowledge and experience levels of general anesthesia and reanimation physicians, who are at high risk of encountering traumatic dental injury (TDI) cases, regarding dentoalveolar and temporomandibular joint injuries during endotracheal intubation. Additionally, the study aimed to determine their training status in this area.

Despite advances in intubation techniques and devices, preoperative dental damage remains one of the most common adverse events associated with anesthetic administration. It accounts for the largest proportion of malpractice claims against anesthetists, comprising more than 33% of all complaints.[17,18] Retrospective studies of hospital records, anesthesia residency programme directors' reports and insurance company records have shown that the incidence of dental trauma in patients treated under general anesthesia ranged from 0.02% to 0.27% over an 11-year period. In contrast, prospective studies reported a higher incidence compared to retrospective data (12.1%-25.0%).[14]

Research indicates that between 11% and 40% of patients suffering from dental injuries related to anesthesia make claims to insurance companies for the cost of dental restoration.[14] However, only a limited number of these studies have been conducted with the views of anaesthetists.[14,19] In our study, 28.2% (n=64) of anesthetists reported experiencing preanesthetic dental trauma (PADT) in pediatric patients, while 67.4% (n=183) reported such experiences in adult patients during their careers. Notably, the rate of PADT reported in adult patients in this study was higher compared to previous studies. This discrepancy is believed to stem from the fact that iatrogenic injuries occurring in the preanesthetic period are more likely to be recalled by anesthetists than accurately reflected in retrospective hospital records.

Existing studies, similar to our study, show that anaesthetists do not have sufficient experience in TDI, dental avulsion management and PADT.[11,14] In the study by Dubey et al.,[11] only 30% of anaesthetists stated that the tooth should be implanted immediately. This rate was only 4.4% in our study. In addition, in the study by Dubey et al.,[11] almost half of the participants (40%) did not want to reimplant on their own because they thought it was not their specialty, or they did not have enough information. In our study, 79.7% of anaesthetists said, 'I refer to the relevant department in dentistry." The positive change in this rate can be attributed to the increase in awareness of specialties in dentistry over the years.

In case of a delay in reimplantation, the avulsed tooth should be stored in a suitable environment to prevent the loss of vitality of the periodontal tissues around the avulsed tooth.[20] Dubey et al.[11] found that almost half of the anaesthetists (40%) thought that the avulsed tooth should be kept in gauze. However, the most ideal medium for storing an avulsed tooth is considered to be Hank's solution.[18] Similarly, in our study, 30% of the participants said, 'I wrap it in a moist sponge/tissue'.

Our study demonstrated that the management differences between those who experienced temporomandibular joint dislocation during endotracheal intubation (26.4%) and those who did not (73.6%) were statistically significant, suggesting that the experience of dislocation may affect the management approach. There is almost no study evaluating the opinions of anaesthetists about TMJ dislocation during endotracheal intubation. As a result of damage to the TMJ and surrounding structures, the use of mouth guards should become mandatory to prevent postoperative TMJ and facial pain.[21]

Consistent with previous research, the data obtained indicate that these professional groups are generally not trained in TDI, with the vast majority (91.2%) lacking any formal training background on this subject.[16,19,22,23] Moreover, 93% of the respondents believe that training programs on this topic should be implemented.

A comprehensive preclinical evaluation is essential for mitigating the risk of dental injuries during anesthesia. The anesthetist must meticulously evaluate potential risk factors, such as poor oral hygiene, mobile teeth and a history of difficult intubation.[24] In cases where such risks are present, it is recommended that patients be referred to a dentist prior to the planned surgical procedure. Preoperative dental interventions can reduce these risks by treating caries, replacing loose restorations, splinting or extracting removable teeth. In addition, a suitable protective appliance can be provided for use during surgery.[25] In the survey, only 5.3% of participants reported using a protective appliance. The paraglossal straight blade technique is an effective alternative for reducing the risk of dental injury in patients with removable anterior teeth or missing right maxillary molars. This technique offers a lower risk compared to the traditional Macintosh laryngoscope and is a practical method to prevent tooth damage.[26] Dental injury is more likely when using the Macintosh blade. It is therefore recommended that the Miller blade be selected in patients at risk of dental trauma. In addition, it is advised that the size of the laryngoscope be reduced in order to prevent dental trauma.[12] In addition, specialized designs such as the 'dental protective blade', enhanced laryngoscope blade' and 'callander laryngoscope blade' have been developed to protect the teeth during direct laryngoscopy and have been widely adopted for clinical use. Devices used to protect teeth include individually adaptable thermoplastic shields and pre-moulded dental shields. Shields made of thermoplastic material, cellulose acetate foil or ethylene vinyl-acetate can be customized to the patients' oral structure, while pre-engineered dental shields offer a more practical and faster solution, contributing to the prevention of dental trauma.[27]

CONCLUSION

This study set out to investigate the prevalence of dentoalveolar and temporomandibular joint injuries occurring during endotracheal intubation in anesthetic practice, and the level of awareness of these conditions. The findings show that such

injuries have a high prevalence and that adequate precautions are generally not taken. In particular, it was determined that the use of protective devices was at a very low level and the majority of healthcare professionals did not receive adequate training in this field. It is vital to prioritise prevention and effective management of dental and temporomandibular joint injuries in order to enhance patient safety and reduce medico-legal risks. In this context, a comprehensive oral and dental health assessment, identification of risk factors and appropriate protective measures should be taken prior to anesthesia procedures. Furthermore, the development of training programmes for such injuries and the raising of awareness among healthcare professionals will play an important role in reducing possible complications. In conclusion, increasing awareness among anaesthetists and implementing standardized protective measures can significantly reduce the incidence of perioperative dental and temporomandibular joint injuries. The findings of this study contribute to fill the existing gaps in the literature and provide a reference for future research.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Mersin University Clinical Researches Ethics Committee (Date: 10.07.2024, Decision No: 2024-644).

Informed Consent

All participants signed a free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

All 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 the quality and reliability of YouTube videos related to hallux rigidus

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ABSTRACT

Aims: This study aims to evaluate the scientific accuracy, informational value, and content quality of YouTube videos about hallux rigidus, marking the first study to assess videos on this topic.

Methods: Two systematic searches were conducted by two orthopedic surgeons using the YouTube search bar with the keywords "hallux rigidus" and "hallux limitus." Each video was evaluated based on the following features: title, content, source, duration (seconds), number of views, number of days since upload, view ratio (views/time since upload), number of likes, number of dislikes, like ratio (likes×100/likes+dislikes), and Video Power Index (VPI).

Results: A total of 50 videos meeting the inclusion criteria were evaluated. Among these, 39 (78%) were uploaded by healthcare professionals. Despite this, 25 videos (50%) were categorized as low quality according to the DISCERN score, and 33 videos (66%) were classified as low quality based on the YouTube hallux rigidus score. The DISCERN and JAMA scores demonstrated a statistically significant relationship with the video source ($p<0.001$). Videos created by physicians had significantly higher DISCERN and JAMA scores compared to those created by non-physician healthcare professionals ($p=0.015$, $p=0.01$). Similarly, videos by non-physician healthcare professionals scored significantly higher than those prepared by patients or for advertisement purposes ($p=0.031$, $p=0.026$). Additionally, videos uploaded more than three years ago had a significantly higher like rate compared to more recent videos ($p<0.001$).

Conclusion: The use of platforms such as YouTube for health-related information is increasing. However, the overall quality of videos about hallux rigidus remains low, underscoring the need for higher-quality content to better support public health outcomes.

Keywords: Hallux rigidus, hallux limitus, Youtube, video, quality

INTRODUCTION

Hallux rigidus is a progressive form of arthritis that causes pain and restricted movement in the big toe joint, significantly impairing patients' quality of life.[1-3] With the increasing digitalization of health information, platforms such as YouTube have considerable potential to contribute to public health by reaching large audiences.[1,2] However, research indicates that the quality of information in YouTube videos is generally low to moderate and often includes incomplete or misleading content, which may influence patients' health decisions.[6,7] Hallux rigidus is a progressive form of arthritis that causes pain and limited movement in the big toe joint, significantly impairing patients' quality of life by restricting their daily activities. Raising awareness about the diagnosis and treatment of this condition is critical for promoting early intervention and encouraging individual self-care.[3-5]

With the increasing digitalisation of health information, platforms such as YouTube hold significant potential to contribute to public health by reaching large audiences. Today, YouTube is one of the largest media-sharing platforms, with over 30 million daily active users and 1 billion monthly active users.[1,2] However, the accuracy and reliability of health-related content on this platform are often questioned. Research indicates that the informational quality of YouTube videos is generally low to moderate and frequently includes incomplete or misleading content that may influence patients' health decisions.[6,7] These concerns became more apparent during global health crises, such as the COVID-19 pandemic, where the quality of information on the platform was under increased scrutiny.[8]A high-quality video on hallux rigidus should provide a comprehensive overview of the condition,

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including its description, symptoms, available treatment options and associated risks, rehabilitation protocols, and prognosis. Additionally, the content should be grounded in credible and evidence-based sources.[9]

To date, no study in the literature has assessed the scientific accuracy and quality of YouTube videos related to hallux rigidus. Therefore, this study aims to evaluate the scientific accuracy, informational value, and content quality of hallux rigidus-related videos available on YouTube.

METHODS

Ethics committee approval was not required for this study. All procedures were carried out in accordance with the ethical rules and the principles.

Two systematic searches were conducted by two orthopaedic surgeons using the YouTube search bar. The searches were performed on 8 September 2024 via a web browser without any saved history or cookies, using the keywords "hallux rigidus" and "hallux limitus". Videos were filtered solely based on relevance. Videos that were not in English, lacked audio and/or video, were shorter than one minute, or were repetitive were excluded from the study. Data were obtained by analysing the first 50 videos that met these inclusion criteria.

The videos were categorised by source into four groups: physician, non-physician healthcare professional, patient, and advertisement. Each video was evaluated for the following features: title, content, duration (in seconds), number of views, days since upload, view rate (number of views/time since upload), number of likes, number of dislikes, like rate [likes×100/(likes+dislikes)], and Video Power Index (VPI).[10]

The accuracy and reliability of the video information were assessed using the Journal of the American Medical Association (JAMA) score, while the DISCERN score was used to evaluate video quality and content.[11] Additionally, video quality and content were evaluated using the newly developed YouTube hallux rigidus score (YHR), based on previous studies.[9] Video quality was categorised as follows: excellent (13-16), good (9-12), fair (5-8), and poor (0-4) (**Table 1**). The measurement and evaluation was carried out by two surgeons.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0. Descriptive statistics were presented as median (minimum–maximum) for continuous variables and frequency (percentage) for categorical variables. The Shapiro-Wilk test was used to evaluate data distribution. Non-parametric tests were employed for variables that did not meet the assumption of normality.

Group comparisons were conducted using the Kruskal-Wallis test, and pairwise comparisons were performed using the Mann-Whitney U test when significant differences were identified. Correlations between continuous variables were assessed using Spearman's rank correlation coefficient. A significance level of $p<0.05$ was considered statistically significant.

Table 1. YouTube hallux rigidus score

Anatomy	1 point
Timing	1 point
Age	1 point
Gender	1 point
Associated pathology	1 point
Clinical diagnosis	1 point
Radiological diagnosis	1 point
Differantial diagnosis	1 point
Conservative treatment	1 point
Surgical indications	1 point
Surgical contraindications	1 point
Surgical techniques	1 point
Implant type and description	1 point
Additional procedures	1 point
Immobilization detail description	1 point
Complication	1 point
TOTAL	16 point

RESULTS

In this study, 50 videos meeting the inclusion criteria were evaluated. Of the uploaded videos, 21 (42%) were from physicians, 18 (36%) were from non-physician healthcare professionals, 2 (4%) were from patients, and 9 (18%) were uploaded for advertising purposes.

In the evaluation of the DISCERN score, 8 (16%) videos were classified as having very poor quality, 17 (34%) as poor, 12 (24%) as fair, 9 (18%) as good, and 4 (8%) as excellent. In the YHR score evaluation, 33 (66%) videos were rated as poor, 12 (24%) as fair, 2 (4%) as good, and 3 (6%) as excellent. Descriptive information about the videos is given in **Table 2**.

Table 2. Descriptive of the results

	Minimum	Maximum	Median
Video duration (min)	1	34.5	3.8
Number of views	132	900000	14000
View ratio	0,5	357	95
Number of likes	1	16000	125
Number of dislikes	0	457	75
Like ratio	57	100	99
Video Power Index	0,5	346	12
DISCERN	18	72	38
JAMA	0	4	3
Halluks rigidus score	0	16	4

Video duration, number of views, number of likes, number of dislikes, view rate, like rate, Video Power Index (VPI), DISCERN score, and JAMA score were evaluated based on video sources. Among these parameters, only the DISCERN score and JAMA score showed a statistically significant

relationship with the video source (p<0.001). In pairwise comparisons, physician-generated videos had significantly higher DISCERN and JAMA scores compared to videos created by non-physician healthcare professionals (p=0.015, p=0.01, respectively). Similarly, videos from non-physician healthcare professionals had significantly higher DISCERN and JAMA scores than videos prepared by patients or for advertisement purposes (p=0.031, p=0.026, respectively).

In the correlation analysis between variables, video duration was significantly correlated with the number of likes, view rate, VPI, and DISCERN score (p=0.001, p=0.011, p=0.011, and p=0.01, respectively). Additionally, a strong statistical correlation was found between the DISCERN score and the JAMA score (p<0.0001).

Videos were also evaluated based on their upload time (uploaded more than three years ago versus uploaded within the last three years). Of the 50 videos, 24 (48%) were uploaded more than three years ago, while 26 (52%) were uploaded within the last three years. Videos uploaded more than three years ago had a statistically significantly higher like rate compared to more recent videos (p<0.001). However, no significant differences were found between the two groups regarding VPI, DISCERN score, YHR score or JAMA score (p>0.05).

DISCUSSION

This study represents the first to examine the content quality of YouTube videos related to hallux rigidus disease. Consistent with findings from the literature, we observed that the overall quality of videos was generally low.[12] A significant portion of the videos (58%) was uploaded by non-physicians. However, our analysis revealed that the quality of videos produced by physicians and non-physician healthcare professionals was significantly higher compared to other sources (p<0.001). Interestingly, the video source did not have a significant impact on the number of views or likes. The average YHR score was notably low, with a maximum of 16 and a mean of 3.8.

In a study by Uzun et al.[9] evaluating YouTube videos on hallux valgus surgery, it was similarly concluded that video quality was poor. Similarly, Kunze et al.[13] found low-quality content in YouTube videos related to rotator cuff tears. The low quality of videos may stem from the fact that many are uploaded by non-healthcare professionals who lack sufficient expertise, and there is no standard evaluation process for these videos. Our study found that physician-generated videos were of the highest quality, followed by those created by non-physician healthcare professionals. Videos uploaded by patients or for advertisement purposes were significantly lower in quality (p<0.001). Similar findings in the literature confirm that physician-generated video content tends to be of higher quality.[14] In a high-quality video, information regarding the definition of the disease and its symptoms, conservative and surgical treatment options, physiotherapy process, disease progression, and potential complications should be provided based on the existing literature. Health professionals should take these criteria into account when uploading videos. When uploading videos to these platforms, they should undergo review and approval by a supervisory board before being published.

Given the widespread use of the internet for health information, with studies showing that individuals in North America access online health information at least once a month, it is crucial to encourage physicians and non-physician healthcare professionals to produce reliable content.[15] While patients may prefer videos reflecting other patients' experiences, they may also be misled, as evidenced by the inability to differentiate between high- and low-quality information. This misinformation can negatively impact disease management or compliance with treatment after visiting a healthcare institution. Healthcare professionals should assess whether patients have been misinformed during consultations and provide appropriate guidance.

Our study also found that videos uploaded more than three years ago had a statistically higher like rate compared to more recent videos (p<0.001). This may be attributed to improvements in video quality over time. Although previous studies reported that lower-quality videos tend to attract more views, we did not observe a significant relationship between content quality and viewing rates.[16] Contrary to the literature, our study noted a higher frequency of general information and exercise-related videos about hallux rigidus, with fewer videos discussing surgical treatment and prognosis. This lack of content on surgical treatment may deter patients from considering surgery, even though it is recommended for advanced cases by physicians.

The mean YHR score in our study was 3.48 out of 16. In comparison, Kunze et al.[13] reported a mean score of 2.3 out of 5 in a specific scoring system for PCL injuries, while MacLeod et al.[17] found a score of 3.1 out of 16 in a similar system for hip arthritis. Our findings align with the literature, suggesting that YouTube health-related videos often score poorly in specific evaluation systems.

In contrast to Uzun et al.,[9] who found no correlation between video duration and quality scores, our study observed a significant correlation between video duration and metrics such as the number of likes, view rate, Video Power Index, and DISCERN score (p<0.01). This suggests that shorter videos may provide insufficient information, leading to lower quality scores. Additionally, patients may find it difficult to obtain the necessary information from shorter videos, negatively impacting their engagement metrics such as VPI, view rate, and number of likes. Thus, we propose that health-related videos should be of sufficient length to adequately cover essential information.

Limitations

The primary limitation of this study is that it only examined videos on YouTube and may have reached different results if conducted at another time or on different platforms. Video quality may vary across platforms. However, as a cross-sectional study, our research utilized an instantaneous search model and focused on YouTube, one of the most widely used platforms. The limitations of the study also encompassed restricting the analysis to videos in English, evaluating only

the first 50 results, and utilizing only "hallux rigidus" and "hallux limitus" as search terms. However, previous studies have shown that patients often engage with the first videos they encounter. A key strength of this study is the use of three different scoring systems DISCERN, JAMA, and YHR which enhances the robustness of the findings.

CONCLUSION

The use of platforms such as YouTube for health-related information is increasing daily. However, the overall quality of videos about hallux rigidus remains low. Physicians and non-physician healthcare professionals should be encouraged to produce higher-quality content to ensure patients have access to accurate and reliable information. Additionally, patients should be cautioned about the potential for misleading or inaccurate videos. Implementing a pre-evaluation process for health-related videos on YouTube and similar platforms may help improve the quality and reliability of the content. This study is the first to specifically assess the quality of YouTube videos related to hallux rigidus. We believe that further research in orthopaedics and other medical disciplines will contribute to the enhancement of video content quality and the overall trustworthiness of online health information.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethics committee approval was not required for this study.

Informed Consent

Since the study was conducted without the participation of any living being, no written consent form was 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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The relationship between self-efficacy and caregiving burden among parents of children with cerebral palsy

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ABSTRACT

Aims: This descriptive study aimed to determine the relationship between self-efficacy levels and the caregiving burden of parents caring for children with cerebral palsy.

Methods: The sample of the study consisted of 128 parents of children with cerebral palsy attending four special education and rehabilitation centers affiliated with Van Provincial Directorate of National Education. Data were collected between January and August 2023 using the Introductory Information Form, the Parental Self-Efficacy Scale (PSES) and the Burden of Caregiving Scale (CBSS). Data was collected through face-to-face interviews with parents. The principles of scientific ethics and data confidentiality were followed at all stages of the study.

Results: Outcomes showed a moderate negative correlation between PSES and CBSS scores, indicating that higher self-efficacy is associated with lower caregiving burden. Factors such as social insurance, caregiving support, and income level significantly influenced caregiving burden. Parents with fewer children, higher education levels, and children with mild mobility limitations had higher self-efficacy scores. Similarly, caregiving burden was found to be greater among parents of children with intellectual disabilities, lower income levels, feelings of burnout, and future anxiety.

Conclusion: The study highlights the importance of identifying the factors that affect caregiving burden and self-efficacy. Nurses should adopt a multidisciplinary approach to identify parental strengths and weaknesses and provide targeted interventions. Training in this area and targeted interventions to enhance parental self-efficacy could significantly reduce caregiving burdens.

Keywords: Care burden, cerebral palsy, nurse, parental self-efficacy, parent

INTRODUCTION

Cerebral palsy (CP) is a permanent but non-progressive neurodevelopmental disorder, representing a heterogeneous clinical syndrome caused by prenatal, perinatal, or intrapartum brain injury.[1] The prevalence of CP ranges from 2.3 to 3.6 per 1,000 children, though this rate varies between and within countries.[2] From the prenatal period through the neonatal period, one or more risk factors affecting the developing brain may result in CP. The most common risk factors include premature birth, low birth weight, placental abnormalities, hypoxia, intrauterine infections, intracranial hemorrhage, neonatal asphyxia, multiple pregnancies, periventricular leukomalacia, and vascular disorders.[3]

In addition to motor impairments, children with CP may experience intellectual disabilities, epileptic seizures, pain, sensory impairments (such as hearing and vision problems), as well as musculoskeletal, respiratory, gastrointestinal, oral-motor, sleep, and behavioral challenges. These issues can significantly impair their overall health, functionality, social interactions, comfort, sleep patterns, and quality of life.[1,4]

Parents play a pivotal role in the treatment, care, and rehabilitation of children with CP.[5] They often spend the majority of their time caring for their child,[6] and some may even neglect their own needs.[1,7] Caring for a child with CP can lead to feelings of hopelessness, anxiety, and depression, as well as physical health issues and social isolation for the parents.[6] Consequently, children with CP frequently require lifelong comprehensive care and rehabilitation, placing a significant psychological, physical, financial, and caregiving burden on their families.[8]

This caregiving burden can negatively impact parents' self-efficacy levels.[2,9] At this point, nurses can identify parents' strengths and weaknesses in the care process and provide counseling and support to increase their self-efficacy, thus helping to alleviate the burden of care for parents.[6] Higher self-efficacy enables parents to better manage both their own health and the health of their children.[10] Improved parental self-efficacy may lead to better quality care and treatment for children with CP,[6] as well as increased comfort for the child.[2,9]

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The aim of this study was to examine the care burden and self-efficacy levels of parents of children with CP and to evaluate the relationship between them. Although various studies have been conducted in the literature on the difficulties and burden of care faced by parents of children with CP, it is seen that this issue has been addressed less in terms of self-efficacy. In particular, it is understood that comprehensive data on the effect of parents' self-efficacy levels on their children's quality of care and family life are limited. This study aims to fill this gap in the existing literature and to guide both nurses and families with the findings obtained.

Objective

The aim of this study is to determine the relationship between the self-efficacy levels of parents caring for a child with CP and their caregiving burden.

METHODS

Ethics

Prior to the study, approval was obtained from the Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 29.07.2022, Decision No: 2022-7/14) and the necessary institutional permissions for the study were obtained from their affiliated institutions. During the research data collection process, the principles of the Declaration of Helsinki, scientific ethics and data confidentiality principles were followed.

Research Questions

- Is there a relationship between self-efficacy levels of parents caring for children with cerebral palsy and care burden?
- Do parents' demographic characteristics (age, gender, educational status, socioeconomic status, etc.) affect their self-efficacy levels?
- Do parents' demographic characteristics (age, gender, educational status, socioeconomic status, etc.) affect the burden of care?
- Do parents' self-efficacy levels have an effect on burden of care?

Design

This study utilized a descriptive survey model to investigate the relationship between self-efficacy levels and the caregiving burden of parents caring for a child with cerebral palsy. Additionally, a relational survey model was employed to define the relationships between these variables, explain the findings, and develop recommendations. This combined approach allowed for both a comprehensive overview and an in-depth analysis of the topic.

Study Location and Timeframe

The study was conducted in four special education and rehabilitation centers from January 2023 to August 2023. No specific selection was made in the sample selection; instead, all parents (n = 128) who had a child with CP between the ages of 1 and 18 years and agreed to participate in the study during the specified time period were included. Only three parents with communication problems were excluded from the study. Written and verbal informed consent was obtained from all parents who agreed to participate in the study before data collection. The data were collected by the researchers in a meeting room using a 15-minute face-to-face interview method.

Data Collection Methods and Tools

In the study, the Descriptive Information Form,[4,11] Parental Self-Efficacy Scale[12] (PSES) and Burden of Caregiving Scale[13] (CBSS) prepared in line with the literature were used.

Descriptive Information Form: This form consists of 24 questions about the sociodemographic characteristics of the parents (educational status, economic status, occupation, etc.) and identifying characteristics of the child (age, gender, etc.).

Parental Self-Efficacy Scale: Parental Self-Efficacy Scale is a scale adapted into Turkish by Diken[14] and updated by Cavkaytar et al.[12] and used to measure the self-efficacy perceptions of parents of children with disabilities regarding their parenting skills. The scale is a Likert-type rating tool from 1 to 7. The scale consists of a total of 17 items with a minimum score of 17 and a maximum score of 119. Self-efficacy increases as the score level increases. Cronbach's Alpha internal consistency coefficient of the scale was found to be 0.95. In this study, it was found to be 0.74.

Caregiving Burden Scale: This scale, which was developed to assess the stress experienced by caregivers of the elderly or individuals in need of care, was adapted to Turkish culture and its validity and reliability study was conducted by İnci and Erdem[13] in 2006. The Caregiver Burden Scale is a 22-item Likert-Type Scale ranging from 0 to 4. A minimum score of 0 and a maximum score of 88 can be obtained from the scale. A high scale score indicates that the distress experienced is high. A score between 0-20 indicates "no care burden," between 21-40 indicates "light care burden," between 41-60 indicates "moderate care burden" and between 61-88 indicates "heavy care burden." The internal consistency coefficient of the scale was determined as 0.95. In this study, it was found to be 0.75.

Statistical Analysis

Descriptive statistics for continuous variables are presented as means, standard deviations, minimum, and maximum values. For categorical variables, frequencies are presented as numbers and percentages. To compare the scale scores across participant groups, the Independent Sample T test and One-way Analysis of Variance (ANOVA) were used. For comparisons involving more than two groups, Duncan post hoc test was employed to identify the groups showing significant differences. Pearson correlation coefficients were calculated to assess the relationship between the scale scores. In addition, linear regression analysis was conducted to examine the predictive value of the scales. Statistical significance was set at $p<.05$.

RESULTS

This section presents the findings obtained from analyses conducted in line with the study's objectives.

When Table 1 was analyzed to determine differences between groups, a significant difference was found in the variables of social insurance, support in care, and income level in relation to PSES, based on the demographic data obtained from the

Table 1. Findings related to the variables in which significant differences were found between independent variables groups							
Variables	**n (%)**	**PSES X±SE**	**T/F**	**p**	**CBSS X±SE**	**T/F**	**p**
Parents age							
29-52 years old	54 (42.19)	84.75±11.15			34.2±8.83		
30-39 years old	36 (28.13)	85.05±12.47	.523	.594	35.3±9.31	.451	625
Over 40 years old	38 (29.69)	86.54±11.24			35.52±8.13		
Total	128 (100)	85.45±11.62			34.67±8.76		
Parenting situation							
Mum	104 (81.25)	91.23±11.22			37.73+8.28		
Father	24 (18.75)	93.71±9.44	.571	.568	36.70+9.32	.041	.968
Total	128 (100)	92.47±10.33			37.215±8.80		
Intellectual disability							
Yes	89 (69.5)	86.11±12.82	-1.438	.154	37.55±9.84	3.600	.001*
No	39 (30.5)	89.21±10.42			31±8.56		
Total	128 (100)	87.05±12.18			35.55±9.91		
Movement restriction							
Light	30 (23.4)	b94.77±8.3			a29.07±5.41		
Middle	31 (24.2)	a87.55±12.25	10.458	.001*	b33.81±10.81	13.990	.001*
Heavy	67 (52.3)	a83.37±12.08			c39.27±9.41		
Total	128 (100)	87.05±12.18			35.55±9.91		
Social insurance							
Yes	91 (71.1)	90.04±10.38	4.248	.001*	33.2±8.63	-4.160	.001*
No	37 (28.9)	79.7±13.25			41.35±10.58		
Total	128 (100)	87.05±12.18			35.55±9.91		
Number of children							
One	20 (15.6)	b91.2±8.84			35.9±9.81		
Two	55 (43)	b88.53±12.72	3.393	.037*	34.6±10.28	.463	.630
Three or more	53 (41.4)	a83.96±12.13			36.42±9.66		
Total	128 (100)	87.05±12.18			35.55±9.91		
Care support							
Yes	68 (53.1)	89.46±11.01	2.420	.017*	33.81±8.89	-2.152	.033*
No	60 (46.9)	84.33±12.94			37.53±10.69		
Total	128 (100)	87.05±12.18			35.55±9.91		
Parents education level							
Elementary school	62 (48.4)	a81.35±10.95			36.61±11.44		
Secondary school	30 (23.4)	b90.13±10.89	17.889	.001*	33.33±8.77	1.109	.333
High school and above	36 (28.1)	b94.31±10.54			35.58±7.64		
Total	128 (100)	87.05±12.18			35.55±9.91		
Income level							
Income<expenditure	55 (43)	83.27±12.38	-3.155	.002*	39.15±10.72	3.607	.001*
Income≈expenditure	73 (57)	89.9±11.29			32.85±8.35		
Total	128 (100)	87.05±12.18			35.55±9.91		
Employment status							
Working	26 (20.3)	83±14.31	-1.681	.057	45.96±10.36	6.002	.001*
Not working	102 (79.7)	88.09±11.42			32.9±7.87		
Total	128 (100)	87.05±12.18			35.55±9.91		
Burnout							
Yes	35 (27.3)	85.83±14.61	-.697	.487	38.43±11.23	2.037	.044*
No	93 (72.7)	87.52±11.18			34.47±9.2		
Total	128 (100)	87.05±12.18			35.55±9.91		
Anxiety about the future							
Yes	100 (78.1)	86.59±12.47	-.815	.417	36.53±10.01	2.133	.035*
No	28 (21.9)	88.71±11.11			32.07±8.86		
Total	128 (100)	87.05±12.18			35.55±9.91		

*: p<.05, a, b, c: Shows different groups, PSES: Parental Self-Efficacy Scale, SE: Standard deviation, CBSS: Burden of Caregiving Scale

participant parents (p<.05). Specifically, it was observed that participants with social security, those receiving support in caregiving, and those whose income was equal to their expenses had statistically significantly higher PSES scores. Additionally, when examining variables with more than two subgroups, children with mild mobility restrictions scored higher in PSES compared to those with moderate or severe mobility restrictions. Similarly, parents with 1 or 2 children had higher PSES scores than those with 3 or more children. Parents with secondary, high school, or higher education levels also scored higher than those with primary school education. In contrast, no significant differences were observed in PSES across other demographic variables (p>.05). Similarly, when analyzing the demographic data in terms of CBSS, significant differences were identified in the variables of intellectual disability, social security, support in care, income level, employment status, burnout, and future anxiety (p<.05). Specifically, CBSS levels were higher for parents with children who had intellectual disabilities, those without social security, those not receiving support in caregiving, those whose income was less than their expenses, those who were employed, and those experiencing burnout or future anxiety. Among variables with more than two subgroups, a significant difference was found only in the mobility limitation variable, where CBSS levels increased as the child's mobility limitation became more severe (p<.05). No significant differences were found in CBSS across other demographic subgroups (p>.05).

Furthermore, as shown in Table 2, the study examined whether the mean PSES and CBSS scores of participant parents differed according to subgroups such as speaking status, consanguineous marriage, type of home, child's gender, and the effects of the condition on relationships, responsibilities, anger, unhappiness, sadness, and compassion.

Table 2. Findings related to variables for which no significant difference was found between independent variables groups

Variables	n(%)	PSES X±SE	T/F	p	CBSS X±SE	T/F	p
Speech status							
Yes	30 (23.4)	86.37±12.33	-.352	.725	36.8±11.2	.785	.434
No	98 (76.6)	87.27±12.19			35.17±9.51		
Total	128 (100)	87.05±12.18			35.55±9.91		
Consanguineous marriage							
Yes	28 (21.9)	86.68±13.41	-.184	.854	36.29±8.99	.440	.661
No	100 (78.1)	87.16±11.88			35.35±10.19		
Total	128 (100)	87.05±12.18			35.55±9.91		
House type							
Detached house	81 (63.3)	85.72±12.63	-1.644	.103	36.26±10.47	1.056	.293
Apartment	47 (36.7)	89.36±11.12			34.34±8.84		
Total	128 (100)	87.05±12.18			35.55±9.91		
Gender of the child							
Girl	65 (50.8)	85.52±11.99	-1.452	.149	36.75±11.03	1.401	.164
Boy	63 (49.2)	88.63±12.27			34.32±8.52		
Total	128 (100)	87.05±12.18			35.55±9.91		
Effects on relationships							
Slightly affected	17 (13.3)	85.94±12.89	-.404	.687	35.65±8.46	.041	.967
Highly affected	111 (86.7)	87.23±12.12			35.54±10.15		
Total	128 (100)	87.05±12.18			35.55±9.91		
Effects on responsibilities							
Slightly affected	23 (18)	88.83±8.89	.967	.339	34.13±9.05	-.760	.449
Highly affected	105 (82)	86.67±12.79			35.87±10.1		
Total	128 (100)	87.05±12.18			35.55±9.91		
Effects on anger							
Yes	30 (23.4)	88.4±11.93	.690	.491	36.07±10.1	.322	.748
No	98 (76.6)	86.64±12.28			35.4±9.9		
Total	128 (100)	87.05±12.18			35.55±9.91		
Unhappiness							
Yes	41 (32)	89.1±11.44	1.306	.194	34.76±9.92	-.624	.534
No	87 (68)	86.09±12.46			35.93±9.94		
Total	128 (100)	87.05±12.18			35.55±9.91		
Anger							
Yes	30 (23.4)	88.4±11.93	.690	.491	36.07±10.1	.322	.748
No	98 (76.6)	86.64±12.28			35.4±9.9		
Total	128 (100)	87.05±12.18			35.55±9.91		
Sadness							
Yes	78 (60.9)	87.4±12.8	.396	.692	35.37±9.95	-.260	.795
No	50 (39.1)	86.52±11.24			35.84±9.95		
Total	128 (100)	87.05±12.18			35.55±9.91		
Compassion							
Yes	87 (68)	86.63±11.86	-.570	.570	35.7±10.1	.243	.809
No	41 (32)	87.95±12.94			35.24±9.61		
Total	128 (100)	87.05±12.18			35.55±9.91		

PSES: Parental Self-Efficacy Scale, SE: Standard deviation, CBSS: Burden of Caregiving Scale

When Table 2 is examined, as a result of the analyzes, it was determined that the variables in the table did not cause a significant difference in the scales (p>.05).

When Table 3 is examined, it is seen that the participant parents had a mean score of 87.05±12.18 from the ESLS, where the total mean score can vary between 17-119 (the lowest score of 17 points can be obtained from the scale and the highest score of 119 points can be obtained). Similarly, the participants had a mean score of 35.55±9.91 on the BVLS, where the total mean score can vary between 0-80 (minimum score of 0 and maximum score of 88 can be obtained from the scale). A high scale score indicates that the distress experienced is high. A score between 0-20 indicates "no care burden", between 21-40 indicates "light care burden", between 41-60 indicates "moderate care burden" and between 61-88 indicates "heavy care burden").

Table 3. General descriptive statistics of the scales

Scale	n	Min	Max	Mean	SD	Skewness	Kurtosis
PSES	128	47.00	108.00	87.05	12.18	-.543	-.079
CBSS	128	15.00	70.00	35.55	9.91	.989	.850

Min: Minimum, Max: Maximum, SD: Standard deviation, PSES: Parental Self-Efficacy Scale, CBSS: Burden of Caregiving Scale

The results of the correlation analysis, which aimed to determine the relationship between PSES and CBSS among the participant parents, and the linear regression analysis, which explored the predictive power of these variables, are displayed in Table 4.

Table 4. Correlation and linear regression analyses

Variable	B	SE	Beta	T	p.	R	Adj. R2
Constant*	76.741	5.185		14.799	.001*	-.581	.333
PSES	-.473	.059	-.581	-8.019	.001*		

*: Dependent variable: CBSS: Burden of Caregiving Scale, SE:Standard error, PSES: Parental Self-Efficacy Scale

Upon examining Table 4, a moderate negative linear relationship (0.30<r<0.70) was found between PSES and CBSS (r=-0.581, p<0.05). This indicates that as PSES scores increase, CBSS scores decrease. The independent variable (PSES) explains 33.3% of the variance in the dependent variable (CBSS), and this relationship is statistically significant. When the regression coefficients are analyzed, it is observed that for each unit increase in PSES, CBSS decreases by approximately 0.473 units, and this effect is statistically significant (p < 0.05).

The analysis of regression shows that PSES accounts for 33.3% of the total variance in CBSS, meaning that PSES explains a substantial portion of the variation in CBSS. These findings demonstrate that PSES is a moderate predictor of CBSS, with a negative relationship between the two. The model generally provides a good fit, and PSES is confirmed as a significant predictor of CBSS, with results statistically significant.

DISCUSSION

In this study, which examined the relationship between PSES and caregiving burden in caregivers of children with cerebral palsy, several evaluations regarding the relationship between these variables were made based on the obtained findings. Researchers who focus on the psychosocial development of children with developmental disorders suggest that parental self-efficacy can significantly impact a child's development.[15,16] Drawing on Bandura's social-cognitive theory, parental self-efficacy is defined as an individual's belief in their ability to organize and perform tasks necessary to achieve a specific success.[17] Parents with high PSES can effectively shape their thoughts and behaviors to best support their children's development.[18] In other words, even when confronted with numerous stressors, parents with high PSES contribute to positive developmental outcomes for their children.[5]

High self-efficacy is a key factor enabling parents to exhibit appropriate behaviors towards their children with developmental delays.[19] Similarly, when PSES levels are high, parents are believed to provide more suitable feedback to their children by managing challenging and stressful situations effectively.[20] In the literature, parental self-efficacy levels have been found to be either high[11,20] or moderate[21] in studies involving parents of children diagnosed with disabilities or at risk of developmental delays. In this study, the PSES levels of parents were found to be high (Table 3). This elevated level of parental self-efficacy is believed to result from institutional support, where parents regularly receive training for their needs and can easily access relevant information through the internet.

Caring for children with cerebral palsy is a stressful and challenging task for primary caregivers, especially parents. Parents of children with CP experience a greater caregiving burden than those caring for healthy children.[8] As the score on the caregiving burden scale increases, so does the caregiving burden perceived by parents.[22] Karahan and Islam[23] found a moderate caregiving burden in a study involving 23 mothers of children with CP. Similarly, Wijesinghe et al.[24] examined caregiving difficulties among mothers of children with CP using the "Caregiver Difficulties Scale" and identified a moderate level of burden. In this study, the caregiving burden among parents was observed to be comparatively lower (Table 3). This is thought to be a result of the demographic and socioeconomic characteristics of the parents who participated in the study, the support they received, the environmental factors they experienced, and the fact that they saw the care burden as a part of the parental role rather than a burden and acted to help their children.

When the relationship between PSES and CBSS was analyzed, it was found that PSES was a significant predictor of CBSS, and the results were statistically significant. Accordingly, the findings showed that as parental self-efficacy increased, the perceived caregiving burden decreased (Table 4). These results are consistent with previous studies, which have also demonstrated a negative relationship between CBSS and PSES.[25] Parents with high self-efficacy tend to exhibit more supportive behaviors in caring for and treating their children. Supporting parents of children with chronic disabilities, such as CP, in caregiving and education can increase parental self-efficacy and, in turn, promote the child's development. Reducing parents' caregiving burden is thought to strengthen the parent-child bond and encourage parents to take a more active role in their child's care.

Social insurance provides both financial and emotional support to parents in meeting the special care needs of their children. These services alleviate the financial burden on parents, enabling them to feel more confident in addressing their children's health, education, and overall care needs.[26] Research indicates that parents with access to social security exhibit higher self-efficacy, as these supports make them feel better equipped and more confident.[27] In our study, it was found that the PSES scores of parents with social security were significantly higher. Thus, social security appears to positively impact parenting self-efficacy by enhancing parents' ability to provide improved care for their children.

Caring for children with cerebral palsy often requires considerable physical and mental effort.[28] External care support has been shown to positively influence parents' self-efficacy, as it helps them manage daily tasks more effectively and allows for increased quality time with their children. This external support also bolsters parents' belief that they can provide better care for both themselves and their children.[26] In addition, a study revealed that mothers who received support from their spouses or other relatives tended to report higher parenting self-efficacy.[29] Similarly, in our study, parents who received assistance from care centers demonstrated higher self-efficacy. However, it is suggested that parents who receive support from care centers but not from family members may still experience lower PSES scores due to the physical, mental, and emotional challenges of childcare, leading to feelings of inadequacy.

The literature reveals that parenting self-efficacy tends to increase with higher levels of education. In Dursun and Bıçakçı's[30] study, mothers with undergraduate degrees exhibited higher self-efficacy compared to those with only primary school education, while Öztürk and Giren[31] found that mothers with high school diplomas had higher self-efficacy than those with primary school education. In our study, significant differences in PSES scores were observed based on educational status. This may be because some parents, because of their profession or educational background, possess greater knowledge of child development, which may contribute to higher self-efficacy. Additionally, these differences may be related to the content of the education received by the parents.

Several studies have noted that low-income parents often experience heightened anxiety about caring for their children, which negatively impacts their parenting self-efficacy.[32,33] Government support programs and social security services can help mitigate these effects, though the accessibility and quality of such services often depend on income levels.[28] In our study, parents whose income matched their expenses demonstrated significantly higher PSES scores. In general, parents with higher income levels may have higher self-efficacy because they can access more resources for their children's care, while low-income parents face more challenges in this regard.

Children with cerebral palsy often have motor disorders accompanied by intellectual disabilities, sensory issues, respiratory and nutritional problems, as well as communication, perception, and behavioral difficulties, leading to significant impairments.[34] As the child's level of dependency increases, the caregiving burden on parents may also rise. It is hypothesized that parents' self-efficacy may diminish due to reduced expectations from their child, compounded by the learned helplessness that can develop over time in response to the child's lifelong condition.[35] Our study found that parents of children with mild mobility limitations had significantly higher PSES scores compared to those with moderate or severe mobility limitations (**Table 1**). This relationship may be attributed to the increased caregiving demands, which, in turn, negatively affect parents' self-efficacy.

Research indicates that having many children can create additional stress for parents, potentially reducing their perception of self-efficacy. Parents with multiple children may struggle to balance the needs of a child with cerebral palsy (CP) with those of their other children.[27] Our study found that parents with one or two children reported higher mean PSES scores compared to those with three or more children. This suggests that a larger number of children may increase parental stress, thereby reducing self-efficacy and complicating the balance of caregiving responsibilities.

Caring for a child with an intellectual disability can impose a significant burden on family members, which is often influenced by the caregiver's personal perceptions and responses during caregiving.[36] Üstün et al.[22] found a significant relationship between the child's mental disability status and the parents' caregiving burden. Other studies have shown that as the degree of a child's disability increases, so does the caregiving burden.[37,38] Our study also identified a positive relationship between caregiving burden and the child's intellectual disability (**Table 1**). Despite support from care centers, the presence of intellectual disability in children with CP extends the caregiving time, which significantly increases the burden on parents.

As children's mobility limitations increase, so does the caregiving burden on their parents. Children with severe mobility restrictions require more assistance with daily activities, leading to increased physical, emotional, and time-related responsibilities for parents.[39] Ribeiro et al.[40] observed that as mobility limitations in children intensified, the caregiving burden also increased. Our study's multiple comparison test results similarly showed that the CBSS levels increased with greater mobility limitations in the child (**Table 1**). Even with physical care and rehabilitation support, parents of children with severe mobility limitations expend more time and energy, further raising the CBSS.

Social insurance plays a crucial role in mitigating the caregiving burden for parents.[41] Literature suggests that many parents of children with CP lack social security.[42,43] However, our study found that most parents had social security and those without it experienced a higher caregiving burden (**Table 1**). This underscores the importance of social security in alleviating the caregiving burden. Financial and moral support provided through social security can facilitate a more sustainable and higher-quality caregiving process.

The availability of caregiving support significantly impacts the caregiving burden for parents of children with CP.[41] Our

study found that parents who did not receive caregiving support reported higher CBSS levels (Table 1). Even with care center support, the lack of assistance from spouses and family members can create additional challenges in caring for children with CP and increase the overall caregiving burden.

The income level of parents of children with CP significantly impacts the burden of caregiving. Taşçıoğlu et al.[44] found that caregiving burden varies according to parental income levels. Bufteac et al.[45] suggested that income level can be either a protective or risk factor for children diagnosed with CP, as it influences access to treatment opportunities. Their study indicated that parents whose income was insufficient to cover their expenses reported higher levels of caregiving burden (Table 1). While high-income families can afford more services and support for their children's care, low-income families often face financial difficulties that exacerbate their caregiving burden.

Employment status also plays a crucial role in the caregiving burden experienced by parents.[46] Ahanotu et al.[47] found that parents' employment status directly affects the caregiving burden they experience for their children with epilepsy. In a similar vein, this study found a statistically significant difference between the employment status of parents of children with CP and their mean CBSS scores ($p<0.05$) (Table 1). The higher caregiving burden reported by working parents, despite receiving external professional support, is likely due to the challenges in balancing work and caregiving responsibilities.

As caregiving burden and difficulties increase, parents are prone to burnout[48] and future anxiety[49]. The caregiving burden score was lower among those experiencing burnout and anxiety compared to those who did not (Table 1). Despite receiving institutional support and having lower caregiving burden scores, the stress and challenges associated with the disease, along with concerns about the future particularly uncertainties regarding their children's lives after their own aging or death may heighten parents' future anxiety and contribute to burnout.

It is thought that there is a negative relationship between care burden and parental self-efficacy. High care burden may reduce parents' self-confidence and their belief in their ability to meet their children's needs. On the other hand, it has been observed that parents with high self-efficacy are better able to manage care burden and experience less psychological distress. Therefore, interventions aimed at increasing parents' self-efficacy may be effective in reducing the negative effects of care burden.[50]

Limitations

This study was conducted with parents of children with cerebral palsy using self-report scales. It should be noted that the study was conducted in one region, which may limit the generalizability of the findings to other populations. The limitations of self-report scales, such as potential bias or inaccuracy in responses, also apply. Additionally, the cross-sectional design of the study restricts the ability to infer causality. Despite these limitations, the findings contribute to a better understanding of the relationship between parents' care burden and self-efficacy and may inform future research in this area.

CONCLUSION

The study's results indicate that the care burden experienced by parents of children with cerebral palsy is influenced by various factors. Parents with higher levels of self-efficacy manage this burden more effectively. Elevated self-efficacy enables parents to provide better care, reduces the care burden, and supports their children's development. Factors such as social security, caregiving support, parents' education, and income levels enhance both the parents' self-efficacy and the quality of care they provide. In conclusion, multiple factors affect the care burden and self-efficacy of parents of children with cerebral palsy. Nurses, as healthcare professionals, should assess parents' strengths and weaknesses and provide multidisciplinary interventions. These interventions can improve the quality of life for both parents and children by helping parents assume a more supportive role in their children's care. Nurses need to increase general and clinically based interventions, especially on important issues such as self-efficacy and burden of care. Planning training programmes to increase self-efficacy, conducting research that examine the relationship between care burden and care burden in more depth, and developing interventions that can be applied in the clinical environment will contribute to providing a more effective care process at both individual and social levels.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Van Yüzüncü Yıl University Non-interventional Clinical Researches Ethics Committee (Date: 29.07.2022, Decision No: 2022-7/14).

Informed Consent

Signed and informed consent forms were obtained from all parents.

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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Development of the Parental Knowledge-Attitude Scale for children's use of digital devices: a methodological study*

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ABSTRACT

Aims: This study focuses on creating a comprehensive scale to measure parents' knowledge and attitudes about children's digital device use and rigorously examining its validity and reliability to ensure its effectiveness.

Methods: The study was designed and conducted using a methodological approach. A 43-item question pool was created for the Parental Knowledge-Attitude Scale for children's use of digital devices. After receiving expert opinions on the items and conducting a pilot study, the number of items was reduced to 19. A field study was conducted for the 19-item scale. The research was carried out in the pediatric clinics of a university training and research hospital between February and March 2023. The universe of the study consisted of parents (n=416) whose children between the ages of 6 months and 6 years were hospitalized in the pediatric clinics of the specified hospital for any reason between the specified dates, and who did not have any chronic diseases or psychological problems, and who were open to communication and cooperation. The study was conducted with the entire population without using the sampling method. Statistical analysis of the data was performed using SPSS and AMOS software. The statistical significance level was accepted as 5%. Ethical principles have been adhered to.

Results: It was determined that the obtained data were suitable for factorization and the sample size was sufficient. Exploratory factor analysis was performed to discover construct validity. The number of factors was decided according to the eigenvalue criteria, explained variance, and scree plot graph. Scale items had 3 components and there was a significant correlation among them. The total variance explained by the factors was 61.3%. The total score average of the scale was 75.95±10.7 and the reliability Cronbach alpha coefficient was 0.979. The item discrimination method was used for the internal consistency of the scale, it was determined that each item distinguished the measured phenomenon and was statistically significant ($p<0.001$). Exploratory factor analysis revealed a latent construct, and to confirm and strengthen its validity, a subsequent confirmatory factor analysis was conducted. The analysis results obtained were found to be within the good fit [CMIN/df: 1.679; RMSEA: 0.04; SRMR: 0.045; CFI: 0.978; AGFI: 0.925; NNFI (TLI): 972], acceptable fit (NFI: 0.947; GFI: 0.946; RFI: 0.934; PNFI: 0.759; PGFI: 682) according to the fit measurement table and were lower than the AIC, CAIC and ECVI values of the compared model.

Conclusion: A three-dimensional, 19-item scale, which is 5-point Likert-type and tested for validity and reliability, was developed to measure parents' knowledge and attitudes toward children's use of digital devices.

Keywords: Child, digital devices, parent, pediatric nurse

*The data from this study were presented as an oral presentation at the 4th International Mediterranean, 3rd International, and 8th National Pediatric Nursing Congress, held in Erzurum, Turkiye, on June 1-3, 2023.

INTRODUCTION

New technologies such as mobile and interactive display media have taken hold of a young child's daily life.[1] While electronic devices have revolutionized learning, communication, and the dissemination of information, it has been shown that screen media has long-term negative effects on children's health, which is a concerning issue from a public health perspective.[2-4] The World Health Organization (WHO) and the American Academy of Pediatrics (AAP) recommend limiting screen time for children aged 2-4 years to a maximum of one hour per day. They further highlight that this time should focus on educational content and be supervised by a responsible adult.[5] AAP strongly discourages any screen exposure for children under the age of two.[6]

However, touchscreen devices are often used as "electronic babysitters" to calm or soothe crying or restless babies.[7] Over the past two decades, it has been reported that screen time has doubled in children aged 0-2 years.[8] Previous findings have indicated that increased screen time may contribute to various

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physical and mental health challenges, including a heightened risk of obesity, sleep disturbances, depression, diminished self-esteem, and reduced academic achievement.[9-11]

While today's children can quickly adapt to technology as digital natives, some parents may struggle to cope with this speed because they lack the necessary technical skills.[12] Especially during the coronavirus pandemic, curfews/lockdown and virtual education, affected children's developmental processes, and digital worlds offered an alternative environment for play and interaction.[12,13] It was noted that when parents were doing housework or busy with something, they used mobile devices to calm their children, put them to sleep, or distract them, as well as preferred them for rewarding, punishment, and behavior management purposes.[14] Research carried out in Turkiye revealed that parents encouraged children under the age of 2 to use screens and digital devices, often employing these devices to distract children under 5, particularly during mealtimes.[15] The existing literature predominantly focuses on the negative effects of digital devices on child development. However, there is a significant gap in scales designed to assess parental knowledge and attitudes toward digital device use during early childhood. Studies on digital parenting have primarily targeted older age groups (>6 years) and have not thoroughly addressed parents' knowledge levels and guidance roles. For instance, the scale developed by İnan Kaya et al.[16] focuses on parents of children aged 6-18 years. Similarly, another study in Turkiye evaluated the attitudes of parents of 6th and 7th-grade students toward the use of information and communication technologies.[17] To date, no scale has been developed to assess parental knowledge and attitudes regarding digital device use in children aged 6 months to 6 years.

This study aims to develop the first valid and reliable scale specifically designed to evaluate parental knowledge and attitudes toward digital device use in children aged 6 months to 6 years. Understanding the health implications of digital device exposure during early childhood and increasing parental awareness are essential for both child development and public health. According to the literature, more than 90% of children are introduced to digital devices between the ages of 6 and 12 months, with an average daily screen time of approximately 2 hours.[18] Unless parental attitudes shift, children's exposure to digital devices is likely to increase as they grow older. Therefore, focusing on early childhood represents a critical opportunity to mitigate the adverse effects of screen exposure and promote effective parental guidance. This study not only provides a robust tool to assess parental knowledge and attitudes toward digital device use during early childhood but also lays the foundation for evidence-based advancements in digital parenting strategies.

METHODS

Ethical Procedure

Approval for the study was granted by the Atatürk University Faculty of Nursing Ethics Committee (Date: 15.02.2023, Decision No: 2023-1/13). The development of the scale adhered to the ethical guidelines outlined in the Helsinki Declaration. Informed consents were obtained from every participant before the surveys.

In ensuring the scale's validity, its development process and steps were meticulously carried out following the guidelines outlined in the literature.[19,20] A diagram of the scale development process is given below (**Figure 1**).

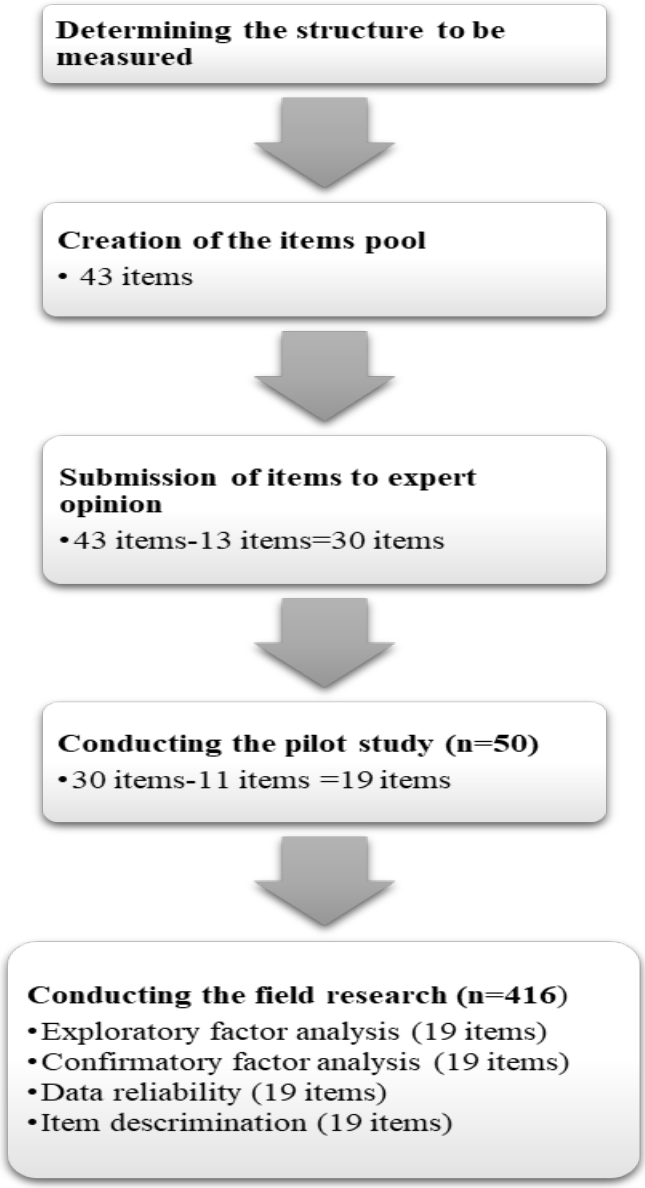

Figure 1. The scale development process

The structure to be measured: In the modern era of rapid technological advancements, digital devices have become integral to the lives of children, alongside individuals of all age groups.[21] Prolonged use of digital devices during childhood may adversely impact various aspects of development, including cognitive, physical, emotional, and social growth.[22] At this point, parents' attitudes towards their children's use of digital devices play an important role.[14] The structure to be measured through the scale is to determine parents' knowledge and attitudes regarding their children's use of digital devices.

Creation of the items pool: Two ways were followed to create the item pool.[23] A comprehensive literature review was initially performed, and relevant sentences were revised and incorporated into the item pool. Secondly, the information obtained from interviews with specializers was itemized. Consequently, a preliminary pool comprising 43 items was established.

Obtaining expert opinions: To ensure content validity, 10 subject-matter experts were consulted to determine the extent to which each item accurately represented the intended construct.[24] The draft scale items were sent to academicians and professionals specialized in pediatric nursing, child health, child development, measurement, and evaluation. Experts were asked to evaluate whether the prepared items were appropriate in terms of language, content, and scope and whether they measured the implicit phenomenon.[25]

Feedback reports from 10 experts were evaluated according to the Lawshe technique.[24] According to the technique, the content validity ratio for each item was examined and it was understood that the items had a content validity between 0.54 and 1.00. The content validity criterion value for 10 experts is 0.62 at the 0.05 significance level.[25] Thirteen items had a score below 0.62. It was observed that these 13 items overlapped in meaning with other items. As a result of expert evaluation, 13 items with a score below 0.62 were removed from the item pool.

The content validity ratio (CVR) of the remaining 30 items ranges from 0.76 to 1.00, which is above the critical value of 0.62. The content validity index (CVI) rate calculated for all 30 items is 0.82 and has a score above 0.60.

Conducting the pilot study: The 30-item draft scale was evaluated through a pilot study.[26] The scale's applicability, comprehensibility, and technical suitability were tested in this pilot study.[27] The pilot study involved 50 parents of children aged between 6 months and 6 years who were regular users of digital devices.[28] Of those who participated in the pilot study, 50% (n=25) were mothers and 50% (n=25) were fathers.

The pilot study data were analyzed using statistical methods. The draft scale, comprising 30 items, demonstrated a reliability coefficient (α) of 0.76, with item-total correlation coefficients ranging from 0.28 to 0.69. Three items with low correlation coefficients were excluded from the draft scale.[27] It was determined that removing these items would increase the reliability coefficient to 0.80.

In addition, exploratory factor analysis (EFA) was conducted on the pilot study data to explore underlying latent constructs. The first component of the scale has 10 items, the second component has 6 items, and the third component has 3 items. The remaining 8 items were excluded from the draft scale because they overlapped with other scale items.[29]

As a result, 11 items were removed from the draft scale with 30 items due to the low correlation coefficient of 3 items and overlapping problems of 8 items. Thus, the number of draft scale items was refined to 19.

Conducting Field Research to Test the Draft Scale in a Large Sample Group

Statistical procedure: The data of the study were analyzed using SPSS 26 and AMOS 24 statistical package programs. In the tables; sample size (n), percentage (%), mean and standard deviation (X±SD), statistical significance (p), large (>) and small (<), chi-square (X^2) were shown. For the normality test, the kurtosis and skewness values of the data were taken as basis, if this value was between -1.5 and +1.5, it was accepted that the data set provided a normal distribution.[30] Cronbach's Alpha coefficient (α) was used for reliability tests.[31] Since the test conditions were met, an independent sample T test was applied.[32] Pearson's correlation coefficient was used in correlation analyses.[33] It was understood that the obtained data provided the necessary conditions for exploratory and confirmatory factor analysis.[34] Analysis results were evaluated within the 95% ($p<0.05$) confidence interval determined for social sciences.[31]

Questionnaire: A structured questionnaire was developed to evaluate the draft scale, incorporating both a personal information section and the preliminary scale items. Each participant's response to the items was measured on a 5-point Likert Scale, spanning from strongly disagree to strongly agree.

Participants: The research was carried out in the pediatric clinics of a university training and research hospital between February and March 2023. The study population comprised parents (n=416) of children aged six months to six years who were hospitalized in the pediatric clinics of the designated hospital during the specified timeframe. These parents had no chronic illnesses or psychological disorders and were willing to engage in communication and collaboration. The research was carried out with the entire population without using the sampling method. According to scale development literature, the sample size is recommended to be between 300-400 people[28] and in this study, the sample size was 416.

67.3% of the participants were mothers and 32.7% were fathers. 26.9% of the participants were in primary school, 21.6% were in secondary school, 21.6% were in high school, 24.5% were university graduates, and 5.3% had a master's/doctorate. 41.1% of the participants had low, 49.3% had medium and 9.6% had high economic income. 18.5% had 1 child, 36.5% had 2 children, and 45% had 3 or more children. The average age of the participating parents was 33.5±7.5 years (**Table 1**).

RESULTS

Exploratory (EFA) and confirmatory (CFA) factor analyses were performed to establish the construct validity of the draft scale.[26,35]

Findings Regarding Factorization

First, the data was checked to determine whether it was suitable for factoring.[36] The relationships between the items should be examined before performing factor analysis on the data obtained through field research. The correlation coefficients in these relationships should not be too high or too low.[21,37]

Table 1. Demographic and social characteristics of the study participants		
Variables	**n**	**%**
Parents		
Mother	280	67.3
Father	136	32.7
Education		
Primary school	112	26.9
Secondary school	90	21.6
High school	90	21.6
University	102	24.5
MA/PhD	22	5.3
Income		
Income is less than the expense (low)	171	41.1
Income equals expense (middle)	205	49.3
Income is more than the expense (high)	40	9.6
Number of children		
1	77	18.5
2	152	36.5
3+	187	45.0
Total	416	100.0
Age (mean and standard division)	X=33.5 and SD=7.5	

SD: Standard deviation

Both situations adversely affect the correct factorization. The results showed that the item-total correlation coefficients for the draft scale ranged between 0.406 and 0.699. The fact that the correlation coefficients are not below 0.30 or above 0.90 indicates that the item-total correlation coefficients are within the desired range for factorization (Table 2).

Table 2. Findings for factorization			
		Values that should be*	**Findings**
Item-total correlation coefficient (min-max)		0.30-0.90	0.406-0.699
Determinant of inter-item correlation matrix		>0.00001	0.00002954
Anti-image correlation matrix diagonals value		>0.50	0.750
Communalities value		>0.50	0.516
Kaiser-Meyer-Olkin sample adequacy value		>0.70	0.892
Bartlett's sphericity test	Chi-square value		4253.969
	Degree of freedom		171
	p	<0.05	<0.001

*These values were obtained from different sources in the literature on scale development, Min: Minimum, Max: Maximum

Additionally, there should be no multicollinearity problem in the correlation matrix between the items.[36,38] For this, it is a requirement for proper factorization that the matrix determinant value is greater than 0.00001 and the diagonal value of each value in the matrix is greater than 0.50.[39] In the data obtained by field research, the diagonal values of the anti-image correlation matrix were found to be 0.75 and it was understood that there was no multicollinearity problem (>.00001) (Table 2).

It is not enough to look at correlation values alone to determine whether data are suitable for factoring. It is expected that each item in the scale contributes highly to the factor it is included in. The fact that the communality values of an item are close to 1 means that the item fully represents the factor it is associated with, and this is a desired situation.[40,41] According to Karasar,[37] items with communality values of .50 and below should be removed from the scale because it affects adversely factorization. The smallest commonality value of the data obtained through field research was .516 (Table 2).

In addition, it is recommended to use the Bartlett Sphericity test to test whether the correlations between the examined variables are suitable for factorization. [37] As a result of this test, the p-value is expected to be less than 0.05 and therefore the null hypothesis is rejected.[42] In this study, Bartlett's test of sphericity yielded statistically significant results (p<0.001) (Table 2).

The reliability of factorization is affected by sample size, but there is no consensus on sample size. [21] However, the Kaiser-Meyer-Olkin (KMO) value provides important information about the adequacy of the sample size. If the result of the analysis is greater than 0.7, it shows that the sample size is suitable for factorization.[36] In this study, the KMO value was .892 (Table 2).

All these data have shown that factor analysis can be performed with the data obtained.

Findings on Exploratory Factor Analysis (EFA)

Principal component analysis is the most preferred method thanks to its simpler structure and psychometric properties.[41] Moreover, this method reveals the latent variable(s) by grouping the items under a certain factor or factors.[35] In this study, the principal components analysis method was used since it was aimed to determine under which components (latent variables) the draft scale items were grouped.

With factor rotation, the loading of an item on a factor is attempted to be maximized while the loading of the same item on other factors is attempted to be minimized.[21] Since the existence of a relationship between items is assumed in social sciences, oblique rotation is recommended as a rotation method.[29] In this study, the direct oblique rotation method was selected because it was assumed that there was a correlation between the items.

The number of factors is determined by attempting to maximize the percentage of variance explained, but this must be consistent with the underlying theoretical construct.[36] The number of factors was determined according to four criteria that are frequently used in the literature. The first of these is the Kaiser (eigenvalue) criterion. The eigenvalue of a factor indicates the amount of information it contains about the construct to be measured, and this value must be greater than 1.[41] The second is the variance percentages criterion. The cumulative explained variance ratio must be at least 0.50.[42] The third is the criterion of contribution to the explained variance. The variance explained by each factor/component should not be less than 5%.[40] The last is the scree plot criterion (Table 3). By looking at the scree plot, researchers can determine the number of factors based on the point at which the slope decreases significantly (Figure 2).[34]

Table 3. Findings for exploratory factor and reliability analysis				
I. factor: Parental knowledge and attitudes about the harms caused by digital device use to children	**Factor loading**	**Eigenvalue**	**Explained variance**	**Cronbach α**
Item-16	.853	6.500	34.209%	0.907
Item-17	.835			
Item-18	.830			
Item-19	.830			
Item-15	.792			
Item-14	.691			
Item-13	.673			
Item-12	.648			
Item-11	.646			
Item-10	.619			
II. factor*: Parental attitudes and behaviors in the use of digital devices				
Item-2	.834	2.983	15.595%	0.839
Item-8	.782			
Item-4	.780			
Item-1	.701			
Item-9	.671			
Item-3	.635			
III. faktor*: Instrumentalization of the children in the use of digital devices				
Item-6	.932	2.181	11.477%	0.909
Item-5	.895			
Item-7	.888			
Total		11.664	61.281%	0.979
Total average of the Draft Scale: 75.95±10.7				
	Estimate	**Standard error**	**Composite reliability**	**p**
I.<-->II.	0.306	0.025	4.501	<0.001
I.<-->III.	0.263	0.023	4.545	<0.001
II.<-->III.	0.308	0.032	4.748	<0.001
*Items are reverse-coded				

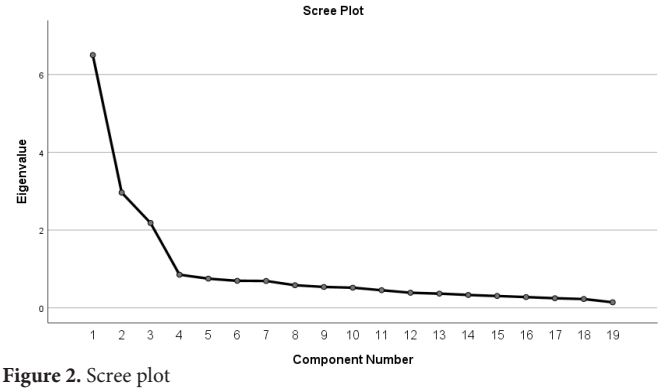

Figure 2. Scree plot

There were three component eigenvalues greater than 1 (the Kaiser criterion). Each component explained more than 5% of the variance (Table 3). When Figure 3 is examined, it is evident the line levels off following the third component (Figure 2). These criteria revealed that the draft scale consists of 3 components. The first factor, called "parental knowledge and attitudes about the harms caused by digital device use to

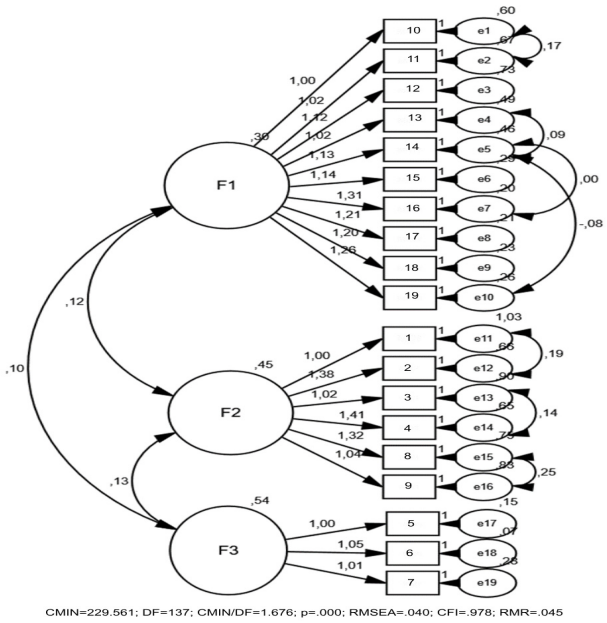

Figure 3. Confirmatory factor analysis results of Draft Scale

children" explained 34.3% of the total variance, the second factor, called "parental attitudes and behaviors in the use of digital devices" explained 15.6% of the total variance, and the third factor, called "instrumentalization of children in the use of digital devices" explained 11.5% of the total variance. The entire draft scale consisting of 19 items explained 61.3% of the total variance, which is above the 50% value accepted in the scale development literature.[29] Item factor loadings ranged from 0.619 to 0.853 for the first component, 0.635 to 0.834 for the second component, and 0.888 to 0.932 for the third component. All components' factor loadings were above 0.45.[38] A statistically significant correlation was found between the first and second components ($r=0.306$, $p<0.001$), between the first and the third components ($r=0.263$, $p<0.001$), and between the second and third components ($r=0.308$, $p<0.001$). The mean total score of the draft scale was 75.95±10.7.

Findings on Confirmatory Factor Analysis (CFA)

CFA was performed to verify the structural validity of the draft scale derived from the EFA results.[26] The analysis was performed using AMOS 24 and the analysis output includes some modification suggestions. Some changes were made for variables with high covariance values and improvements were observed in model fit indices (**Figure 3**). Some modifications were made for variables with high covariance values.[26] The analysis results were evaluated by comparing them according to the confirmatory factor analysis fit criteria table (**Table 4**).[43]

Multiple fit indices were evaluated to assess the model's suitability. The Tucker-Lewis Index (NNFI-TLI), Comparative Fit Index (CFI), Adjusted Goodness of Fit Index (AGFI), Goodness of Fit Index (GFI), Root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR) demonstrated a strong model fit. Furthermore, the Normed Fit Index (NFI), Relative Fit Index (RFI), and Parsimony Goodness of Fit Index (PGFI) fell within the range of acceptable fit. Additionally, model values smaller than the thresholds for the Akaike information criterion (AIC), consistent Akaike information criterion (CAIC), and Expected Cross Validation Index (ECVI) further confirmed the model's acceptability.[43]

Findings on Data Reliability

Cronbach's alpha coefficients were calculated to assess the internal consistency of the data (Table 3). The reliability for the first component, 'parental knowledge and attitudes regarding the harms of digital device use on children,' was 0.907. The second component, 'parental attitudes and behaviors in digital device usage,' had a reliability of 0.839, while the third component, 'instrumentalization of children in digital device usage,' showed a reliability of 0.909. The overall reliability of the draft scale was 0.979, with all values exceeding the acceptable threshold of 0.70.[31]

Item discrimination was analyzed to evaluate the internal consistency of the draft scale (**Table 5**). Following the arrangement of total scores in descending order, 112 participants (27%) with the highest and lowest scores were selected for item analysis. An independent samples t-test was conducted to identify differences in scale scores between the lower and upper groups. Each item showed a statistically significant difference ($p<0.001$), confirming that the items effectively differentiated the measured construct.[44]

DISCUSSION

Today, children's digital device uses and addiction is one of the important health problems. At this point, it is frequently stated in the literature that parental attitudes play a decisive role in children's digital device use.[45,46] This study aimed to develop a scale to measure parents' knowledge and attitudes regarding their children's digital device use and to test its validity and reliability by conducting a field study. For this purpose, the scale development process and steps were followed.[19,20]

For content and scope validity, an item pool was created by reviewing the literature, the item pool was presented to field

Table 4. Findings of CFA and comparing to fit indices

Fit indices	Acceptable fit	Good fit	Findings of CFA	Results
$\chi 2/df$	$2\leq\chi 2/df\leq 3$	$0\leq\chi 2/df\leq 2$	1.676	Gf
SRMR	$0.05\leq SRMR\leq 0.08$	$0.00\leq SRMR\leq 0.05$	0.045	Gf
RMSEA	$0.05\leq RMSEA\leq 0.10$	$0.00\leq RMSEA\leq 0.05$	0.040	Gf
NFI	$0.90\leq NFI\leq 0.95$	$0.95\leq NFI\leq 1.00$	0.947	Af
CFI	$0.90\leq CFI\leq 0.95$	$0.95\leq CFI\leq 1.00$	0.978	Gf
GFI	$0.90\leq GFI\leq 0.95$	$0.95\leq GFI\leq 1.00$	0.946	Af
AGFI	$0.85\leq AGFI\leq 0.90$	$0.90\leq AGFI\leq 1.00$	0.925	Gf
NNFI (TLI)	$0.90\leq$ NNFI (TLI)≤ 0.95	$0.95\leq$ NFI (TLI)≤ 1.00	0.972	Gf
RFI	$0.90\leq RFI\leq 0.95$	$0.95\leq RFI\leq 1.00$	0.934	Af
PNFI	$0.50\leq PNFI\leq 0.95$	$0.95\leq PNFI\leq 1.00$	0.759	Af
PGFI	$0.50\leq PGFI\leq 0.95$	$0.95\leq PGFI\leq 1.00$	0.682	Af
AIC	The model compared is smaller than the AIC value		335.561<380.000	Af
CAIC	The model compared is smaller than the CAIC value		602.188<1778.76	Af
ECVI	The model compared is smaller than the ECVI value		0.809<0.916	Af

CFA: Confirmatory, SRMR: Standardized root mean square residual, RMSEA: Root mean square error of approximation, NFI: Normed Fit Index, CFI: Comparative Fit Index, GFI: Goodness of Fit Index, AGFI: Adjusted Goodness of Fit Index, TLI: Tucker-Lewis Index, RFI: Relative Fit Index, PGFI: Parsimony Goodness of Fit Index, AIC: Akaike information criterion, CAIC: Consistent Akaike information criterion, ECVI: Expected Cross Validation Index

Table 5. Findings on item discrimination

		X	SD	t	p			X	SD	t	p
I-1	Lower	2.8	1.2	-10.87	0.000	I-11	Lower	2.9	1.2	-7.578	0.000
	Upper	4.4	0.9				Upper	4.1	1.0		
I-2	Lower	2.3	0.9	-12.98	0.000	I-12	Lower	3.2	1.1	-7.645	0.000
	Upper	4.1	1.1				Upper	4.2	0.9		
I-3	Lower	2.8	1.1	-10.88	0.000	I-13	Lower	3.3	1.1	-7.504	0.000
	Upper	4.3	1.0				Upper	4.2	0.8		
I-4	Lower	2.4	1.0	-14.44	0.000	I-14	Lower	2.9	1.1	-9.172	0.000
	Upper	4.3	0.9				Upper	4.2	0.9		
I-5	Lower	3.9	1.1	-9.54	0.000	I-15	Lower	3.4	1.0	-7.848	0.000
	Upper	4.9	0.2				Upper	4.4	0.7		
I-6	Lower	4.0	1.1	-8.35	0.000	I-16	Lower	3.2	1.0	-8.809	0.000
	Upper	4.9	0.2				Upper	4.3	0.8		
I-7	Lower	3.9	1.2	-7.79	0.000	I-17	Lower	3.4	0.9	-10.260	0.000
	Upper	4.9	0.5				Upper	4.5	0.6		
I-8	Lower	2.6	1.1	-13.15	0.000	I-18	Lower	3.5	1.0	-9.459	0.000
	Upper	4.4	1.0				Upper	4.5	0.6		
I-9	Lower	3.0	1.2	-12.151	0.000	I-19	Lower	3.5	0.9	-10.168	0.000
	Upper	4.6	0.7				Upper	4.5	0.6		
I-10	Lower	3.3	1.0	-10.935	0.000						
	Upper	4.6	0.7								

t: Independent samples T test, lower (n)=112, upper (n)=112, SD: Standard deviation

experts for their opinions, and a pilot study was conducted.[26,47] After the revisions, a field study was conducted on a large sample for the 19-item, 5-point Likert-Type Scale.[34]

Exploratory and confirmatory factor analysis was conducted to determine the construct validity of the scale.[26,35] The determination of the number of factors was guided by eigenvalues, percentage of variance explained, contribution to total variance, and an evaluation of the scree plot.[34] EFA revealed a three-factor structure explaining 61.3% of the total variance, exceeding the 50% minimum threshold recommended in scale development.[36] CFA was performed to test the construct validity of the factor analysis results. CFA confirmed the EFA structure, demonstrating good and acceptable model fit across all indices.[43] The Cronbach alpha coefficient of 0.979 indicated excellent internal consistency,[31] and item discrimination analyses validated the scale's ability to measure the intended constructs.[44] As a result of the procedures performed for content, scope, and structural validity, it was determined that the scale consisted of 19 items and 3 factors.

This study developed the 'parental knowledge and Attitude Scale for children's use of digital devices,' focusing on children aged 6 months to 6 years, which distinguishes it from existing scales in the literature that predominantly target older age groups.[16,17] The lack of comprehensive measurement tools addressing early childhood digital device use highlights a significant gap in the field. By addressing this gap, the study contributes to the literature by revealing the multidimensional nature of parental attitudes toward digital device use.

CONCLUSION

The final scale comprised 19 items across three sub-dimensions, presented in a 5-point Likert format (Appendix-1). The "Parental Knowledge-Attitude Scale for children's use of digital devices" is a valid and reliable instrument that enables researchers and practitioners to assess parental knowledge-awareness and attitudes toward children's digital device use.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Atatürk University Faculty of Nursing Ethics Committee (Date: 15.02.2023, Decision No: 2023-1/13).

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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Evaluation of intravenous iloprost use in critically ill pediatric patients: a single-center experience

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ABSTRACT

Aims: Iloprost is a prostacyclin analog that has vasodilatation properties at the systemic level, inhibiting platelet aggregation and adhesion and triggering angiogenesis. Our experience with intravenous (IV) administration of iloprost as a vasodilator in pediatric intensive care units is limited. The present study investigates the characteristics of patients subjected to IV iloprost therapy and their response to treatment.

Methods: A 15-month period, all patients who received IV iloprost treatment were included. Data including age, gender, reason for hospitalization, cause of vascular damage, affected vessel, iloprost dosage, treatment duration, necessity of surgery, and occurrence of treatment-related complications were retrieved from retrospective patient files.

Results: During the study, IV ten patients receiving iloprost treatment were examined. The starting dose of the drug was 0.5 ng/kg/min in all patients, and the initial dose was continued in seven patients. Duration of iloprost use was 17.8±10.8 (min 1, max 28) days. 50% (n=5) of the reasons for hospitalization were non-traumatic reasons. Amputation was performed in three patients (30%). In the clinical classification of those with damage to the extremities, there were four patients in stage 1 (44.5%), two patients in stage IIa (22.2%), and three patients in stage IIb (33.3%). Amputation was applied to three patients in stage IIb, and this is the patient group where the dose was started at a dose of 0.5 ng/kg/min and the dose was increased.

Conclusion: Intravenous iloprost treatment is a safe therapeutic option with minimal side effects, beneficial for preventing hypoxia and tissue cellular damage in cases of vascular injury.

Keywords: Child, iloprost, pediatric intensive care, vasodilation

INTRODUCTION

Iloprost is a prostacyclin analog that has vasodilatation properties at the systemic level and triggers angiogenesis by inhibiting platelet aggregation and adhesion. The administration of intravenous (IV) iloprost infusions has come to the fore as a new treatment alternative in acute arterial occlusive diseases in recent years.[1,2] Although iloprost is commonly used as an inhaler for treating pulmonary hypertension in pediatric intensive care units (PICU), there is insufficient experience regarding its use in vasodilator therapy. This lack of experience is particularly pronounced with its IV administration.

Acute arterial occlusive diseases are clinical syndromes that occur as a result of arterial tissue or organ ischemia. Acute limb ischemia develops as a result of a sudden decrease in arterial perfusion in the limb. Symptoms and signs of acute limb ischemia vary depending on the duration of ischemia and the location of arterial obstruction. Vasculopathies occur secondary to septic shock, peripheral artery disease, iatrogenic vascular injury, or as a result of acute traumatic ischemia.[1,2]

Acute traumatic ischemia is the general definition of injuries caused by a high-energy trauma that can cause skin, soft tissue, bone, tendon, nerve, or vascular damage that blocks blood flow to the tissue and is a part of crush syndrome. It appears as a result of many situations that threaten tissue integrity, such as open fractures, gunshot and sharp object injuries, and frostbites. Acute limb ischemia also occurs as a serious complication of septic shock. Ischemia in the extremities may occur as a result of local inflammation of the skin, hypoperfusion, severe vasoconstriction, hypoxia, and disseminated intravascular coagulation.[1,2]

It has been reported that iloprost therapy has positive effects on healing trophic lesions, relieving rest pain, decreasing amputation rates, and reducing overall mortality.[1,2] These positive effects are achieved by increasing iloprost microcirculation. The ideal dose for iloprost treatment should be one that minimally affects blood pressure and has minimal side effects. In many clinical studies, it has been demonstrated

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that administering IV iloprost infusion at a dose of 0.5-2 nanograms (ng)/ kilogram (kg)/ minute (min) for six hours daily achieves the desired optimal results safely and without serious side effects.[1-3] This retrospective study aimed to contribute to the literature by examining the characteristics and treatment response of IV iloprost administered patients who were followed up and treated as inpatients in PICU over 15 months.

METHODS

All patients aged between one month and 18 years who received IV iloprost treatment during a 15-month period starting from January 2023 were included in our tertiary PICU. Data on patients' age, gender, reason for admission to the PICU, duration of PICU and hospital stay, cause of vascular damage, affected vessel, iloprost dose, treatment duration, clinical classification of extremity ischemia, treatment outcomes, use of anticoagulants, necessity of surgery and treatment-related complications were obtained from retrospective patient files. Approval for the study was received from Mersin University Non-interventional Clinical Researches Ethics Committee (Date: 22.04.2024, Decision No: 2024/364). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The reasons for admission to PICU were classified as trauma and non-traumatic causes. Causes of vascular damage were categorized into acute traumatic ischemia, damage secondary to septic shock and iatrogenic vascular injury. Amputation, if performed, was further divided into minor and major categories. Minor amputation refers to limb loss that occurs distal to the metatarsophalangeal joint in the lower extremities and metacarpophalangeal joint in the upper extremities, without significant impact on daily function or work capacity. Major amputation was defined as all amputations starting from the transmetatarsal level in the lower extremity and the metacarpal level in the upper extremity. Acute limb ischemia is a decrease in blood supply that endangers tissue viability. Clinical classification is made by evaluating loss of sensation, muscle dysfunction, and arterial and venous Doppler findings (Table 1).[4,5]

Statistical Analysis

Statistical Package for Social Sciences (SPSS for Windows 20.0 version) statistical program was used for statistical evaluation. Number and percentage values are used in categorical data; minimum, maximum, and mean±standard deviation values are given for descriptive statistical measurements.

RESULTS

Included in the study were 10patients aged between 1 month and 18 years who received IV iloprost therapy in the tertiary pediatric intensive care unit over a 15-month period, as of January 2023, 60% (n=6) of whom were female. The age was 9.7±5.3 (min 1, max 16) years and the body weight was 35.0±21.87 (min 6, max 70) kg. The PICU stay was 54.8±62.2 (min 5, max 180) days and the hospital stay was 68.4±59.3 (min 15, max 185) days. Initially, all patients started iloprost at a dose of 0.5 ng/kg/min. During treatment, the dose was increased to 2.0 ng/kg/min for 1 patient, 1.0 ng/kg/min for 2 patients, while 7 patients continued with the initial dose. No complications related to the drug were detected and the duration of iloprost use was 17.8±10.8 (min 1, max 28) days.

The reasons for admission to the PICU were 50% (n=5) trauma and 50% (n=5) non-traumatic reasons. Forty percent (n=4) of the patients had compartment syndrome and 50% (n=5) crush syndrome. When the areas where vascular damage develops are examined, 20% (n=2) are in the upper extremities, 70% (n=7) are in the lower extremities, and one patient is in the abdomen. The injured vessel in the abdominal area was the portal vein (V. portae hepatitis), while the other injuries (n=9, 90%) were arterial vessel injuries. Among the damaged arteries, 3 of them (30%) were arteria (A) tibialis anterior, 2 (20%) were A. tibialis posterior, 2 (20%) were A. poplitea, 1 (10%) was A. radialis and 1 (10%) was A. ulnaris.

Anticoagulant treatment could be given to five of the patients (50%); low molecular weight heparin was used in anticoagulant therapy. Amputation was performed in three patients (30%), minor amputation was performed in one (10%) patient, and major amputation was performed in two (20%) patients. The characteristics of the patients are shown in Table 2. When nine patients with damage to the vessels in the extremities were examined in terms of clinical classification, it was found that there were four patients in stage 1 (44.5%), two patients in stage IIa (22.2%), and three patients in stage IIb (33.3%). Amputation was applied to three patients in stage IIb, and this is the patient group in which the dose was started at a dose of 0.5 ng/kg/min and the dose was increased.

DISCUSSION

At 15-month period, IV parenteral ten patients receiving iloprost treatment were examined. The starting dose of the drug was 0.5 ng/kg/min in all patients, and the initial dose was continued in seven patients. Duration of iloprost use was min 1 days, and max 28 days. 50% (n=5) of the reasons for hospitalization were non-traumatic reasons. Amputation was performed in three patients. In the clinical classification of

Table 1. Clinical classification of acute limb ischemia[4,5]

Stage		Loss of sensation	Muscle dysfunction	Arterial Doppler flow	Venous Doppler flow
1. Alive	No direct threat	No	No	Yes	Yes
2a. Threat at the border	Can be saved with urgent intervention	None/minimal	No	None	Yes
2b. Serious threat	Can be saved with very urgent intervention	Common, with rest pain	Mild	None	Yes
3. Irreversible ischemia	Major tissue damage, permanent nerve damage	Deep, anesthetic	Deep	None	None

Table 2. Assessment of patients receiving iloprost therapy

Patients	Age (years)	Gender	Reason for hospitalization	Affected vessel	Initial iloprost dose (ng/kg/min)	Max Iloprost dosage (ng/kg/min)	Number of days using iloprost	Anticoagulant treatment	Amputation
Patient 1	1	Female	Septic shock, menigococcemia	Bilateral popliteal artery	0.5	2.0	21	+	Bilateral minor amputation
Patient 2	15	Male	Trauma	Left ulnar artery	0.5	0.5	21	+	-
Patient 3	8	Male	Traumatic pancreatitis	Portal vein	0.5	0.5	1	-	-
Patient 4	6	Male	Septic shock, autoimmune encephalitis	Bilateral radial artery	0.5	0.5	28	+	-
Patient 5	12	Female	Septic shock, purpura fulminans	Left tibilias anterior artery	0.5	0.5	28	-	-
Patient 6	16	Female	Trauma	Left tibialis posterior artery	0.5	0.5	28	+	-
Patient 7	13	Female	Septic shock, purpura fulminans	Bilateral tibialis posterior	0.5	0.5	28	+	-
Patient 8	2	Female	Trauma	Right popliteal artery	0.5	1.0	6	-	Right major amputation
Patient 9	15	Female	Trauma	Left tibialis anterior artery	0.5	0.5	5	-	-
Patient 10	8	Male	Trauma	Left tibialis anterior artery	0.5	1.0	12	-	Left major amputation

ng: Nanogram, kg: Kilogram, min: Minute

those with damage to the extremities, there were four patients in stage 1, two patients in stage IIa, and three patients in stage IIb. Amputation was applied to three patients in Stage IIb, and this is the patient group where the dose was started at a dose of 0.5 ng/kg/min and the dose was increased. In this study, we aimed to present our experiences with parenteral iloprost use to the literature.

Damage to vessels, whether caused by trauma, iatrogenic factors or shock, leads to a slowdown or deterioration of circulation, resulting in hypoxia and cellular damage in the tissue supplied by the affected vessel. Our goal in treatment is to increase tissue oxygenation of the damaged area and improve perfusion.[6,7]

In vasodilator treatment in the adult age group, there are studies and experiences regarding IV iloprost.[2,3] Although iloprost is frequently used as an inhaler in the treatment of pulmonary hypertension in PICU, our experience with IV administration in vasodilator therapy is limited.[1,4,8,9] In this study, we present our experiences with ten critically ill pediatric patients who received IV iloprost treatment due to vascular damage.

In a study conducted by Zulian et al.,[1] IV treatment was administered to 15 pediatric patients with severe finger ischemia due to connective tissue disease. It has been reported that iloprost infusion is a safe and effective treatment for ischemic finger and digital ulcers. Tanyıldız et al.,[9] in their 2023 publication on managing earthquake victims in PICU, reported administering vasodilator treatment to eight patients. Although they mentioned using nitroglycerin, milrinone, and iloprost infusion, they did not specify the number of patients treated with iloprost. IV iloprost was administered as an infusion at a rate of 0.5-1 ng/kg/min.

Headaches, rash, nausea, and vomiting are common drug-related side effects. The ideal dose for iloprost treatment should be the dose that does not affect blood pressure and has minimal side effects.[10] In our study, no drug-related complications were detected in our patients. While no complications were observed in 47% (n=7) of the patients during IV iloprost treatment administered to children with connective tissue disease; drug-related complications seen in other patients have been reported to include nausea, vomiting, headache, and hypotension.[1] In our study, the starting dose of medication was 0.5 ng/kg/min in all patients. The dose was increased to 2.0 ng/kg/min in one patient and 1.0 ng/kg/min in two patients, and the initial dose was continued in seven patients. Studies have shown that the lowest infusion rate at which vasodilatation and platelet aggregation inhibition begins is 0.5 ng/kg/min. It has been reported that high doses of iloprost do not increase the effect. It is believed that doses higher than 0.5-2.0 ng/kg/min do not further enhance the therapeutic effect of iloprost, potentially due to increased vasodilatation and blood leakage from the skin into the muscle tissue.[11-13] In our study, the maximum dose was found to be 2.0 ng/kg/min.

Distal limb ischemia is a serious complication of septic shock. Ischemia may occur in the extremities as a result of local inflammation of the skin, hypoperfusion, severe vasoconstriction, hypoxia and disseminated intravascular coagulation. One therapeutic method used to interrupt this series of events is iloprost, a prostacyclin analogue known for its systemic vasodilatory properties. It inhibits platelet aggregation and adhesion while promoting angiogenesis. It can prevent progression to necrosis and amputation in patients whose lesions are peripheral and have digital involvement.[2,3,8,14] In the article, four patients in the pediatric

age group who developed limb ischemia as a result of septic shock were presented. It was reported that two patients responded to iloprost treatment, while the response to iloprost treatment could not be evaluated in the other two patients who died due to multiple organ failure resulting from meningococcemia.[8] In our study, four patients received vasodilator treatment due to acute extremity ischemia resulting from septic shock. While cure was achieved in three patients, one patient underwent minor amputation. One of our patients received IV iloprost treatment for one day due to iatrogenic injury to the portal vein during an abdominal operation. Iloprost infusion was administered. While our average duration of iloprost use was 17.8±10.8 days, with a maximum of 28 days, this duration aligns with similar studies reported in the literature. Guidelines for critical limb ischemia also recommend parenteral iloprost treatment for 7-28 days.[15]

Acute artery occlusion is followed by clinical findings. Patients are monitored for pain in the relevant area, pulselessness, pallor, sensory impairment, and motor losses.[5] In addition, evaluation is performed with Doppler ultrasonography in the area with a clinical picture of acute limb ischemia. Doppler works on the principle of detecting the movement of blood and is used together with other diagnostic tests to detect vascular diseases. In a normal artery, the waveform is triphasic. During cardiac systole, there is forward flow in the artery. At the beginning of diastole, the flow reverses. The normal triphasic signal changes if stenosis develops in the vessel. If the stenosis is minimal, signal loss distal to the lesion or disappearance of the forward flow component in mid-diastole results in a biphasic signal. As the stenosis becomes more severe, the signal becomes monophasic. The location of the stenosis can be determined by evaluating the Doppler signal in different parts of the extremity.[16] Our patients were followed with repeated clinical examinations and Doppler ultrasonography examinations, and as a result of these evaluations, the number of days and dosage of parenteral vasodilator treatment were determined. Amputation may be life-saving in extremity gangrene that cannot be corrected despite all treatments. It should be performed at the appropriate time above the demarcation line formed in the unfed area. Three of our patients underwent an amputation.

Limitations

In the study, five patients received anticoagulant therapy in addition to iloprost treatment. This may have contributed to the treatment success of these patients. Not comparing the patients who received anticoagulant therapy and those was a limitation of the study. The biggest limitation of our study is that we could not statistically examine the factors that could affect it due to the lack of a sufficient number of cases. However, since there is limited information in the literature about the use of parenteral iloprost in pediatric intensive care patients, we wanted to convey our experiences in this study.

CONCLUSION

Intravenous iloprost therapy is a safe therapeutic approach with minimal side effects. It effectively prevents hypoxia and cellular damage in tissues supplied by damaged vessels, addressing circulation slowdown or deterioration caused by vessel injury. There is a need for further studies of this issue involving larger patient cohorts.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Mersin University Non-interventional Clinical Researches Ethics Committee (Date: 22.04.2024, Decision No: 2024/364).

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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Ultrasonographic evaluation of Caval Aortic Index in gestational and pregestational diabetes: a predictor of perinatal outcomes?

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ABSTRACT

Aims: Diabetes mellitus (DM), including gestational (GDM) and pregestational diabetes (pre-GDM), adversely affects maternal and fetal outcomes due to hyperglycemia and vascular changes. The Caval Aortic Index, a non-invasive measure of blood volume, could provide insights into these complications. In our study, we aimed to determine the functional changes in inferior vena cava (IVC) and aorta (Ao) diameters as well as the importance of caval aortic index in predicting perinatal outcomes in diabetic pregnant women.

Methods: This prospective case-control study included 120 DM patients and 100 controls. DM patients were divided into pre-GDM, diet-regulated GDM, and insulin-regulated GDM groups. Ultrasound measurements of inferior vena cava and aortic diameters were performed, alongside Doppler evaluations. Statistical analyses were conducted to assess the association of these parameters with adverse perinatal outcomes.

Results: Although the IVC and aortic diameters of the pregnant women with DM were higher compared to the control group and a statistically significant difference ($p<0.001$) was found between the groups, the Caval-Aortic Index was similar between the groups. Adverse outcomes (APGAR 5 min <7, need for mechanical ventilation, need for continued positive airway pressure, respiratory distress syndrome, transient tachypnea of the newborn and neonatal intensive care unit admission and neonatal low cord blood pH) were higher in DM groups but showed no direct correlation with IVC or aortic parameters. IVC diameter was the most predictive parameter in DM patients and the cut-off was >3.81 mm (AUC: 0.674).

Conclusion: Ultrasonographic IVC and aortic diameters reflect vascular adaptations in diabetic pregnancies but lack predictive value for adverse outcomes. While the Caval Aortic Index provides limited prognostic utility, integrating these measurements into comprehensive models may enhance perinatal risk assessment.

Keywords: Gestational diabetes, pregestational diabetes, Caval Aortic Index, perinatal outcomes, ultrasonography, vascular adaptations

INTRODUCTION

A collection of illnesses known as diabetes mellitus (DM) are typified by hyperglycemia brought on by an issue with the secretion and/or action of insulin.[1] Gestational diabetes mellitus (GDM) is the term for glucose intolerance that first appears in the second or third part of pregnancy, whereas pregestational diabetes mellitus (pre-GDM) is the term for glucose intolerance that already exists before pregnancy or is identified in the first trimester.[2,3] On average, 1.3% of pregnancies are affected with pre-GDM, whereas 7-11% are affected by GDM. As maternal age and obesity rise, this rate also rises.[2,4] Macrosomia, congenital abnormalities, perinatal mortality, hypertrophic cardiomyopathy, fetal growth restriction (FGR), preterm birth, respiratory distress syndrome (RDS), and newborn hypoglycemia are all more common in pregnancies affected by diabetes mellitus. Among the long-term consequences of diabetes mellitus are obesity, type 2 diabetes, and an increased risk of cardiovascular disease.[5-7]

As pregnancy goes on, maternal insulin resistance rises as a result of elevated levels of estrogen, progesterone, cortisol, and human placental lactogen acting as counter-regulatory hormones to insulin and influencing glucose homeostasis.[8] As a result, maternal carbohydrate metabolism changes during

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pregnancy.[9,10] Through the fetoplacental circulation, elevated maternal glucose is passed to the fetus, resulting in reactive hyperinsulinemia and hyperglycemia. Moreover, elevated oxidative stress is linked to a hyperglycemic setting.[9] Vascular abnormalities in fetuses of diabetes moms can be caused by endothelial dysfunction brought on by elevated fetal oxidative stress and the production of inflammatory cytokines. Furthermore, around one-third of fetuses born to pregnant mothers with diabetes may develop hypertrophy of the aortic and pulmonary trunk muscle layers, which may change the volume of blood in circulation.[11,12]

Venous blood is transported from the lower body to the right atrial chamber by the inferior vena cava (IVC). Variations in circulating blood volume and central venous pressure affect the IVC's size.[13] Originally used to evaluate the body's fluid state, the caval aortic index is a non-invasive technique that is calculated as the ratio of the diameter of the descending aorta to the diameter of the inferior vena cava (IVA/Ao).[14,15]

Along with functional alterations in IVC and Ao diameters in pregnant women with diabetes, our study sought to determine the relevance of Caval Aortic Index in predicting perinatal outcome.

METHODS

The Ankara Etlik City Hospital Clinical Researches Ethics Committee gave its permission to the study protocol (Date: 18.10.2023, Decision No: AESH-EK1-2023-621). Every participant provided written consent after being told about the study. The Declaration of Helsinki's guiding principles were followed when conducting the study. This prospective case-control study was carried out in the Ankara Etlik City Hospital's Perinatology Clinic from November 2023 to August 2024. The study population was divided into four groups: group 1: 40 patients diagnosed with pre-GDM, group 2: 40 patients with diet-regulated gestational diabetes (DR-GDM), group 3: 40 patients with insulin-regulated gestational diabetes mellitus (IR-GDM) and group 4: 100 healthy control patients.

GDM was diagnosed based on the American College of Obstetricians and Gynecologists' (ACOG) Committee's criteria.[2,3] Our clinic used a two-stage oral glucose tolerance test (OGTT), which was advised for all pregnant women between weeks 24 and 28. Following 50 grams of oral glucose solution, a 1-hour glucose measurement was first carried out in the vein. Patients whose 1-hour glucose result was greater than 140 mg/dl were next subjected to a diagnostic OGTT using 100 grams. GDM was identified in women who had two or more abnormal 3-hour OGTT results. In the OGTT, abnormal values were defined as fasting glucose ≥95 mg/dl, first-hour glucose ≥180 mg/dl, second-hour glucose ≥155 mg/ dl, and third-hour glucose ≥140 mg/dl. Pre-GDM was identified if the random fasting plasma glucose level was ≥126 mg/dl, the 2-hour glucose value in the 75-g-OGTT surpassed ≥200 mg/dl, or the glycosylated hemoglobin (HbA1c) was ≥6.5 before to pregnancy or during the first trimester.[1] When necessary, diet or treatment was started for patients with diabetes mellitus. Patients who began insulin treatment were placed in the IR-GDM group, while those who maintained their pregnancy on diet were placed in the DR-GDM group. Based on the first day of the last menstrual cycle, the study participants' weeks of gestation were determined. The crown-rump length, which was obtained during the first trimester ultrasound examination, was used to calculate the gestational age in patients who were unaware of their most recent menstruation. The study involved women who were 28-41 weeks pregnant. The control patients were selected on the basis of their gestational age. Patients who discontinued follow-up, patients with smoking, alcohol consumption, congenital anomalies, multiple pregnancies, chronic maternal diseases (such as hypothyroidism, hypertension) and patients with obstetric complications other than DM diagnosis (such as isolated FGR, intrahepatic cholestasis in pregnancy) were excluded from the study. All of the study's patients had their demographic data, including their body-mass index (BMI), weight gain during pregnancy, and maternal age, gathered. Maternal venous blood was used to calculate the HbA1c value.

The patients were examined by transabdominal sonography using the Voluson S10 Expert sonography device (GE Healthcare, Milwaukee, Wisconsin, USA) by the same perinatology specialist (GK) under the supervision of an experienced supervisor (ZVY). The patient was positioned supine or semi-recumbent at 15° to 30° for Doppler exams, with the head and chest slightly raised to avoid caval compression. Pulsatility Index (PI) of the umbilical artery (UA) and systolic/diastolic ratio (S/D), PI of the middle cerebral artery (MCA), peak systolic velocity (PSV) and S/D values, and S/D and PI values of the uterine artery (UtA) were recorded for the Doppler evaluation. Every measurement was carried out in compliance with the International Society of Ultrasound in Obstetrics and Gynecology's (ISUOG) guidelines. The UA waveform was measured and recorded from the free-floating portion of the cord in the absence of minimal fetal activity and fetal respiration. The circle of Willis was seen using the color Doppler in the axial portion of the fetal head while the MCA Doppler was being inspected. The insonation angle was consistently near 0° during the measurement, which took place in the proximal third of the MCA, which is derived from the circle of Willis. A sagittal cut of the uterus was produced to locate the cervical canal in order to do the Doppler measurement of the uterine artery. The measurement was taken prior to the uterine artery giving off the arcuate branch.[16] The diameter of the IVC was measured from inner edge to inner edge in the parasagittal section and in the bicaval view. The anteroposterior diameter of the IVC increases during expiration and decreases during inspiration. Therefore, the measurement was repeated and averaged for 3 respiratory cycles to account for the changes during breathing. The aortic diameter was examined on the descending aorta at the end of systole. The Ao diameter in the fetus's coronal section was measured from inner edge to inner edge, which represents the upper and lower ends of the iliac and renal arteries, respectively. At least three measurements were made, and the mean of them was used (**Figure 1**).[13]

In our clinic, decisions on the follow-up care and delivery of patients diagnosed with DM are made according to the criteria

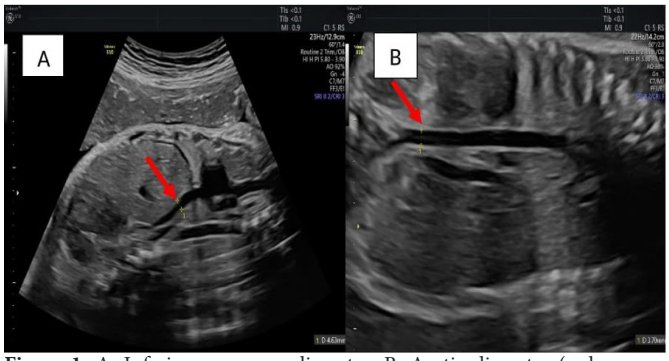

Figure 1. A: Inferior vena cava diameter, B: Aortic diameter (red arrows: inner wall to inner wall vessel diameter measurement)

of the American College of Obstetricians and Gynecologists (ACOG) committee.[2,17] In patients with pre-GDM and IR-GDM, delivery was decided at 36^{+0}-38^{+6} weeks in the case of a complicated pregnancy and at 39^{+0}-39^{+6} weeks in the case of an uncomplicated pregnancy. In DR-GDM patients, expectant management was applied until 40^{+6} weeks of gestation. If the estimated fetal weight was ≥4500 g, a decision for cesarean section was made. Patients' birth information, birth weight, APGAR 1/APGAR 5 scores and neonatal morbidities were recorded. Composite adverse perinatal outcome (CAPO) was defined as at least one of the following: APGAR 5 min <7, need for mechanical ventilation (MV), need for continued positive airway pressure (CPAP), RDS, transient tachypnea of the newborn (TTN), admission to the neonatal intensive care unit (NICU), and low cord blood pH.

Statistical Analysis

IBM Corporation SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) was used to conduct the statistical analysis. The conformance to the normal distribution was examined using the Kolmogorov-Smirnov test. For continuous variables with a normal distribution, descriptive statistics are displayed as "mean±standard deviation". and for those who don't, as the "median (interquartile range)". When comparing more than two groups, the Analysis of Variance (ANOVA) test was employed. The number of groups was taken into consideration while determining the ANOVA test's statistical significance. 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. The optimal cutoff values based on the Youden Index were found by calculating and comparing the areas under the curve (AUC) using the ROC curve. For all tests, a p-value of less than 0.05 was considered statistically significant.

The number of people to be included in the study was determined using the G-Power 3.1.9.7 software (University of Dusseldorf, Dusseldorf, Germany). When calculating the estimated sample size, the Caval-Aorta Index was used as the primary variable; the sample size was calculated using the student's paired test with 80% power, a probability of error of α=0.05 and the Cohen effect size as 'medium'. Accordingly, it was considered appropriate to conduct the study with at least one hundred and eighty patients, ensuring the robustness of the study's findings.

RESULTS

One hundred control participants and 120 DM patients participated in this study. The maternal features and ultrasonography results of the DM and control patients are displayed in Table 1. The pre-GDM group had a greater maternal age than the control group, which was a significant difference (p<0.001). Gravida of the pre-GDM group was higher than that of the DR-GDM, IR-GDM and control groups (p=0.037). All four groups had similar parity and gestational weeks at evaluation (p=0.537, p=0.142). The control group and the pre-

Table 1. Comparison of maternal characteristics and ultrasound parameters of the groups

	Pre-GDM n=40	DR-GDM n=40	IR-GDM n=40	Control n=100	p-value
Maternal age (year)	32.9±5	30.9±6	31.1±6	28.2±5.1	<0.001[a]
Gravida	3 (2)	2 (2)	2 (3)	2 (2)	0.037[b]
Parity	1 (1)	1 (2)	1 (2)	1 (2)	0.142[b]
BMI (kg/m²)	32.4±4.2	31.7±6.2	33.2±5.2	29.4±4.9	<0.001[a]
Gestational week at examination	34 (4)	34 (4)	33 (4)	34 (3)	0.537[b]
UA S/D	2.58 (0.76)	2.33 (0.76)	2.34 (0.54)	2.50 (0.63)	0.240[b]
UA PI	0.92 (0.28)	0.85 (0.31)	0.81 (0.21)	0.89 (0.25)	0.335[b]
UtA S/D	1.98 (0.45)	1.94 (0.59)	2.05 (1.12)	1.94 (0.70)	0.379[b]
UtA PI	0.75 (0.30)	0.73 (0.35)	0.83 (0.50)	0.75 (0.37)	0.577[b]
MCA PSV	47.19 (10.36)	43.13 (15.08)	49.39 (11.67)	47.80 (16.29)	0.522[b]
MCA S/D	5.10 (2.17)	4.38 (2.19)	4.55 (1.34)	4.96 (2.33)	0.305[b]
MCA PI	1.68±0.33	1.55±0.41	1.61±0.31	1.60±0.35	0.428[a]
SDVP (mm)	65 (30)	66 (43)	64 (24)	50 (15)	<0.001[b]
IVC diameter (mm)	3.98 (0.77)	4.12 (1.35)	3.97 (0.80)	3.53 (0.84)	<0.001[b]
IVC diameter (z-score)	-0.01±0.83	0.07±1.34	-0.20±0.98	-0.75±1.06	<0.001[a]
Aortic diameter (mm)	4.70±0.91	4.86±0.75	4.91±0.76	4.51±0.69	0.012[a]
Aortic diameter (z-score)	-1.28±1.15	-1.28±1.31	-1.29±1.19	-1.9±1.19	0.003[a]
IVC/Ao index (mm)	0.85±0.16	0.86±0.23	0.82±0.14	0.80±0.17	0.240[b]
IVC/Ao index (z-score)	0.15±0.97	-0.65±8.88	0.25±2.05	0.74±1.71	0.337

[a]: Analysis of variance with Bonferroni test, [b]: Kruskal-Wallis test, Pre-GDM: Pregestational diabetes mellitus, DR-GDM: Diet regulated gestational diabetes mellitus, IR-GDM: Insulin regulated gestational diabetes mellitus, BMI: Body-mass index, UA: Umbilical artery, S/D: Systolic/diastolic ratio, PI: Pulsatility Index, UtA: Uterine artery, MCA: Middle cerebral artery, PSV: Peak systolic velocity, SDVP: Single deepest vertical pocket, IVC: Inferior vena cava, Ao: Aorta, Data are expressed as mean±standard deviation or median (interquartile range) where appropriate

GDM and IR-GDM groups had significantly different BMIs (p=0.012 and p=0.001, respectively). UA S/D, UA PI, MCA S/D, PI, PSV, UtA S/D, and PI were comparable among groups on ultrasonographic evaluation (p=0.240, p=0.335, p=0.305, p=0.428, p=0.522, p=0.379, p=0.577, respectively). In the single deepest vertical pocket (SDVP), there was a substantial correlation between control and pre-GDM, DR-GDM, and IR-GDM (p<0.001, p<0.001, and p=0.001, respectively). The control and DR-GDM groups differed considerably in IVC diameter, with the DR-GDM group showing a thicker IVC diameter (p<0.001). Between the control and IR-GDM groups, there was a significant difference in the aortic diameter, with the IR-GDM group's Ao diameter being thicker (p=0.012). The Z-score evaluation revealed a significant difference between the control group and the pre-GDM, DR-GDM, and IR-GDM groups in terms of the Z-score of the IVC (p=0.002, p<0.001, and p=0.005, respectively). The aortic Z-score of the pre-GDM, DR-GDM, and IR-GDM groups differed significantly from that of the control group (p=0.006, p<0.001, and p=0.008, respectively). All four groups' IVC/Ao index (mm) and IVC/Ao index (Z-score) values did not differ significantly (p=0.240 and p=0.337, respectively).

Table 2 displays the birth characteristics and perinatal outcomes of the study participants. According to gestational week, there was a significant difference between control and pre-GDM, DR-GDM, and IR-GDM (p<0.001, p=0.001, and p<0.001, respectively). Fetal distress, birth weight, and the APGAR score at one minute were comparable among groups (p=0.604, p=0.294 and p=0.104, respectively). Significant differences were observed between the groups in terms of neonatal hypoglycemia, APGAR 5. minute, prematurity, cesarean section rate, NICU admission, TTN, antenatal corticosteroid use, RDS, CPAP, MV need, and phototherapy need (p=0.023, p=0.018, p=0.005, p=0.004, p<0.001, p=0.001, p=0.012, p=0.002, p=0.008, p=0.002, p=0.004).

Table 3 compares IVC/Ao index, IVC and aortic diameter (mm, Z-score), birth characteristics and perinatal outcomes of newborns between patients with pre-GDM or GDM and control patients. Both the IVC and Ao diameters (mm) were significantly different between the two groups, and the DM group's diameters increased (p<0.001, p=0.002) (Figure 2). Additionally, there were substantial differences in both groups' IVC and Ao Z-scores (p<0.001, p<0.001). Both groups' IVC/Ao indexes (mm) and Z-scores were similar (p=0.078, p=0.136). he rates of fetal distress and the need for phototherapy were comparable in both groups when comparing the neonatal outcomes (p=0.147, p=0.515). However, the DM group had significantly higher rates of cesarean section, prematurity, NICU admission, neonatal hypoglycemia, TTN, RDS, CPAP, and MV needs (p=0.011, p=0.001, p<0.001, p=0.033, p=0.004, p=0.001, p=0.006, and p=0.004, respectively).

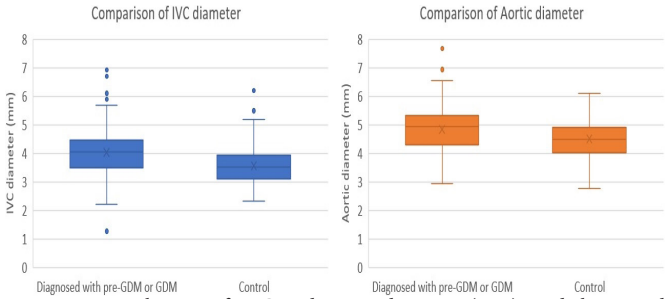

Figure 2. Distribution of IVC and aortic diameter (mm) in diabetes and control groups

IVC: Inferior vena cava

Table 4 compares the Doppler measurements of the groups in DM that had and did not have CAPO. IVC diameter (mm), IVC diameter (Z-score), Ao diameter (mm), Ao diameter (Z-score), IVC/Ao index (mm), and IVC/Ao index (Z-score) did not significantly differ across the groups (p=0.504, p=0.473, p=0.986, p=0.066, p=0.510, p=0.526, respectively).

Table 2. Birth characteristics and perinatal outcomes of the newborns

	Pre-GDM n=40	DR-GDM n=40	IR-GDM n=40	Control n=100	p-value
Gestational age at delivery (week)	37 (2.4)	37 (1.35)	37 (2.5)	39 (1.55)	<0.001[a]
Prematurity (<37 weeks)	14 (35%)	9 (22.5%)	12 (30%)	11 (11%)	0.005[b]
Cesarean section	35 (87.5%)	24 (60%)	30 (75%)	58 (58%)	0.004[b]
Birth weight (gram)	3287±511	3219±575	3238±537	3124±447	0.294[c]
Apgar score at 1st minute	9 (1)	9 (1)	9 (1)	9 (0)	0.104[a]
Apgar score at 5th minute	10 (1)	10 (1)	10 (1)	10 (0)	0.018[a]
NICU admission	20 (50%)	11 (27.5%)	10 (25%)	9 (9%)	<0.001[b]
Umbilical cord pH	7.37 (0.07)	7.36 (0.15)	7.38 (0.16)	7.42 (0.07)	0.247[a]
Transient tachypnea of the newborn	8 (20%)	9 (22.5%)	2 (5%)	4 (4%)	0.001[b]
Antenatal corticosteroid	12 (30%)	7 (17.5%)	11 (27.5%)	10 (10%)	0.012[b]
Fetal distress	2 (5%)	1 (2.5%)	1 (2.5%)	8 (8%)	0.604[b]
Respiratory distress syndrome	6 (15%)	4 (10%)	5 (12.5%)	1 (1%)	0.002[b]
Continues positive airway pressure	8 (20%)	10 (25%)	4 (10%)	6 (6%)	0.008[b]
Mechanical ventilation	7 (17.5%)	3 (7.5%)	2 (5%)	1 (1%)	0.002[b]
Phototherapy for neonates	6 (15%)	0 (0%)	0 (0%)	3 (3%)	0.004[b]
Neonatal hypoglycemia	3 (7.5%)	1 (2.5%)	2 (5%)	0 (0%)	0.023[b]

[a]: Kruskal-Wallis test, [b]: Pearson chi-square, [c]: Analysis of variance with Bonferroni test, Pre-GDM: Pregestational diabetes mellitus, DR-GDM: Diet regulated gestational diabetes mellitus, IR-GDM: Insulin regulated gestational diabetes mellitus, NICU: Neonatal intensive care unit

Table 3. Comparison of IVC/Ao index, IVC and aortic diameter (mm, z-score), birth characteristics and neonatal outcomes of newborns according to patients diagnosed with pre-GDM or GDM

	Diabetes mellitus (Pre-GDM+DR-GDM+IR-DM) n=120 (54.5%)	Control n=100 (45.5%)	p-value
IVC diameter (mm)	4.03±0.90	3.57±0.68	<0.001[a]
IVC diameter (z-score)	-0.5±1.07	-0.74±1.06	<0.001[a]
Aortic diameter (mm)	4.82±0.81	4.51±0.69	0.002[a]
Aortic diameter (z-score)	-1.28±1.21	-1.90±1.19	<0.001[a]
IVC/Ao index (mm)	0.84±0.17	0.80±0.16	0.078
IVC/Ao index (z-score)	-0.08±5.26	0.74±1.71	0.136[a]
Cesarean section	89 (74.2%)	58 (58%)	0.011[b]
Fetal distress	4 (3.3%)	8 (8%)	0.147[c]
Prematurity (<37 weeks)	35 (29.2%)	11 (11%)	0.001[b]
NICU admission	41 (24.2%)	9 (9%)	<0.001[b]
Neonatal hypoglycemia	6 (5%)	0 (0%)	0.033[c]
Transient tachypnea of the newborn	19 (15.8%)	4 (4%)	0.004[c]
Respiratory distress syndrome	15 (12.5%)	1 (1%)	0.001[c]
Continues positive airway pressure	22 (18.3%)	6 (6%)	0.006[b]
Mechanical ventilation	12 (10%)	1 (1%)	0.004[c]
Phototherapy for neonates	6 (5%)	3 (3%)	0.515[c]

[a]: Student T test, [b]: Pearson chi-square, [c]: Fisher's exact test, Pre-GDM: Pregestational diabetes mellitus, DR-GDM: Diet regulated gestational diabetes mellitus, IR-GDM: Insulin regulated gestational diabetes mellitus, IVC: Inferior vena cava, Ao: Aorta, NICU: Neonatal intensive care unit, A p-value of <0.05 indicates a significant difference and statistically significant p-values are in bold

Table 4. Comparison of Doppler measurements of groups with and without composite adverse perinatal outcomes in DM

	With CAPO n=51 (23.1%)	Without CAPO n=169 (76.9%)	p-value
IVC diameter (mm)	0.81±0.19	0.83±0.17	0.504[a]
IVC diameter (z score)	-0.27±1.19	-0.39±1.1	0.473[a]
Aortic diameter (mm)	4.69±0.87	4.69±0.75	0.986[a]
Aortic diameter (z score)	-1.28±1.32	-1.65±1.2	0.066[a]
IVC/Ao index (mm)	3.76±0.93	3.85±0.82	0.510[a]
IVC/Ao index (z score)	0.61±2.23	0.20±4.47	0.526[a]

[a]: Student T test, IVC: Inferior vena cava, Ao: Aorta, CAPO: Composite adverse perinatal outcomes, APGAR 5 min <7, need for mechanical ventilation, need for continued positive airway pressure, respiratory distress syndrome, transient tachypnea of the newborn and neonatal intensive care unit admission and neonatal low cord blood pH, data are expressed as mean±standard deivation or median (inter quartile range) where appropriate

The evaluation of the IVC/Ao index, IVC and aortic diameter (mm, Z-score) in the diabetes and control groups using the ROC analysis is shown in Table 5. The value of the IVC/Ao index (Z-score) (AUC: 0.590, cut-off: <0.28 p=0.022) shows limited significance for the diagnosis of DM. The IVC diameter (mm) cut-off value was found to be >3.81, which led to a 60% sensitivity and a 60.8% specificity (AUC: 0.674, p<0.001). With a sensitivity of 61.7% and a specificity of 64% (AUC: 0.679, p<0.001), the determined cut-off value for IVC diameter (Z-score) was >-0.35. The Ao diameter (mm) cut-off value was >4.63, which produced a 62.5% sensitivity and a 58% specificity (AUC: 0.623, p=0.002). With a sensitivity of 60% and a specificity of 59% (AUC: 0.632, p<0.001), the computed cut-off value for Ao diameter (Z-score) was >-1.64 (Figure 3).

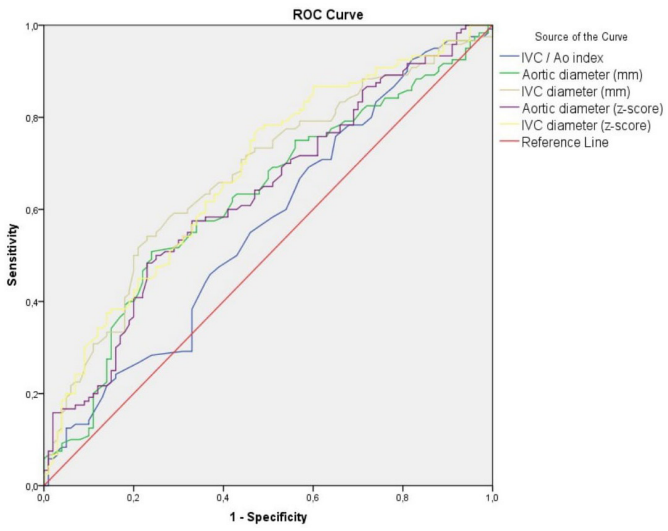

Figure 3. ROC analysis of IVC/Ao index, IVC and aortic diameter (mm, Z-score) by ROC analysis in diabetes and control groups

ROC: Receiver operating characteristic, IVC: Inferior vena cava

Table 5. Evaluation of IVC/Ao index, IVC and aortic diameter (mm, Z-score) in diabetes and control groups by ROC analysis

	LR+	LR-	Cut-off*	Sensitivity	Specificity	AUC	95% CI	p-value
IVC/Ao index (Z-score)	1.32	0.77	<0.28	55%	58.3%	0.590	0.515-0.665	0.022
IVC diameter (mm)	1.88	0.59	>3.81	60%	60.8%	0.674	0.60-0.75	<0.001
IVC diameter (z score)	1.71	0.60	>-0.35	61.7%	64%	0.679	0.61-0.75	<0.001
Aortic diameter (mm)	1.49	0.65	>4.63	62.5%	58%	0.623	0.55-0.70	0.002
Aortic diameter (z score)	1.46	0.68	>-1.64	60%	59%	0.632	0.56-0.71	0.001

*Cut-off values were found according to Youden Index. IVC: Inferior vena cava, ROC: Receiver operating characteristic, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, AUC: Area under the curve, CI: Confidence interval, Ao: Aorta

The comparison of IVC and aortic diameter (Z-score) of the DM-diagnosed group and the control group by week of gestation is shown in Table 6. There were 29 patients diagnosed with DM at 32 weeks' gestation and 14 control patients. Before 32 weeks, the IVC diameter (Z-score) of the DM group was 0.02±1.25, while that of the control group was -0.25±0.99. There was no noticeable difference between the two groups (p=0.480). Between 32 and 37 weeks, 72 individuals were diagnosed with diabetes mellitus, while 73 patients served as controls. Between 32 and 37 weeks, the DM group's IVC diameter (Z-score) was -0.01±0.95, while the control group's was -0.75±1.06; the two groups' differences were statistically significant (p<0.001). Thirteen patients in the control group and 19 in the DM group were older than 37 weeks. There was a significant difference between the two groups (p=0.026), with the IVC diameter (Z-score) in the DM patients after 37 weeks being -0.30±1.24 and in the control group being -1.27±1. There was no significant difference between the two groups (p=0.114), with the Ao diameter (Z-score) in the DM patients under 32 weeks being -0.86±1.29 and in the control group being -1.46±0.69. Between 32 and 37 weeks, the DM group's Ao diameter (Z-score) was -1.31±1.17, whereas the control group's was -1.89±1.22. The two groups' differences were statistically significant (p=0.004). The DM group's Ao diameter (Z-score) was -1.8±1.02 over 37 weeks, whereas the control group's was -2.37±1.3. There was no significant difference between the two groups (p=0.172).

Table 6. Comparison of IVC and aortic diameter (Z-score) of the group diagnosed with pre-GDM or GDM and the control group according to gestational week

		Diagnosed with pre-GDM or GDM n=120 (54.5%)		Control n=100 (45.5%)		
		z score	n	z score	n	p-value
IVC diameter (z score)	<32 week	0.02±1.25	29	-0.25±0.99	14	0.480[a]
	32-37 week	-0.01±0.95	72	-0.75±1.06	73	<0.001[a]
	>37 week	-0.30±1.24	19	-1.27±1	13	0.026[a]
Aortic diameter (z score)	<32 week	-0.86±1.29	29	-1.46±0.69	14	0.114[a]
	32-37 week	-1.31±1.17	72	-1.89±1.22	73	0.004[a]
	>37 week	-1.8±1.02	19	-2.37±1.3	13	0.172[a]

[a]: Student T test, pre-GDM: Pregestational diabetes mellitus, IVC: Inferior vena cava, GDM: Gestational diabetes mellitus

DISCUSSION

This study demonstrated that the IVC and Ao diameters are impacted by gestational diabetes. The DM group had higher IVC diameter (mm, Z-score) and Ao diameter (mm, Z-score) than the control group, but the IVC/Ao index (Z-score) was lower. The IVC diameter was the most important parameter in the DM patients compared to the control patients. The determined cut-off value for IVC diameter (mm) was >3.81 and resulted in a sensitivity of 60% and a specificity of 60.8% (AUC: 0.674, p<0.001). The identified cut-off value for IVC diameter (Z-score) was >-0.35, which corresponds to a sensitivity of 61.7% and a specificity of 64% (AUC: 0.679, p<0.001). No correlation was found between IVC diameter (mm, Z-score), Ao diameter (mm, Z-score) and IVC/Ao index and CAPO. To our knowledge, our study is the first to investigate the effects of changes in IVC and aortic wall diameter on maternal and fetal circulation in diabetic pregnancies.

The first known study on fetal aortic diameter was conducted by Tonge et al.[18] This study showed that the aortic diameter increased with the increase in fetal blood volume over the course of the gestational week. Following a stillbirth, Szpinda et al.[19] carried out an autopsy investigation to provide reference values for the descending aorta's diameters at various weeks of gestation. This study showed that the fetal gender had no influence on the assessment of the aortic diameter, the aortic thickness was similar in both sexes and the aortic thickness increased with gestational week. Skilton et al.[20] compared aortic thickness in patient groups. This study was based on the measurement of aortic wall thickness by ultrasound in 25 FGR newborns and 25 normal birth weight infants. Maximum aortic diameter was significantly higher in infants with FGR (810 µm) than in infants without FGR (743 µm, p=0.02), and a significant increase in aortic diameter was observed in neonates with FGR. This suggests that prenatal events may favor a later cardiovascular risk. Aortic diameter was also considerably greater in FGR patients than in control patients, according to Cosmi et al.'s[21] research of FGR patients. This difference was observed both intrauterine (1.9 mm vs. 1.15 mm; p<0.001) and postnatally (2.4 mm vs. 1.03 mm; p<0.001). The IVC transports venous blood to the right atrium of the heart from the abdominal cavity and lower limbs.[22] According to Çilingir et al.[23] the IVC width was smaller in FGR patients than in control patients and varied with gestational age. The reason for this was attributed to decreased blood flow from the placenta, kidneys, lower extremities and peripheral organs such as the pelvis. They argued that the thickness of the IVC changes with the relative influence of blood flow to the IVC. The IVC/Ao-index was used for the first time in 2014 for the assessment of vascular fluid and is a non-invasive, objective assessment method.[14] The change in IVC/Ao index with intravascular volume in healthy volunteers was investigated by Bilgin et al.[24] In this study, changes in IVC/Ao index and IVC diameter due to blood loss were observed. In this investigation, the highest IVC diameter was 17.3±0.3 mm, and after 500 ml of blood loss, a 6% change was noted. Denizli et al.[13] used this index to assess the thickness change that may occur in FGR patients with endothelial dysfunction. The IVC/Ao index was comparable in both groups, despite the fact that the IVC and aortic diameter values were substantially lower in FGR patients than in the control group. IVC/Ao (Z-score), Ao diameter, and IVC diameter were all greater in our study than in the control group. Nevertheless, CAPO was not linked to these factors. Increased IVC and aortic diameters in diabetic pregnancies could be related to vascular adaptations and endothelial dysfunction. Fetal and maternal hyperglycemia triggers oxidative stress and inflammatory processes that can lead to changes in vessel wall thickness. The IVC diameter in particular is the most important parameter in diabetic pregnant women. Although long-term vascular complications develop in DM patients due to inflammation and endothelial dysfunction, these are not present in every patient. The ability to measure vessel wall thickness in fetuses using a non-invasive technique such as ultrasound may be an early sign of

atherosclerosis. This could be an important step in predicting the long-term effects after birth. Larger studies are needed for CAPO and long-term complications.

Maternal and fetal hyperglycemia causes hemodynamic changes in DM patients through vascular changes and high oxidative stress effects.[25] As a result, the uteroplacental blood flow may decrease. A brain-protective effect occurs when prenatal adaptation redirects blood flow from the peripheral to the brain rather than the internal organs. The development of the brain-protective effect can manifest itself in a decrease in MCA S/D, PI and an increase in UA S/D, PI. Doppler ultrasonography measures can be used to identify these hemodynamic alterations.[26] Rane et al.[27] analyzed a total of 10 prospective and 5 retrospective studies in a review. The predictive accuracy of Doppler ultrasonography data in forecasting adverse perinatal outcomes in DM pregnancies was examined in this study. UA Doppler measurements showed significant prognostic value for neonatal hypoglycemia, hyperbilluribinemia, NICU admission, RDS, and preterm labor. In their investigation of 138 GDM patients, Leung et al.[28] discovered no association between CAPO and UA and MCA Doppler measures, despite the fact that the CAPO rate was 27.5%. This situation shows that Doppler parameters will not play a role in every patient diagnosed with DM. Similarly, another meta-analysis that examined 151 publications found that pregnancies with diabetes had significantly greater UtA PI and S/D ratios than pregnancies without diabetes, but that there was no difference in UA PI, UA S/D ratio, MCA PI, and MCA S/D ratio.[26] The control and DM groups in our study had comparable values for UA PI, S/D, UtA PI, UtA S/D, MCA PI, MCA S/D, and MCA PSV. In pregnant women diagnosed with DM, the rates of cesarean section, need for MV, TTN, RDS, need for CPAP, neonatal hypoglycemia, NICU admission, and preterm delivery were significantly higher in the DM group than in the control group. However, no correlation was found between CAPO and these Doppler parameters.

Limitations

There are limitations on the study. The results' generalizability may be limited by the fact that it was only carried out at one location. In addition, the low prognostic value of the IVC/Ao index suggests that this parameter alone is not a sufficient tool. To validate these findings, larger patient groups and various centers should be the focus of future research. It is also advised to conduct research on how alterations in IVC and aortic diameter affect long-term perinatal outcomes.

The fact that this study was carried out in a broad patient group using a prospective strategy is one of its main advantages. The opportunity to examine the distinctions between pregestational and gestational diabetes was given by four distinct groups, which included individuals with both illnesses.

CONCLUSION

The present study examined the predictive power of alterations in IVC, aortic diameter, and Caval-Aortic Index in perinatal outcomes in pregnancies complicated by diabetes. Our results showed significant differences in IVC and aortic diameter between diabetic and non-diabetic pregnancies, suggesting that these parameters reflect the effects of diabetes on maternal and fetal circulation. However, the limited prognostic value of the Caval-Aortic Index shows that this parameter alone is not sufficient for risk assessment. Although an increased IVC and aortic diameter was observed in diabetic pregnancies, no direct correlation between these changes and an adverse perinatal outcome could be established. However, integrating these parameters into a comprehensive risk assessment model can provide additional information on maternal and fetal health. In conclusion, this study highlights the impact of gestational and pregestational diabetes on ultrasonographic vascular parameters, suggesting potential vascular adaptations during pregnancy. Given the long-term cardiovascular risks associated with diabetes, future research should focus on postnatal follow-up studies assessing both maternal and neonatal vascular health. A longitudinal approach may provide deeper insights into the implications of these vascular changes beyond the perinatal period.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara Etlik City Hospital Clinical Researches Ethics Committee (Date: 18.10.2023, Decision No: AESH-EK1-2023-621).

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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The hidden impact: frailty and malnutrition in patients with diabetic foot ulcers

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ABSTRACT

Aims: Diabetic foot ulcers (DFUs) are a significant complication affecting over 30% of individuals with diabetes, leading to increased morbidity and mortality. This study investigates the relationships between frailty, nutritional status, and quality of life in patients aged 50 and older diagnosed with DFUs.

Methods: A total of 100 participants with DFUs were prospectively included in the study, with assessments conducted using the Edmonton Frailty Scale and the Mini Nutritional Assessment Scale. Quality of life was evaluated using the EQ-5D-3L scale. Demographic data, concomitant diseases, medications, HbA1c levels, and participants' height, weight, and circumferences of the upper arm, calf, and waist were recorded. The data analysis was performed using statistical software.

Results: The findings revealed that 50% of patients exhibited varying degrees of frailty, and 85% were at risk of malnutrition. Both frailty and malnutrition were associated with a significant decline in quality of life. Notably, patients with normal nutritional status reported higher quality of life scores compared to those at risk of malnutrition or malnourishment.

Conclusion: This study underscores the need for a holistic approach to managing DFUs that integrates frailty and nutritional status assessments. Targeted interventions addressing these factors are essential for improving health outcomes and enhancing the quality of life for individuals living with diabetes. The findings advocate a shift from a narrow focus on wound management to a broader, more comprehensive care strategy.

Keywords: Diabetic foot ulcers, frailty, nutrition, quality of life

INTRODUCTION

The prevalence of diabetes worldwide is increasing, especially among the elderly, due to longer life expectancies.[1] Frailty is an increasingly significant complication of diabetes in older adults. It refers to a state of diminished physiological reserve, which heightens an individual's vulnerability to negative health outcomes, including an increased mortality risk. Frailty is characterized as a multidimensional condition that enhances vulnerability in older individuals, leading to a decline in health status reduced resilience, and increased functional impairment.[2,3] This condition is associated with various physical changes, including reduced bone density, muscle weakness, low blood pressure, impaired vision, and problems with joints and hearing.[3,4] The recognition of frailty is increasingly emphasized in diabetes management guidelines for older adults. These recommendations often lack specificity and fail to consider the varying levels of frailty and other factors that impact clinical outcomes.[5]

Diabetic foot ulcers (DFUs) affect more than 30% of individuals with diabetes at some point in their lives. The global healthcare burden associated with DFUs is expected to rise significantly in the coming years. This increase is primarily due to the growing prevalence of DFUs, which is occurring alongside an aging population that is more vulnerable to both foot ulcers and other types of diabetic foot complications.[6] Individuals with DFUs have a higher risk of mortality compared to those with diabetes who do not have DFUs. This connection between DFUs and increased mortality cannot be explained by other major diabetes complications that also raise the risk of death.[7] The relationship between DFUs and frailty is significant, as frailty has been identified as an independent risk factor for poor healing outcomes and increased re-hospitalization rates in patients with DFUs.[8] It is also possible that a DFU is a marker of increased medical frailty, necessitating increased healthcare provider vigilance in the care of the patient.[7]

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Nutritional status significantly contributes to frailty, making it a modifiable risk factor. Studies indicate that dietary changes can play a crucial role in preventing and treating frailty.[9,10] Patients with DFUs often have poor nutritional status, which is associated with an impaired healing process. These patients require comprehensive care from a multidisciplinary team to optimize wound healing. However, one crucial aspect often overlooked is their nutritional status.[11] Research has shown that nutrition deficiencies are linked to an increased risk of amputation[12] and mortality[13] in patients with DFUs.

A recent literature review indicates that DFUs significantly impact patients' physical and mental health-related quality of life. Patients with DFU exhibit a more pronounced decline in quality of life across multiple domains, including social, psychological, physical, and economic aspects.[14] As a result of reduced mobility and associated lifestyle modifications, there is a further deterioration in the quality of life in these patients. The impact of DFUs on quality of life is so significant that patients with diabetic foot amputations who can mobilize have a higher quality of life than patients with DFUs.[15] Quality of life is a crucial indicator of active aging, significantly affecting life expectancy and mortality rates among older populations. The quality of life for older adults can be greatly affected by factors such as frailty and nutritional status.[16]

A holistic approach to diabetic foot management can help reduce the risk of complications. Although numerous studies have focused on individuals with diabetes, research examining the connection between frailty, nutritional status, and quality of life in patients with diabetic foot complications is still limited. This study investigates frailty, nutritional status, and quality of life in patients with DFUs. By addressing these factors through targeted interventions, the study seeks to provide recommendations to improve health outcomes and promote overall well-being for individuals with diabetes.

METHODS

Ethics and Study Desing

Patients with DFUs admitted to our outpatient clinic were consecutively and prospectively included in this study between February 2023 and May 2024. The research was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Kayseri Clinical Researches Ethics Committee (Date: 31.01.2023, Decision No: 794). Informed consent was obtained from each participant. A total of one hundred individuals aged 50 years and older who were diagnosed with DFUs and agreed to participate by signing the consent form were included in the study. Patients who did not cooperate were excluded from the study.

A questionnaire was administered using a face-to-face interview method to all participants. Demographic data, concomitant diseases, and medications used were noted in the questionnaire form. Glycosylated hemoglobin A1c (HbA1c) was recorded from patient files. The same investigator measured all participants' height, weight, upper arm, calf circumference, and waist circumference and recorded these measurements.

Frailty

The Edmonton Frailty Scale, developed by Rolfson et al.,[17] assesses frailty in patients. Aygör[18] validated and ensured its reliability in Turkiye. The scale consists of 11 questions and is evaluated on a 0-20 point scale. If the score obtained from the scale is in the range of 0-4, the elderly individual is not frail; 5-6 is visibly vulnerable; 7-8 is mildly frail; 9-10 is moderately frail, and 11 points and above is considered severely frail. This scale assesses frailty in older adults, including those with various health conditions, such as foot disorders. One study specifically aimed to evaluate the Edmonton Frailty Scale's validity, reliability, and sensitivity in predicting frailty outcomes in elderly patients with foot disabilities, which include conditions like diabetic foot syndrome.[19]

Assessment of Nutrition Statement

We utilized the mini nutritional assessment (MNA) scale to evaluate the nutritional status of participants. This scale is recommended by the European Society of Clinical Nutrition and Metabolism, the International Association of Gerontology and Geriatrics, and the International Academy of Nutrition and Aging. The MNA was first applied to patients in 1994 and consists of four sections with a total of 18 questions.[20]

The sections include;

Anthropometric assessment: This evaluates body mass index (BMI), weight, and arm and calf circumference measurements.

General assessment: This covers lifestyle factors, the number of medications taken, mobility, and symptoms of depression and dementia.

Short nutritional assessment: This focuses on meal frequency, food and fluid intake, and autonomy in nutrition.

Subjective assessment: This gathers information on individuals' self-perception of health and nutrition.

These assessments were conducted with the participants at the start of the study. The MNA scale was selected for nutritional evaluation due to its extensive validation as a reliable tool for assessing malnutrition across various populations, including older adults and individuals with chronic conditions.[20] MNA scores below 17 points indicate malnutrition, between 17 and 23.5 points indicate malnutrition risk, and ≥24 points indicate no malnutrition risk.

Quality of Life

The patients' quality of life was assessed with the EQ-5D 3L version of the general Quality of Life Scale (QOLS). The EQ-5D-3L QOLS is a general health scale. It consists of two parts. The EQ-5D-3L index score consists of 5 dimensions: movement, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients also assessed their health on the EQ Visual Analog Scale (EQ-VAS). 100 mm indicates "the best imaginable health state," and 0 mm indicates "the worst imaginable health state".[21]

Statistical Analysis

The data collected in the study were analyzed using the IBM SPSS version 25 software package (SPSS Inc, Chicago, IL, USA). In descriptive statistics, continuous data were

presented as mean, standard deviation, median, minimum, and maximum values, and categorical data were presented as number and percentage values.

The chi-square test was used for statistical comparison of categorical data. Kolmogorov-Smirnov analysis evaluated normal distribution for continuous data, and one-way ANOVA and Kruskal Wallis tests were used to compare groups. Post hoc analysis of significance between frailty groups was performed using one-way ANOVA and Tamhane's T2 test. After the Kruskal-Wallis test, Bonferroni correction and Mann-Whitney U test were used. A p-value less than 0.05 was considered statistically significant at a 95% confidence interval. In chi-square post hoc analysis, significance was determined with Bonferroni correction for values less than 0.01 for the subgroups of the Frailty Scale and less than 0.017 for the Mini Nutrition Scale, and adjusted p values were used in other post hoc evaluations. The statistical tests used to create the tables are indicated as footnotes.

RESULTS

A total of 100 patients were included in the study. The mean age of the study participants was 66.75±7.14 years. It was found that 27.0% of the individuals in the sample were female, 91.0% of these individuals were married, 64.0% were primary school graduates, and 85.0% had income equal to expenses (**Table 1**).

The mean value of the Edmonton Frailty Scale was 6.35±3.04. It was also found that 8.0% of the individuals were severely frail, 22.0% were mildly frail, and 20.0% were moderately frail (**Table 1**).

Patients were categorized into five classes based on the Edmonton Frailty Scale. No significant differences were found between the demographic data and clinical characteristics (**Table 2**).

Our study also evaluated the EQ-5D-3L general QOLS. According to the scale, an increase in value indicates a decrease in quality; it was observed that quality of life decreased with increasing frailty. In addition, it was found that on a scale of 0-100, where patients rated their health status, the value rated by the patients decreased significantly with increasing frailty (**Table 3**).

The mean, median values, and distribution of the patients according to the Mini Nutrition Scale are given in **Table 3**.

According to the frailty score, 15 of the non-frail patients, 18 of the visibly vulnerable patients, 19 of the mildly frail patients, 15 of the moderately frail patients and 7 of the severely frail patients were at risk of malnutrition. It was determined that the mean value of the total assessment score decreased from the non-frail group to the severely frail group, while the patients were predisposed to malnutrition, with a significant difference between the groups (**Table 4**).

When the patients were classified according to the Mini Nutrition Score, a decrease in the general QOLS score from Normal Nutrition to Malnutrition, i.e., a decrease in the general quality of life, was determined (**Table 5**).

DISCUSSION

This study found that 50% of patients with diabetic foot disease aged 50 and over in our outpatient clinic exhibited varying degrees of frailty. Moreover, 25% of these patients were identified as vulnerable and at risk of developing frailty. Additionally, 85% were malnourished, and these results were associated with decreased quality of life. Wound healing in diabetic foot patients is associated with the patient's frailty,[8] nutritional status,[11] and quality of life.[22] The results of this study highlight the need for new strategies to improve the care of patients with DFUs. These strategies could encourage a shift from a limited focus on wound management to a broader, more holistic approach to patient care.

Diabetes is a complex condition that affects multiple body systems, including the vascular, neurological, and immune systems. A holistic approach to the management of diabetes involves an examination of the interactions between these systems and their contribution to diabetic foot complications.[23] This approach requires a comprehensive assessment of the individual's medical history, nutritional status, physical activity, and psychosocial factors in order to identify risk factors and enable individualized interventions.[24]

Few studies have investigated frailty in patients with DFUs, and the high frailty rate observed in this study aligns with the findings of those studies.[3,6,8] Frailty is a key predictor of clinical outcomes, and early detection can help slow functional decline. However, screening for frailty is often inadequate due to the lack of a universally accepted definition. Frailty indicates extreme vulnerability to low-intensity stressors, resulting from challenges in maintaining homeostasis and a loss of functional reserve. It represents a multisystem dysregulation and a pre-disability state marked by declining health and loss of independence. Additionally, frailty can be identified early through recognition of a pre-frailty state.[25] Frailty in patients with DFUs occurs at a younger age and is associated with impaired wound healing.[8] It is crucial to recognize frailty and identify individuals who are at risk. Health promotion, proper nutrition, social engagement, and light physical activity are effective strategies for preventing frailty.[26]

Our study, as well as other studies,[11,27-33] shows that malnutrition is very common in patients with DFU, but this is often overlooked.[11,27] Nutrient deficiencies are among the major risk factors in DFU development and healing. Nutrient deficiencies modify the physiological responses to infection by diminishing the immune response, predisposing the skin to become thin and flaky, thereby increasing the likelihood of developing a wound. The deficiencies also decrease subcutaneous fat at pressure points, exacerbating the vulnerability to pressure wounds. Nutrient deficiencies also reduce the collagen synthesis required for wound healing and promote immobility due to diminished energy reserves. Malnutrition adversely affects the complex wound-healing process.[27] In our study, 11% of patients were malnourished, and 74% were at risk of malnutrition. This result is similar to the proportions at risk of malnutrition (49% to 70%) or malnourished (15% to 62%) found in randomized controlled trials.[28] Dietary recommendations for patients

Table 1. Comparison of the stratification of frailty score categories and demographic data

Variable	No frailty group 1 n: 25	Visibly vulnerable group 2 n: 25	Mild frailty group 3 n: 22	Moderate frailty group 4 n: 20	Severe frailty group 5 n:8	p
Age (mean±SD)	66.40±5.38	66.12±6.01	65.73±7.59	64.88±6.92	64.88±6.92	0.084[a]
HbA1c (%) (mean±SD)	8.53±1.95	9.08±2.23	8.08±2.15	8.59±1.72	9.88±2.69	0.249[a]
Duration of diabetes (years) median (min-max)	18 (1-30)	18 (1-35)	14 (1-40)	20 (1-30)	21 (10-30)	0.485[b]
Gender (male), n	21	17	18	13	4	0.243[b]
Wagner grade, n						
2	14	7	6	8	0	0.090[b]
3	9	13	14	11	8	
4	2	5	2	1	0	
Marital status (married), n	24	22	20	18	7	0.883[b]
Health insurance, n						
Pension fund	4	8	4	4	1	0.749[b]
SSK	18	11	12	11	4	
Self-employed	3	4	3	4	3	
No insurance	0	2	3	1	0	
Education status, n						
Illiterate	1	2	0	5	1	0.195[b]
Primary school	11	15	17	14	7	
Secondary school	5	5	2	0	0	
High school	8	2	2	1	0	
License	0	1	1	0	0	
Occupation, n						
Housewife	3	7	4	7	4	0.125[b]
Retired	16	15	16	12	3	
Officer	2	2	0	1	0	
Self-employment	3	0	1	0	0	
Worker	1	1	0	0	1	
Other	0	0	1	0	0	
Income level, n						
Less than expenses	1	3	0	3	1	0.668[b]
Equals expenses	24	21	22	13	5	
More than expenses	0	1	0	4	2	
Occupation, n						
Working	0	1	0	0	0	0.109[b]
Not working	2	2	2	0	1	
Retired	20	17	16	12	3	
Housewife	3	5	4	8	4	
Living situation, n						
Alone	1	1	3	1	1	0.790[b]
Wife and children	8	10	4	4	2	
Wife	13	12	11	13	5	
Family	2	1	4	0	0	
With relatives	0	1	0	1	0	
Children	1	0	0	1	0	
Alcohol intake, n (yes)	1	1	0	0	1	0.418[b]
Smoking, n (yes)	3	5	6	3	0	0419[b]
Insulin therapy, n (yes)	18	21	18	19	8	0.198[b]

[a]One way ANOVA test (Tamhane's T2 test), [b]Kruskal Wallis test, [c]Mann-Whitney U test, p<0.01, was considered significant. There is a significant difference between group 1 and group 3, between group 1 and group 4, between group 1 and group 5, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 2. EQ-5D-3L General Quality of Life Scale and comparison results with frailty groups

Variable	No frailty group 1	Visibly vulnerable group 2	Mild frailty group 3	Moderate frailty group 4	Severe frailty group 5	p
EQ-5D-3L total[b] (median, min-max)	8 (5-15)	9 (6-11)	9 (5-14)	12 (9-15)	13 (8-14)	<0.001[a]
Current health status (%)[c] (median, min-max)	70 (15-100)	60 (40-100)	50 (0-90)	50 (5-80)	45 (0-70)	<0.001[a]

[a]Kruskal Wallis test, [b]Mann-Whitney U test, p<0.01 was considered significant. There is a significant difference between group 1 and group 2, group 1 and group 3, group 1 and group 4, and group 1 and group 5. There is a significant difference between group 2 and group 4; between group 2 and group 5. There is a significant difference between group 3 and group 4. [c]Mann Whitney U test, p<0.01, was considered significant. There is a significant difference between group 1 and group 4 and between group 1 and group 5. There is a significant difference between group 2 and group 4, Min: Minimum, Max: Maximum

Table 3. Mini Nutrition Assessment Scale evaluation results

Variable	Mean±SD	Median	Min-max
Evaluation		11.50	8.0-15.0
Screening score		9.0	4.0-14.0
Total evaluation	20.57±3.35		12.0-28.0

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

with DFUs should prioritize proper wound healing through the consumption of adequate energy sources and essential nutrients.[29] Nutritional supplementation with antioxidants,[30] other essential micronutrients,[31] and proteins, along with nutritional education,[32] may accelerate the wound healing process in patients with DFUs. National and international guidelines for wound healing are lacking, leading to the recent publication of an expert consensus and guidelines for nutritional interventions in adults with DFUs.[33]

Our study found a significant link between malnutrition and frailty in patients with DFU, both of which contribute to a reduced quality of life. Patients with DFUs often report a poor quality of life, which can deteriorate further if the ulcer recurs or fails to heal. Several factors influence this quality of life, including older age, weight, educational background, foot self-care practices, and the presence of peripheral neuropathy.[34] Frailty correlates with disability, lower quality of life, and cognitive impairment, with studies reporting a strong association in those examining these outcomes.[35] Pre-frailty and frailty are associated with increased risks of mortality and cardiovascular events, leading to higher healthcare utilization in patients with type 2 diabetes mellitus.[36] Reducing frailty can enhance the quality of life.[37] Frailty is a considerable concern for the aging population, and dietary nutrition is considered a key factor in preventing frailty.[38,39] Malnutrition in patients with diabetic foot conditions is linked to various factors. First, patients with higher grades of foot complications are at a greater risk of malnutrition compared to those with lower grades. This increased risk is due to the higher protein demands and susceptibility to malnutrition, that comes with more severe conditions. Additionally, wounds are linked to malnutrition because they trigger active inflammatory responses, raising metabolic rates and increasing protein breakdown. Strict dietary restrictions for glycemic control may also result in insufficient nutrient intake.[40] Nutritional interventions for patients with DFU may enhance wound healing, reduce frailty, and improve overall quality of life.[9,10,31,35,36,41]

Wound care, infection control, off-loading, glycemic control, vascular assessment, advanced therapies, and patient education are the primary treatments commonly discussed for DFUs.[42] In recent years, the individualization of treatment for DFUs has become an essential topic of discussion.[43] In this context, alongside the main treatments, it is necessary to consider factors such as frailty and nutrition when individualizing treatment plans, according to the current study's findings.

Table 4. Distribution of malnutrition and mean scores of participants

Variable	No frailty group 1	Visibly vulnerable group 2	Mild frailty group 3	Moderate frailty group 4	Severe frailty group 5	Total, n
Malnutrition score						
Normal nutrition (24-30 points)	9	4	1	1	0	15
Malnutrition risk sub. (17-23.5 points)	15	18	19	15	7	74
Malnutrition (<17 points)	1	3	2	4	1	11
Total evaluation (mean±SD)	22.74±3.15	20.94±3.15	19.73±2.53	19.33±3.48	18.06±2.67	p<0.001[a]

[a]Kruskal Wallis test, [b]Mann Whitney U test, p<0.01 was considered significant. It was observed that there was a difference between group 1 and group 3 in favor of group 1 and group 1 and group 5 in favor of group 1. SD: Standard deviation

Table 5. Association between Mini Nutrition Scale score and overall quality of life

Variable	Mini nutrition score categories, median (min-max)			
Overall quality of life	**Normal nutrition**	**At risk of malnutrition**	**Malnutrition**	**p**
Total score (points)	8 (5-10)	9 (5-14)	10 (6-15)	0.009[a]
Health status level today %	70 (40-100)	50 (0-100)	50 (0-90)	0.003[a]

[a]Kruskal Wallis test, [b]Mann Whitney U test, p<0.017 was considered significant. It was observed that there was a difference between normal nutrition and at risk of malnutrition in favor of at risk of malnutrition and between normal nutrition and malnutrition in favor of Malnutrition. [c]Mann Whitney U test, p<0.017 was considered significant. It was observed that there was a difference between normal nutrition and at risk of malnutrition in favor of at risk of malnutrition and between normal nutrition and malnutrition in favor of malnutrition, Min: Minimum, Max: Maximum

Limitations

The study has several limitations that should be acknowledged. Firstly, the sample size of 100 participants may limit the generalizability of the findings to a broader population of DFU patients. The cross-sectional design restricts the ability to establish causal relationships between frailty, nutritional status, and quality of life. Furthermore, reliance on self-reported measures for assessing quality of life and nutritional status may introduce bias, and the lack of an intervention component limits the evaluation of specific management strategies.

CONCLUSION

In conclusion, this study highlights the critical interrelationship between frailty, nutritional status, and quality of life in patients with DFUs. The findings indicate that a significant proportion of older adults with DFUs exhibit varying degrees of frailty and malnutrition, both of which adversely affect their overall quality of life. As frailty emerges as a key predictor of clinical outcomes, healthcare providers need to adopt a holistic approach to DFU management that encompasses not only wound care but also the assessment and improvement of nutritional status. The evidence presented underscores the necessity for targeted interventions that address the multifaceted needs of patients with DFUs. By integrating nutritional support and frailty assessment into routine care, healthcare professionals can enhance healing outcomes and improve the quality of life for these vulnerable individuals. Future research should focus on developing and implementing comprehensive care strategies that prioritize the prevention and management of frailty and malnutrition in diabetic patients, ultimately contributing to better health outcomes and a reduction in the burden of diabetic foot complications.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kayseri Clinical Researches Ethics Committee (Date: 31.01.2023, Decision No: 794).

Informed Consent

All patients signed a free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

All 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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Prognostic importance of the pan-immune-inflammation value and potential serological biomarkers of complicated peritonsillar abscesses

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ABSTRACT

Aims: A peritonsillar abscess (PTA) is the most common deep infection of the head and neck and can sometimes be associated with life-threatening complications. Clinical symptoms in patients with a complicated peritonsillar abscess (CPTA) may not always reflect the severity of this disease. Therefore, monitoring these patients with inexpensive and easily accessible hematological parameters is essential. Recently, certain inflammatory monitoring markers have gained acceptance. In this study, we aimed to determine the role of the pan-immune-inflammation value (PIV) in patients with a PTA at a high risk of complications.

Methods: Patients aged 18 years and older who were diagnosed with a PTA and hospitalized in our clinic between October 10, 2022, and October 1, 2024 were retrospectively analyzed. The patients were divided into the CPTA group and the uncomplicated peritonsillar abscess (UPTA) group. Demographic characteristics, laboratory findings, and complications observed in the emergency department were evaluated.

Results: A total of 104 patients were included in the study, with 71 in the UPTA group and 33 in the CPTA group. PIV values were significantly higher in the CPTA group compared to the UPTA group. The diagnostic value of PIV in predicting PTA-related complications was assessed using receiver operating characteristic curve analysis. A PIV cutoff value of 989.6 (AUC: 0.838; 95% confidence interval: 0.753-0.903) demonstrated a sensitivity of 72.7% and a specificity of 85.9%, indicating superior predictive power for PTA-related complications compared to NLR, MLR, and SII.

Conclusion: Our findings suggest that the PIV is a rapid, simple, and reliable marker for predicting the severity of PTAs and potential complications.

Keywords: Complication, emergency department, pan-immune-inflammation value, peritonsillar abscess

INTRODUCTION

A peritonsillar abscess (PTA) is characterized by the accumulation of suppuration in the space between the tonsillar capsule and the superior constrictor muscles. A PTA is the most common deep infection of the head and neck observed in the emergency department (ED) and frequently occurs in young adults.[1] Delayed or inadequate treatment of severe progressive infections can lead to the spread of the infection into the deep cervical spaces of the neck, resulting in serious or life-threatening complications.[2] Therefore, complicated peritonsillar abscesses (CPTAs), which have clinical importance, most commonly affect the retropharyngeal, parapharyngeal, and peritonsillar spaces. These abscesses may lead to severe morbidity and mortality, particularly when associated with conditions such as mediastinitis, sepsis, and airway obstruction.[3]

Needle aspiration is essential for a definitive diagnosis of a PTA, while surgical drainage and antimicrobial therapy constitute the cornerstone of treatment. In patients with a PTA, who often require hospitalization, surgical intervention and tonsillectomy may also be necessary.[4] Most PTAs resolve without complications with abscess drainage and appropriate antibiotic therapy. However, as the infection spreads to deep neck spaces, surrounding tissues, or distant tissues via hematogenous dissemination, clinical deterioration occurs.[5] Early diagnosis and prompt, effective treatment of this severe infection are crucial. In patients with CPTA, the clinical presentation is highly variable, and early symptoms may not always reflect the severity of this disease.[6] Therefore, monitoring patients with a CPTA using inexpensive and easily accessible hematological parameters is necessary.

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Recently, the use of various inflammatory biomarkers derived from complete blood count parameters as prognostic indicators of severity in infections and sepsis has become increasingly common.[7-9] These biomarkers include C-reactive protein (CRP), the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), the monocyte-to-lymphocyte ratio (MLR), and the Systemic Immune-Inflammation Index (SII). Additionally, the pan-immune-inflammation value (PIV), which is calculated as the neutrophil count×platelet count×monocyte count)/lymphocyte count, is a novel inflammatory index developed to assess patients' levels of inflammation and their prognoses. The PIV can be calculated easily from routine complete blood count tests without incurring additional costs and is commonly available in most clinical laboratories. Previous studies have shown that the PIV is an accurate marker for determining the clinical severity and prognosis of various types of cancer, such as esophageal, colorectal, and breast cancers, as well as conditions such as rheumatoid disease and septic shock.[10-14] Inflammation is prominently observed in PTAs, thus resulting in changes in the PIV. Therefore, the PIV is likely to be a predictive factor for complications of PTAs. To the best of our knowledge, there have been no prior studies on the use of the PIV in the follow-up and treatment process of PTAs in adults. The utility of the PIV as a predictor for distinguishing uncomplicated peritonsillar abscesses (UPTAs) from CPTAs has yet to be clarified.

Therefore, this study aimed to evaluate whether serological biomarkers with prognostic significance, such as the NLR, PLR, MLR, SII, and PIV, which can be derived easily from a complete blood count, can be used to predict PTAs. Additionally, we aimed to assess whether the PIV, a novel serological biomarker, is a reliable predictor for CPTAs.

METHODS

Study Design and Participants

This study was conducted in the Emergency Department of Ankara Etlik City Hospital, which is a tertiary care center with an annual average of 850,000 patient visits, between October 10, 2022 and October 1, 2024. Ethical approval for the study was obtained from the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee before its commencement (Date: 06.11.2024, Decision No: AEŞH-BADEK-2024-962). The study was conducted in accordance with the Declaration of Helsinki, and the patient data collected by the researchers were kept confidential. Informed consent was not obtained because the study involved retrospectively collected data. The inclusion criteria were as follows: 1) patients older than 18 years of age who presented to the ED with a sore throat; 2) patients whose diagnosis was confirmed by an otolaryngology specialist through needle aspiration, laboratory tests, ultrasonography (US), and computed tomography (CT), and who were hospitalized for clinical treatment; and 3) patients with complete medical records available for inclusion in the study. The exclusion criteria were as follows: patients who did not accept hospitalization; patients referred from external centers; pregnant patients; patients with trauma, active infection of other sites, a history of inflammatory disease, fever of unknown origin, or active hematological or liver disease; patients diagnosed with a tumor according to pathology results; patients who have had any surgery in the last 3 months or who developed symptoms after surgery; patients without complete records; and patients diagnosed with peritonsillar cellulitis owing to the absence of pus in peritonsillar drainage.

Procedure, Data Collection, and Laboratory Analyses

In the ED, patients with medially displaced tonsils underwent US to evaluate suspected PTA and CT imaging to assess the potential spread of deep neck infections. During the consultation, the otolaryngology specialist performed a 1-cm incision using a No. 15 scalpel and aspiration with an 18-gauge needle at the most prominent area of swelling, which was located at the junction of the upper pole of the medially swollen tonsils and the base of the uvula. Patients with pus drainage were diagnosed with a PTA.

The patients were divided into the UPTA group and the CPTA group. The UPTA group comprised patients who were diagnosed with UPTA. The CPTA group consisted of patients who showed airway obstruction, tongue base abscess, para- or retropharyngeal abscess or phlegmon, mediastinitis, carditis, or sepsis, or required tracheostomy or intubation. These conditions were based on imaging obtained during their ED visit or clinical follow-up during hospitalization. Data for both groups were obtained using the hospital's electronic database. Laboratory parameters from complete blood samples taken during the patients' initial ED visits, along with neck US and CT findings, demographic data, clinical characteristics, complications, and laboratory values (white blood cell, neutrophil, monocyte, lymphocyte, and platelet counts, and CRP concentrations) were recorded. In patients with a PTA confirmed both clinically and radiographically in the ED, the PIV was calculated as an indicator of clinical outcomes. The data of patients in the CPTA group were then compared with those of patients in the UPTA group.

Routine blood samples collected from patients during ED visits were drawn into tubes containing ethylenediaminetetraacetic acid. A complete blood count analysis was performed using a XN (Sysmex, Kobe, Japan) analyzer. The following ratios and indices were calculated: the NLR, MLR, PLR, SII, (calculated as platelet count×neutrophil count/lymphocyte count),[7,8,15] and the PIV (calculated as neutrophil count×platelet count×monocyte count)/lymphocyte count).[9]

Statistical Analysis

The data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 26 (IBM SPSS Inc., Armonk, NY, USA). In the evaluation of the collected data, descriptive statistical methods (percentage calculations, median, mean, and standard deviation) were calculated. Continuous variables are expressed as the mean±standard deviation (SD) or median (minimum-maximum value) according to the normality of distribution, while categorical variables are expressed as numbers and percentages. The normal distribution of the data was evaluated using the Kolmogorov-Smirnov test. The student T test was used to compare continuous variables with a normal distribution, and the Mann-Whitney U test was used

to compare variables without a normal distribution. Pearson's chi-squared or Fisher's test was used to compare categorical variables. The diagnostic ability of the variables that were statistically significant in-group comparisons was evaluated by a receiver operating characteristic (ROC) curve analysis, and the Youden Index was used to determine the cutoff value. In the tests used, p values <0.05 were considered statistically significant.

RESULTS

During the study period, ED physicians requested a total of 4,015 emergency consultations from the otolaryngology clinic. Of these, 263 patients (15.2%) were suspected of having a PTA. A total of 159 patients were excluded from the study for the following reasons: 15 patients were referred from external centers; 45 patients had comorbidities, such as hypertension, diabetes, metabolic syndrome, coronary heart disease, thyroid dysfunction, renal or hepatic dysfunction, malignancy, a history of surgery within the past 3 months, nasal septum deviation, systemic inflammatory diseases, anemia, or chronic obstructive pulmonary disease, or they smoked, were on medications for chronic inflammation, or had other inflammatory diseases; 73 patients were diagnosed with peritonsillar cellulitis owing to the absence of pus during peritonsillar drainage; 6 patients declined admission to the otolaryngology clinic; and 20 patients had incomplete medical records or lacked imaging studies. A total of 104 patients were included in the study, with 71 in the UPTA group and 33 in the CPTA group.

The mean age of the patients was 34.4±9.7 years in the UPTA group and 34.7±11.1 years in the CPTA group. Male patients constituted 54.7% of the UPTA group and 61.6% of the CPTA group. There was no significant difference in age or sex between the groups. The demographic data and hematological parameters of the patients included in the study are shown in Table 1. The median NLR and mean MLR were significantly higher in the CPTA group than in the UPTA group [3.52 (2.61-4.19) vs. 2.45 (1.83-3.86), p=0.005; 0.39±0.19 vs. 0.68±0.36, p<0.001, respectively]. Additionally, the median SII and mean PIV values were significantly higher in the CPTA group than in the UPTA group [1011 (795-1314) vs. 705 (559-1172), p=0.004; 1201.9±401.6 vs. 695.6±380.6, p<0.001, respectively]. There was no significant difference in PLR values between the CPTA and UPTA groups (p=0.055).

In the 33 patients with complications, the most common complication observed was upper respiratory tract obstruction, which occurred in 78.8% of the patients. One patient required tracheostomy, and another required intubation. The types and frequencies of complications that developed following PTA in the study population are shown in Figure 1. A ROC curve analysis was performed to calculate the diagnostic values of the NLR, MLR, PLR, SII, and PIV in predicting complications associated with PTAs. The area under the curve (AUC) value for the NLR was 0.673 [95% confidence interval (CI): 0.574-0.761], that for the MLR was 0.776 (95% CI: 0.684-0.852), that for the PLR was 0.617 (95% CI: 0.517-0.711), that for the SII was 0.674 (95% CI: 0.575-0.763), and that for the PIV was 0.838 (95% CI: 0.753-0.903). The highest diagnostic value was found for the PIV, with an AUC of 0.838 (95% CI: 0.753-0.903), which indicated that the PIV was a stronger predictive tool than the NLR, MLR, SII, and PLR alone. The optimal cutoff values were 2.98 for the NLR (69.7% sensitivity, 67.6% specificity), 0.51 for the MLR (63.6% sensitivity, 76.0% specificity), 130.6 for the PLR (63.7% sensitivity, 60.5% specificity), 802.2 for the SII (75.7% sensitivity, 61.9% specificity), and 989.6 for the PIV (72.7% sensitivity, 85.9% specificity) (Table 2). The ROC curve of PIV evaluating CPTA is shown in Figure 2.

Table 1. Comparison of peritonsillar abscess patients with and without complications

	Peritonsillar abscess		
Variables	Complication absent (n=71)	Complication present (n=33)	p-value
Age, (years)	34.4±9.7	34.7±11.1	0.978
Male gender,	58 (54.7%)	61 (61.6%)	0.317
WBC (x10^9/L)	15.7±4.4	18.1+±2.7	0.006
Neutrophil, (x10^9/L)	6.07 (4.89-7.64)	7.01 (4.81-8.39)	0.082
Monocyte, (x10^9/L)	0.86±0.41	1.22±0.44	<0.001
Lymphocyte, (x10^9/L)	2.39±0.84	2.05±0.78	0.092
Platelet, (x10^9/L)	303.1±67.5	296.9±61.4	0.655
CRP mg/dl	134.8±91.2	168.1±57.0	0.002
NLR	2.45 (1.83-3.86)	3.52 (2.61-4.19)	0.005
MLR	0.39±0.19	0.68±0.36	<0.001
PLR	124.6 (105.2-175.8)	146.6 (118.2-199.8)	0.055
SII	705 (559-1172)	1011 (795-1314)	0.004
PIV	695.6±380.6	1201.9±401.6	<0.001

Data are presented as mean±standard deviation, median (25%-75% quartiles) or n (%), WBC: White blood cell, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic İmmune-İnflammation Index, PIV: Pan-immune-inflammation value

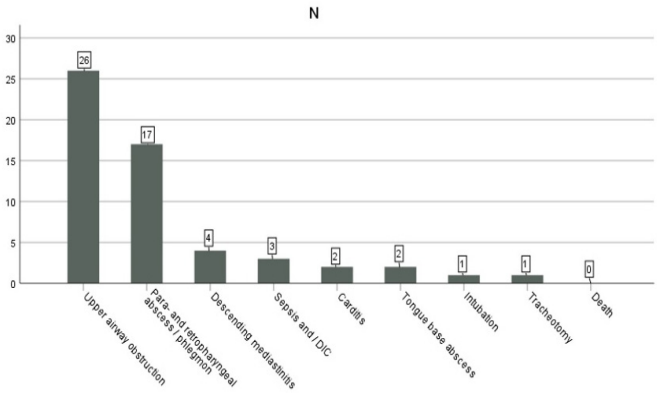

Figure 1. Types and rates of complications following peritonsillar abscess in the study population. *Since some patients experienced more than one complication, the total number of complications exceeded the number of patients with complications (n=56)

DISCUSSION

A PTA is one of the most common causes of deep space head and neck infections, and it represents the most frequent otolaryngology emergency because of its life-threatening complications.[16,17] Radiological methods, such as US and CT, are used in the diagnosis of PTAs and the investigation of their associated complications.[18,19] However, these imaging modalities have certain disadvantages. US requires an

Table 2. Analysis of the area under the ROC curve for NLR, MLR, PLR, SII, and PIV in patients with complicated peritonsillar abscess

Variables	NLR	MLR	PLR	SII	PIV
AUC (95% CI)	0.673 (0.574-0.761)	0.776 (0.684-0.852)	0.617 (0.517-0.711)	0.674 (0.575-0.763)	0.838 (0.753-0.903)
Cut-off value	>2.98	>0.51	>130.6	>802.2	>989.6
Sensitivity	69.7%	63.6%	63.7%	75.7%	72.7%
Specificity	67.6%	76.0%	60.5%	61.9%	85.9%
+LR	2.15	2.66	1.61	1.99	5.16
-LR	0.45	0.48	0.60	0.39	0.32
PPV	50.0%	55.3%	42.9%	48.1%	70.6%
NPV	82.8.6%	81.8%	78.2%	84.6%	87.1%

ROC: Receiver operating characteristic, NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic Immune-Inflammation Index, PIV: Pan-immune-inflammation value, AUC: Area under the ROC curve, CI: Confidence interval, +LR: Positive likelihood ratio, -LR: Negative likelihood ratio, PPV: Positive predictive value, NPV: Negative predictive value

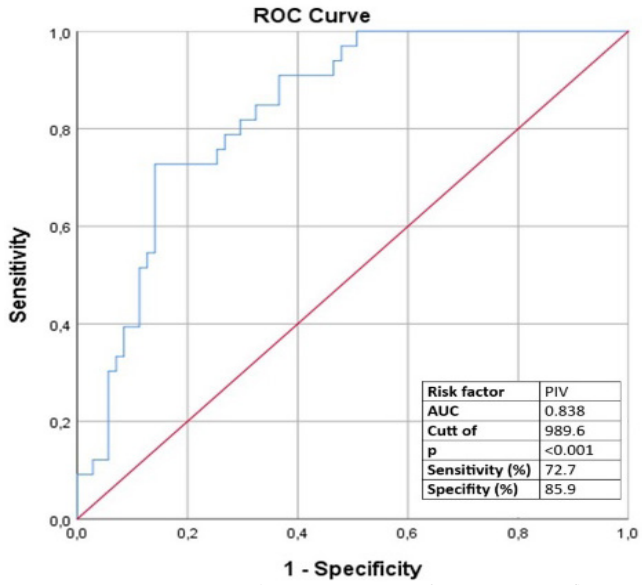

Figure 2. Receiver-operating characteristic curve of pan-immune-inflammation value for prediction of complicated peritonsillar abscess

experienced radiologist, has a limited field of view, and faces challenges in evaluating deep tissues. CT is associated with higher costs, a prolonged hospital stay, the requirement for intravenous contrast agents, and exposure to radiation.[20-22] A complete blood count can be performed in most EDs, and biomarkers calculated from complete blood count parameters are easily accessible because of their relatively low cost. In recent years, the use of biomarkers has gained considerable popularity.[23] The use of novel serological biomarkers in conjunction with imaging modalities may assist ED physicians in managing treatment and predicting the prognosis of UPTAs and CPTAs. To the best of our knowledge, the role of the PIV in distinguishing between UPTAs and CPTAs remains unclear. Therefore, in this study, we investigated whether the PIV can differentiate between a UPTA and a CPTA.

In this study, we found significantly higher PIV values in patients with CPTAs than in those with UPTAs. The AUC value of the PIV in predicting CPTAs was higher than the AUC values of the NLR, MLR, PLR, and SII when considered individually. We found that patients with a PTA and a PIV >989.6 had a higher risk of developing CPTA than those with a lower PIV value. In the ROC curve analysis, the PIV showed a sensitivity of 72.7% and a specificity of 85.9% in predicted CPTAs (AUC: 0.838). These findings suggest that the PIV could serve as a useful and prognostic biomarker in predicting CPTAs.

The NLR has been reported as a reliable biomarker for distinguishing patients with suspected infections from those without infections in EDs.[23] Furthermore, de Jager et al.[24] showed that the NLR outperformed CRP concentrations, white blood cell count, and neutrophil count in identifying bacteremia in patients who presented to the ED. Baglam et al.[25] studied a pediatric patient population and proposed a cutoff value of 5.4 for the NLR as a predictor of deep neck infections resulting from acute bacterial tonsillitis. Şentürk et al.[2] found that an NLR of 3.08 was the optimal cutoff value, and the sensitivity, specificity, positive predictive value, and negative predictive value were all 90.9%. They found that the NLR in the pre-treatment PTA group was higher than that in the post-treatment PTA group and the control group. Additionally, they reported a decrease in the NLR after treatment compared with pre-treatment. In our study, we found that the NLR had a sensitivity of 69.7% and a specificity of 67.6% in predicting complications in patients with PTA. We consider the NLR an important biomarker for distinguishing between complicated and uncomplicated cases of PTAs.

The SII has been reported as a prognostic biomarker that reflects the host's inflammatory response in various diseases and conditions.[26,27] A recent study proposed that an SII cutoff value of 2975 serves as a predictor of a high risk of complications in deep neck infections.[7] Additionally, this SII cutoff value is associated with airway obstruction requiring tracheostomy, an increased risk of mediastinitis, and a higher mortality rate. In our study, we found that an SII cutoff value of 802.2 showed a sensitivity of 75.7% and a specificity of 61.9% in predicting CPTAs. Despite variations in threshold values, we believe that the SII could be an important biomarker for distinguishing between complicated and uncomplicated PTA cases.

The recently discovered PIV is a Next-Generation Comprehensive Inflammatory Index that has been reported as a prognostic biomarker in various conditions, such as peritoneal dialysis, malignancies, autoimmune diseases, and sepsis.[28] A large-scale cross-sectional study showed an association between the PIV and stage III/IV periodontitis.[29] An association between the PIV and mortality has been

investigated in various coronary diseases.[30] However, the role of the PIV in patients with PTAs at a high risk of complications has not been previously evaluated. In our study, the PIV was significantly higher in patients with CPTAs than in those with UPTAs. We found that a PIV cutoff value of 989.6 was a predictor of a high risk of complications in patients with PTAs.

The PIV is derived from neutrophil, platelet, monocyte, and lymphocyte counts measured during admission to the ED. Therefore, the PIV can be calculated to identify patients at a high risk of complications. The accessibility and low cost of obtaining the PIV make it a useful tool in ED for assessing PTAs, which are one of the most common causes of deep neck space infections. The PIV is useful for predicting disease severity, potential complications, and the requirement for surgical intervention.

Limitations

Our study has certain limitations. First, because of the retrospective design of the study, the data were obtained by reviewing electronic patient records, and patients with incomplete data or those referred from external hospitals were excluded. These factors may have affected the PIV results. Second, the study was limited by its single-center design and relatively small cohort size. Third, we calculated the NLR, MLR, PLR, SII, and PIV using blood samples collected at the time of ED admission. We were unable to examine post-treatment changes in these indices by repeated measurements. Finally, the study lacked a healthy control group, which limits the ability to compare the findings with baseline values in a non-diseased population.

CONCLUSION

Delayed diagnosis and inadequate treatment in patients with PTAs can lead to life-threatening morbidities. Therefore, early diagnosis and close monitoring of PTAs are crucial for such patients. The PIV, with a cutoff value of 989.6, is useful in predicting complications in patients with PTAs. The accessibility and ease of calculation of the PIV make it a useful tool for assessing disease severity and potential complications. Moreover, the PIV can be effectively used in emergency settings in which access to imaging is limited or contraindicated, such as in pediatric or pregnant patients. Larger multicenter studies with broader patient populations are required to validate our findings and enhance the clinical utility of this biomarker.

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: 06.11.2024, Decision No: AEŞH-BADEK-2024-962).

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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Exploring Turkish equivalents of terms for musculoskeletal radiology: insights for a standardized terminology

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ABSTRACT

Aims: This study aimed to provide an analysis of Turkish equivalents of English terms for musculoskeletal radiology.

Methods: The present study focuses on a global endorsement of English terms in musculoskeletal radiology, and explores how their Turkish equivalents are used in reference books (Turkish translation of the books, Diagnostic Imaging: Musculoskeletal: Trauma and Diagnostic Imaging: Musculoskeletal: Non-Traumatic Disease). Furthermore, the study attempts to provide a picture of how AI-based tools (i.e. neural machine translation tools such as DeepL, Google Translate and an AI Chatbot, ChatGPT) vary in the translation of these terms.

Results: The study found that the most common translation strategies for musculoskeletal radiology terms were borrowing and literal translation, with several combined strategies used for complex terms. AI-based tools like DeepL, Google Translate, and ChatGPT showed a high similarity to human translations, but differences were observed in word choice, strategy use, and orthographic variations. These differences, though minor, highlight the challenges of achieving consistency and accuracy in AI-generated medical translations.

Conclusion: The present study provides a list of Turkish equivalents for musculoskeletal terminology in English, and presents an analysis of translations by radiology specialists and AI-based tools. Careful evaluation of AI translations is essential to ensure accuracy and consistency in the translation of medical terminology, particularly in subspecialities such as musculoskeletal radiology.

Keywords: Radiology, musculoskeletal radiology, AI-based translation tools, terminology

INTRODUCTION

In the relevant literature, there have been several studies investigating how terminology is used in radiology, particularly in radiological reports. Radiologists and the referring physicians might use different lexicons, which will result in confusion with radiology reporting.[1] With the technological advancements, this is also crucial today for automatic radiology report generation.[2] A survey was conducted with radiologists and primary care physicians to understand their interpretation of the presence of metastatic disease based on the terminology used in a fictitious report.[1] The results demonstrated an agreement between the two groups, yet radiologists gave a higher likelihood for several phrases when compared to the primary care physicians. In an earlier study, a group of researchers investigated the extent of the agreement between radiologists and non-radiologists in terms of the use of terms to convey diagnostic certainty in radiology reports[3]. To this end, they administered an interview with 12 randomly selected radiologists from 6 different subspecialties, and identified the 15 most frequently used words and phrases. The researchers prepared a questionnaire including these words and phrases in a random order and asked radiologists and other physicians to rank these terms in order of the diagnostic certainty. The results revealed that there was poor agreement, thereby suggesting the need for a standardization of terminology. The radiology community has recognized that a standard terminology is essential to improve the clarity of radiology reports, to decrease variation, to facilitate access to imaging data, and to enhance the quality of practice. To this end, there have been attempts to develop a controlled terminology for radiology. For instance, Radiological Society of North America (RSNA) has built RadLex to provide a standardized and comprehensive set of terms for radiology reporting, teaching and conducting research.[4] Furthermore, there have been attempts to enhance RadLex[5] and converting it into a structured hierarchical text report.[6] Additionally, researchers have provided lists of standardized terms for particular topics. To illustrate, a recent study attempted to present a consensus glossary for thoracic

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radiology in Portuguese.[7] The experts from Brazil and Portugal presented a consensus statement for reporting chest images. The list included 60 terms in total including acinus, air trapping, fungus ball, broncholith, etc. In another study, researchers aimed to provide a standardized terminology for liver imaging for research, education and clinical care of patients.[8] The aim of the present study is to focus on a global endorsement for musculoskeletal radiology terminology,[9] their Turkish equivalents and how AI-based tools translate these terms.

Terminology for Musculoskeletal Radiology

Over the past 100 years, musculoskeletal radiology has evolved into a major imaging subspecialty.[10] Along with the developments in the field, there have been few studies on the terms of musculoskeletal radiology across the world. For instance, a recent study addressed the need for a standardized terminology in MRI descriptions of musculoskeletal inflections.[11] To this end, the Society of Skeletal Radiology developed a consensus on nomenclatures and identified the definition, diagnosis as well as controversies and rationale for each term through discussions and endorsements. They presented a list of 19 terms related to the categories including soft tissue, joints/tendon sheaths, bone surface, medullary space, and necrosis. The challenges posed by inconsistent terminology in describing musculoskeletal findings on MRI were also discussed.[12] It was emphasized that ambiguous terms such as meniscal tears, bone bruises, joint subluxation, etc. might lead to miscommunication among radiologists and clinicians, and thus influencing patient care. More recent and comprehensive study was administered by Palmer et al.[9] The researchers compiled a list of terms for musculoskeletal radiology. The authors included members of the International Skeletal Society, representing Asia, Australia, Europe and the USA. They selected 101 terms for inclusion and obtained consensus agreement from 19 musculoskeletal radiology societies worldwide.

The anatomical structures, disease processes, and syndromes that are essential to the musculoskeletal lexicon are the main topics of the glossary. The researchers reported that they prioritized the terms that potentially have problematic meaning, and due to the prevalence of musculoskeletal disorders and derangement, many terms related to neoplasm, spine, intervention, and pediatrics were excluded from the glossary. The final list of terms was formed with the global endorsement of the 19 societies. Due to the significant consensus and large terminology included in Palmer et al.,[9] the present study attempted to provide a general picture of how Turkish equivalences of these terms are used in books and journal articles by radiologists in Turkiye. Furthermore, the present study will also present a discussion of how AI-based translation tools (DeepL, Google Translate and ChatGPT within the scope of this study) translated these terms.

Translation of Medical Terminology

Medical translation has always remained an important topic throughout the human history. Medical translation "is the most universal and the oldest field of scientific translation.[13]Mombasa and Manila It is often regarded to be limited to extremely specialist materials and complex medical terminology.[14] Nevertheless, medical translation is of great importance for clinical practice, physician-patient communication, education and research, particularly in today's world. Medical terminology has a special place from a translation perspective. The level of formality, technicality, and the means of communication in medical language varies depending on the genre and context.[15] Medical language has a large number of Greek and/or Latin-derived terms that frequently have equivalents in ordinary everyday language (e.g. hemorrhage vs. bleeding).[16] There might also be multiple equivalents for the same term (e.g. adhesive capsulitis vs. frozen shoulder or scapulohumeral periarthritis) in formal settings. Neologisms are a reflection of the ever-evolving field of medical research and ongoing discoveries and developments. Every year, the World Health Organization (WHO) reports that thousands of new terms are coined as a consequence of new research, theoretical shifts, or duplications of existing medical concepts.[14] This level of varieties in medical terminology might be challenging for translation, and thus communicative situations in healthcare. In a recent study, for instance, researchers explored the elements of medical terminology which are particularly challenging for translation, the examples of which included acronyms, culture-specific items, terminological variations, and neologisms.[14]

In the relevant literature, even though there have been some attempts to present standardized terminologies for various subspecialities and topics, there have been very few studies addressing the translation strategies used to cope with medical terminology. There is a thorough summary of the primary translation issues, the varied definitions of fidelity in translation, and potential translation procedures pointed out in the relevant literature such as exoticism, cultural borrowing, calque, transliteration, cultural transplantation, etc.[16] In another study, researchers analyzed the strategies for translating medical terminology about COVID-19 from English into Macedonian.[14] They examined a corpus of 130 terms, highlighting challenges in conveying accurate and consistent terminology for diverse audiences including medical professional and the public. Relying on Vinay and Darbelnet's model,[17] the study identified methods for structured terminology, ensuring clarity and effective communication. More recently, the English translation strategies for Mongolian medical terminology were explored, emphasizing specificity, scientific basis, and cultural distinctiveness.[18] The study underscored the challenges in translating the terms into English, given their strong ties to Mongolian cultural heritage and their technical complexity. It outlined four key translation strategies: literal translation, transliteration, free translation, and a combined approach, which are used to preserve the cultural and professional essence while ensuring accessibility and comprehensibility for audiences.

Due to the dynamic and varied nature of translation strategies for medical terminology, the present study relied on Vinay and Darbelnet's model, which presents a clear picture of the translation categories and strategies, and widely used

to ensure effective and context-dependent translation. The model outlines 7 translation strategies divided into two categories, namely direct translation and oblique translation.[17] Direct translation is used when it is possible to transpose a source language element by element into a target language. The translation strategies in this category include borrowing (using the same word for the source language, e.g. 'aspirin'), calque (a literal translation of expressions or phrases, e.g. 'skyscraper' in English becomes 'gökdelen' in Turkish, structurally similar, as well), and literal translation (word-for-word translation from one language to another). On the other hand, oblique translation is employed when greater linguistic or cultural differences and it consist of the following strategies; transposition (alteration of word class, e.g. verb to noun), modulation (shifting perspectives or viewpoints, e.g. 'negative test result' becomes 'test sonucu temiz'), equivalence (expression of the same idea with culturally appropriate terms), and adaptation (modifying concepts to suit cultural norms, e.g. translating 'pediatrician' to 'çocuk doktoru' for cultural relevance).

AI-based Tools in Musculoskeletal Radiology and Terminology

Artificial intelligence (AI) has gained major attention in musculoskeletal radiology. There have many studies highlighting how AI might be utilized throughout the entire imaging workflow.[19,20] A current study examined the diagnostic performance of ChatGPT based on textual vs. visual information in musculoskeletal radiology and they provided a comparison with the radiologists' diagnostic performance.[21] To this end, they provided medical history and imaging findings input into GPT-4- based ChatGPT and GPT-4V-based ChatGPT. Furthermore, two radiologists, including a radiology resident and a board-certified radiologist, provided diagnoses for all cases. GPT-4-based ChatGPT (accuracy rate: 43%) demonstrated a comparable performance to the radiology resident (41%), yet lower than that of the board-certified radiologist (53%). GPT-4V-based ChatGPT had the lowest performance (accuracy rate: 8%). In another study, it was explored how AI might shape the entire imaging workflow in musculoskeletal radiology.[22] More precisely, they attempted to show the transformative potential of AI in both interpretive tasks (e.g., image analysis and diagnosis) and noninterpretive tasks (e.g., scheduling and reporting). A group of researchers sought to test how AI algorithm performed against experienced radiologist in musculoskeletal radiology.[23] They used four datasets of conventional hand, wrist, and scaphoid radiographs for training and diagnosing scaphoid fractures. Furthermore, the AI algorithm was compared with the analysis of 5 experienced musculoskeletal radiologists. The results revealed that the algorithm detected the fractures at the level of experienced radiologists and might be utilized in order to shorten their reading time.

Research has indicated that ChatGPT has the potential to revolutionize radiology reporting by ensuring precision and standardization.[24,25] Given that recent studies have argued the role and performance of AI on various applications such as diagnosis, classification, and radiology report generation,[26] it might be notable to explore how AI-based tools such as DeepL, Google Translate and ChatGPT translate these terms into other languages. AI-based translation tools have a great potential and contribution especially in terms of translation accuracy and speed.[27] Exploring the performance of NMT tools, DeepL and Google Translate, the researchers found that these tools provided accurate results in informative texts,[28] yet had challenges in narrative and functional texts. In another study, the performance of ChatGPT was examined and it was reported that the AI tool produced publishable texts with human post-editing.[29] Therefore, the present study seeks to explore how AI-based translation tools performed at translating musculoskeletal terminology. This study focuses on the translation of English terms into Turkish, and provides a comparison between the results of these tools and the translations by the radiology specialists.

METHODS

The study was carried out without involvement of any animate beings. Hence, an ethics committee approval was not required. All steps were carried out in accordance with the ethical rules and the principles.

Materials

The materials for exploring the Turkish equivalents of the terms included the reference books for musculoskeletal radiology translated into Turkish and AI-based translation tools, namely DeepL, Google Translate and ChatGPT. There were two reference books examined in detail for the Turkish equivalents. These included the Turkish translations of the books entitled "musculoskeletal: trauma" and "musculoskeletal: non-traumatic disease" from diagnostic imaging series. The former was authored by Sonin, Manaster, Andrews, Crim, and Tuite, and the 1st edition was published in 2010. The latter was authored by Manaster, Roberts, Petersilge, Moore, Hanrahan, and Christopher, and the 1st edition was published in 2012.

The books were translated from English into Turkish under the leadership of Prof. Dr. Remide Arkun and with contributions of several other radiology specialists in the field of musculoskeletal radiology. The first book entitled "diagnostic imaging, musculoskeletal: trauma" was translated as "diagnostic imaging, kas-iskelet: travma". The book consisted of 7 chapters including an introduction, shoulder and humerus, elbow, wrist and hand, hip and pelvis, knee, and ankle and foot. The second book entitled "diagnostic imaging, musculoskeletal: non-traumatic disease" was translated as "diagnostic imaging, kas-iskelet: travma dışı hastalıklar" and it comprised 12 chapters. These chapters were arthritis, osseous tumors and tumor-like conditions, soft tissue tumors, congenital and developmental abnormalities, dysplasias, systemic diseases with MSK involvement, orthopedic implants or arthrodesis, infection, bone marrow, bone marrow edema and necrosis, metabolic bone disease, and drug-induced and nutritional MSK conditions.

Palmer et al.[28] selected and received consensus on a list of 101 terms for musculoskeletal radiology. The same list was checked in the Diagnostic Imaging reference books for musculoskeletal radiology. There were only 5 terms which were not found

either in the English source texts or in the Turkish translation texts. Therefore, there were 96 terms examined in the present study. Furthermore, the same list of 96 terms were translated by using the well-known neural machine translation tools, namely DeepL and Google Translate, and ChatGPT, which is frequently employed in AI-based research on radiology.

RESULTS

The present study, thus, attempted to provide an analysis of the Turkish equivalents of the terms which previously received a global endorsement for musculoskeletal radiology, how they were translated into Turkish. To this end, the reference books translated from English into Turkish were examined. There were 96 terms identified in the English source texts and its Turkish translations. Furthermore, given that AI-based technology has also started to be used in image processing, diagnosis and report generation in radiology, the present study aimed to explore how AI-based tools translated these terms in Turkish, as well. Therefore, the result part presents an analysis of how English terms were used by Turkish radiology specialists in the translation of the reference books for musculoskeletal radiology. Afterwards, the translation suggestions by AI-based tools (DeepL, Google Translate and ChatGPT within the scope of this study) are explored and further discussed.

Turkish Equivalents of Terms for Musculoskeletal Radiology

The Turkish translations of the terms for musculoskeletal radiology were examined based on the translation strategies suggested by Vinay and Darbelnet's model. When all the terms and the translation strategies were considered, the most frequently used strategy were borrowing (n: 83), e.g. translating 'adhesive capsulitis' into Turkish as 'adeziv kapsülit' and literal translation (n: 53), e.g. translating 'groin pain' into Turkish as 'kasık ağrısı'. Given that some terms included multiple words, there were also more than one strategy used in the translations of each term, as well. The translation strategies employed included 10 different patterns in general as follows: adaptation+borrowing (n: 1), borrowing+literal translation (n: 23), borrowing (n: 41), borrowing+literal translation+addition (n: 2), borrowing+equivalence (n: 2), literal translation+equivalence (n: 1), literal translation (n: 11), literal translation+borrowing (n: 14), borrowing+addition+literal translation (n: 1), and calque+literal translation (n: 2). In the translation of medical terms for musculoskeletal terminology, thus the most frequent patterns were borrowing, borrowing+literal translation, literal translation+borrowing, and literal translation respectively (see appendix for **Table 1 and 2** illustrating the Turkish equivalents of the English terms for musculoskeletal radiology: an analysis of how the terms were used in the reference books).

Adaptation+borrowing: There is only 1 example for this pattern, which is for the translation of 'boutonniere deformity'. Boutonniere means 'yaka çiçeği' in Turkish, another name for Boutonniere deformity in English is button hole deformity. Due to this difference, the Turkish preference was adapted as translation for this term. Nevertheless, the word 'deformity' is received only with minor orthographic changes in transliteration (i.e. spelling the term according to the alphabetical characters of the target language). Thus, a combination of both adaptation and borrowing is observed.

Borrowing+literal translation: This patter in observed in 23 examples. For the terms which comprises more than one words, a combination of borrowing and literal translation strategies is quite frequently preferred. For instance, 'atypical femoral fracture' is translated as 'atipik femur kırığı', where the first two words are borrowed, yet the last word 'fracture' is translated into Turkish as 'kırığı".

Borrowing: For the terms which consist of only one word or two words, employing merely 'borrowing' strategy was observed in 41 cases. To illustrate, 'chondromalacia' was used as 'kondromalazi', merely with minor orthographic changes in transliteration.

Borrowing+literal translation+addition: In 2 examples, there were also additions to the term in the Turkish translation. The terms were 'ankle, anterior (anteromedial, anterolateral) impingement' and 'ankle, posterior (posteromedial) impingement'. In the Turkish translations, the word 'sendromu' was also added, so the translation ended, for instance, as 'anterior (anteromedial, anterolateral) sıkışma sendromu, ayak bileği'.

Borrowing+equivalence: In 2 cases, the pattern of borrowing and equivalence was observed. For instance, 'carpal boss' was translated as 'karpal kemik' where the Turkish equivalence for boss was used, and for 'cyclops syndrome', the word 'lezyon' was preferred and the term was translated as 'siklops lezyonu', where the word 'siklops' was borrowed, yet an equivalent word was used for syndrome.

Literal translation+equivalence: There was only 1 case of literal translation and equivalence. For 'bone bruise', the translation choice was 'kemik kontüzyonu'. Bone is translated as 'kemik', which is a word-to-word translation. Bruise, on the other hand, has a literal translation, which is 'çürük', yet it is translated as 'contusion'.

Literal translation: The mere use of literal translation as a translation strategy was observed in 11 examples. For instance, 'bone island' was translated word-to-word as 'kemik adası', and 'sprain' was translated as 'burulma'. The translation of 'O'Donoughe's triad' was also accepted as an example of literal translation. The full term in English is 'O'Donoughe's unhappy triad'. However, the full term is not found in the original English source text, nor in the Turkish translations. In the English text, only 'unhappy triad' is used, which is literally translated into Turkish as 'mutsuz üçlü'. Therefore, instead of excluding the term from the analysis, the word was accepted as an example of literal translation within the scope of the present study.

Literal translation+borrowing: The pattern of literal translation and borrowing was also quite frequent with 14 cases. Although the same strategies with the pattern of 'borrowing and literal translation' was employed, this pattern was also categorized additionally to underline that the literal translation was first employed for initial words

Table 1. Turkish equivalents of the English terms for musculoskeletal radiology: an analysis of how the terms were used in the reference books

Nr.	English term	Turkish equivalent [reference books]	Translation strategies
1	Acetabular labral tear	Asetabular labrum yırtığı	Borrowing+literal translation
2	Acetabular retroversion	Asetabular retroversiyon	Borrowing
3	Adhesive capsulitis	Adeziv kapsülit (other usages: donum omuz/ scapulohumeral periartrit)	Borrowing
4	Ankle, anterior (anteromedial, anterolateral) impingement	Anterior (anteromedial, anterolateral) sıkışma sendromu, ayak bileği	Borrowing+ literal translation+addition
5	Ankle, posterior (posteromedial) impingement	Posterior (posteromedial) sıkışma sendromu, ayak bileği	Borrowing+ literal translation+addition
6	Anterolateral ligament of the knee	Anterolateral bağ	Borrowing+literal translation
7	Atypical femoral fracture	Atipik femur kırığı	Borrowing+literal translation
8	Avulsion fracture	Avülziv yaralanma/avülziyon kırığı	Borrowing+literal translation
9	Bone bruise	Kemik kontüzyonu	Literal translation+equivalence
10	Bone island	Kemik adası	Literal translation
11	Bone marrow edema	Kemik iliği ödemi	Literal translation
12	Bone mineral density	Kemik mineral yoğunluğu	Literal translation
13	Boutonniere deformity	Düğme iliği deformitesi	Adaptation+borrowing
14	Brodie's abscess	Brodie absesi	Borrowing
15	Buford complex	Buford kompleks	Borrowing
16	Cancellous bone	Sesamoid kemik/süngerimsi kemik	Literal translation
17	Carpal boss	Karpal kemik	Borrowing+equivalence
18	Carpet lesion		
19	Chondromalacia	Kondromalazi	Borrowing
20	Compartment syndrome	Kompartman sendromu	Borrowing
21	Coracoacromial arch	Korokoakromiyak ark	Borrowing
22	Cortical bone	Kortikal kemik	Borrowing+literal translation
23	Crescent sign of osteonecrosis	Kresent işareti	Borrowing+literal translation
24	Cyclops syndrome	Siklops lezyon	Borrowing+equivalence
25	Denervation myopathy	Denervasyon miyopati	Borrowing
26	Double line sign in osteonecrosis	Osteonekrozu çift çizgi işareti	Literal translation+borrowing
27	Enthesopathy	Entesopati	Borrowing
28	Epicondylitis	Epikondilit	Borrowing
29	Femoral diaphyseal stress injury	Femur diyafiz stres hasarı	Borrowing+literal translation
30	Friction syndrome	Sürtünme sendromu	Literal translation+borrowing
31	Geyser sign	Geyser işareti	Borrowing+literal translation
32	Glenoid retroversion	Glenoid retroversiyon	Borrowing
33	Groin pain	Kasık ağrısı	Literal translation
34	Haglund's syndrome	Haglund sendromu	Borrowing
35	Heterotopic ossification	Heterotopic osifikasyon	Borrowing
36	Hill-Sachs defect	Hill-Sachs defekt	Borrowing
37	Hip impingement, cam deformity	Kalça sıkışma sendromu, cam deformitesi	Literal translation+borrowing, borrowing
38	Hip impingement, femoroacetabular	Femoral asetabular sıkışma	Borrowing+literal translation
39	Hip impingement, ischiofemoral	Iskifemoral sıkışma	Borrowing+literal translation
40	Hip impingement, pincer deformity	Kıskaç/pincer tip sıkışma	Literal translation/borrowing+addition+literal translation
41	Iliotibial band friction syndrome	İliotibiyal bant sürtünme sendromu	Borrowing+literal translation
42	Impingement syndrome	Sıkışma sendromu	Literal translation+borrowing
43	Intersection syndrome	Kavşak sendromu	Literal translation+borrowing
44	Ivory vertebra	Fildişi vertebra	Literal translation+borrowing
45	Lisfranc joint	Linsfrank eklemi	Borrowing+literal translation
46	Looser zone	Looser hatları/milkman kırıkları/yalancı kırıklar	Borrowing+literal translation
47	Medial tibial stress syndrome	Medial tibial stres sendromu	Borrowing
48	Metallosis	Metalozis	Borrowing
49	Mucoid change	Mukoid değişiklik	Borrowing+literal translation
50	Muscle injury	Kas yaralanması	Literal translation
51	Myonecrosis	Kas enfarktı	Literal translation+borrowing (muscle infarction, alternative to myonecrosis)
52	Myopathy	Miyopati	Borrowing
53	Myositis	Miyozit	Borrowing
54	Myositis ossificans	Miyozitis osifikans	Borrowing
55	Myotendinous junction	Kas-tendon bileşkesi	Calque+literal translation
56	Myotendinous unit	Kas-tendon ünitesi	Calque+literal translation
57	Necrotizing fasciitis	Nekrozitan fasiit	Borrowing

Table 1. Turkish equivalents of the English terms for musculoskeletal radiology: an analysis of how the terms were used in the reference books (continues)

Nr.	English term	Turkish equivalent [reference books]	Translation strategies
58	O'Donoghue's triad	Mutsuz üçlü	Literal translation (O'Donoghue's unhappy triad; "O'Donoghue" is omitted both in English source text and in Turkish text).
59	Osteitis condensans ilii	Osteitis kondensans ilii	Borrowing
60	Osteochondral defect	Osteokondral defekt	Borrowing
61	Osteochondritis dissecans	Osteokondritis disekans	Borrowing
62	Osteonecrosis	Osteonekroz	Borrowing
63	Osteoporosis	Osteoporoz	Borrowing
64	Paratenonitis	Tenosinovit	Borrowing
65	Pathologic fracture	Patolojik kırık	Borrowing+literal translation
66	Periosteal reaction	Periost reaksiyonu	Literal translation
67	Plantar plate	Plantar fasya	Borrowing+literal translation
68	Pseudarthrosis	Psödoartroz	Borrowing
69	Quadrilateral space syndrome	Kuadrilateral mesafe sendromu	Borrowing+literal translation
70	Ramp lesion		
71	Reaction to metal		
72	Reactive arthritis	Reaktif artrit	Borrowing
73	Rice bodies	Pirinç cisimleri	Literal translation
74	SAPHO syndrome	SAPHO	Borrowing
75	Sarcopenia		
76	Serous atrophy of bone marrow	Seröz atrofi, kemik iliği	Borrowing+literal translation
77	Shoulder, glenohumeral instability	Omuz, glenohumeral instabilite	Literal translation+borrowing
78	Shoulder, posterosuperior impingement	Omuz, posterosuperior sıkışma	Literal translation+borrowing
79	Shoulder, rotator cuff tear (full thickness)	Omuz, rotator cuff/kılıf yırtığı (tam kat)	Literal translation+borrowing
80	Shoulder, rotator cuff tear (overview)	Omuz, rotator cuff/kılıf yırtığı (tam kata yakın)	Literal translation+borrowing
81	Shoulder, rotator cuff tear (partial thickness)	Omuz, rotator cuff/kılıf yırtığı (kısmi)	Literal translation+borrowing
82	Shoulder, SLAP tear (superior labrum anterior-to-posterior	SLAP yırtık	Borrowing+literal translation
83	Shoulder, subacromial impingement	Omuz, subakromiyal sıkışma	Literal translation+borrowing
84	Skier's thumb	Kayakçı başparmağı	Literal translation
85	Sprain	Gerilme/burkulma	Literal translation
86	Stress fracture	Stres kırığı	Borrowing+literal translation
87	Stress response	Stres cevabı	Borrowing+literal translation
88	Subchondral insufficiency fracture	Subkondral yetmezlik kırığı	Borrowing+literal translation
89	Subluxation	Subluksasyon	Borrowing
90	Swan neck deformity	Kuğu boynu deformitesi	Literal translation+borrowing
91	Synovitis	Sinovit	Borrowing
92	Tendinopathy	Tendinopati	Borrowing
93	Tophus	Tofüs	Borrowing
94	Torsion	Torsiyon	Borrowing
95	Transient osteoporosis	Transiyet kemik iliği ödem sendromu	Borrowing+literal translation
96	Trochanteric syndrome	Trokanterik sendrom	Borrowing
97	Tubulation	Tubulasyon	Borrowing
98	Tunnel syndrome	Tünel sendromu	Borrowing
99	Ulnar impaction syndrome	Ulnar impaksiyon sendromu	Borrowing
100	Version	Retroversiyon (bileşik halde kullanılıyor)	Borrowing
101	Wolff's law		

and later word(s) was kept and borrowing strategy was preferred. Otherwise, in terms of the usage of strategies, both patterns might be considered similar. An example of literal translation+borrowing was the translation of 'swan neck deformity', which was 'kuğu boynu deformitesi'. The first two words 'kuğu boynu' are the examples of literal translation, whereas 'deformitesi' is an example of borrowing strategy. Additionally, the translation of 'myonecrosis' was also accepted as an example of 'literal translation+borrowing'. An alternative term for myonecrosis in the literature is muscle infarction, for the Turkish translation, 'kas enfarktı' is preferred, where 'kas' is an example of literal translation and 'enfarktı' is an example of borrowing.

Borrowing+addition+literal translation: There was also 1 example of borrowing+addition+literal translation, where 'hip impingement, pincer deformity' was translated as 'pincer tip sıkışma'. This term defines one subtype of hip impingements. Even though the word 'tip (i.e. type in English) is not in the English term, it is also included in the Turkish translation to highlight the type of impingement.

Calque+literal translation: The last example of the pattern for translation strategies included calque and literal translation. There were 2 cases, including the word 'myontendinous' where myo means 'related to muscle' and tendinous refers to 'related to tendon'. The word was translated into Turkish

Table 2. Turkish translations of the English terms for musculoskeletal radiology: an analysis of how NMT and AI-based tools translate medical terms

Nr.	English Term	DeepL	Google Translate	ChatCPT
1	Acetabular labral tear	Asetabular labral yırtık	Asetabular labral yırtığı	Asetabular labrum yırtığı
2	Acetabular retroversion	Asetabular retroversiyon	Asetabular retroversiyon	Asetabular retroversiyon
3	Adhesive capsulitis	Yapışkan kapsülit	Adhesif kapsülit	Adeziv kapsülit
4	Ankle, anterior (anteromedial, anterolateral) impingement	Ayak bileği, anterior (anteromedial, anterolateral) sıkışma	Ayak bileği, anterior (anteromedial, anterolateral) sıkışma	Ayak bileği, ön (anteromedial, anterolateral) sıkışma
5	Ankle, posterior (posteromedial) impingement	Ayak bileği, posterior (posteromedial) sıkışma	Ayak bileği, posterior (posteromedial) sıkışma	Ayak bileği, arka (posteromedial) sıkışma
6	Anterolateral ligament of the knee	Dizin anterolateral bağı	Diz anterolateral bağı	Diz anterolateral bağ
7	Atypical femoral fracture	Atipik femur kırığı	Atipik femoral kırık	Atipik femur kırığı
8	Avulsion fracture	Avülsiyon kırığı	Avulsiyon kırığı	Avulsiyon kırığı
9	Bone bruise	Kemik çürüğü	Kemik çürüğü	Kemik kontüzyonu
10	Bone island	Kemik adası	Kemik adası	Kemik adacığı
11	Bone marrow edema	Kemik iliği ödemi	Kemik iliği ödemi	Kemik iliği ödemi
12	Bone mineral density	Kemik mineral yoğunluğu	Kemik mineral yoğunluğu	Kemik mineral yoğunluğu
13	Boutonniere deformity	Yaka çiçeği deformitesi	Boutonniere deformitesi	Boutonniere deformitesi
14	Brodie's abscess	Brodie'nin apsesi	Brodie apsesi	Brodie apsesi
15	Buford complex	Buford kompleksi	Buford kompleksi	Buford kompleksi
16	Cancellous bone	Kansellöz kemik	Süngersi kemik	Spongiyöz kemik
17	Carpal boss	Karpal patron	Karpal çıkıntı	Karpal kemik çıkıntısı
18	Carpet lesion	Halı lezyonu	Halı lezyonu	Halı lezyonu
19	Chondromalacia	Kondromalazi	Kondromalazi	Kondromalazi
20	Compartment syndrome	Kompartman sendromu	Komppartman sendromu	Kompartman sendromu
21	Coracoacromial arch	Korakoakromiyal kemer	Korakoakromial ark	Korakoakromial ark
22	Cortical bone	Kortikal kemik	Kortikal kemik	Kortikal kemik
23	Crescent sign of osteonecrosis	Osteonekrozun hilal işareti	Osteonekrozun hilal işareti	Osteonekrozun hilal belirtisi
24	Cyclops syndrome	Cyclops sendromu	Siklops sendromu	Cyclops sendromu
25	Denervation myopathy	Denervasyon miyopatisi	Denervasyon miyopatisi	Denervasyon miyopatisi
26	Double line sign in osteonecrosis	Osteonekrozda çift çizgi işareti	Osteonekrozda çift çizgi işareti	Osteonekrozda çift çizgi belirtisi
27	Enthesopathy	Entesopati	Entesopati	Entezopati
28	Epicondylitis	Epikondilit	Epikondilit	Epikondilit
29	Femoral diaphyseal stress injury	Femoral diyafiz stres yaralanması	Femoral diafiz stres yaralanması	Femur diyafiz stres yaralanması
30	Friction syndrome	Sürtünme sendromu	Sürtünme sendromu	Sürtünme sendromu
31	Geyser sign	Gayzer işareti	Gayzer işareti	Geyser belirtisi
32	Glenoid retroversion	Glenoid retroversiyonu	Glenoid retroversiyon	Glenoid retroversiyon
33	Groin pain	Kasık ağrısı	Kasık ağrısı	Kasık ağrısı
34	Haglund's syndrome	Haglund sendromu	Haglund sendromu	Haglund sendromu
35	Heterotopic ossification	Heterotopik kemikleşme	Heterotopik kemikleşme	Heterotopik ossifikasyon
36	Hill-Sachs defect	Hill-Sachs defekti	Hill-Sachs defekti	Hill-Sachs defekti
37	Hip impingement, cam deformity	Kalça sıkışması, kam deformitesi	Kalça sıkışması, kam deformitesi	Kalça sıkışması, cam deformitesi
38	Hip impingement, femoroacetabular	Kalça sıkışması, femoroasetabular	Kalça sıkışması, femoroasetabular	Kalça sıkışması, femorosatabular
39	Hip impingement, ischiofemoral	Kalça sıkışması, iskiyofemoral	Kalça sıkışması, iskiofemoral	Kalça sıkışması, ischiofemoral
40	Hip impingement, pincer deformity	Kalça sıkışması, kıskaç deformitesi	Kalça sıkışması, pens deformitesi	Kalça sıkışması, pincer deformitesi
41	Iliotibial band friction syndrome	İliotibial bant sürtünme sendromu	İliotibial bant sürtünme sendromu	İliotibial bant sürtünme sendromu
42	Impingement syndrome	Sıkışma sendromu	Çarpışma sendromu	Sıkışma sendromu
43	Intersection syndrome	Kesişme sendromu	Kesişim sendromu	İnterseksiyon sendromu
44	Ivory vertebra	Fildişi omur	Fildişi omur	Fildişi vertebra
45	Lisfranc joint	Lisfranc eklemi	Lisfranc eklemi	Lisfranc eklemi
46	Looser zone	Daha gevşek bölge	Daha gevşek bölge	Looser zonu
47	Medial tibial stress syndrome	Medial tibial stres sendromu	Medial tibial stres sendromu	Medial tibial stress sendromu
48	Metallosis	Metallosis	Metalozis	Metallozis
49	Mucoid change	Mukoid değişim	Mukoid değişim	Mukoid değişim
50	Muscle injury	Kas yaralanması	Kas yaralanması	Kas yaralanması
51	Myonecrosis	Miyonekroz	Myonekroz	Miyonekroz
52	Myopathy	Miyopati	Miyopati	Miyopati
53	Myositis	Miyozit	Miyozit	Miyozit
54	Myositis ossificans	Miyozit ossifikans	Miyozit ossifikans	Miyozitis ossifikans
55	Myotendinous junction	Miyotendinöz kavşak	Miyotendinöz kavşak	Miyotendinöz bileşke
56	Myotendinous unit	Miyotendinöz ünite	Miyotendinöz ünite	Miyotendinöz ünite
57	Necrotizing fasciitis	Nekrotizan fasiit	Nekrotizan fasiit	Nekrotizan fasiit
58	O'Donoghue's triad	O'Donoghue'nun üçlüsü	O'Donoghue triadı	O'Donoghue triadı

Table 2. Turkish translations of the English terms for musculoskeletal radiology: an analysis of how NMT and AI-based tools translate medical terms (continues)

Nr.	English Term	DeepL	Google Translate	ChatCPT
59	Osteitis condensans ilii	Osteitis condensans ilii	Osteitis condensans ilii	Osteitis kondensans ilii
60	Osteochondral defect	Osteokondral defekt	Osteokondral defekt	Osteokondral defekt
61	Osteochondritis dissecans	Osteokondritis dissekans	Osteokondritis dissekans	Osteokondritis dissekans
62	Osteonecrosis	Osteonekroz	Osteonekroz	Osteonekroz
63	Osteoporosis	Osteoporoz	Osteoporoz	Osteoporoz
64	Paratenonitis	Paratenonit	Paratenonit	Paratenonit
65	Pathologic fracture	Patolojik kırık	Patolojik kırık	Patolojik kırık
66	Periosteal reaction	Periosteal reaksiyon	Periosteal reaksiyon	Periosteal reaksiyon
67	Plantar plate	Plantar plaka	Plantar plak	Plantar plak
68	Pseudarthrosis	Psödartroz	Psödartroz	Psödoartroz
69	Quadrilateral space syndrome	Dörtgen boşluk sendromu	Dörtgensel boşluk sendromu	Dörtgen boşluk sendromu
70	Ramp lesion	Rampa lezyonu	Rampa lezyonu	Ramp lezyonu
71	Reaction to metal	Metale karşı reaksiyon	Metale reaksiyon	Metale reaksiyon
72	Reactive arthritis	Reaktif artrit	Reaktif artrit	Reaktif artrit
73	Rice bodies	Pirinç gövdeleri	Pirinç cisimleri	Pirinç cisimcikleri
74	SAPHO syndrome	SAPHO sendromu	SAPHO sendromu	SAPHO sendromu
75	Sarcopenia	Sarkopeni	Sarkopeni	Sarkopeni
76	Serous atrophy of bone marrow	Kemik iliğinde seröz atrofi	Kemik iliğinin seröz atrofisi	Kemik iliği seröz atrofi
77	Shoulder, glenohumeral instability	Omuz, glenohumeral instabilite	Omuz, glenohumeral instabilite	Omuz, glenohumeral instabilite
78	Shoulder, posterosuperior impingement	Omuz, posterosuperior sıkışma	Omuz, posterosuperior sıkışma	Omuz, posteriyosuperior sıkışma
79	Shoulder, rotator cuff tear (full thickness)	Omuz, rotator manşet yırtığı (tam kalınlık)	Omuz, rotator manşet yırtığı (tam kalınlık)	Omuz, rotator manşet yırtığı (tam kalınlık)
80	Shoulder, rotator cuff tear (overview)	Omuz, rotator manşet yırtığı (genel bakış)	Omuz, rotator manşet yırtığı (genel bakış)	Omuz, rotator manşet yırtığı (genel bakış)
81	Shoulder, rotator cuff tear (partial thickness)	Omuz, rotator manşet yırtığı (kısmi kalınlık)	Omuz, rotator manşet yırtığı (kısmi kalınlık)	Omuz, rotator manşet yırtığı (kısmi kalınlık)
82	Shoulder, SLAP tear (superior labrum anterior-to-posterior	Omuz, SLAP yırtığı (superior labrum anterior-posterior)	Omuz, SLAP yırtığı (üst labrum ön-arka)	Omuz, SLAP yırtığı (üst labrum ön-arka)
83	Shoulder, subacromial impingement	Omuz, subakromiyal sıkışma	Omuz, subakromial sıkışma	Omuz, subakromial sıkışma
84	Skier's thumb	Kayakçının başparmağı	Kayakçının baş parmağı	Kayakçı başparmağı
85	Sprain	Burkulma	Burkulma	Burkulma
86	Stress fracture	Stres kırığı	Stres kırığı	Stres kırığı
87	Stress response	Stres tepkisi	Stres tepkisi	Stres yanıtı
88	Subchondral insufficiency fracture	Subkondral yetmezlik kırığı	Subkondral yetersizlik kırığı	Subkondral yetmezlik kırığı
89	Subluxation	Subluksasyon	Subluksasyon	Subluksasyon
90	Swan neck deformity	Kuğu boynu deformitesi	Kuğu boynu deformitesi	Kuğu boynu deformitesi
91	Synovitis	Sinovit	Sinovit	Sinovit
92	Tendinopathy	Tendinopati	Tendinopati	Tendinopati
93	Tophus	Tophus	Tophus	Tofüs
94	Torsion	Burulma	Torsiyon	Torsiyon
95	Transient osteoporosis	Geçici osteoporoz	Geçici osteoporoz	Geçici osteoporoz
96	Trochanteric syndrome	Trokanterik sendrom	Trokanterik sendrom	Trokanterik sendrom
97	Tubulation	Tübülasyon	Tübülasyon	Tübülasyon
98	Tunnel syndrome	Tünel sendromu	Tünel sendromu	Tünel sendromu
99	Ulnar impaction syndrome	Ulnar impaksiyon sendromu	Ulnar impaksiyon sendromu	Ulnar çarpma sendromu
100	Version	Versiyon	Sürüm	Versiyon
101	Wolff's law	Wolff yasası	Wolff yasası	Wolff yasası

as 'kas-tendon'. For instance, 'myontendinous junction' was translated into Turkish as 'kas-tendon bileşkesi', where 'kas-tendon' is an example of calque in the same structure and 'bileşkesi' is an example of literal translation, where it is translated word-to-word in an appropriate form.

To sum up, the study explored the Turkish translations of musculoskeletal radiology terms, focusing on the strategies proposed by Vinay and Darbelnet's model. Borrowing and literal translation emerged as the most frequently employed strategies, reflecting the technical and precise nature of medical terminology. Multi-word terms often required combining strategies, resulting in ten distinct patterns such as borrowing+literal translation. While the borrowing strategy dominated single-word or straightforward terms, more complex phrases demanded nuanced combinations including adaptation+borrowing or calque+literal translation. Thus, the analysis emphasizes the also highlighted the need for translators to reconcile the linguistic fidelity with the functional clarity of medical terms in the target language. This comprehensive investigation underscores the complexity of achieving accurate, culturally relevant translations in specialized fields, as in musculoskeletal radiology.

AI-based Tools and Translation of Medical Terms

The terms for musculoskeletal radiology were also translated through neural machine translation tools such as DeepL and Google Translate and an AI chatbot, namely ChatGPT. There were differences identified between the Turkish translations by radiology specialists in the reference books and the translations by AI-based tools. Nevertheless, the percentage of similarity was quite high. It was 55.20% for DeepL and likewise 55.20% for Google Translate, whereas the similarity was even higher for Chat GPT with 59.37% (see Appendix for the Turkish translations of the English terms for musculoskeletal radiology: An analysis of how NMT and AI-based tools translate medical terms). Even though the differences were due to minor alterations and alternative usages in the field, which does not heavily influence understanding, these variations should be avoided for ensuring standardized and accurate usage. The sources of differences included three major categories, namely word choice, choice of strategy use (e.g. using literal translation and borrowing instead of otherwise around), and variations in orthographic writing. For instance, for the term 'acetabular labral tear', the reference book used the translation 'asetabular labrum yırtığı' by employing borrowing and literal translation strategies. However, DeepL and Google Translate translated the term with a difference choice of borrowed word and gave the output of 'asetabular labral yırtık' (DeepL) and 'asetabular labral yırtığı' (Google Translate).

The choice of translation strategy use also leads to differences in the output. For instance, for 'bone bruise', the reference book used 'kemik kontüzyonu'by employing literal translation (for 'bone', 'kemik') and equivalence (for 'bruise', 'kontüzyonu') strategies, yet both DeepL and Google Translate translated the term word to word as 'kemik çürüğü', whilst ChatGPT suggested 'kemik kontüzyonu'. Another example is the translations of 'heterotopic ossification'. In the reference book, the borrowing strategy was used and the term was translated as 'heterotopik osifikasyon'. DeepL and Google Translate, on the other hand, translated the term as 'heteropik kemikleşme', suggesting a literal translation for the word 'ossification'.

The last type of source of differences included variations in orthographic writing. For instance, for 'heterotopic ossification', ChatGPT also followed the borrowing strategy, yet suggested the Turkish equivalent with double 's', 'heterotopik ossifikasyon'. How to write the word where borrowing strategy was used leads to the question of orthographic writing in several other ways, as well. The examples of these terms include Pseudarthrosis, Tophus, Osteitis condensans ilii, etc., where the challenge is to decide which letters to keep or change in accordance with the Turkish writing rules.

The distribution of the types of differences for DeepL can be listed as strategy use in translation (43.47%), word choice (28.26%), and orthographic writing (28.26%) respectively. The leading reason behind the difference between the translation of the radiology specialists and DeepL emerges to be strategy use. In other words, while the radiology specialist preferred to use literal translation, for instance, 'kas-tendon ünitesi' for myotendinous unit, DeepL suggested 'miyotendinöz ünite'. For Google Translate, it is word choice (45.23%), orthographic writing (33.33%), and strategy use (21.42%). In other words, word choice is the leading factor when it comes to Google Translate. For instance, Google Translate suggested 'kesişim sendromu' for 'intersection syndrome while the radiology specialist used 'kavşak sendromu' in the reference book. Lastly, for Chat GPT, the distribution is more consistent, strategy use (36.58%), word choice (31.70%) and orthographic writing (31.70%).

All in all, the present study compared the Turkish translations of musculoskeletal radiology terms from the reference books by the radiology specialists to those generated by neural machine translation (NMT) tools, DeepL and Google Translate, as well as AI-based tools, ChatGPT. While the AI tools exhibited a high percentage of similarity with the specialist translations-55.20% for DeepL and Google Translate, and 59.37% for ChatGPT-key differences were noted in word choice, translation strategy, and orthographic conventions. These differences, though minor, highlight the challenges of achieving standardization in medical translations. The findings emphasize the need for careful evaluation of AI-generated translations to ensure accuracy and consistency in specialized medical contexts.

DISCUSSION

The results of the present study align with and extend the findings of previous research in the field of medical terminology translation. Palmer et al.[9] emphasized the importance of achieving global consensus on musculoskeletal radiology terminology. Nevertheless, it is important to acknowledge the challenges posed by translating these terms into various languages. The Turkish translations analyzed in this study reveal that borrowing and literal translation were the most frequently used strategies, reflecting a similar tendency toward linguistic fidelity and technical precision observed in international studies. This adherence to established translation strategies underscores the universal difficulty in reconciling linguistic and functional equivalence in specialized fields like radiology.

Consistent with findings of some researchers, who highlighted the role of borrowing in medical terminology to preserve technical accuracy,[30] this study found that borrowing was predominantly employed, especially for single-word terms such as 'chondromalacia' ('kondromalazi'). However, the analysis also revealed nuanced patterns, such as the combined use of borrowing and literal translation for multi-word terms, highlighting the flexibility required in translating complex terms. These results point to a broader insight in medical translation, where standardization is crucial yet challenging due to linguistic and cultural variability.

The role of AI-based tools in medical translation was also explored, adding a novel dimension to the discussion. Consistent with the findings of a study, which demonstrated the potential of AI-based tools, the present study found a high degree of similarity (55.20%-59.37%) between translations by AI-based tools and those in the reference books. However, differences in strategy use, word choice, and orthographic conventions highlight limitations in the AI tools' ability to achieve standardized translations. For instance, the term

'acetabular labral tear' was translated differently by DeepL, Google Translate and ChatGPT, revealing variability in borrowing strategy implementation. These inconsistencies resonate with the concerns about the lack of contextual and domain-specific sensitivity in machine translations.

The study also sheds light on the challenges posed by orthographic variations, which were a significant source of differences in AI-generated translations. Orthographic consistency is critical for standardizing medical terminology. For instance, terms such as 'pseudarthrosis' require careful adaptation to Turkish orthography without compromising technical accuracy. The study's detailed categorization of translation strategies provides valuable insights into how AI tools might be improved to better align with the nuanced strategies employed by human specialists.

The present study focused on a recent study conducted by Palmer et al.,[9] which presented a consensus agreement globally on the English terms in the field of musculoskeletal radiology, and sought to provide an analysis of their Turkish equivalents so that a standardized terminology might be achieved for the use of radiology specialists and referring physicians.

Limitations

Furthermore, this study examined how AI-based tools translated the same terms into Turkish, as well, and discussed their similarities and differences. Nevertheless, the present study only relied on two reference books which were translated from English into Turkish. Even though, the translations were managed under the supervision of a radiology expert and with contributions of several other radiology specialists, the use of Turkish equivalents of these terms might vary in radiology reports as well as in academic publications. Future research might examine how these terms are used in the samples of radiology reports in Turkiye or in academic publications in Turkish, and gather comments and suggestions of the radiologists. Furthermore, radiology specialists might also show variance depending on individual differences such as their age range. Thus, future research might provide a comparison between terminology use of different age groups in radiology reports. Lastly, this study only focused on the Turkish translations of the English terms for musculoskeletal radiology, researchers might also explore the terminology equivalents in various language pairs as well as in other medical fields and subspecialties.

CONCLUSION

Overall, the results emphasize the need for standardized guidelines in the translation of medical terminology, particularly in specialized fields such as musculoskeletal radiology. While borrowing remains the dominant strategy, the use of hybrid strategies reflects the complexity of achieving functional clarity alongside linguistic fidelity. AI tools demonstrate potential but require refinement to address contextual and orthographic challenges more effectively. This study contributes to the growing body of literature on medical translation by highlighting the interplay between traditional human strategies and emerging AI capabilities.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out without involvement of any animate beings. Hence, an ethics committee approval was not required.

Informed Consent

Since the study was conducted without the participation of any living being, no written consent form was obtained.

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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The effect of physical activity level on quality of life in women with postmenopausal osteoporosis

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ABSTRACT

Aims: Physical activity increases and maintains bone mineral density (BMD) and reduces the risk of bone fractures. Several factors may affect quality of life (QoL) in postmenopausal osteoporosis (PMO). This study aimed to evaluate the effect of physical activity level on QoL in women with PMO.

Methods: Demographic and clinical characteristics were recorded in this cross-sectional study. Physiological parameters, including handgrip strength (HGS), one-leg standing time, and ability to squat down on the floor, were collected. The BMDs at L1–L4 total, femur neck (FN), and femur total (FT) were measured by dual-energy X-Ray absorptiometry device. Physical activity level was calculated as metabolic equivalent of task (MET) value using the International Physical Activity Questionnaire (IPAQ) and patients were classified as 'low, moderate and high'. The European Osteoporosis Foundation Quality of Life Questionnaire (QUALEFFO-41) was used to evaluate QoL.

Results: This study included 179 postmenopausal women with a mean age of 62.72±7.83 years. The average values of HGS and one-leg standing time were determined as 24.6±8.1 kg and 17.6±27.6 seconds, respectively. According to the IPAQ categories, 66.5% of the participants had low level of physical activity, and the median IPAQ score was 2286 MET. The mean QUALEFFO-41 total score was found to be 46.2±17.6. All QUALEFFO-41 questionnaire subscores, IPAQ categories, and IPAQ MET scores were significantly correlated with one-leg standing time. Additionally, all QUALEFFO-41 questionnaire subscores were negatively correlated with the HGS but positively correlated with the IPAQ category. All subscores of QUALEFFO-41 were significantly higher in inactive patients, indicating a worse QoL.

Conclusion: Low physical activity levels in women with PMO negatively impact their QoL. Additionally, physical activity level correlates with muscle strength and balance. Thus, interventions to increase muscle strength, balance and physical activity levels should be included in the treatment to improve patients' QoL with PMO.

Keywords: Quality of life, physical activity levels, postmenopausal osteoporosis

INTRODUCTION

Osteoporosis is a globally prevalent health burden and its prevalence is predicted to rise as the global population ages.[1-5] The burden of osteoporosis considering epidemiological aspects, socioeconomics, and health-related quality of life (HRQoL) has been documented.[2,4,6,7] It is well-known that osteoporosis is associated with increased fracture risk.[2,3,8] Osteoporotic fractures impair the patient's quality of life (QoL) by leading to pain and causing loss of independence.[3-6,8-10]

Previous studies indicated that independent of fragility fractures postmenopausal women with osteoporosis have worse QoL compared to the ones with normal bone mineral density (BMD).[9-13] Nevertheless, it has also been reported that women with osteoporotic fracture(s) have poorer overall QoL than those without a fracture.[3,5,7,9-12,14-20] QoL is a crucial measure of people's health, thus identifying the risk factors is essential to halt its deterioration.[3] Age, marital status, educational and financial status, functional impairment, severity of postural deformities, stage of the disease, and sedentary lifestyle are among the factors affecting the QoL of patients with postmenopausal osteoporosis (PMO).[5,9,13-15,18,19,21,22]

Physical activity has long been considered a significant modifiable factor associated with BMD and fracture risk.[23-25] Wee et al.[23] found that postmenopausal women with moderate physical activity levels on the International Physical Activity Questionnaire (IPAQ) scale had a lower likelihood of

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worsening BMD at the following 2 years. In a cross-sectional clinical study, Dallanezi et al.[24] assessed the level of physical activity using the IPAQ questionnaire in postmenopausal women with low BMD. They concluded that the rate of sedentary lifestyles was higher in osteoporotic women than in those with either osteopenia or normal BMD and the daily amount of time sitting was highest in the osteoporotic group. Conversely, Schöffl et al.[26] reported that habitual physical activity and exercise do not influence BMD in elderly postmenopausal women. A systematic review stated that the potential benefits of exercise in enhancing bone formation and reducing bone resorption biomarkers in individuals with osteoporosis.[27] Engaging in moderate to vigorous physical activity reduces the secretion of sclerostin and helps increase BMD.[25] Furthermore, increasing physical activity within an appropriate range may reduce the risk of hip fracture but not wrist fracture in older women.[28]

This study aimed to determine the physical activity level of women with PMO and evaluate the relationship between physical activity and HRQoL.

METHODS

The study protocol was approved by the Hacettepe University Non-interventional Clinical Researches Ethics Committee (Date: 31.05.2016, Decision No: GO 16/209-02). Written informed consent was obtained from all participants before the study. The study was carried out according to the principles of the Declaration of Helsinki.

A total of 179 women aged over 50 years with a diagnosis of PMO based on the classification by the World Health Organization were included in this cross-sectional study. The exclusion criteria were as follows: conditions and/or drug use that may result in secondary osteoporosis, neurological disorders, vestibular diseases, malignancy, severe cardiopulmonary diseases and instrumentation in the spine and/or joints in the lower extremities.

Firstly, the patient's age, age for menopause and T-scores at the lumbar spine (L1-L4 total), femur neck (FN), and femur total (FT) measured by dual-energy X-Ray absorptiometry (DXA) (Hologic) were noted. Then, the participants were asked to complete the questionnaires.

The IPAQ is used to determine the patient's physical activity level in the metabolic equivalent of task (MET). The IPAQ included questions about the frequency, intensity, and duration of physical activity that participants had engaged in during their everyday lives over the past seven days. Three levels of physical activity have been assigned to the participants: low, moderate, and high. Participants with a moderate physical activity level engage in vigorous physical activity for 3 or more days a week, with at least 20 minutes per day, or they engage in walking or moderate-intensity physical activity for 5 or more days a week, with at least 30 minutes per day or 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 600 MET-min/week. High physical activity levels are achieved by participating in at least 3 days of vigorous-intensity physical activity, accumulating at least 1500 MET minutes per week, or by engaging in a combination of vigorous physical activity, moderate-intensity physical activity, or walking for 7 or more days, achieving a total of at least 3000 MET minutes per week. Low-level physical activity included participants with the lowest activity levels and did not meet moderate or high physical activity criteria.

Quality of life was assessed by the European Osteoporosis Foundation Quality of Life Questionnaire (QUALEFFO-41), widely used as a disease-specific questionnaire in osteoporosis patients.[29,30] The reliability and validity of its Turkish version have been demonstrated.[31] It includes 41 questions and comprises 5 main domains: pain, physical function, social activity, general health, and mental health. The results were analyzed using the algorithm proposed by the International Osteoporosis Foundation, applying a scale from 0 to 100 where 0 represents the best and 100 represents the worst QoL.

Lastly, hand grip strength (HGS), one-leg standing time and the ability to squat on the floor were tested as physiological parameters. Jamar hydraulic hand dynamometer was used to measure the HGS while the participants were sitting on a chair with their elbows flexed at a 90° angle. It was repeated three times, resting 15 seconds between trials, and the mean value was recorded in kilograms. Then, the subjects were instructed to stand on their dominant foot and keep their eyes open, and the time to stand on one leg was measured. Finally, they were asked to squat vertically in a stable position and then rise again. The squat-on-the-floor test outcomes were marked as yes or no.

Statistical Analysis

The data analysis used IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA). For continuous variables, the mean, standard deviation (SD), or median (min-max) were utilized; for categorical variables, percentages and numbers were employed. The Kolmogorov-Smirnov test found the data to have a normal distribution, and the Pearson correlation was used to determine the relationship between the parametric variables. A p-value of 0.05 was taken into account. Since few patients had high activity levels, those with moderate and high activity levels were combined and compared with those with low activity levels.

RESULTS

The mean age of the participants was 62.7+7.8 years. It has been found that 66.5% of the patients had low level of physical activity. The demographic characteristics, T scores, physiological parameters, IPAQ and QUALEFFO-41 scores are given in **Table 1**. While HGS and one-leg standing time were significantly higher in individuals with moderate to high activity levels compared to those with low activity level, the ability to squat on floor was found to be similar (**Table 2**). Among physiological parameters, only one-leg standing time correlated with IPAQmet values (r=-0.153, p=0.041).

All subscores of QUALEFFO-41 were significantly higher in patients with low activity level indicating a worse QoL (**Table 2**). Besides, all subscores were negatively correlated with HGS and one-leg standing time (**Table 3**).

Table 1. The demographic features, clinical properties, physiological parameters and quality of life scores of the patients

	n=179
Age (years) (mean±SD)	62.7±7.8
Age for menopause (years) (mean±SD)	45.7±5.6
Body-mass index (kg/m2) (mean±SD)	27.32±4.82
Handgrip strength (HGS) (kg) (mean±SD)	24.60±8.07
One leg standing time (s) (mean±SD)	17.60±27.62
Ability to squat down on the floor (yes)	150 (83.8%)
Bone densitometry (mean±SD)	
Femoral neck T score	-1.98±0.77
Femur total T score	-1.65±0.85
Lumbar L1-L4 total T score	-2.96±0.67
Physical activity level IPAQ MET (median)	**2286**
Low-level physical activity	66.5%
Moderate-level physical activity	22.9%
High-level physical activity	10.6%
QUALEFFO-41 scores	
Pain (mean±SD)	47.10±28.27
Physical function (mean±SD)	33.15±21.16
Social function (mean±SD)	67.76±22.18
General health perception (mean±SD)	60.75±20.29
Mental function (mean±SD)	50.95±18.08
QUALEFFO-41 total score (mean±SD)	46.17±17.63

SD: Standard deviation, HGS: Handgrip strength, IPAQ: International Physical Activity Questionnaire, MET: Metabolic equivalent of task, QUALEFFO-41: The European Osteoporosis Foundation Quality of Life Questionnaire

Table 2. Physiological parameters and quality of life scores according to physical activity level

	Low-level physical activity	Moderate and high-level physical activity	p-value
One-leg standing time	14.61±18.79	25.52±39.27	0.041
Handgrip strength (HGS) (kg)	23.34±7.58	27.07±8.50	0.003
Ability to squat down on the floor			
Yes	97	53	0.288
No	22	7	
QUALEFFO-41 scores			
QUALEFFO-41 pain	53.15±25.76	35.38±28.79	<0.001
QUALEFFO-41 physical function	38.14±21.52	22.86±16.61	<0.001
QUALEFFO-41 social function	74.51±18.69	53.54±23.01	<0.001
QUALEFFO-41 general health perception	65.27±19.08	51.89±19.38	<0.001
QUALEFFO-41 mental function	54.30±16.76	44.23±18.96	0.001
QUALEFFO-41 total score	51.13±16.19	36.01±16.53	<0.001

HGS: Handgrip strength, QUALEFFO-41: The European Osteoporosis Foundation Quality of Life Questionnaire

Table 3. Relationship between balance and grip strength with quality of life

	Time to balance on one leg	Handgrip strength
QUALEFFO-41 pain	r=-0.156* p=0.037	r=-0.261* p<0.001
QUALEFFO-41 physical function	r=-0.331* p<0.001	r=-0.451* p<0.001
QUALEFFO-41 social function	r=-0.447* p<0.001	r=-0.273* p<0.001
QUALEFFO-41 general health perception	r=-0.280* p<0.001	r=-0.355* p<0.001
QUALEFFO-41 mental function	r=-0.301* p<0.001	r=-0.308* p<0.001
QUALEFFO-41 total score	r=-0.378* p<0.001	r=-0.435* p<0.001

QUALEFFO-41: The European Osteoporosis Foundation Quality of Life Questionnaire

DISCUSSION

Postmenopausal osteoporosis and fragility fractures deteriorate HRQoL to varying degrees. Women with a history of bone fractures, especially a femoral neck fracture, have a lower overall QoL than females without fractures.[5,7,9,11] Vertebral fractures were also found to be specifically linked to decreased physical domain of HRQoL and pain.[3,5,32] Several studies have shown that pain was associated with poor QoL in women with osteoporosis and pain intensity negatively affects HRQoL in women with osteoporosis with or without a vertebral fracture.[3,9] It was detected that women with osteoporosis exhibit a lower QoL in various QUALEFFO-41 subscales, regardless of bone fractures.[5,9-11,13,15,33] A systematic review indicated that individuals with osteoporosis who did not have a vertebral fracture had clinically significant declines in the domains of physical role, general health, vitality, and mental health, as well as the mental component summary score SF36. Using QUALEFFO-41, pain and physical function were worse in these patients.[12] Similarly, Godala et al.[19] concluded that osteoporosis patients have a lower QoL than healthy controls in all subscores of QUALEFFO-41. Furthermore, they stated that the QUALEFFO-41's 'mental function' domain received the worst score. Rizzo reported that compared to persons with normal BMD, subjects with osteoporosis scored lower on the QUALEFFO questionnaire regarding physical and social function.[33] Singh et al.[18] indicated that significant differences were observed in the three domains of QUALEFFO-41, consisting of pain, physical, and social function among normal BMD, osteopenic, and osteoporotic postmenopausal women. Postmenopausal women with osteopenia and osteoporosis had a lower QoL than women with normal BMD. Ciubean et al.[10] showed that women with PMO had considerably lower scores in all SF-36 domains except for the energy/fatigue dimension. Between osteoporotic women with and without fragility fractures, they noticed statistical significance in terms of leisure/social activities, mental function, and total score of QUALEFFO-41. However, no significant difference was found between the two groups in SF-36 domains except the pain domain.[10] According to Bączyk et al.,[5] the normal BMD group showed higher QoL (QUALEFFO-41) regarding pain, social function, health perception, and mental function than osteoporotic and osteopenic women. Additionally, they found a significant difference in pain, physical function, and total QUALEFFO-41 scores between osteoporotic women with fractures and those without fractures. Similarly, a significant difference in pain and total QUALEFFO-41 scores were also detected among osteopenic women between those with fractures and without

fractures. In the study of de Oliveira Ferreira et al,[16] women with PMO had lower QoL scores in both of the SF-36 and QUALEFFO-41 subscores. Furthermore, the overall QoL was also considerably lower in women with vertebral fractures than in those without fractures. Pamuk et al.[15] reported that a substantial difference was observed between the patients with and without osteoporosis in all subgroup scales of QUALEFFO-41.

In most of the above-mentioned studies, the factors which deteriorate QoL were also investigated. In a study evaluating the factors that predict QoL in postmenopausal women with osteoporosis, it has been determined that marital, educational and financial status have a statistically significant effect on QoL.[9] Pamuk et al.[15] indicated that parameters such as age, education level, employment status, income level, exercise habit, and activity level had a significant impact on QoL, based on QUALEFFO-41 outcomes. According to Bączyk et al.,[5] secondary and higher education, self-perceived back deformity, prior fractures, reduced height, and anxiety were the related factors for total QUALEFFO-41. In the study by Rizzo et al.,[33] high BMI and high FRAX score were identified as the main variables associated with deterioration in QoL. De Oliveira Ferreira et al.[16] demonstrated that a sedentary lifestyle and a BMI above 25 were associated with a lower QoL, whereas paid work was linked to a higher QoL. According to Singh et al.,[18] BMI significantly influences the physical and social function dimensions of QoL for women who are osteopenic or osteoporotic. Miyakoshi et al.[21] suggested that decreased lean muscle mass, increased thoracic kyphosis, and generalized muscle weakness could be linked to a lower QoL in osteoporosis patients.

In this study, women with PMO were evaluated for the impact of their physical activity level on their QoL. Patients with low level physical activity had significantly higher QUALEFFO-41 subscores, indicating a lower QoL. Previous studies investigating the relationship between physical activity level and QoL in patients with osteoporosis have similar findings. Stanghelle et al.[3] determined that lower levels of HRQoL were significantly related to poorer levels of physical function assessed by walking speed, and higher pain levels. Walking speed was highly correlated with four of the six subscales of the QUALEFFO-41 (except pain and mood). In another study, it has been determined that those who performed exercises for osteoporosis had significantly better scores in all subgroups of the QUALEFFO-41 except the mental function than patients who did not exercise.[34] In accordance with these studies, Pamuk et al.[15] reported that postmenopausal women with osteoporosis who exercised regularly and were more active had higher QUALEFFO-41 scores. However, they did not specify how they had measured physical activity levels in their study.

Additionally, we examined the relationship between QoL and physiological characteristics including HGS, one-leg standing time and the ability to squat on the floor and found that HGS and one-leg standing time have negative correlations with all scores of the QUALEFFO-41 questionnaire domains. Furthermore, HGS and one-leg standing time were significantly higher in individuals with moderate to high activity levels compared to those with low activity level. Previous studies have shown that HGS and one-leg standing time were positively correlated with BMD values, but their relationships with the patients' physical activity level and QoL have not been investigated.[35-40]

It is well-known that sedentary adults lose bone more quickly. A cause of older people's avoidance of physical activity is osteoporosis.[2,22,41,42] In individuals with osteoporosis, kinesiophobia may be linked to decreased levels of physical activity and QoL. Gunendi et al.[20] found that patients with osteoporosis had greater levels of kinesiophobia than healthy control participants and there was a strong link between the QUALEFFO-41 total score and the kinesiophobia score in patients with osteoporosis. As older adults' mobility and physical activity levels diminish, the risk of falling increases.[2,22,40,42] Studies have indicated that sedentary older adults experience a higher risk of hip fracture compared to more active ones.[2] Thus, exercise interventions are crucial for PMO in women.[2,4,22,40,43-49] Exercise recommendations for older adults with osteoporosis or osteoporotic vertebral fractures incorporate resistance and balance training.[43] Multimodal exercise regimens emphasizing postural balance and muscle strength are beneficial in lowering fall and fracture risk factors. Exercise regimens have also been shown to enhance kinesiophobia, mood, and QoL in osteoporosis patients.[20,48,49] In addition to medication, moderate-to-intense exercise, including weight-bearing and non-weight-bearing activities, may dramatically improve BMD and QoL in older adults with osteoporosis.[4,20,41,46] Physical activity may include 30-40 minutes of weight-bearing and resistance exercise three to four times weekly.[2,4,14] The level of evidence is higher for higher-dose exercise regimens involving multiple exercise types seem more beneficial.[2,14,42] Nevertheless, some reports suggest that patients may benefit from even low-intensity exercise.[42] In addition to helping to prevent osteoporosis, physical activities may enhance the QoL in osteoporotic patients by reducing pain, increasing mobility, and both.[2,3,14,22,42,45,46,49]

Limitations

Our study has some limitations. The findings of our study apply only to the women with PMO and do not address osteoporosis from other causes. The study's lack of male participants restricts the generalizability of the results. In our study, the participants' fracture history was not evaluated and a history of anti-osteoporotic medical treatment was not recorded. Lastly, the IPAQ questionnaire's recall bias and subjective scores are problematic when evaluating physical activity levels.

CONCLUSION

In conclusion, our study investigating the relationship between physical activity levels and QoL in women with PMO revealed that PMO patients with low physical activity levels had worse QoL. Higher HGS and one-leg standing time values were also found to be associated with better QoL in these patients. Thus, these findings suggest that interventions to increase muscle strength, balance, and physical activity levels should be incorporated into the treatment to enhance patients' QoL with PMO.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Hacettepe University Non-interventional Clinical Researches Ethics Committee (Date: 31.05.2016, Decision No: GO 16/209-02).

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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Does the presence of comorbidities in rheumatoid arthritis patients impact initial tumor necrosis factor inhibitor treatment response and retention rates?

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ABSTRACT

Aims: We aimed to evaluate the effect of comorbidities on the first tumor necrosis factor inhibitor (TNFi) treatment response and retention in patients with rheumatoid arthritis (RA).

Methods: The study included adult RA patients (with M05 and M06 ICD codes) registered in the TURKBIO database and receiving their first TNFi treatment. Data on demographic, clinical, and laboratory features, disease activity scores, and other follow-up parameters (at the beginning and months 6 and 12) were collected. The Log-Rank test and Kaplan-Meier curve were used to determine the TNFi retention rates.

Results: There were 1172 bio-naive RA patients who initiated their first TNFi treatments. The median age (IQR) of the patients was 53 (51-61), and 79.8% (n=935) were women. The most commonly used TNFi was etanercept (38.9%), followed by adalimumab (27.9%), certolizumab (13.8%), golimumab (10.8%), and infliximab (8.7%). The most prevalent comorbidities in patients were hypertension (32.6%), obesity (32.6%), osteoporosis (22.3%), asthma/COPD (17.9%), and diabetes mellitus (15.7%). The presence of comorbidities at the beginning of TNFi treatment did not affect DAS28 CRP responses at months 6 and 12 (p=0.18 and p=0.83, respectively) and the continuation rates of the first TNFi drug. After conducting a thorough analysis that factored in variables including gender, age over 60 years, smoking, serologic status, presence of erosion, and basal disease activity scores, it was determined that there were no statistically significant hazard ratios (HR) for the first TNFi persistence. However, there was a 5% decrease in adherence to the first TNFi drug with an increase in median disease duration (HR 0.95, 95% CI=0.90-1.00, p=0.048).

Conclusion: It has been observed that the presence of comorbidities in patients with RA does not significantly affect the TNFi treatment response and retention rate. However, evidence suggests that as the duration of the disease increases, the continuation of the first TNFi drug may decrease.

Keywords: Comorbidity, rheumatoid arthritis, first TNFi drug survival

*The article was presented as a poster at the EULAR 2020 congress in Madrid.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder primarily affecting the joints, leading to synovium inflammation and cartilage damage.[1] The prognosis for individuals with RA has significantly improved with the use of biological agents and close patient monitoring to succeed in low disease activity or remission. However, the presence

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of comorbidities can lead to functional limitations[2] and premature mortality in patients with RA.[3] Comorbidities may manifest in RA patients as a consequence of treatments or as a direct association with RA itself. Of the 5,317 patients, 18.3% displayed at least one comorbidity, according to the Charlson Comorbidity Index (CCI).[4] In RA, the prevalence of multimorbidity is remarkably high and is associated with a faster progression compared to individuals without RA.[5] The presence of comorbid conditions presents challenges in the management of RA, such as contraindications for medications or patient noncompliance with treatment.[6] Additionally, there is growing recognition of the significant impact that comorbidities have on the development of difficult-to-treat RA.[7]

Tumor necrosis factor inhibitors are frequently prescribed biologic agents for the treatment of RA patients who have not shown improvement with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). But, approximately 30-40% of patients treated with tumor necrosis factor inhibitor (TNFi) cannot be continued due to primary/secondary ineffectiveness or side effects.[8-10] However, the patient population in clinical trials may differ from real-life patients regarding associated comorbid conditions and additional medications, potentially leading to differences in drug survival outcomes. With this study, we aimed to assess the impact of comorbidities on the persistence of the first TNFi in patients with RA and present real-life data.

METHODS

Ethics

Ethical approval for the use of TURKBIO data was granted under protocol number 304-SBKAEK, with all participating patients having provided written informed consent. The study was carried out with the permission of the Dokuz Eylül University Faculty of Medicine Ethics Committee (Date: 07.06.2013, Decision No: 107354). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Population

The study focuses on a patient population obtained from the TURKBIO registry, a multicenter observational cohort in Turkiye dedicated to patients receiving biologic treatments for rheumatic diseases. The TURKBIO database is the Turkish version of the Danish DANBIO rheumatology database established in 2011. Patient data are entered into an online system by physicians at three-month intervals or in response to any changes in medication. In Turkiye, the administration of TNFi treatments for RA is restricted to patients with a 28-joint count disease activity score (DAS28) exceeding 5.1, who have not responded adequately to at least three standard disease-modifying antirheumatic drugs (DMARDs), one of which must be methotrexate (MTX).

The inclusion criteria for this analysis comprised adult patients diagnosed with RA, identified through specific diagnostic codes (M05 and M06 ICD), who were beginning their first course of treatment with TNFi. The study targeted biologic-naive RA patients satisfying the 2010 ACR/EULAR classification criteria,[11] thereby ensuring a well-defined cohort for evaluation.

Data Collection

The study thoroughly evaluated demographic and clinical characteristics encompassing age, gender, disease duration, smoking status, body-mass index (BMI), and acute phase reactants, notably C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Serologic status indicators, including rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP), as well as disease activity scores (such as the Clinical Disease Activity Index, DAS28, and the Visual Analogue Scale Global), were meticulously assessed. Furthermore, the Health Assessment Questionnaire-Disability Index, X-Ray evidence of erosion, and various comorbidities were documented.

Comorbidities under examination included hypertension, diabetes mellitus, coronary artery disease, dyslipidemia, cerebrovascular disease, obesity, osteoporosis, depression, chronic lung disease, liver disease, peripheral vascular disease, peptic ulcer disease, and renal disease. Additionally, patients with at least two comorbidities were defined as multi-comorbidities. The presence or absence of concomitant csDMARD and corticosteroid use was systematically recorded. However, dose calculation for these medications was not undertaken in this study. The exclusion criteria specified for the study were (i) patients lacking follow-up data and (ii) those who withdrew their informed consent.

The study assessed the persistence of the first TNFi treatment by calculating the duration between the first and last prescriptions. Drug retention was analyzed using Kaplan-Meier methods and a log-rank test to compare survival distributions. During anti-TNF therapy, disease activity was measured at baseline, 6 months, and 12 months. The data point closest to each time point was selected for analysis in cases with multiple visits within the specified intervals. Clinical responses were assessed using the DAS28 scale. A change in the DAS28 score greater than 1.2 is considered a significant improvement.

Statistical Analysis

Demographics and descriptive data are presented as median [interquartile range (IQR)] or mean (SD). The variables were checked for normal distribution using visual and analytical methods. Chi-square analysis was used for categorical variables, and the Mann-Whitney U test was used for pairwise group comparisons with non-normally distributed numerical variables. The adherence rates for the first TNFi were calculated using the Kaplan-Meier method. Risk factors associated with firstTNFi discontinuation were determined using Cox Regression analysis. Statistically significant results were considered at type-1 error levels below 5%.

RESULTS

The median age (IQR) of the RA patients was 53 (51-61) years, and 79.8% (n=935) were women. 23.2% (n=256) of the patients were smokers. RF was positive in 55.6% (n=404), and anti-CCP antibody was positive in 58.2% (n=430). At least one erosion on the radiographs was found in 61.9% of the patients (n=317). In the studied cohort, 44.2% of patients used concomitant csDMARDs, and 40.3% were prescribed

corticosteroids. The distribution of biologic therapies was as follows: etanercept was prescribed to 38.9% (n=456) of the patients, adalimumab to 27.9% (n=326), certolizumab to 13.8% (n=162), golimumab to 10.8% (n=126), and infliximab to 8.7% (n=102). The most commonly occurring coexisting disease included hypertension, which was present in 32.6% (n=262) of the patients, osteoporosis in 22.3% (n=178), asthma or chronic obstructive pulmonary disease in 17.9% (n=143), and diabetes mellitus in 15.7% (n=126). Around one-third of the patients exhibited a body-mass index of 30 or higher. The median CRP value among patients was 7 mg/L (3-18), while the median ESR was 26 mm/h (14-44). The study revealed that 66.3% (n=197) of seropositive RA patients exhibited at least one erosion on their radiographs, marking a statistically significant increase compared to seronegative patients (p=0.001). The demographic and clinical attributes of the bio-naive RA patients have been briefly outlined in Table 1.

Table 1. Demographic and clinical characteristics of patients

	n (%)
Gender (female)	935 (79.8)
Age*	53 (51-61)
Smoker	256 (23.2)
Rheumatoid factor positivity	404 (55.6)
Anti-cyclic citrullinated peptide positivity	430 (58.2)
Presence of erosion	317 (61.9)
Disease activity score 28 CRP*	3.9 (2.5-5.1)
CRP (mg/L)*	7 (3-18)
Erythrocyte sedimentation rate (mm/h)*	26 (14-44)
Visual Analogue Scale Global *	50 (20-70)
Health Assessment Questionnaire-Disability Index*	0.88 (0.38-1.25)
Comorbidities	
Hypertension	262 (32.6)
BMI ≥30	254 (32.6)
Osteoporosis	178 (22.3)
Pulmonary disease	143 (17.9)
Depression	126 (15.8)
Diabetes mellitus	126 (15.7)
Dyslipidemia	69 (8.7)
Kidney disease	47 (5.9)
Coronary artery disease	46 (5.7)
GERD/peptic ulcer	44 (5.5)
Hepatic disease	38 (4.7)
Peripheric vascular disease	16 (2)
Cerebrovascular disease	14 (1.7)

*Median, IQR: Interquartile range, CRP: C-reactive protein, BMI: Body-mass index, GERD: Gastroesophageal reflux disease

The first TNFi was initiated 9.2 (5.0-14.6) years after diagnosis in seropositive patients and 7.3 (2.8-11.5) years in seronegative patients (p=0.001). The median adherence rate of RA patients with at least one comorbid disease started on infliximab as the first bDMARD was 117.6 (±37.4) months. The presence of comorbidity did not affect the drug retention rate in RA patients using infliximab as their first TNFi (p=0.065). There was no statistically significant variance observed between the drug survival rates of etanercept users with or without comorbidities. (71.2 months and 87.3 months, respectively, p=0.56). No correlation existed between comorbidities and TNFi persistence in those using golimumab (p=0.66). The drug survival rate in patients initiated on certolizumab for RA was not found to be affected by the presence or absence of comorbidities (p=0.055). Similarly, there is no statistically significant variance between comorbidities and drug persistence when treated with adalimumab (p=0.94). Concomitant use of csDMARDs and/or steroids had no significant effect on the duration of the first TNFi (p=0.064, p=0.30, respectively).

The influence of hypertension, diabetes mellitus, coronary artery disease, or cerebrovascular disease on the adherence to the initial TNFi drug was insignificant (p=0.570, p=0.143, p=0.213, p=0.907, respectively). Similarly, dyslipidemia, peripheral vascular disease, pulmonary disease, or depression did not affect the first TNFi survival (p=0.140, p=0.631, p=0.199, and p=0.996). Notably, chronic kidney damage showed a marginally significant effect on drug persistence (p=0.051). At the same time, a body-mass index ≥30 did not affect the first TNFi drug survival (p=0.471). Having multi-comorbidity also did not affect retention on the first TNFi drug (p=0.829). Moreover, the presence of comorbidities at the beginning of TNFi treatment demonstrated no impact on DAS28 CRP responses at months 6 and 12 (p=0.18 and p=0.83, respectively). Overall, in rheumatoid arthritis, it was observed that comorbidities did not impact retention rates to the first TNFi drug (as illustrated in Figure) or the treatment response.

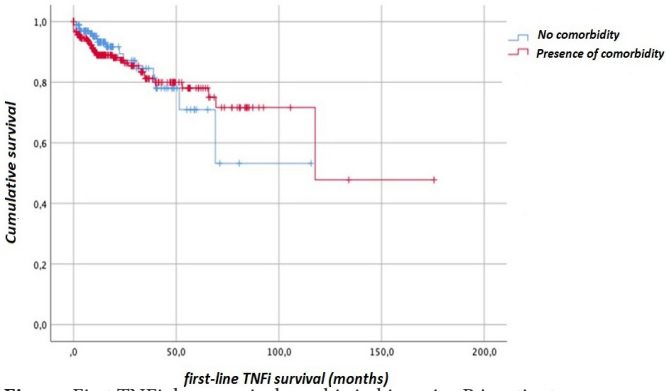

Figure. First TNFi drug survival graphic in bio-naive RA patients

TNFi: Tumor necrosis factor inhibitor, RA: Rheumatoid arthritis

Using variables including gender, age >60 years, smoking, seropositivity status, presence of erosion on X-Rays, and basal disease activity scores, no significant hazard ratios were obtained in the Cox proportional hazard analysis for the first TNFi persistence. In contrast, with the increase in median disease duration, adherence to the first TNFi decreases by 5% (HR 0.95, 95% CI: 0.90-1.00, p=0.048) (Table 2).

Table 2. Cox proportional hazard analysis for discontinuation of the first TNF inhibitor

Variable	HR	95% CI		p
Gender (male)	1.55	0.68	3.50	0.294
Age ≥60 years	0.72	0.31	1.67	0.446
Median disease duration (years)	0.94	0.89	1.00	0.052
Smoker	2.18	0.78	6.11	0.137
RF positivity	1.55	0.69	3.49	0.293
Presence of erosion	1.45	0.65	3.24	0.362
Basal HAQ	1.15	0.66	2.02	0.627
Basal DAS28-CRP	0.61	0.28	1.35	0.223
Basal CDAI	1.06	0.97	1.15	0.191
Basal ESR	0.99	0.97	1.01	0.393
Basal VAS global	1.01	0.98	1.03	0.594
Infliximab	0.00	0.00		0.980
Etanercept	1.22	0.50	2.93	0.663
Golimumab	1.74	0.36	8.43	0.490
Sertolizumab	0.86	0.11	6.86	0.887
Adalimumab	0.88	0.24	3.25	0.853
Final model				
Median disease duration (years)	0.95	0.90	1.00	0.048

TNF: Tumor necrosis factor, HR: Hazard ratio, CI: Confidence interval, RF: Rheumatoid factor, HAQ: Health Assessment Questionnaire, DAS 28: Disease activity score 28, CRP: C-reactive protein, CDAI: Clinical Disease Activity Index, ESR: Erythrocyte sedimentation rate, VAS: Visual Analog Scale

DISCUSSION

This study, conducted in the TURKBIO registry, suggests that comorbidity in bio-naive patients with RA starting the first TNFi treatment is not associated with a decreased treatment response and shortened retention rate. It is notable that previously identified factors, including gender, age, RF positivity, basal disease activity scores, and smoking, also did not appear to have a significant impact on drug survival for the first TNFi in our cohort.

In most studies presenting real-life data, approximately 50% of patients discontinued biologic therapy or had to switch to an alternative agent within five years after the first bDMARD.[12] The persistence of TNFi treatment in RA patients depends on its effectiveness and tolerability. Prolonged drug survival may indirectly indicate longer remission in RA patients, making it crucial to analyze the contributing factors. Comorbidities play a significant role in affecting the quality of life in RA patients[13] and can potentially limit treatment options. Comorbidities may lead to a preference for less intensive treatment than is indicated. For instance, a study demonstrated that the likelihood of bDMARD usage decreased by 11% with each additional chronic disease.[14] Patients with more than two comorbidities also experienced a longer median time to first biologic agent prescription than those without multimorbidities.[15] This study did not identify a significant relationship between multi-comorbidity and TNFi persistence.

According to the UK cohort, comorbidities such as respiratory and cardiovascular diseases are significantly prevalent in newly diagnosed RA patients.[16] Additionally, RA patients had higher 3-year comorbidity incidence than controls.[17] The European League Against Rheumatism has emphasized the importance of screening for comorbid conditions like infection, accelerated atherosclerosis, osteoporosis, gastrointestinal disorders, malignancies, and depression in RA patients.[18] Additionally, according to the EULAR working group, comorbidities in difficult-to-treat RA may affect the assessment of inflammatory activity.[19] Considering the potential for obesity, infections, malignancies, and fibromyalgia to cause an overestimation of inflammatory markers and/or disease activity, it is crucial to consider these factors in the assessments.[20] In the CORRONA registry, RA patients with more comorbidities are less likely to respond to therapy.[21] However, the UK inception cohort data indicated no correlation between baseline comorbidities and DAS28 outcome at 5 and 10 years.[22] Furthermore, the survival rate with first-line bDMARD was similar for those with and without comorbidities in the Spanish cohort.[23] Similarly, the results of our study suggested that there was no impact of comorbidities on the initial TNFi drug survival or treatment response rates.

Continuation rates of TNFi treatment indirectly show us the effectiveness and safety of the drug. In a study evaluating the real-life 10-year survival of the first TNFi drugs for inflammatory arthritis, 28% discontinued treatment due to ineffectiveness and 24.8% due to side effects.[24] British Society for Rheumatology Biologics Register revealed that 50% of patients discontinued their initial TNFi treatment during a median follow-up of 2 years.[25] Combining with a csDMARD improves bDMARD survival,[25,26] but the RF is negatively associated with biological drug survival.[27] In a multicenter study, higher baseline disease activity and female gender were associated with early TNFi discontinuation.[28] In the Israeli population, the prolonged duration of the first bDMARD medication is associated with male gender, concurrent csDMARD use, and the initiation of bDMARD treatment in earlier calendar years.[29] The use of oral steroids in combination with TNFi treatment has been shown to increase the risk of discontinuation in the ANSWER cohort.[30] In our study, we found that age, gender, baseline activity scores, or RF positivity did not affect the first-line TNFi retention rate.

Limitations

It's important to highlight that this study has some limitations that should be considered. Firstly, the reasons for treatment discontinuation, whether due to lack of efficacy or adverse events, were not explicitly stated. Another limitation is that we did not use a standard comorbidity index such as CCI. Dose calculation for concomitant csDMARD and steroid was not undertaken. Furthermore, we could not differentiate between the effects of the original and biosimilar TNFi.

CONCLUSION

The comorbidities in RA raise essential considerations regarding the impact on disease activity, functional status, and treatment response. However, our study suggests that comorbidities may not be associated with the decreased first TNFi treatment response and lower retention rate. Notably,

previously identified factors such as gender, seropositivity, disease activity scores, and structural damage presence did not significantly impact drug survival for the first TNFi in our cohort. However, it is essential to acknowledge the need for further prospective research to understand how multimorbidity affects disease outcomes and treatment survival comprehensively.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Dokuz Eylül University Faculty of Medicine Ethics Committee (Date: 07.06.2013, Decision No: 107354).

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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Hypertension awareness among university students: the impact of education and societal factors

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ABSTRACT

Aims: Hypertension (HT) is a leading global cause of morbidity and mortality, contributing significantly to the burden of cardiovascular diseases. Despite its widespread prevalence, HT is often underdiagnosed and poorly managed, particularly among younger populations. This study investigates HT awareness among university students, focusing on the impact of education, gender, and lifestyle practices.

Methods: A cross-sectional online survey was conducted among 546 students from various academic disciplines using an online questionnaire that assessed demographics, HT awareness, lifestyle factors, and blood pressure monitoring habits. Statistical comparisons were performed using independent t-tests, Mann-Whitney U tests, and correlation analyses.

Results: Study results revealed notable disparities in HT awareness and behaviors. Medical students demonstrated higher awareness of risk factors, diagnostic thresholds, and BP monitoring practices compared to non-medical students. Females consistently exhibited healthier lifestyle behaviors, including lower smoking prevalence, greater physical activity, and proactive BP monitoring. Awareness of dietary factors contributing to HT was moderate (62.8%), but knowledge of diagnostic BP thresholds was alarmingly low (22.9%), even among medical students. Family history of cardiovascular diseases positively influenced HT awareness, while beliefs about COVID-19's impact on BP regulation highlighted gaps in health literacy.

Conclusion: The findings underscore the critical role of formal education and targeted interventions in enhancing HT awareness. Integrating basic health education into non-medical curricula, addressing gender-specific disparities through tailored campaigns, and promoting familial health education are vital strategies for mitigating the long-term cardiovascular risks associated with undiagnosed and uncontrolled hypertension among young adults.

Keywords: Hypertension, awareness, university students, young

INTRODUCTION

Hypertension (HT), is a leading cause of morbidity and mortality globally.[1] It contributes significantly to the burden of cardiovascular diseases, and is responsible for approximately 10.8 million deaths annually.[2] Despite its prevalence and devastating consequences, HT is often underdiagnosed and inadequately managed, primarily due to a lack of awareness and knowledge about the condition among the general population.[3] This gap is particularly concerning among younger demographics, who are traditionally perceived as being at lower risk for HT but increasingly exhibit risk factors such as obesity, sedentary lifestyles, and poor dietary habits.[4,5]

The rising prevalence of HT in youth necessitates targeted educational interventions to enhance awareness and promote early preventive measures.[6] Early detection and management of HT are critical, as elevated blood pressure (BP) during adolescence and early adulthood can predispose individuals to persistent HT and associated complications later in life.[7] Furthermore, awareness of modifiable and non-modifiable risk factors is essential to mitigate the public health burden of this condition.[8] University students, representing a highly dynamic and educated segment of society, provide a unique cohort for assessing HT awareness. This group is at a transitional stage of life, where lifestyle habits are often formed and consolidated.[9]

Previous studies have primarily focused on the general adult population, with limited research targeting young adults and university students. This study seeks to fill this gap by evaluating the awareness of HT among undergraduate students from diverse academic disciplines. By investigating their knowledge of HT risk factors, lifestyle practices, and monitoring habits, this research aims to identify critical gaps and opportunities for intervention. Furthermore, the study explores the influence of medical education, gender, and family medical history on HT awareness, providing a comprehensive

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understanding of the factors shaping health behaviors in this population.

METHODS

Ethics

Ethical approval for the study was obtained from the Ufuk University Non-interventional Clinical Researches Evaluation Ethics Committee (Date: 09.01.2025, Decision No: 25.01.09.02/16). Prior to participation, an online informed consent was obtained from all individuals. The collected data were anonymized and securely stored to uphold participant confidentiality and ensure compliance with data protection regulations. All procedures adhered to the ethical principles outlined in the Declaration of Helsinki.

Study Design

This was a cross-sectional study aimed at evaluating HT awareness, lifestyle practices, and associated factors among undergraduate students. The study utilized an online survey format, ensuring broad accessibility and convenience for participants. This design allowed for a rapid and cost-effective method of data collection while minimizing potential biases associated with in-person surveys.

Study Population

The target population comprised undergraduate students enrolled in various academic disciplines, including medicine and non-medical fields, across multiple universities. A total of 546 students participated in the study, representing a diverse cohort in terms of academic background, gender, and lifestyle practices. The inclusion of medical and non-medical students provided a comparative perspective on the impact of educational exposure to health-related topics on HT awareness. The inclusion criteria comprised undergraduate students aged 18-30 years old. Exclusion criteria encompassed individuals with incomplete survey responses. The latter were omitted from the final analysis to ensure the integrity and quality of the data.

Data Collection

The study utilized a structured online questionnaire, meticulously developed to address the objectives of the research. The survey comprised four primary sections. The first section focused on demographics and lifestyle information, including variables such as age, gender, academic discipline, smoking habits, physical activity, and body-mass index (BMI). The second section assessed participants' awareness of HT, exploring their knowledge of risk factors, diagnostic thresholds, and the significance of BP monitoring. This section also included questions on dietary components influencing BP, symptoms of high BP, and the organs most affected by HT. The third section evaluated BP monitoring practices, examining participants' ownership of sphygmomanometers, frequency of BP measurement, and awareness of ideal conditions for accurate BP measurement. The final section investigated the influence of social and medical factors, including family history of cardiovascular diseases, diabetes, and HT, alongside perceptions of the impact of COVID-19 on BP regulation. The questionnaire was initially pretested to a small group of students to ensure clarity, relevance, and ease of understanding. Feedback from this pilot test was used to refine the survey before full deployment. The Participation was voluntary, and respondents were informed about the study's purpose, confidentiality of their responses, and the option to withdraw at any time.

Statistical Analysis

The numerical data obtained in the study will be presented as mean±standard deviation (SD), while categorical data will be reported as frequency (n) and percentage (%). The normality of the data distribution will be assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For normally distributed data, paired sample T tests will be used for dependent groups, and independent sample t-tests for independent groups. For non-normally distributed data, the Wilcoxon signed-rank test will be used for dependent groups, and the Mann-Whitney U test for independent groups. The chi-square test will be applied for the comparison of categorical variables.

Correlation analyses will be conducted to examine the relationships between hypertension awareness and demographic or behavioral factors. Pearson's correlation test will be used for parametric datasets, and Spearman's correlation test for non-parametric datasets. To identify the factors influencing hypertension awareness levels, a multivariate logistic regression model will be constructed. This model will include variables found to be significant in univariate analyses ($p<0.05$) as well as other variables deemed biologically significant. Data analysis was done using SPSS version 21.0 for windows (IBM Corp., USA).

RESULTS

Among the 546 undergraduate students surveyed, comprising 328 medical and 218 non-medical students, notable disparities in HT awareness and health behaviors were observed. While 46.9% of participants believed that they led a healthy lifestyle, this perception was significantly more common among medical students compared to non-medical students (54.3% vs. 35.8%, $p<0.01$), with females reporting higher adherence to healthy habits than males. Smoking prevalence was 27.1%, with medical students and females exhibiting notably lower rates than their counterparts. Nearly half of the participants (48.9%) engaged in regular physical activity, and the mean BMI was 23.1±3.5 kg/m^2, once again medical students and females demonstrating lower values. Awareness of HT risk factors varied, with 62.8% identifying dietary contributors but only 22.9% recognizing diagnostic BP thresholds; medical students significantly outperformed non-medical students in both areas (all p-vales <0.01) (**Table**).

Blood pressure monitoring practices were prevalent, with 61.9% owning a sphygmomanometer and 65.8% measuring their BP at least once in the past year, trends more pronounced among medical students and females. Knowledge of the ideal BP measurement conditions was observed in 56% of participants, predominantly among medical students (77.4% vs. 23.9%, $p<0.01$). Family history of cardiovascular diseases was positively associated with higher HT awareness ($p<0.01$), while the belief that COVID-19 could influence BP regulation was noted in 25.3% of participants but did not significantly impact awareness levels.

Table. Distribution of responses to survey questions on hypertension awareness and related behaviors among university students, stratified by faculty of study

Survey questions	Rates of correct answers among participants n (%)			
	Total (n=546)	Faculty of medicine (n=328)	Other faculties (n=218)	p-value
Do you believe that you lead a healthy lifestyle?	256 (46.9)	178 (54.3)	78 (35.8)	p<0.01
Do you smoke?	148 (27.1)	48 (14.6)	100 (45.9)	p<0.01
Do you know which food components can raise blood pressure?	343 (62.8)	230 (70.1)	113 (51.8)	p<0.01
Do you exert regular physical exercise?	267 (48.9)	168 (51.2)	99 (45.4)	0.34
Body-mass index (kg/m^2)	23.1±3.5	22.8±3.7	23.5±3.2	0.02
Do you have a sphygmomanometer at home?	338 (61.9)	216 (65.9)	122 (56.0)	0.15
Have you measured your blood pressure in the last year?	360 (65.8)	248 (75.6)	112 (51.4)	p<0.01
Do you know the ideal conditions for measuring blood pressure?	306 (56)	254 (77.4)	52 (23.9)	p<0.01
What are the blood pressure thresholds?	125 (22.9)	100 (30.5)	25 (11.5)	p<0.01
What is the most common symptom of high blood pressure?	289 (52.9)	224 (68.3)	60 (27.5)	p<0.01
Which organ is most commonly affected by hypertension?	289 (52.9)	212 (64.6)	97 (44.4)	p<0.01
Do you have a family history of hypertension?	284 (52)	178 (54.3)	106 (48.6)	0.37
Do you have a family history of diabetes?	198 (36.3)	118 (36)	80 (36.7)	0.89
Do you have a family history of high cholesterol?	286 (52.4)	172 (52.4)	114 (52.3)	0.98
Do you have a family history of cardiovascular diseases?	224 (41)	124 (37.8)	100 (45.9)	0.15
Do you have a family history of stroke?	58 (10.6)	36 (11)	22 (10.1)	0.75
Do you have a family history of kidney diseases?	56 (10.3)	36 (11)	20 (9.2)	0.52
Do you believe that COVID-19 infection or vaccination can affect blood pressure levels?	138 (25.3)	72 (22)	66 (30.3)	0.06

DISCUSSION

This study evaluated HT awareness among undergraduate students, highlighting differences between medical and non-medical students, gender disparities, and the influence of familial and social factors, including perceptions related to the COVID-19 pandemic. The findings provide a comprehensive overview of the current awareness levels and practices, offering insights for future educational and public health initiatives.

Numerous studies highlight the critical role of formal education in promoting health literacy and positive health-promoting lifestyle.[10] For instance, a study demonstrated that medical students possess a higher level of health literacy, which is crucial for preventing diseases and promoting healthy life style.[11] In parallel to this, our study showed that medical students have a significantly higher levels of awareness regarding HT risk factors, diagnostic thresholds, and the importance of BP monitoring compared to their non-medical counterparts. This disparity underscores the critical role of formal education in shaping health knowledge and behaviors. Medical curricula likely provide exposure to preventive cardiology concepts, practical training in BP measurement, and discussions on lifestyle modifications, all of which contribute to enhanced awareness. Conversely, non-medical students, lacking this exposure, showed notable gaps, particularly in identifying BP thresholds and ideal measurement conditions. This gap emphasizes the need to integrate basic health education into non-medical curricula to ensure broader public awareness.

Another aspect of HT awareness is gender disparities, studies have shown that women are generally more likely to adhere to health guidelines and engage in preventive behaviors, which may be influenced by societal norms and expectations.[12] In our study, gender-based differences about HT awareness were evident, with females consistently exhibiting greater HT awareness and healthier behaviors compared to males. Lower smoking prevalence, better adherence to regular physical activity, and more proactive BP monitoring practices among females was also observed. Cultural and societal norms may also play a role, as women often face greater emphasis on maintaining health, which could explain these disparities. However, males demonstrated higher engagement in behaviors linked to cardiovascular risk, such as smoking, which may hinder their overall awareness and predispose them to long-term health issues. Addressing these gender disparities through targeted public health campaigns could encourage men to adopt healthier practices and improve their understanding of HT.

On the other hand, nutritional awareness is essential, as it promotes healthier eating behaviors that can significantly improve dietary choices, playing a crucial role in managing HT effectively.[13] Although 62.8% of the participants in our study were aware of dietary factors contributing to HT, like many college students, they often encounter challenges when adapting to new food environments, which can substantially influence their eating habits.[14] Such challenges highlight the need for targeted interventions in campus dining facilities to promote healthier food choices, thereby potentially reducing the risk of HT.

Awareness of HT within the population reveals notable gaps, particularly in understanding diagnostic criteria, emphasizing the importance of targeted educational initiatives.[15] In our study, only 22.9% correctly identified BP thresholds for diagnosing HT. This finding is concerning, as knowledge of diagnostic criteria is essential for recognizing and addressing high BP early. Even among medical students, who exhibited better knowledge than non-medical peers, this gap highlights the need for enhanced emphasis on HT in medical education. Practical training modules that focus on recognizing and interpreting BP values could bridge this gap and improve diagnostic proficiency.

Studies showed that personal experiences with diseases can enhance awareness and prompt individuals to seek medical advice more proactively.[16] In our study, participants with a family history of cardiovascular diseases showed higher HT awareness. However, family histories of diabetes and HT alone did not show a similar impact. This discrepancy may indicate varying levels of perceived risk associated with different health conditions, as individuals may prioritize awareness and management of conditions they perceive as more immediately threatening, such as cardiovascular diseases, suggesting the need for targeted interventions focusing on familial health education to better connect these conditions to HT awareness.

The COVID-19 pandemic has significantly heightened public awareness of health-related issues, particularly cardiovascular diseases, while also creating opportunities for the spread of misinformation.[17,18] In our study, 25.3% of participants believing that the infection or vaccination could affect BP regulation. This perception was more prevalent among non-medical students, potentially reflecting greater susceptibility to misinformation. While this belief did not significantly impact HT awareness, it underscores the importance of clear communication from health authorities to address misconceptions and provide evidence-based information.

The study's findings highlight the need for comprehensive public health initiatives to improve HT awareness among young adults. Integrating health education into non-medical curricula could ensure that all students, regardless of academic discipline, receive basic knowledge about HT and its management. Gender-specific campaigns that address the unique health behaviors of males and females could also help reduce disparities. Additionally, leveraging familial relationships to promote health education could further enhance awareness and engagement in preventive practices.

Limitations

This study has several limitations that should be acknowledged. The reliance on self-reported data introduces the potential for response bias, as participants may overestimate their health behaviors or knowledge levels. Additionally, the cross-sectional design captures awareness at a single point in time, limiting the ability to infer causal relationships. The study also excluded postgraduate young students, who may exhibit different awareness levels and behaviors. Future research could address these limitations by employing longitudinal designs and including a broader range of participants.

CONCLUSION

This study underscores the importance of education, gender, and familial influences in shaping HT awareness among undergraduate students. While medical students and females demonstrated greater awareness and healthier behaviors, critical gaps, particularly in understanding diagnostic thresholds, persist across the cohort. Addressing these gaps through targeted educational interventions and public health campaigns could significantly improve HT awareness and prevention among young adults, contributing to long-term cardiovascular health.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ufuk University Non-interventional Clinical Researches Evaluation Ethics Committee (Date: 09.01.2025, Decision No: 25.01.09.02/16).

Informed Consent

Prior to participation, an online informed consent was obtained from all individuals.

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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Association of thrombocytopenia on secondary infection and mortality in pediatric intensive care unit patients receiving continuous renal replacement therapy

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ABSTRACT

Aims: Continuous renal replacement therapy (CRRT) is a widely used treatment modality in pediatric patients. We aimed to evaluate the susceptibility of thrombocytopenia to secondary infection and mortality during intensive care unit admission and the initiation of CRRT in patients admitted to the pediatric intensive care unit.

Methods: We conducted a retrospective study of patients in a tertiary pediatric intensive care unit who underwent CRRT between February 2021 and July 2024. The study included 34 patients who underwent CRRT.

Results: The study population consisted of patients with a median age of 26 months and 58.8% were male. At pediatric intensive care units (PICU) admission, 10 (29.4%) patients had thrombocytopenia, whereas 15 (44.1%) had thrombocytopenia at CRRT initiation. Patients with thrombocytopenia at the start of CRRT had a greater risk of mortality. Mortality approached significance in patients with thrombocytopenia at PICU admission. The risk of infection was significantly increased in patients with thrombocytopenia at the start of CRRT according to univariate and multivariate regression analyses (p=0.01).

Conclusion: The detection of thrombocytopenia at the beginning of CRRT is associated with a higher secondary infection rate and mortality during pediatric intensive care hospitalization. CRRT and thrombocytopenia negatively impact immune function, and further prospective studies are needed to assess their association with subsequent infection risk.

Keywords: Continuous renal replacement therapy, pediatric intensive care, secondary infection, thrombocytopenia, mortality

INTRODUCTION

Continuous renal replacement therapy (CRRT) is a widely used treatment modality in pediatric patients. However, the prognosis of pediatric patients is poor, with mortality rates ranging from 30% to 60% in pediatric intensive care units (PICU).[1-2] Although CRRT is increasingly used in clinical practice, the relationship between the survival rate does not increase in parallel. Its proven safety and efficacy make it the preferred treatment for critically ill pediatric patients. CRRT is an adjuvant treatment modality that removes fluid overload (FO), uremic toxins, endotoxins, proteins, and inflammatory mediators in critically ill patients.[3] The timing and indications for initiating CRRT are still under discussion. The most common indications for CRRT include acute kidney injury (AKI), FO, removal of toxic metabolites, inborn errors of metabolism, sepsis, and poisoning, as well as nonrenal indications such as removal of inflammatory mediators. AKI and FO are common in critically ill children and increase mortality.

The pathophysiology of sepsis-associated AKI is thought to involve microcirculatory dysfunction, inflammation, autophagy, the inflammatory pathway, vitamin D levels, and immunosuppression.[4] In patients undergoing CRRT for sepsis, immunosuppression also develops due to the elimination of cells responsible for body defense, such as platelets and leukocytes. CRRT also provides the removal of inflammatory mediators that cause sepsis. Sepsis is associated with the development of secondary infection by causing immunosuppression in both AKI and CRRT used in the treatment of sepsis.

Platelets are key components of both innate and adaptive immunity.[5] It is possible that platelet loss, which plays a role in innate and adaptive immunity, may lead to subsequent infection. Platelet depletion after the initiation of CRRT has been associated with increased mortality and a lack of renal recovery in survivors.[6] Thrombocytopenia is common in critically ill patients and is often associated with a negatively impacted prognosis. The incidence of thrombocytopenia varies among studies, ranging from 35% to 55% in studies of pediatric patients.[7] Decreased platelet production or increased destruction associated with therapeutic

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interventions and underlying diseases such as sepsis are causes of thrombocytopenia. Sepsis and multiorgan failure are the most important risk factors for the development of thrombocytopenia in intensive care patients, and markers related to disease severity, such as the need for mechanical ventilation and the duration of vasopressor use, have also been shown to be risk factors for thrombocytopenia. Thrombocytopenia is common in critically ill patients who require dialysis and negatively impacts prognosis. Thrombocytopenia developing before CRRT initiation and during follow-up is associated with increased intensive care unit mortality.[8]

AKI and thrombocytopenia, especially when secondary to sepsis, are common in critically ill children requiring dialysis. Thrombocytopenia is an independent risk factor for AKI and a marker of disease severity.[8] There is insufficient information in the literature about the incidence and outcome of thrombocytopenia in pediatric patients. In this study, we aimed to evaluate whether thrombocytopenia at admission to the intensive care unit and initiation of CRRT would be an independent risk factor for secondary infection and mortality in patients admitted to the PICU.

METHODS

The study was approved by the İzmir Bakırçay University Non-interventional Clinical Researches Ethics Committee (Date: 10.07.2024, Decision No: 1688). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This retrospective analysis included all hospitalized patients who underwent CRRT in the Pediatric Intensive Care Unit of Manisa City Hospital between February 2021 and July 2024. Many demographic and clinical variables, such as age, sex, laboratory results, PRISM III score, pediatric sequential organ failure assessment (pSOFA) score on the day that CRRT was initiated, number of days on mechanical ventilation, CRRT indication, dialysis catheter location, and culture results, were documented in the study. Also recorded were the platelet value at initiation of CRRT, number of days on CRRT, day on which CRRT was initiated in the ICU, time from initiation of CRRT to platelet nadir, and time from discontinuation of CRRT to discharge from the ICU. The study included individuals aged between 29 days and 18 years who underwent CRRT during their PICU stay and had complete and available data. AKI, fluid excess greater than 10% of the normal body volume, electrolyte imbalance, severe metabolic acidosis and acute metabolic disorder episodes are classified as criteria for CRRT. The total percent fluid overload (FO%) was calculated by employing the following formula: [(total fluid intake-total fluid output) (in liters)/admission body weight in kg]×100. The Vasopressor Index score (VIS) was calculated via the following equation: the sum of the dopamine dosage (g/kg/min), dobutamine dose (g/kg/min), 100 times the epinephrine dose (g/kg/min), 10 times the milrinone dose (g/kg/min), 10,000 times the vasopressin dose (U/kg/min), and 100 times the norepinephrine dose (g/kg/min).[9]

CRRT was initiated in critically ill children with FO>10% when diuretics failed to achieve or maintain negative fluid balance. Percutaneous insertion of double-lumen central venous catheters is often performed through the right internal jugular vein. While subclavian vein access was used in one patient due to thrombosis, femoral vein access was preferred in three patients. The PRISMAFLEX hemofiltration system apparatus was used for CRRT. Modifications were applied to the CRRT parameters, with blood flow rates ranging from 4 to 10 cc/kg/min. Adjustments were made to the dialysate and replacement settings following the clearance dose of 2000 cc/hour/1.73 m^2. Unfractionated heparin was used for anticoagulation.[10] However, patients with platelet counts less than $50\times10^3/mm^3$ were not anticoagulated, a larger catheter was placed, or the blood flow rate was kept high. The criteria for termination of CRRT are increased urine output, no fluid overload, decreased need for vasoactive drugs, and patient death. Patients with platelet counts $<100\times10^3/\mu l$ at PICU admission and CRRT initiation were evaluated as having thrombocytopenia. Patients who developed sepsis during CRRT or after CRRT was terminated and had positive blood cultures were considered to have secondary infection. Secondary infection was defined as a new antibiotic prescription for possible infection during CRRT and in the post-CRRT intensive care unit and subsequent detection of proven infection. Another endpoint evaluated as a secondary outcome was the development of septic shock during ICU follow-up, defined as suspected infection, hypotension refractory to fluid resuscitation, or at least 2 SIRS criteria positive and lactate elevation. Finally, mortality was defined as survival to discharge during the ICU stay.

The primary outcome included the development of a secondary infection in patients with platelet counts <100×103/μl at PICU admission and CRRT initiation. The secondary outcome was the association between secondary infection and mortality in patients with thrombocytopenia at PICU admission and the initiation of CRRT.

Statistical Analysis

The data analyses were performed via SPSS 22 software (SPSSX Inc., Chicago, IL, USA). The characteristics of the study population were described via frequency distributions for categorical variables and mean and standard deviation (SD) values, medians, and ranges for continuous variables, on the basis of the normal distribution of the data. The Kolmogorov-Smirnov test was used to evaluate the homogeneity of the data distribution. The statistical significance of continuous variable comparisons was determined via Student's t-test or the Mann-Whitney U test in pairs, depending on the distribution of the analyzed variable; if necessary, it was evaluated via one-way ANOVA or the Kruskal-Wallis test in multiple groups. The relationships among the parameters were investigated via Pearson correlation analysis. Comparisons of categorical variables were carried out via the chi-square test or Fisher's exact test. The power analysis of thrombocytopenia patients who underwent CRRT in adult intensive care was determined as 80%. In our study, 0.05 (1-alpha) and 0.8 effect sizes were calculated according to the sample number, and 80% power was calculated according to the independent samples t-test analysis.[11] All the statistical tests were two-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS

The study included a cohort of 34 patients who underwent CRRT from February 2021 to July 2024. Table 1 shows the patient characteristics. The study population consisted of patients with a median age of 26 months and an interquartile range (IQR) of 8-138 months. Additionally, 58.8% of the patients were male. The most common comorbidity in the entire sample was metabolic/genetic disease, which occurred in 15 individuals (44.1%). Sepsis was responsible for most PICU admissions, accounting for 47.1% of cases. At PICU admission, 10 (29.4%) patients had thrombocytopenia, whereas 15 (44.1%) had thrombocytopenia at CRRT initiation. The mortality rate in the PICU was determined to be 35.3%.

Patients with thrombocytopenia at the start of CRRT were younger than those without thrombocytopenia (p=0.01). Patients with thrombocytopenia at the start of CRRT had a greater rate of developing infection during PICU follow-up (p=0.01). Mortality was greater in patients with thrombocytopenia at PICU admission, but this difference was not statistically significant. Mortality was significantly greater in patients with thrombocytopenia at CRRT initiation (p=0.007) (Table 2).

The multivariate analysis included the following outcome measures; age, sex, PRISM III score, comorbidities, PICU admission diagnosis, VIS score, duration of mechanical ventilation, and duration of PICU stay. Regression analysis revealed that the risk increased with age in patients with thrombocytopenia at PICU admission and increased mortality. Patients with thrombocytopenia at the start of CRRT had a greater risk of mortality. Mortality approached significance in patients with thrombocytopenia at PICU admission. The risk of infection was significantly increased in patients with thrombocytopenia at the start of CRRT according to univariate and multivariate regression analyses (p=0.01) (Table 3).

Table 1. Patient use of CRRT

Characteristics	Total (n=34)
Age (month), median (IQR)	26 (8-138)
Sex, n (%)	
Female	14 (41.2)
Male	20 (58.8)
PRISM III score, median (IQR)	27.5 (20-32)
Comorbid condition, n (%)	
Genetic/metabolic	15 (44.1)
Other	19 (55.9)
PICU admission diagnosis, n (%)	
Sepsis	16 (47.1)
Respiratory system diseases	8 (23.5)
Acute attacks of metabolic diseases	2 (5.9)
Acute renal failure	4 (11.8)
Other	4 (11.8)
Need for inotrope, n (%)	28 (82.4)
Vasoactive inotropic score, median (IQR)	37.5 (20-90)
Thrombocytopenia at PICU admission, n (%)	10 (29.4)
Thrombocytopenia at the initiation of CRRT, n (%)	15 (44.1)
Infection after CRRT, n (%)	15 (44.1)
Invasive mechanical ventilation, n (%)	29 (85.3)
Duration of mechanical ventilation (days), median (IQR)	12 (7-15)
Duration of PICU stay (days), median (IQR)	14.5 (11.5-20)
PICU mortality, n (%)	12 (35.3)

CRRT: Continuous renal replacement therapy, IQR: Interquartile range, PRISM III score: Pediatric risk of mortality score, PICU: Pediatric intensive care units

Table 2. Comparison of primary and secondary outcomes in thrombocytopenia at PICU admission patients and in patients who had thrombocytopenia at CRRT initiation

	Thrombocytopenia at PICU admission			Thrombocytopenia at the initiation of CRRT		
Outcomes	**Yes (n=10)**	**No (n=24)**	**p-value**	**Yes (n=15)**	**No (n=19)**	**p-value**
Age (month), median (IQR)	17.5 (7-138)	29.5 (8-140)	0.55	9 (5-32)	86 (24-174)	0.01
PRISM III score, median (IQR)	24.5 (18.7-35.2)	29 (20-32)	0.93	25 (20-32)	28 (20-32)	0.97
Infection after CRRT, n (%)	6 (60)	4 (40)	0.22	10 (66.7)	5 (33.3)	0.01
Duration of mechanical ventilation (days), median (IQR)	12.5 (9.2-16.2)	12 (7-15)	0.85	10 (6-14)	14 (12-17)	0.05
Duration of PICU stay (days), median (IQR)	14.5 (5.7-21.2)	14.5(12-17.5)	0.87	14 (6-23)	15 (12-16)	0.93
Mortality	6 (60)	4 (40)	0.05	9 (60)	6 (40)	0.007

PICU: Pediatric intensive care units, CRRT: Continuous renal replacement therapy, IQR: Interquartile range

Table 3. Associations between variables and thrombocytopenia according to univariate and multivariate regression analyses

	Thrombocytopenia at PICU admission			Thrombocytopenia at the initiation of CRRT		
Variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age (month)						
Univariable	0.999	0.988-1.009	0.80	0.986	0.973-0.998	0.02
Multivariable	0.999	0.987-1.010	0.08	0.969	0.946-0.993	0.01
Infection after CRRT						
Univariable	0.400	0.088-1.813	0.235	0.179	0.041-0.786	0.02
Multivariable	0.404	0.080-2.031	0.271	0.018	0.001-0.413	0.01
Mortality						
Univariable	0.222	0.046-1.065	0.06	0.125	0.025-0.62	0.01
Multivariable	4.330	0.867-21.63	0.07	0.119	0.021-0.66	0.01

PICU: Pediatric intensive care units, CRRT: Continuous renal replacement therapy, OR: Odds ratio, CI: Confidence interval

DISCUSSION

Our results suggest that in children undergoing CRRT in the PICU, the thrombocytopenia at PICU admission and CRRT initiation are associated with an increased risk of infection and mortality during PICU follow-up. Mortality was increased in patients with thrombocytopenia at PICU admission, but this difference was not statistically significant. Mortality was significantly greater in patients with low platelet counts at CRRT initiation. Although thrombocytopenia is known to be associated with an increased rate of infection, one study showed that thrombocytopenia at CRRT initiation is independently associated with subsequent infection and mortality.[8]

Sepsis that develops during follow-up in patients with AKI is the most common cause of death, and AKI is also the most common organ dysfunction in sepsis patients. Impaired immune function due to malnutrition in patients undergoing CRRT can lead to infection.[12] Furthermore, uremia and acidosis frequently have negative effects on immunity because they interfere with white blood cell function, phagocytosis, and endothelial function in AKI patients.[13] Secondary infection is a significant source of morbidity and mortality in patients treated with CRRT, and CRRT is known to have a bidirectional relationship with sepsis.[14] In the PICARD study, 49% of patients who were followed for AKI and received RRT developed sepsis, and the mean time to onset of sepsis was 4 days (IQ range 2-7 days) after the start of RRT.[15] In a study conducted with 55 pediatric intensive care patients who underwent CRRT, 78.2% had one or more infections during or after CRRT. Catheter-related infections are common in 64.3% of cases.[16] Immunosuppression in patients with hemodialysis catheters placed for CRRT in intensive care patients or due to both sepsis and therapies used may be associated with an increased rate of secondary infection.

The risk of infection during follow-up was significantly increased according to multivariate regression analysis in patients with thrombocytopenia at the initiation of CRRT (p=0.01). Infection was detected in 6 (60%) patients with thrombocytopenia at PICU admission, and secondary infections were detected in 10 (66.7%) patients with thrombocytopenia at the start of CRRT. The agents isolated in culture were *Pseudomonas aeruginosa* in 6 (17.6%) patients, *Klebsiella pneumoniae* in 5 (14.7%) patients, *Acinetobacter baumannii* in 1 (2.9%) patient, and *Candida albicans* in 3 (8.8%) patients. Gram-negative bloodstream infection was detected in 48.8% of thrombocytopenic patients and was significantly more common than in patients without thrombocytopenia (p=0.007).[17] Similarly, in our study, the agents isolated from patients were gram-negative, and no gram-positive agents were detected.[18] Catheter retention has been associated with a higher risk of infection and mortality.[19] Our patients also had dialysis catheters and central venous catheters, which created a predisposition to infection.

In our study, thrombocytopenia during PICU admission was not significantly associated with mortality according to the univariate analysis (p=0.06). The univariate and multivariate statistical analyses revealed that mortality in patients with thrombocytopenia at the initiation of CRRT was substantial (p=0.01). A study in pediatric intensive care patients reported that a low platelet count may indicate a poor prognosis and may also be independently associated with mortality in critically ill children. They concluded that thrombocytopenia is generally associated with sepsis and a higher mortality (p=0.0053) rate than that in nonthrombocytopenic patients.[20] In a study of 541 adult patients, a platelet count <150×10^3/µl at the start of CRRT was associated with mortality. The observed in-hospital mortality also increased significantly with worsening thrombocytopenia (p=0.05).[8] In a study of 797 CRRT patients discharged from an adult intensive care unit, a platelet count reduction of >40% from pre-CRRT was associated with an increase in post-ICU infections, independent of the presence of baseline thrombocytopenia.[21] Therefore, risk factors associated with thrombocytopenia should be closely monitored by physicians to determine the outcome in critically ill children because of their association with poor prognosis and mortality.

Limitations

This study has several limitations. Tests were not available to diagnose potentially significant thrombocytopenia, such as heparin-induced thrombocytopenia, but heparin was used less frequently and was not used at all in patients with low platelet counts (50×10^3/µl). This study is a retrospective examination conducted at one PICU. There is a need for further prospective studies that include larger cohorts of patients. Furthermore, the sample size is limited, diminishing our estimations' accuracy and posing difficulties in extrapolating general conclusions from the identified associations.

CONCLUSION

Thrombocytopenia is a prevalent condition in patients requiring dialysis in pediatric intensive care and impacts negatively on their survival. The detection of thrombocytopenia at the beginning of CRRT is associated with a higher secondary infection rate during pediatric intensive care hospitalization. Thrombocytopenia present at the beginning of CRRT is associated with higher pediatric intensive care mortality. CRRT and thrombocytopenia negatively impact immune function, and further prospective studies are needed to assess their effects on subsequent infection risk.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the İzmir Bakırçay University Non-interventional Clinical Researches Ethics Committee approved the study (Date: 10.07.2024, Decision No: 1688).

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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Cardiac rhythm disturbances associated with hydroxychloroquine and azithromycin combination in children with COVID-19 pneumonia

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ABSTRACT

Aims: At the beginning of the COVID-19 pandemic; it has been shown that receiving hydroxychloroquine and azithromycin treatment decrease viral carriage of coronavirus in patients. In this study, we aimed to evaluate electrocardiography (ECG) abnormalities in pediatric patients with COVID-19 pneumonia receiving combined therapy with hydroxychloroquine and azithromycin.

Methods: In this study; ECG and laboratory parameters of 24 children with COVID-19 pneumonia who were treated with hydroxychloroquine and azithromycin at Health Sciences University between June 2020 and November 2020 were analyzed retrospectively. P wave dispersion (PWd), QT interval (QT), QT dispersion (QTd), QTc interval (QTc), QTc dispersion (QTcd), Tpeak-Tend interval (Tp-e), Tp-e dispersion (Tp-ed), Tp-e/QT, Tp-Te/QTc ratios were evaluated with 12 lead ECG. ECG parameters and QTc interval were compared before and after (5 days) the treatment.

Results: The mean age was 13±4.5 years and 62.5% were female. Median hospitalization length was 6 days. There was no statistically significant difference between the PWd, QT and QTc interval, QTd, QTcd, Tp-e interval, Tp-e dispersion, Tp-e/QT, Tp-e/QTd measurements and ratios of the before and after treatment. A significant difference was found for the decrease in hearth rate in regard to the measurement before and after the treatment.

Conclusion: In our study, there were no rhythm problems which were observed on ECG in pediatric patients receiving hydroxychloroquine and azithromycin combination therapy for COVID-19 pneumonia. We also found that laboratory parameters were not specific for COVID-19 pneumonia in children.

Keywords: Azithromycin, COVID-19, D-dimer, hydroxychloroquine, side effects, QTc prolongation

INTRODUCTION

COVID-19 (Coronavirus disease 2019) is primarily known as a respiratory infection due to the SARS-CoV-2 virus. But it has been shown to be a multisystemic disease involving the cardiovascular, gastrointestinal, hematopoietic and immune systems.[1] Although data and treatments related to adult patients were mostly published at the beginning of the pandemic, publications began to appear on diagnosis and treatment in children over time.[2] Following the start of the COVID-19 pandemic in Turkiye, a data announced by the Ministry showed that there were 198.284 COVID-19 cases in Turkiye as of June 28, 2020, and 14.388 of them were children aged 15 and under (7.3%).[3] It was observed that clinical and laboratory findings in children were different from those in adults. Laboratory findings regarding COVID-19 in children were found to be similar to findings in other coronavirus infections. In studies; WBC was mostly normal or low and CRP was reported as normal. In severe cases, high D-dimer levels have been reported.[4,5]

However, there were differences in the protocols implemented by countries and recommended by ministries of health during the new COVID-19 epidemic. While hydroxychloroquine was recommended in some countries, it was not recommended in some countries due to its side effects.[6-8] Chloroquine, which was started to be used in the treatment of malaria in the 1950s, also used for anti-inflammatory treatment of lupus erythematosus and rheumatoid arthritis. Studies

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have been published showing that it is also effective against viruses in the COVID-19 pandemic.[9,10] After these studies, it was included in the treatment protocol of the COVID-19 treatment in some countries such as Turkiye and China. But later that, hydroxychloroquine and azithromycin combined therapy was published to increased mortality, viral spread, hospitalization and cardiac side effects.[6-8] And later this combination was ceased due to side effects. The most feared side effect in combined therapy is QTc prolongation, which has been reported to occur in 0.67% of adult patients.[11,12] Food and drug administration (FDA) cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems.[13]

In the treatment protocol of the Ministry of Health in Turkiye, hydroxychloroquine and azithromycin treatment was recommended firstly in adult patients. Also, it was added to the pediatric COVID-19 pneumonia treatment protocol in March 2020, in Turkiye.[14] After FDA notification, the Turkish Ministry of Health removed the combined therapy from the pediatric treatment protocol on May 2021.[15,16] But this cases gave the opportunity to evaluate the rhythm disturbances among children who had this combination therapy.

In this study, we aimed to evaluate ECG abnormalities (cardiac repolarization inhomogeneity and QTc prolongation) in pediatric patients with COVID-19 pneumonia receiving combined therapy with hydroxychloroquine and azithromycin.

METHODS

The study was carried out with the permission of the Kütahya Health Sciences University Rectorate Non-interventional Clinical Researches Ethics Committee (Date: 30.06.2021, Decision No: 2021/11-17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this study, 24 pediatric COVID-19 pneumonia patients treated with hydroxychloroquine and azithromycin combination between June 2020 and November 2020 in the pediatric pandemia service at Kütahya Health Sciences University of Health Sciences were retrospectively analyzed for cardiac dysrhythmia before and after the treatment. Patients with congenital or acquired heart disease, patients diagnosed with myocarditis and patients being treated in intensive care unit were excluded from the study. All patient's echocardiography and 12 lead ECG analysis were evaluated by a pediatric cardiologist. We evaluated ECG and laboratory parameters in patients with COVID-before treatment and on the fifth day of treatment, retrospectively. P wave dispersion (PWd), QT interval (QT), QT dispersion (QTd), QTc interval (QTc), QTc dispersion (QTcd), Tpeak-Tend interval (Tp-e), Tp-e dispersion (Tp-ed), Tp-e/QT, Tp-Te/QTc ratios and also other arrhythmias were evaluated with 12 lead electrocardiography.

Treatment dose of hydroxychloroquine loading dose 10 mg/kg (max: 600 mg/dose), then 3 mg/kg (max: 200 mg/dose) for 4 days period and the total treatment duration was five days) and azithromycin (loading dose 10 mg/ kg and maintenance dose 5 mg/kg daily on the days of 2-5) were given orally for 5 days.[14] All patients were received ceftriaxone to address potential secondary bacterial infections.

Electrocardiographic Analysis

Heart rate (per minute), QRS, corrected QT (cQT), Tpeak-Tend interval (Tpe), corrected Tpe (cTpe), and cTpe/cQT intervals were analyzed from 12-derived ECG by pediatrician and a pediatric cardiologist who were blinded to the patients' data. Examinations were performed on the leads II and V5 at least for measurement. QRS was measured from the beginning of the QRS to the end of the S wave and reflects ventricular depolarization. The QT interval was measured from the beginning of the QRS complex to the end of the tangent of T wave at the point of the isoelectric line. The Tpe interval was measured from the peak point of T wave to the end of the tangent of T wave crossing isoelectric line (the difference between QT interval and QT peak interval).[12] cQT and cTpe were measured by means of Bazett formula: $cQT=QT\sqrt{}$ (R-R interval) and $cTpe=Tpe\sqrt{}$ (R-R interval), respectively.

Laboratory Analysis

Demographic data, blood parameters [white blood cell (WBC) count, lymphocyte count, neutrophil count, hemoglobin, platelet, platecrit, C-reactive protein (CRP), D-dimer, fibrinogen, troponin-I] levels, clinical course, comorbid diseases, medications were evaluated from the medical records.

Statistical Analysis

All statistical analyses were performed using the SPSS software, version 21.0 for Mac (SPSS Inc, Chicago IL, USA). Continuous variables were shown median with interquartile range values. Categorical variables were shown as number and rate. The Kalmogorov-Smirnov test was used to assess the normality of distribution. A paired sample T test or Wilcoxon signed rank test, was employed to calculate the difference between each before-and-after pair of measurements. The categorical values were stated in units of numbers (n) and percentages. The data were analyzed at a 95% confidence level and considered significant at a p-value of less than 0.05.

RESULTS

The mean age was 13±4.5 years (min 1.9 years-max 17 years) and 62.5% were female of patients. Median hospitalization length was 6±1 day (min 5-max 8 day). There was no statistically significant difference between the PWD, QT and QTc interval, QTd, QTcd, Tp-e interval, Tp-e dispersion, Tp-e/QT, Tp-e/QTd measurements and ratios of the before and after treatment. Only a decrease in heart rate was found statistically significant before and after the treatment (**Table 1**). The patients' laboratory parameters were evaluated. Only D-dimer levels were found above the reference range, but no statistically significant difference was found (**Table 2**). No rhythm abnormalities were observed in all COVID-19 pneumonia patients receiving hydroxychloroquine and azithromycin therapy.

Table 1. Comparison of electrocardiographic measurements of the COVID-19 pneumonia patient before and after the treatment

ECG parameters	Before treatment mean (IQR 25%-75%)	After treatment mean (IQR 25%-75%)	p-value*
Heart rate (/min)	93 (79-99)	81 (75-92)	0.008
P wave duration (ms)	80 (80-100)	80 (80-100)	0.202
P dispersion (ms)	20 (20-40)	20 (12-35)	0.275
QT interval (ms)	340 (320-360)	360 (340-377)	0.140
QT dispersion (ms)	20 (20-35)	20 (20-37.5)	0.964
QTc interval (ms)	405 (392-428)	408 (380-430)	0.877
QTc dispersion (ms)	30 (20-58)	30 (21-46)	0.762
Tp-e interval (ms)	70 (60-95)	75 (60-80)	0.369
Tp-e dispersion (ms)	20 (20-40)	20 (20-37.5)	0.418
Tp-e/QT ratio	0.20 (0.17-0.28)	0.20 (0.17-0.25)	0.475
Tp-e/QTc ratio	0.17 (0.15-0.22)	0.16 (0.15-0.20)	0.394

*Wilcoxon signed rank test, p-value <0.05, ECG: Electrocardiography, IQR: Interquartile range, QT: The time from the beginning of the Q wave to the end of the T wave

Table 2. Evaluation of blood parameters of patients with COVID-19 pneumonia

Blood parameters	Median (25-75%)	Reference values
WBC (10^3/ul)	6.635 (4.660-9.402)	4.0-10.0
Lymphocyte (%)	35.75 (22.49-42.35)	19-44
Neutrophil (%)	56.25 (48.50-67.70)	41-73
Hemoglobin (g/dl)	13.75 (12.45-14.85)	11-16
Platelet (10^3/ul)	240 (185.2-296.7)	130-400
Fibrinogen (mg/dl)	366.83 (312.5-360.2)	200-400
D-dimer (ng/ml)	788.9 (338.5-450.0)	170-550
Platecrit (%)	0.20 (0.17-0.26)	0.10-0.28
Troponin-I (ng/ml)	1.6 (0.5-1.5)	0-19.8
CRP (mg/L)	2.5 (1.3-16.8)	<5

WBC: White blood cell, CRP: C-reactive protein

DISCUSSION

Studies have reported that combination therapy of hydroxychloroquine and azithromycin may cause fatal side effects such as arrhythmia, QTc prolongation or ventricular repolarization.[17,18] As a result of these studies, it was predicted that combination treatments should be careful in terms of cardiac side effects and should be excluded from the routine treatment of COVID-19. Here, in this study, no cardiac repolarization inhomogeneity or QTc prolongation was detected in these patients.

In former studies it was thought to be hydroxychloroquine combined with azithromycin is more effective in treating COVID-19 efficiently than hydroxychloroquine alone, and the *in vivo* mechanisms by which this potential synergy occurs is unknown.[19] Azithromycin is a macrolide antibiotic that can inhibit gram-positive and negative bacteria targeting protein synthesis of bacterial ribosomes.[20] Mortality and morbidity caused by bacteria pneumonia with coinfections maybe reduced by using azithromycin in patients infected by Spanish flu and SARS-CoV-2.[21,22] Although hydroxychloroquine and azithromycin are generally well-tolerated medications used in clinical practice, both can cause corrected QT (QTc) prolongation.[17,18]

Since most studies were conducted in adult patients, it was noted that the pharmacokinetics of hydroxychloroquine in children did not differ significantly compared to adults, except for newborns.[23,24] In addition, recent studies report that hydroxychloroquine is used off-label for interstitial lung disease in addition to the routine treatment of malaria and rheumatic diseases in children.[25,26]

In order to determine whether the combined use of these drugs has an additive or synergistic effect on QT prolongation, a study has been conducted on the scanning of the files in the U.S. Food and Drug Administration's adverse event reporting system (FAERS). According to the analysis of these reports, chloroquine/hydroxychloroquine alone was not found to be associated with QT prolongation and safety signal of torsades de pointes. The use of azithromycin alone or in combination with chloroquine/hydroxychloroquine has been associated with a potential risk of adverse effects. According to this analysis, it has been reported that the use of chloroquine/hydroxychloroquine seems to be partially safe in terms of this specific adverse effect, but more studies are needed on its use in COVID-19 disease.[27] Even though we did not find any rhythm abnormalities in our study, the study was performed in pediatric cases which may be important.

According to Tisdale et al.,[28] there are risk factors associated with QTc prolongation in adult patients. They have been developed into a risk score tool that takes age, sex, diuretic use, potassium level, baseline QTc, acute myocardial infarction, use of QTc prolonging drugs, sepsis and heart failure at adult patients. Also, most of pediatric patients don't have these risk factors for QTc prolongation. In a study from Turkiye, compared to adult COVID-19 patients was treated by either hydroxychloroquine (HCQ) + azithromycin or HCQ alone. The results of the study were as follows; off-label drugs (HCQ/azithromycin combination therapy) have an acceptable cardiac adverse effect in short-term hospitalization.[29] In our study, there was no statistical difference in ECG parameters except for heart rate. The observed decrease in heart rate was deemed associated with the clinical progression of pneumonia in pediatric patients rather than being attributed to a side effect. Since the high heart rate at first admission could be caused by factors such as inflammation, fever, and pneumonia, we thought that returning the heart rate to normal after treatment was an expected result.

However, the relationship between laboratory parameters and especially pneumonia and myocarditis in COVID-19 pediatric patients is not clear. White blood cell (WBC), C-reactive protein (CRP), D-dimer, fibrinogen, troponin-I are the most commonly used markers. The most frequently observed laboratory changes in hospitalized adult and pediatric patients with COVID-19 are characterized by elevations in fibrinogen and D-dimer levels.[30-32] In our study, when we evaluated the blood parameters of our patients at the time of admission; the fact that blood parameters other than D-dimer are within normal limits is a result we expected, consistent with most of the literature.[33,35] However, in our study, the detection of WBC

and CRP within the normal range was found to be compatible with viral COVID-19 pneumonia. In our study, the fact that troponin-I values and ECGs of patients were normal showed that pneumonia was not accompanied by myocarditis at the time of admission.

Furthermore, considering the absence of typical risk factors for QTc prolongation seen in adults, such as hypokalemia and heart failure, no cardiac rhythm side effects were observed in pediatric patients in our study. This observation may also be influenced by our patient selection criteria (excluding individuals with pre-existing heart diseases or other comorbid conditions). It is crucial to emphasize the necessity of careful monitoring for patients with heart diseases or illnesses that can lead to electrolyte imbalances. Additionally, a prospective study could shed light on potential rhythm disturbances under combined therapy with hydroxychloroquine and azithromycin in this specific population.

Limitations

Among the limitations of this study, the number of patients was relatively very small. The number of patients is limited because the combined drug is not preferred in pediatric patients due to side effects in adults and the dual combined treatment is used only in adolescent patients diagnosed with COVID-19 pneumonia. In addition, each clinic applied a different treatment protocol and our study is a single centre retrospective study. For these two drugs, which are rarely used in combination in children, a study with a larger patient group is required. In addition, since it was performed in a single centre; multicentre and a larger number of patients should be analysed.

CONCLUSION

In our study, we found that combined treatment with hydroxychloroquine and azithromycin for COVID-19 pneumonia did not statistically prolong QTc in pediatric patients. However, we analyzed that laboratory parameters did not differ significantly for COVID-19 pneumonia in children.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kütahya Health Sciences University Rectorate Non-interventional Clinical Researches Ethics Committee (Date: 30.06.2021, Decision No: 2021/11-17).

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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Impact of fetal sex combinations on maternal, pregnancy, and neonatal outcomes in dichorionic twin pregnancies

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ABSTRACT

Aims: The aim of this study was to investigate the impact of concordance and discordance in fetal sex on maternal, pregnancy, and neonatal outcomes in dichorionic twin pregnancies.

Methods: This retrospective cohort analysis includes DCDA twin pregnancies delivered at Ankara Etlik City Hospital from January 2023 to December 2024. Pregnancies were categorized into three distinct groups according to the combinations of fetal gender: male-male (group 1), female-female (group 2), and male-female (group 3). Maternal demographic, pregnancy, and neonatal outcome data were compared. Composite adverse perinatal outcome (CAPO) was defined as severe neonatal complications. Chi-square, one-way ANOVA, Kruskal-Wallis, and post-hoc analyses were applied with confounder adjustment.

Results: Male-male pregnancies were also characterized by significantly increased maternal age, BMI, parity, and diabetic disease rates compared with female-female pregnancies ($p<0.05$). Neonatal outcomes indicated a considerable increase in biparietal diameter, head circumference, and abdominal circumference in group 1 and group 3 pregnancies compared with group 2 pregnancies ($p<0.01$). Additionally, male babies from discordant pregnancies weighed considerably more at birth compared to children born from concordant pregnancies ($p=0.04$); no notable differences were seen in female infants ($p=0.84$). Gestational age at birth, preterm labor percentages, and neonatal intensive care unit admission were comparable among groups ($p>0.05$). CAPO rates did not vary between groups significantly ($p=0.396$).

Conclusion: Fetal sex combinations impact neonatal and maternal outcomes of dichorionic twin gestations in varying patterns that differ in male-male versus male-female pregnancies. Greater multicenter numbers are necessary to validate the observations and investigate more fully their consequences for maximally optimizing antenatal treatment and further enhancing perinatal outcome for twin pregnancy.

Keywords: Fetal sex combinations, dichorionic twin pregnancies, maternal and neonatal outcomes

INTRODUCTION

Dichorionic twin pregnancies consist of fraternal twins in which each fetus has its own placenta and account for approximately 70% of all twin pregnancies. This type of pregnancy has a lower risk of complications compared to monochorionic pregnancies.[1] In these pregnancies, the proportion of boy/boy or girl/girl combinations varies between approximately 30-35%, with the boy/girl combination being the most common group with approximately 33-36%.[2]

Twin pregnancies offer a unique model for understanding the consequences of fetal gender and other factors on pregnancy and neonatal outcomes, as multiple fetuses share the same environment. Among these factors, fetal sex has been shown to influence not only pregnancy complications but also neonatal outcomes, revealing sex-based physiological differences.[3] Studies have shown that male fetuses are correlated with an elevated chance of preterm birth, gestational diabetes and macrosomia, whereas female fetuses are associated with preeclampsia and reduced birth weight. These results are often ascribed to hormonal and genetic differences between male and female fetuses, such as androgen exposure and alterations in placental function.[4,5] In twin pregnancies, these sex-related differences may be further accentuated by the presence of a co-fetus. Studies show that male/male twin pregnancies are linked to reduced gestation lengths and increased likelihood of adverse neonatal outcomes such as respiratory distress and low birth weight. In contrast, girl/girl twin pregnancies have shown more favorable outcomes, such as lower rates of neonatal morbidity. Interestingly, mixed-sex pairs (boy/girl twins) may provide a protective effect; it has been suggested that male fetuses may benefit from the presence of a female co-fetus.[6]

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Despite these findings, the interaction among fetal gender combinations and pregnancy outcomes in DCDA twin pregnancies remains understudied. Existing literature has often focused on isolated neonatal parameters or maternal outcomes, leaving a gap in comprehensive assessments of the impact of sex combinations on both pregnancy and neonatal outcomes. To address this gap, this study proposes to assess the outcomes of three distinct fetal gender combinations on maternal, pregnancy and neonatal outcomes in dichorionic-diamniotic twin pregnancies.

METHODS

Approval from the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee was secured for the study protocol (Date: 25.12.2024, Decision No: AEŞH-BADEK-2024-1200), and the study was conducted in keeping with the principals of the Declaration of Helsinki. This retrospective cohort study included DCDA twin pregnancies between January 2023 and December 2024 at the Perinatology Clinic of Ankara Etlik City Hospital. The study evaluated the effect of fetal gender combinations on pregnancy and neonatal outcomes.

The research population comprised all twin pregnancies confirmed to be DCDA by first trimester ultrasound and delivered at or after 24 weeks of gestation. Participants were divided into three groups according to fetal gender combinations: male/male (group1), female/female (group 2), and male/female (group 3). Inclusion criteria were live birth of both fetuses and complete medical records. Exclusion criteria were monochorionic or monoamniotic twins, fetal anomalies, intrauterine infections, twin-to-twin transfusion syndrome (TTTS), stillbirths or pregnancies resulting in neonatal death within the first 24 hours after birth. Cases with incomplete medical records were also excluded.

Data were collected retrospectively from patient records and included maternal demographic information, obstetric history and pregnancy outcomes. Maternal data included maternal age, parity, gestational age at delivery and mode of delivery. Neonatal outcomes included birth weight, Apgar scores at 1 and 5 minutes, neonatal intensive care unit (NICU) admission rates, and combined analysis of adverse neonatal outcomes such as respiratory distress syndrome, sepsis, hypoglycemia and intraventricular hemorrhage.

The primary outcomes were differences in neonatal outcomes, including birth weight, NICU admission rates, and Apgar scores, across the three fetal sex combinations. Secondary outcomes were maternal outcomes. Statistical analyses were performed using SPSS version 25.0. Categorical variables were analyzed using the Chi-square test or Fisher's exact test, while continuous variables were evaluated with one-way ANOVA or the Kruskal-Wallis test, depending on the data distribution. Post-hoc analyses with Bonferroni correction were conducted to identify significant intergroup differences. Logistic regression models were used to adjust for confounding variables, including maternal age, parity, and gestational age at delivery. Statistical significance was defined as $p<0.05$.

For further analysis, fetal sex combinations were categorized as concordant (both fetuses of the same sex: male-male or female-female) and discordant (one male and one female). Concordant pregnancies included group 1 (male-male) and group 2 (female-female), while discordant pregnancies corresponded to group 3 (male-female).

In this study, composite adverse perinatal outcome (CAPO) was defined as the presence of one or more severe neonatal complications. These included an Apgar score below 7 at 5 minutes, the need for NICU admission, respiratory distress, requirement for ventilator support or cardiopulmonary resuscitation, seizures, hypoxic-ischemic encephalopathy (HIE), sepsis, bronchopulmonary dysplasia, necrotizing enterocolitis (NEC), birth injury, perinatal death, or a neonatal arterial blood gas pH below 7.2. The parameters were selected for their clinical relevance in identifying significant neonatal morbidity and mortality.

RESULTS

The demographic details of dichorionic twin pregnancies have been investigated in relation to fetal sex concordance. The maternal age was considerably elevated in the group 1 compared to the group 2 ($p=0.005$). BMI differed significantly among the groups, with the group 3 having a higher BMI than the group 2 ($p=0.039$). Gravidity, parity, and the number of living children did not show a significant difference among the groups ($p=0.69$, $p=0.55$, and $p=0.68$, respectively), as presented in **Table 1**. No significant differences were observed among the groups in terms of hemoglobin levels ($p=0.60$) or the proportion of pregnancies conceived via IVF ($p=0.93$). The prevalence of diabetic diseases showed a significant difference among the groups ($p=0.027$). Post-hoc analysis revealed that the incidence of diabetic diseases was significantly higher in group 1 compared to group 2 ($p=0.008$), and in group 3 compared to group 2 ($p=0.008$). However, no significant difference was observed between group 1 and group 3. The prevalence of hypertensive diseases did not show any significant difference among the groups ($p=0.97$).

The outcomes of biometric measurements in dichorionic twin pregnancies based on fetal sex combinations are summarized in **Table 2**. Gestational week did not differ significantly among the groups ($p=0.863$). The mean birth weights for group 1, group 2, and group 3 were 2182.2±401.7 g, 2033.4±530.6 g, and 2195.3±479.3 g, respectively, with groups 1 and 3 showing higher weights than group 2, though this was not statistically significant ($p=0.09$). No significant differences were noted for weight discordance ($p=0.45$). However, biparietal diameter (BPD) in group 3 compared to group 2. Head circumference (HC) and abdominal circumference (AC) was also larger in groups 1 and 3 compared to group 2. Femur length (FL) showed no significant variation ($p=0.22$). CAPO rates were 44.4% in group 1, 33.3% in group 2, and 40.2% in group 3, without significant differences among the groups ($p=0.396$).

The comparison of birth weight, gestational age and preterm birth outcomes according to fetal sex concordance in dichorionic twin pregnancies is summarized in **Table 3**. In our study, birth weights of male and female newborns

Table 1. Demographic characteristics according to fetal sex

					Post-hoc comprasions, p-value		
	Group 1 (n=90)	Group 2 (n=56)	Group 3 (n=82)	p	Group 1-group 2	Group 1-group 3	Group 2-group 3
Maternal age (years)	33.0±6.2	30.1±8.6	32.1±5.8	0.005[a]	0.004	NA	NA
BMI (kg/m^2)	30.5±6.6	29.9±5.1	32.5±7.4	0.039[a]	NA	NA	0.049
IVF pregnancy	28.9	26.7	26.8	0.931[b]			
Gravidity	2 (3)	2.5 (3)	2 (3)	0.69[c]			
Parity	1 (2)	1 (1)	1 (2)	0.55[c]			
Living children	1 (2)	1 (1)	1 (2)	0.68[c]			
Hemoglobin g/dl	11.9±1.4	11.2±1.7	11.8±1.3	0.60[a]			
Diabetic diseases	10 (11.1)	0	9 (11.0)	0.027[b]	0.008	NA	0.008
Hypertensive diseases	12 (13.3)	8 (13.3)	10 (12.2)	0.97[b]			

BMI: Body-mass index, IVF: In vitro fertilization, a: One-way ANOVA, b: Chi-square test, c: Kruskal-Wallis test, post-hoc analyses were performed using the Bonferroni correction. Group 1: Male-male, Group 2: Female-female, Group 3: Male-female

Table 2. Birth weight, head circumference, and body length measurements according to fetal sex

					Post-hoc comprasions, p-value		
	Group 1 (n=90)	Group 2 (n=56)	Group 3 (n=82)	p	Group 1-group 2	Group 1-group 3	Group 2-group 3
Gestational age at birth (weeks)	33.88±2.16	33.98±3.13	34.07±2.87	0.863[a]			
Birthweight, g	2182.2±401.7	2033.4±530.6	2195.3±479.3	0.09[a]			
Weight Discordance, g	260 (390)	255 (185)	250 (325)	0.454[b]			
Weight Discordance, %	9.84 (15.88)	8.95 (15.70)	7.86 (10.53)	0.426[c]			
BPD, cm	83 (8)	82 (8)	84 (8)	0.005[b]	NA	NA	0.004
HC, cm	305 (23)	302 (27)	306 (18)	0.009[b]	0.006	NA	0.005
AC, cm	292 (36)	268(53)	300 (39)	0.001[b]	0.001	NA	0.001
FL, cm	64 (9)	62 (9)	65 (8)	0.221[b]			
CAPO	40 (44.4)	20 (33.3)	33 (40.2)	0.396[c]			

BPD: Biparietal diameter, HC: Head circumference, AC: Abdominal circumference, FL: Femur length, CAPO: Composite adverse perinatal outcome. a: One-way ANOVA, b: Kruskal-Wallis test, c: Chi-square test, Group 1: Male-male, Group 2: Female-female, Group 3: Male-female

Table 3. Comparison of birth weight, gestational age, and preterm delivery outcomes between fetal sex groups

	Male from concordant pregnancy	Male from discordant pregnancy	p	Female from concordant pregnancy	Female from discordant pregnancy	p
Birth weight, g	2182.2±401.6	2344.7±478.4	0.04[a]	2033.6±530.3	2052.6±439.9	0.84[a]
LBW	66 (73.3)	27 (67.5)	0.49[b]	54 (90.0)	34 (81.0)	0.19[b]
VLBW	7 (7.8)	3 (7.5)	0.95[b]	11 (18.3)	4 (9.5)	0.22[b]
Gestational age at birth, weeks	33.9±2.1	34.1±2.9	0.72[a]	34.2±3.2	34.1±2.8	0.82[a]
NICU	43 (47.8)	15 (35.5)	0.27[c]	23 (38.8)	19 (45.2)	0.48[c]

LBW: Low birth weight, VLBW: Very low birth weight, NICU: Neonatal intensive care unit, SD: Standard deviation, IQR: Interquartile range, a: Student T test, mean±SD, b: Chi-square test, no (%), c: Mann-Whitney U, median (IQR), Group 1: Male-male, Group 2: Female-female, Group 3: Male-female

born from concordant and discordant pregnancies were compared. Among male newborns, the birth weight of those born from group1 (concordant) pregnancies (2182.2±401.6 g) was significantly lower than that of those born from group 3 (discordant) pregnancies (2344.7±478.4 g) (p=0.04). However, among female newborns, there was no significant difference in birth weight between those born from group 2 (concordant) pregnancies (2033.6±530.3 g) and those born from group 3 (discordant) pregnancies (2052.6±439.9 g) (p=0.84). LBW and VLBW rates did not differ significantly between concordant and discordant pregnancies for both male newborns (p=0.49, p=0.95) and female newborns (p=0.19, p=0.22). The gestational age at birth was also similar between the groups, and no significant difference was found for both male newborns (p=0.72) and female newborns (p=0.82). NICU requirement was also not significantly different between the groups. For male newborns, the need for NICU was similar between concordant and discordant pregnancies (p=0.27). Similarly, there was no significant difference in NICU requirement for female newborns (p=0.48).

DISCUSSION

The impact of fetal sex on maternal health, pregnancy course, and neonatal outcome is a topic of continued investigation. Although several studies have indicated that male and female fetuses can differentially affect the physiological aspects of pregnancy, especially in singleton pregnancies, the magnitude of this effect in twin pregnancies is unclear.[4] Dichorionic twin gestations offer a special model for evaluating these influences since they enable comparison of various fetal sex combinations while controlling for confounding factors such as shared placental circulation.[2] The objective of our research was to evaluate whether concordance or discordance of fetal sex influences maternal metabolic parameters, neonatal growth patterns, and perinatal outcomes. The results contribute to the current scientific body of evidence by demonstrating that fetal sex combinations significantly impact maternal body mass index, metabolic status, and fetal biometric parameters but have a modest effect on perinatal morbidity.

The association of fetal sex with maternal demographic characteristics is a controversial issue in the literature. Previous studies have shown that pregnant women carrying a male fetus are correlated with increased maternal age, increased preterm birth rates and some maternal complications.[5] In our study, maternal age was markedly elevated in the group1 group than group 2 (p=0.005), which supports the findings of the literature. Although there was no significant difference between the groups in terms of BMI values in your own study (p=0.039), it has been reported in the literature that BMI may be associated with fetal sex.[6] For example, it was reported that AKR1C1 expression was higher in pregnant women carrying male fetuses and that this was positively correlated with maternal BMI.[6] Moreover, emerging evidence suggests that fetal sex may influence maternal metabolic adaptation during pregnancy. Retnakaran et al.[7] demonstrated that carrying a male fetus is associated with impaired maternal β-cell function and increased postprandial glycemia, leading to a higher risk of gestational diabetes mellitus (GDM). In their study, women carrying male fetuses exhibited higher blood glucose levels during the oral glucose tolerance test (OGTT) and had a 39% increased risk of developing GDM compared to those carrying female fetuses. These findings align with our results, which indicate that diabetic diseases were significantly more common in group 1 and group 3 twin pregnancies than in group 2 pregnancies (p=0.027). This suggests that fetal sex-related metabolic changes may contribute to maternal glucose dysregulation, further supporting the hypothesis that male fetuses impose a greater metabolic burden on the mother.

Nonetheless, no substantial difference was seen between the groups regarding obstetric history parameters such as IVF pregnancy rates, gravida, parity and number of living children and hemoglobin levels (p: 0.93, p: 0.69, p: 0.55, p: 0.55, p: 0.68 and p: 0.60). Our study revealed no disparities between the groups regarding the prevalence of maternal hypertensive diseases, but diabetic diseases were significantly more common in group 1 and group 3 twin pregnancies than in group 2 pregnancies (p=0.027).

In a study conducted by Muhcu et al.[8] in 2014, which is one of the studies evaluating the effect of fetal sex on ultrasonographic measurements, it was reported that male fetuses had higher values in parameters such as birth weight and HC compared to female fetuses. In addition, HC of male fetuses were found to be larger at 35-40 weeks of gestation. Similarly, another study reported that fetal gender may have an effect on ultrasonographic measurements such as BPD, HC, AC, FL and EFW.[9] In our study, there was no significant difference between the groups in terms of birth weight (p=0.09). However, BPD, HC and AC measurements were larger in group 1 and group 3 compared to group 2 and these differences were statistically significant (p=0.005, p=0.009 and p=0.001). These findings are consistent with the literature suggesting that fetal sex may have an effect on birth weight and ultrasonographic measurements. One possible explanation is that male fetuses exhibit higher insulin-like growth factor-1 (IGF-1) levels and greater anabolic activity, contributing to their increased head and abdominal circumference measurements.[10] Additionally, placental function may differ between male and female fetuses, with studies suggesting that placentas from male fetuses may be more efficient in nutrient transport.[11]

Wilms et al.[12] reported that the majority of preterm births were seen in pregnant women carrying a male fetus and that these pregnant women gave birth earlier.However, secondary analyses showed that there was no significant difference in the risk of preterm birth between women carrying male and female fetuses, with the difference being due to ethnicity. According to this analysis, the median gestational age was 37 5/7 weeks in women carrying a male fetus and 38 1/7 weeks in women carrying a female fetus, but there was no significant difference in risk between the two groups. In the study of Melamed et al.[13] on twin pregnancies, there was no significant difference in terms of gestational age at delivery between different fetal sex combinations. In our study, no significant difference was found between the groups in terms of gestational week (p=0.863). The gestational weeks of gestation in group 1, group 2 and group 3 pregnancies were 33.88±2.16, 33.23±3.13 and 34.07±2.87, respectively. CAPO results showed no significant difference between the groups (p=0.396). Although the CAPO rate appeared to be lower in group 2, no statistically significant difference was found. In the literature, there are some studies in which pregnancies carrying a male fetus are associated with higher neonatal risks.[13] However, the high CAPO rates in all groups in our study may be due to the general obstetric and neonatal characteristics of the studied population; therefore, it is thought that the results should be repeated in a larger population.

In our study, we examined the effect of fetal sex concordance or discordance on pregnancy outcomes. As summarized in **Table 3**, birth weights were compared between male and female newborns born from concordant and discordant pregnancies. Among male newborns, the birth weight of those born from group 1 (concordant) pregnancies was significantly lower than those born from group 3 (discordant) pregnancies (p=0.04). In contrast, among female newborns, there was no significant difference in birth weight between those born to group 2 (concordant) pregnancies and those born to group 3 (discordant) pregnancies (p=0.84). These findings appear

to be consistent with some studies in the literature. In the CODATwins study, a large-scale analysis of 67,850 dizygotic twins found that male fetuses were on average 31 g heavier and 0.16 cm longer when they had a female partner than when they had a male partner.[14] However, there was no significant effect of co-twin sex on birth measurements in female fetuses. In addition, the duration of gestation was reported to be shorter in group 1 pairs than in boy-girl and girl-girl pairs. These findings suggest that male fetuses may have a longer gestation period and higher birth size in the presence of a female partner. However, these differences were reported to be attenuated in the presence of birth weight in relation to gestational duration. Similarly, Bayraktar et al.[15] reported that male newborns in male-girl pregnancies had a higher birth weight than male-male pregnancies. In addition, Melamed et al.[13] provided a different perspective, reporting that the growth rate of male fetuses in male-male pregnancies was lower than in male-female pregnancies. In this study, male fetuses showed higher growth rates and longer gestation periods in the presence of a female mate, and hypothesized that male fetuses may have an advantage in competition for food in the presence of a female mate rather than a male mate. However, the mechanisms underlying this observation remain unclear. In contrast, in our study, the birth weight of female newborns born to discordant pregnancies (boy-girl) was slightly higher than that of female newborns born to concordant pregnancies (girl-girl), but this difference was not statistically significant. This finding is consistent with the "girl protective factor" hypothesis proposed in the study by Melamed et al., which states that female fetuses may show better growth dynamics when found with their male twins.

In our study, the NICU needs of newborns in gender concordant and discordant pregnancies were examined and no significant difference was found between the groups (p=0.27 for boys and p=0.48 for girls).

The findings of our study have potential clinical implications for the management of twin pregnancies. Given that male-containing pregnancies (group 1 and group 3) were associated with higher maternal BMI and increased risk of gestational diabetes, closer metabolic surveillance and early screening for gestational diabetes may be warranted in these pregnancies.

Although our study did not find significant differences in perinatal morbidity, future research should explore whether fetal sex concordance impacts long-term neonatal outcomes, including metabolic programming and neurodevelopmental trajectories. The potential influence of fetal sex on placental function and maternal metabolic adaptations also warrants further investigation using molecular and epigenetic approaches.

Limitations

This study has some limitations that should be considered. The relatively small sample size limits the generalizability of our findings, particularly in subgroup analyses based on fetal sex combinations. Second, although we adjusted for confounding variables such as maternal age, parity, and gestational age at delivery, other unmeasured factors, including genetic and environmental influences, may have impacted the outcomes. Finally, the study was conducted in a single center, which may limit the applicability of the results to broader populations. Future prospective, multicenter studies with larger sample sizes are needed to validate our findings and explore the underlying mechanisms of fetal sex-related differences in dichorionic twin pregnancies.

CONCLUSION

This research points to the effects of fetal sex discordance and concordance on neonatal, pregnancy, and maternal outcomes in dichorionic twin pregnancies. The group 1 pregnancies were correlated with increased age of the mother, BMI, parity, and rate of diabetic disease in relation to female-female pregnancies. Neonatal outcome revealed increased biparietal diameter, head circumference, and abdominal circumference in group 1 and group 2 pregnancies, and increased birth weight in male newborns of discordant pregnancies compared to concordant pregnancies. Gestational age, preterm delivery rates, and NICU admission were comparable between groups. These results highlight the effect of fetal sex combinations on neonatal and maternal outcomes. Larger multicenter trials are required to validate these results and to investigate further their implications for maximizing antenatal care in twin pregnancy.

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: 25.12.2024, Decision No: AEŞH-BADEK-2024-1200).

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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Evolution of Leiomyomas with FIGO classification regarding parity, body-mass index and admission symptoms

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ABSTRACT

Aims: To examine the outcomes of leiomyomas classified by FIGO in relation to the demographic, clinical, and laboratory characteristics of patients who underwent laparotomic myomectomy.

Methods: A total of 199 patients were found between September 2019 and September 2023 according to the criteria for study. Data were analyzed and compared in terms of FIGO leiomyoma classification, leiomyoma size, admission symptoms, body-mass index (BMI) and parity. All demographical and operational features were compared in each group for issues including leiomyomas >8 cm, <8 cm; single or multiple leiomyomas; BMI >30, <30; multiparous and nulliparous patients. Moreover, patients' admission symptoms as abnormal uterine bleeding, pelvic pain and compression were also recorded and compared.

Results: The mean leiomyoma size, compression symptoms and pelvic pain of those with abnormal uterine bleeding was 8.5±3.2 cm, 9.6±3.1 cm, and 10.9±3.6 cm; respectively. The mean leiomyoma size of individuals with pelvic pain was significantly larger than that of those with abnormal uterine bleeding ($p<0.05$). Nulliparous patients exhibited a higher incidence of multiple myomas than multiparous patients. Nulliparous patients experienced a lower incidence of abnormal uterine hemorrhage than multiparous patients; however, the incidence of pelvic pain and pressure symptoms was more common ($p=0.013$). The mean leiomyoma size of those with BMI <30 and BMI ≥30 was 9.8±3.6 cm, and 9.2±3.1 cm; respectively. No statistically significant difference was observed between these groups in terms of mean leiomyoma size, operation time, hospital stay and postoperative complications ($p>0.05$).

Conclusion: When evaluating laparotomic myomectomy patients, the patient's parity status, location and size of the leiomyoma should be taken into consideration before surgery.

Keywords: Leiomyomas, parity, FIGO classification, laparotomic myomectomy

INTRODUCTION

Leiomyomas are the most common tumors seen in women that develop from smooth muscle cells.[1,2] The incidence increases with age, but the rate of increase alleviates at older ages. Leiomyomas are more frequent in nulliparous and overweight women.[3] They represent the predominant cause of abnormal uterine bleeding and hysterectomies.[4] Most leiomyomas are small and asymptomatic; nevertheless, several patients with leiomyomas experience substantial issues that disrupt certain facets of their lives and necessitate treatment.[5] Leiomyomas are primarily observed when symptomatic, typically present as abnormal uterine bleeding and/or pelvic pain or pressure.[6] The number, size, and location of the tumors are all factors that contribute to the development of these symptoms. Myomas can occur as single or multiple tumors and can range in size from microscopic to tens of centimeters.

Leiomyomas are classified based on their anatomical position within the uterus, but numerous leiomyomas may possess multiple location designations. The International Federation of Gynecology and Obstetrics (FIGO) has classified myomas according to their location.[7] Intramural myomas (FIGO type 3, 4, 5) are situated within the uterine wall. They may expand to the extent that the uterine cavity or serosal surface is distorted. Certain fibroids may be transmural, extending from the serosal to the mucosal surface. Myometrial cells located beneath the endometrium (the lining of the uterine cavity) are the source of FIGO type 0, 1, 2 leiomyomas. These neoplasms protrude into the uterine cavity. The FIGO/European Society of Hysteroscopy classification system delineates the extent of this protrusion, which is clinically pertinent for predicting the results of hysteroscopic myomectomy.[8] FIGO types 6 and 7 leiomyomas arise from the myometrium at the serosal surface of the uterus, while FIGO type 8 parasitic leiomyomas are situated in the cervix or adnexa, rather than the uterine corpus.

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Treatment options for leiomyoma include medical therapy, non-excisional procedures (e.g., endometrial ablation, uterine artery embolization), and surgical therapy (e.g., myomectomy, hysterectomy). Myomectomy is the surgical excision of leiomyomas from the uterus while preserving the organ. This surgical technique may be executed using abdominal, laparoscopic, hysteroscopic, or vaginal methods.[4]

The size, number, and location of the leiomyoma determine the incidence and severity of symptoms. These also affect surgical treatment options. Consequently, the objective of our investigation was to evaluate the demographic, clinical, and laboratory findings, as well as the results of operational reports, of patients who underwent laparotomic myomectomy. We believe that this analysis data and results of the patients will shed light on the preoperative patient selection and will also help with postoperative patient follow-up.

METHODS

The study was carried out with the permission of the Adana City Hospital Clinical Researches Ethics Committee (Date: 14.09.2023, Decision No: 2826). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective case control study was performed at a territory hospital, between September 2019 and September 2023. During the time period covered, 305 myomectomy procedures were performed. We excluded 5 patients because of missing data, 50 patients because myomectomy was performed at the time of cesarean section, 18 patients because it was performed vaginally, 10 patients because it was hysteroscopic, and 23 patients because other concomitant operations were performed. Finally, 199 patients who underwent laparotomic myomectomy were included the study. The inclusion criteria consisted patients aged 18-45 who underwent laparotomic myomectomy. Patients with uterine anomalies, myomectomies performed without laparotomic way, myomectomies with concomitant operations and patients with malignancy were excluded. Demographic data and clinical features of the patients in the study group were recorded as follows: age, body-mass index (BMI), gravida, parity, preoperative complaints, leiomyoma size, number of leiomyomas, leiomyoma localization according to FIGO leiomyoma uteri classification system. The pre-postoperative hemoglobin (Hb), specimen pathology, incision type, operation time, hospital stay and postoperative complication parameters were also noted.

According to the inclusion criteria, the patients included in the study were grouped separately according to their admission symptoms (abnormal uterine bleeding, compression symptoms and pelvic pain) and BMI limits (below and above 30) and compared in terms of their hospital stay, postoperative complications, myoma sizes and locations.

Statistical Analysis

In order to determine whether continuous data were normally distributed, we implemented the Shapiro-Wilk test. Categorical variables were collected as numbers and percentages. While the mean±standard deviation was employed for continuous variables that were normally distributed, the median (25%-75%) was employed for all other variables. The Mann-Whitney U test was employed for two independent groups in the absence of normal distribution, while the independent samples T test was utilized in its presence. One-way ANOVA was employed to analyze the data across the three categories, and the Tukey test was employed for the post-hoc analysis. We accepted $p<0.05$ as statistically significant.

RESULTS

The study was conducted with a total of 199 myomectomy cases. The study included 126 patients with singular myomas and 73 patients with multiple myomas. 148 of these patients with leiomyoma, the largest leiomyoma diameter was greater than 8 cm, and in 51 of them, the largest myoma diameter was less than 8 cm. The means of age and the BMI were 38.6±9.7 years and 25.8±4.3 kg/m^2 respectively. Demographic and clinical characteristics of all the cases were shown in **Table 1**.

Patients were classified into three groups according to their presenting symptoms (abnormal uterine bleeding, compression symptoms, and pelvic pain). There were 83 (41.7%) patients with abnormal uterine bleeding, 83 (41.7%) patients with pelvic pain, and 33 (16.6%) patients with compression symptoms. Comparison of clinical outcomes among groups regarding of admission complaints was shown in **Table 2**. Accordingly; the mean leiomyoma size of those with abnormal uterine bleeding was 8.5±3.2 cm, the mean leiomyoma size of those with compression symptoms was 9.6±3.1 cm, and the mean leiomyoma size of those with pelvic pain was 10.9±3.6 cm. The mean leiomyoma size of individuals with pelvic pain was significantly larger than that of those with abnormal uterine bleeding ($p<0.05$). No statistically significant difference was observed in mean myoma size between those with compression symptoms and those with abnormal uterine bleeding and pelvic pain ($p>0.05$). In nulliparous patients, the rate of abnormal uterine bleeding was lower, and the rate of compression symptoms and pelvic pain was higher than in multiparous patients ($p<0.05$). Operation time, postoperative complications, and duration of hospital stay did not show statically significant between groups ($p>0.05$). Patients were additionally divided according the Figo leiomyoma classification as type (2, 3, 4, 5) and type (6, 7, 8) and in those with abnormal uterine bleeding, a higher rate of type (2, 3, 4, 5) myoma and a lower rate of type (6, 7, 8) myoma were detected compared to those with pelvic pain ($p<0.05$).

The patients were categorized into two groups based on their BMI and compared with the size of the leiomyoma, the location of the leiomyoma, the duration of the operation, the length of their hospital stay, and the presence of postoperative complications. Comparison of clinical outcomes among groups regarding of BMI was shown in **Table 3**. The mean leiomyoma size of those with BMI <30 was 9.8±3.6 cm, and the mean leiomyoma size of those with BMI ≥30 was 9.2±3.1 cm. Between the groups, there was no statistically significant difference in the mean size of the leiomyomas ($p>0.05$). No statistically significant difference was seen between the groups regarding mean postoperative complications, operation time, and length of hospital stay ($p>0.05$). In addition, the relationship between BMI and leiomyoma size was shown in **Figure**.

Table 1. Demographic and clinical outcomes of all patients

	n=199
Age (years)	38.6±69.7
BMI (kg/m²)	25.8±4.3
Gravida	1 (0-9)
Parity	1 (0-7)
Multipara	128 (64.3%)
Nulliparous	71 (35.7%)
Operation time (minute)	61.2.±21.5
Preoperative Hb (g/dl)	12.0.±1.5
Postoperative Hb (g/dl)	10.2.±1.4
Admission complaint (%)	
Abnormal uterine bleeding	83 (41.7%)
Pelvic pain	83 (41.7%)
Compression symptoms	33 (16.6%)
Leiomyoma size (%)	38.6±69.7
≥8 cm	148 (74.4%)
<8 cm	51 (25.6%)
Number of leiomyomas in the operation (%)	
Single	126 (63.3%)
Multiple	73 (36.7%)
Compression symptoms	33 (16.6%)
FIGO classification (%)	
Type 6	58 (29.1%)
Type 5	54 (27.1%)
Type 4	47 (23.6%)
Type 3	20 (10.1%)
Type 7	9 (4.5%)
Type 8	8 (4%)
Type 2	3 (1.5%)
Incision type (%)	
Pfannenstiel	169 (89.4%)
Lower abdominal longitudinal	24 (12.1%)
Lower and upper abdominal longitudinal	6 (3%)
Pathology results (%)	
Leiomyoma	193 (97%)
Leiomyoma+adenomyosis	4 (2%)
STUMP+leiomyoma	2 (1%)
Postoperative complications (%)	
None	194 (97.5%)
Wound infection	3 (1.5%)
Bowel injury	1 (0.5%)
Relaparotomy	1 (0.5%)

BMI: Body-mass index, Hb: Hemoglobin, FIGO: The International Federation of Gynecology and Obstetrics, STUMP: He uterine smooth muscle tumors of uncertain malignant potential

Table 2. Comparison of clinical outcomes among groups regarding of admission complaints

	Abnormal uterine bleeding n=83	Compression symptoms n=33	Pelvic pain n=83	p-value
Leiomyoma size (cm)	8.5±3.2[a]	9.6±3.1[a,b]	10.9±3.6[b]	0.001
Leiomyoma size (%)				
<8 cm	34 (41%)[a]	6 (18.2%)[a,b]	11 (13.1%)[b]	0.001
≥8 cm	49 (59%)[a]	27 (81.8%)[a,b]	72 (86.7%)[b]	
Operation time (minute)	59.9±18.8	62.7±19.6	61.9±23.8	0.754
Hospital stays (day)	4.2±6.3	3.7±0.9	3.3±0.9	0.442
Postoperative complications (%)				
(+)	3 (3.6%)	1 (3%)	1 (1.2%)	0.753
(-)	80 (96.4%)	32 (97.0%)	82 (98.8%)	
FIGO classification (%)				
Type 2,3,4,5	67 (80.7%)[a]	20 (60.6%)[a,b]	37 (44.6%)[b]	0.001
Type 6,7,8	16 (19.3%)[a]	13 (39.4%)[a,b]	46 (55.4%)[b]	
Number of delivery (%)				
Nulliparous	20 (24.1%)[a]	16 (48.5%)[b]	35 (42.2%)[b]	0.013
Multiparous	63 (75.9%)[a]	17 (51.5%)[b]	48 (57.8%)[b]	

p-value is calculated by ANOVA and Tukey test is used for post-hoc test, different superscripts indicate significant mean differences, FIGO: The International Federation of Gynecology and Obstetrics

Table 3. Comparison of clinical outcomes among groups regarding of BMI

	BMI ≥30 n=167	BMI <30 n=32	p
Leiomyoma size (cm)	9.8±3.6	9.2±3.1	0.354
Leiomyoma size (%)			
<8 cm	44 (26.3%)	7 (21.9%)	0.596
≥8 cm	123 (73.7%)	25 (78.1%)	
Operation time (minute)	61.3±21.5	60.9±21.6	0.935
Hospital stays (day)	3.8±4.5	3.8±0.8	0.682
Postoperative complications (%)			
(+)	4 (2.4%)	1 (3.1%)	0.790
(-)	163 (97.6%)	31 (96.9%)	
FIGO classification (%)			
Type 2,3,4,5	108 (64.7%)	16 (50.0%)	0.117
Type 6,7,8	59 (35.3%)	16 (50.0%)	
Number of delivery (%)			
Nulliparous	62 (37.1%)	9 (28.1%)	0.33
Multiparous	105 (62.9%)	23 (71.9%)	

BMI: Body-mass index, Hb: Hemoglobin, FIGO: The International Federation of Gynecology and Obstetrics

Comparison of clinical outcomes among groups regarding of leiomyomas singularity or multiparity was shown in Table 4. The largest myoma size of those with a single myoma in the patients with 8 cm> and ≥8 cm was 19.0% and 81.0%, respectively, and the ratio of the largest myoma size of those with multiple myomas in the patients with 8 cm> and ≥8 cm was 37.0% and 63.0%; respectively. The mean largest myoma size in the single leiomyoma group was larger than in the multiple leiomyoma group ($p<0.05$). No statistically significant difference was found between the groups in terms of operation time, hospital stay and postoperative complications. The rate of multiple myomas was higher in nulliparous patients than in multiparous patients, and this difference was statistically significant ($p<0.05$).

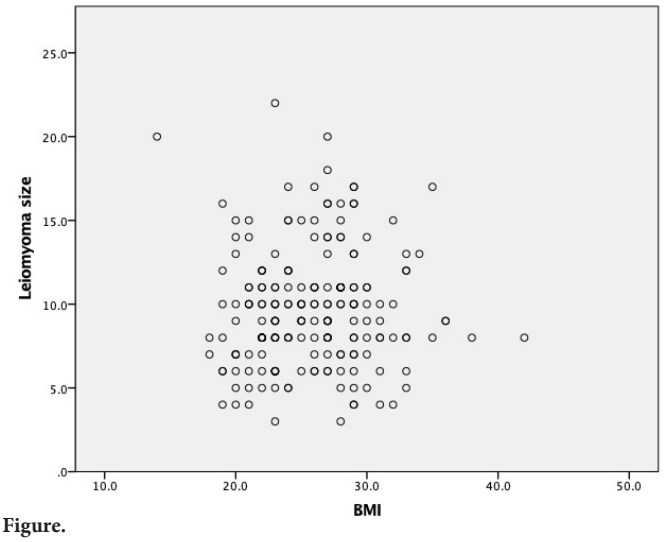

Figure.

Table 4. Comparison of clinical outcomes among groups regarding of leiomyomas singularity or multiparity

	Single n=126	Multiple n=73	p
Leiomyoma size (cm)	10.1±3.4	9.0±3.7	0.044
Leiomyoma size (%)			
<8 cm	24 (19%)	27 (37%)	0.005
≥8 cm	102 (81%)	46 (63%)	
Operation time (minute)	61.0±21.2	61.6±22.0	0.833
Hospital stays (day)	3.8±5.1	3.7±1.1	0.963
Postoperative complications (%)			
(+)	4 (3.2%)	1 (1.4%)	0.756
(-)	122 (96.8%)	46 (63%)	
FIGO classification (%)			
Type 2,3,4,5	80 (63.5%)	44 (60.3%)	0.652
Type 6,7,8	46 (36.5%)	29 (39.7%)	
Number of delivery (%)			
Nulliparous	36 (28.6%)	35 (47.9%)	0.006
Multiparous	90 (71.4%)	38 (52.1%)	

BMI: Body-mass index, Hb: Hemoglobin, FIGO: The International Federation of Gynecology and Obstetrics

DISCUSSION

This study showed that the mean myoma size of patients with pelvic pain was larger than those with abnormal uterine bleeding. In nulliparous patients, the rate of multiple myomas, pressure symptoms and pelvic pain was higher than those who had given birth, while the rate of abnormal uterine bleeding was lower.

The most prevalent pelvic tumors in women are leiomyomas. However, the majority of leiomyomas are asymptomatic. Peak incidence occurs between the ages of 35 and 40 in the reproductive age group.[9] The symptoms associated with leiomyomas correlate closely with their size, number, and location. The histopathological incidence in the population is 80%, as indicated by the study conducted on hysterectomy sections of leiomyomas. Nevertheless, clinical findings are observed in only 20-30% of the samples.[10]

In patients with an indication for myomectomy; If the uterus is larger than the 20th week of pregnancy or if there are more than three myomas larger than 5 cm in size, laparotomic myomectomy is the primary surgical option. The probability of a myomectomy operation performed by experienced surgeons leading to a hysterectomy is less than 1%. In our study, there was no conversion to intraoperative hysterectomy in any of the 199 myomectomies.

In our study, patients with single and multiple myomas were compared according to myoma size. The mean largest myoma size in the single myoma group was larger than in the multiple myoma group and this difference was statistically significant ($p<0.05$). The rate of the largest myoma size being larger than 8 cm in the single myoma group was significantly higher than in the multiple myoma group. The fact that the rate of abnormal uterine bleeding is lower and the rate of pressure symptoms and pelvic pain is higher in nulliparous patients than in patients who have given birth also supports this result. In addition, myoma types 2-5 are more often accompanied by abnormal bleeding. As a result, the larger myoma size in nulliparous patients who underwent surgery may be due to the fact that they have reached the last stage of their pressure complaints. It was also observed that multiple myomas were more common in nulliparous patients. This condition may also be associated with infertility.

In a study conducted by Sato et al.[11] in Japan in 2000, 91 women who underwent hysterectomy due to leiomyoma were compared with age-matched control patients in terms of reproductive factors. It was concluded that women with leiomyoma were more likely to be nulliparous than controls and that the risk of leiomyoma increased as the number of births decreased. Numerous studies indicate that parity diminishes the chance of leiomyoma development, with subsequent pregnancies further decreasing this risk.[12-14] The protective effect of parity on leiomyomas is thought to involve the postpartum uterine involution process.[15,16] In the animal experiment study, research indicates that myocyte autophagy may significantly contribute to uterine involution, myometrial functional adaptations during gestation, and the physiological significance of autophagy in uterine remodeling processes throughout the postpartum phase.[16]

Pelvic pain is a prevalent symptom in individuals with leiomyoma. The two most common symptoms associated with uterine leiomyomas are anormal uterine bleeding and pelvic pain.[17] One epidemiologic study reported that pelvic pain was experienced by 49% of women with symptomatic uterine leiomyomas.[18] In a study by Lacey et al.[19] investigating benign diseases of the uterine corpus, pelvic pain was observed in 30% of cases with large leiomyomas. In our study, 40% of the patients had complaints of pelvic pain, and the mean leiomyoma size of the patients with complaints of pelvic pain was found to be 10.9±3.6, which is similar to the literature data.

In a retrospective study by Puri et al.[20] investigating the relationship between submucosal leiomyomas and severe menstrual bleeding and anemia in 912 women, anemia was recorded more in women with submucosal leiomyomas (34%) than in women with leiomyomas in different

locations (25%). Pelvic pain increased as the leiomyomas approached the serosa and abnormal uterine bleeding increased as the leiomyomas approached the mucosa. In the 2016 study by David et al.,[21] 1548 leiomyoma patients were retrospectively examined using patient questionnaires and ultrasound examinations. The patients' pain was grouped as premenstrual, menstrual and during sexual intercourse. It was found that submucosal myomas were significantly more common in women with severe dysmenorrhea compared to all other myoma localizations. It was concluded that the number of myomas did not have a significant effect on the severity of dysmenorrhea. They also concluded that severity of menstrual pain depended on the location and size of the largest myoma. Although this study has different aspects from our study, it is a good example in terms of showing the relationship between myoma localization and symptoms. Further research is required to elucidate the degree to which the problems experienced by patients with leiomyomas are attributable to the characteristics of the fibroids.

In our study, patients were also categorized into two groups: obese and non-obese. No substantial difference was seen between the groups regarding clinical indicators ($p>0.05$). Different from our results; Cinar et al.[22] in 2016 found a correlation between complications and clinical parameters in 273 women who underwent abdominal myomectomy, comparing obese (BMI ≥30) and non-obese (BMI <30) groups regarding leiomyoma diameter, length of hospital stay, and complications. Patients in the obese group exhibited larger leiomyoma sizes and increased complications, including bleeding, postoperative fever, wound infection, and ileus. Wen et al.[23] also found that obese women were significantly more likely to have both early and late complications, such as increased length of hospital stay. while in another study Gürbüz et al.[24] found that the obese and non-obese women showed no significant difference in terms of the leiomyoma size, complications, and bleeding requiring transfusion.

Limitations

The major strength of our study is evaluating leiomyomas using FIGO classification and comparing clinical parameters among groups in terms of admission complaints, BMI and leiomyomas singularity or multiparity. Retrospective design of the study is the major limiting factor.

CONCLUSION

The mean leiomyoma size was found to be larger in patients with pelvic pain than in those with abnormal uterine bleeding. Nulliparous patients exhibited a higher incidence of multiple leiomyomas than multiparous patients. Nulliparous patients experienced a lower incidence of abnormal uterine bleeding than multiparous patients; however, the incidence of pelvic pain and pressure symptoms was elevated. While the size of the myomas, whether they were single or multiple, the number of pregnancies of the patient and the history of infertility affected the laparotomic surgical approach in myomas, obesity did not. Decisions regarding laparotomic myomectomy surgeries should be made on an individual basis.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Adana City Hospital Clinical Researches Ethics Committee (Date: 14.09.2023, Decision No: 2826).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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The function of oral glucose tolerance test protocols in diagnosing and managing gestational diabetes: can insulin requirements be predicted?

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ABSTRACT

Aims: This study aims to evaluate the effectiveness of diagnostic tests, clinical, and laboratory markers in predicting insulin requirements in pregnant women diagnosed with gestational diabetes mellitus (GDM). Additionally, we assessed differences in maternal and neonatal outcomes between insulin-managed and diet-managed GDM patients.

Methods: A retrospective analysis was conducted on 406 pregnant women diagnosed with GDM at Ankara Etlik City Hospital between October 2022 and December 2024. Patients were categorized based on the diagnostic method used: the one-step 75 g oral glucose tolerance test (OGTT) or the two-step 100 g OGTT following a 50 g OGTT. Clinical, laboratory, and demographic data were compared between insulin-treated and diet-controlled groups. The predictive capacity of fasting plasma glucose (FPG), glucose levels at 1st, 2nd, and 3rd hours during OGTT, and HbA1c for insulin requirement were assessed using receiver operating characteristic (ROC) analysis.

Results: In the 75 g OGTT group, fasting, 1st-hour, and 2nd-hour glucose levels were significantly higher in the insulin-requiring group ($p<0.001$). ROC analysis indicated that fasting glucose >92 mg/dl and 2nd hour glucose >160 mg/dl were predictive of insulin requirement. HbA1c >5.25% was also a significant predictor ($p=0.009$). However, in the 100 g OGTT group, only the 2nd hour glucose level (>169 mg/dl, $p=0.032$) was predictive of insulin need, while HbA1c was not statistically significant. Birth outcomes showed that insulin-treated patients had an earlier gestational age at delivery ($p=0.001$), but neonatal outcomes were not significantly different between insulin-treated and diet-managed groups.

Conclusion: The findings suggest that glucose levels and HbA1c in the 75 g OGTT group are more effective in predicting insulin requirements in GDM patients than the 100 g OGTT. The study underscores the importance of identifying predictive markers for early intervention, potentially guiding clinicians in selecting optimal diagnostic methods and improving patient outcomes.

Keywords: Gestational diabetes mellitus, OGTT, insulin therapy, HbA1c, predictive markers, pregnancy outcomes

INTRODUCTION

Gestational diabetes mellitus (GDM) is a prevalent pregnancy condition identified during the second or third trimester [1]. The incidence of GDM ranges from 9.3% to 25.5%, influenced by ethnicity and the diagnostic methodology employed.[1-3] Besides the risk of acquiring type 2 diabetes mellitus, coronary artery disease, and hypertension later in life for women with GDM, exposure to hyperglycemia during pregnancy may result in long-term detrimental effects for both the mother and the infant.[4-7] GDM is concomitantly linked to numerous obstetric and neonatal complications, including polyhydramnios, macrosomia, preeclampsia, elevated cesarean section rates, preterm birth, birth traumas such as shoulder dystocia, neonatal hypoglycemia, hyperbilirubinemia, and a heightened incidence of neonatal intensive care unit (NICU) admissions.[8-10]

Approximately 15-30% of pregnant women diagnosed with GDM necessitate insulin therapy, which is recognized to reduce unfavorable pregnancy and neonatal outcomes associated with hyperglycemia.[11,12] Several studies have assessed the factors that predict insulin utilization in individuals diagnosed with GDM.[13,14] Given the significance of insulin therapy in regulating hyperglycemia in GDM, assessing prognostic markers may enhance patient management and facilitate timely referrals to appropriate facilities.

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Two approaches are employed for the diagnosis of GDM. The 75-g oral glucose tolerance test (OGTT), regarded as a single-step approach, and the 100-g OGTT conducted subsequent to the 50-g OGTT test, which constitutes a two-step method [Carpenter-Coustan (CC) criteria]. In 2010, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) endorsed the 75 g oral OGTT as a singular screening method for GDM.[15] Research indicates that the single-stage screening test, conducted in accordance with IADPSG guidelines, is more effective in diagnosing diabetes compared to the two-stage GDM screening test advocated by the American College of Obstetricians and Gynecologists (ACOG), which involves a 100-g OGTT following a 50-g OGTT result exceeding 130-140.[16-18] Moreover, research indicates that the single-step test endorsed by IADPSG decreases cesarean rates and composite neonatal outcomes while being cost-effective; yet, other studies assert that there is no distinction between the two methodologies.[17-19] A consensus on the appropriate test to utilize globally remains elusive. The American Diabetes Association (ADA) and ACOG advocate for a two-step diagnostic procedure, however the IADPSG endorses a single-step test.

This study aimed to assess the efficacy of diagnostic tests, clinical, and laboratory indicators in predicting the necessity of insulin treatment in pregnant women diagnosed with GDM. Our secondary objective was to assess the differences in pregnancy and newborn outcomes between pregnant women managing GDM with insulin and those controlling their blood sugar with dietary approaches. We assessed the predictive capacity of HbA1c, fasting blood glucose, and blood glucose levels at the 1st, 2nd, and 3rd hours during diagnostic tests for GDM.

METHODS

Ethics

This study covered patients diagnosed with GDM at Ankara Etlik City Hospital from October 2022 to December 2024. This study followed the Declaration of Helsinki on Research Involving Human Subjects and received approval from the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 25.12.2024, Decision No: AEŞH-BADEK–2024-1199).

Study Participants

A total of 406 individuals diagnosed with GDM using oral glucose tolerance testing at our hospital were included in the study. Patients diagnosed with GDM were divided into two groups: those diagnosed with a one-step method and those diagnosed with a two-step method. Of the 268 patients identified using the single-step approach following the 75 g OGTT test, 138 individuals were diagnosed using the two-step method. In the 75 g OGTT cohort, 49 patients (18.3%) were managed with insulin, whereas in the 100 g OGTT cohort, that number was 120 patients (87%). In our study, patient selection criteria were meticulously determined, and inclusion and exclusion criteria were determined as follows: 406 pregnant women who were diagnosed with GDM by OGTT at Ankara Etlik City Hospital during 24-28 weeks of pregnancy were included in the study. The patients included in the study were diagnosed with either single-stage 75 g OGTT or two-stage 100 g OGTT protocols. Inclusion criteria were gestational age of 18 years and above, being between 24-28 weeks of pregnancy, and GDM diagnosis was made according to the specified criteria. Exclusion criteria included type 1 or type 2 diabetes diagnosed before pregnancy, chronic metabolic diseases (e.g. polycystic ovary syndrome, Cushing syndrome), pregestational obesity (BMI>40 kg/m^2), thyroid diseases, chronic kidney or liver diseases, multiple pregnancies, and steroid use during pregnancy. In addition, patients with incomplete medical records or those for whom the necessary laboratory data could not be obtained were excluded from the study. Determining these criteria aims to conduct our study in a homogeneous patient group and to increase the reliability of the findings obtained. Demographic, clinical, laboratory, and ultrasonographic data of the cases were retrospectively acquired through the hospital data management system.

The sufficiency of the sample size acquired in our investigation was assessed by statistical power analysis. Power analysis is a technique for determining the likelihood of identifying a specific effect magnitude at a designated confidence level. In our investigation, the analyses conducted to assess the markers predicting insulin requirements in pregnant women with gestational GDM were based on an 80% power (1-β) and a 5% significance threshold (α=0.05) to identify significant differences. Based on calculations that accounted for effect sizes reported in analogous studies within the existing literature, it was concluded that the 406 patients included in our investigation constituted an adequate sample size to yield statistically significant results. The findings of our investigation are statistically valid and offer a solid foundation for the generalizability of the acquired data.

Methods for Diagnosing Gestational Diabetes

One step model: After measuring fasting plasma glucose (FPG) in women with 24-28 weeks of pregnancy, 75 g of glucose solution was loaded. Then, glucose levels were measured at 1st and 2nd hours. Patients with at least one positive value were diagnosed with GDM (FPG ≥92 mg/dl, 1st hour glucose ≥180 mg/dl and 2nd hour glucose ≥153 mg/dl).[20,21]

Two step model: Women at 24-28 weeks of gestation underwent a 50-g OGTT. Individuals with a glucose level of 140 mg/dl or higher were deemed positive and underwent a 100-g OGTT. FPG and glucose levels at the 1st, 2nd, and 3rd hours were assessed, and patients exhibiting two positive values were diagnosed as GDM (FPG >95 mg/dl, 1st hour glucose >180 mg/dl, 2nd hour glucose >155 mg/dl, and 3rd hour glucose >140 mg/dl).[20,21]

Statistical Analysis

The data analysis was performed using IBM Corporation SPSS version 22.0 (IBM Corporation, Armonk, NY, USA). The figures were created using Office 2021 (Microsoft, Albuquerque, New Mexico, USA). The Kolmogorov-Smirnov test was used to analyze conformity to normal distribution. Descriptive statistics of continuous variables are shown as "mean±standard deviation" for those with normal

distribution. and as "median (interquartile range)" for those that do not. Categorical variables were compared using the chi-squared test or Fisher's exact test. Continuous variables that were and were not normally distributed were compared using the independent sample T test and the Mann-Whitney U test. respectively. Receiver operating characteristic (ROC) curve was applied to calculate and compare the areas under the curve (AUC) and determine the best cutoff values according to Youden Index. Statistical significance for all tests was defined as p-value of less than 0.05.

RESULTS

Among the patients evaluated using the 75 g OGTT, when comparing the insulin-treatment group with the diet-only group, the mean age of those requiring insulin was significantly lower (31.9±5.9 years) with statistical significance of p=0.016. The frequency of insulin use was significantly lower in the nulliparous cohort (p=0.031). Higher HgbA1c levels were noted in the insulin group (p=0.009), and white blood cell and lymphocyte counts showed statistically significant variations (p=0.014 and p=0.031, respectively). However, serum albumin levels were significantly lower in the insulin group (p<0.001) (Table 1).

Table 1. Characteristics and laboratory results of patients diagnosed with GDM with 75 g OGTT according to need for insulin treatment

	GDM-regulated with insulin n: 49 (18.3%)	GDM-regulated with diet n: 219 (81.7%)	p-value
Maternal age (year)	31.9±5.9	34.2±5.6	0.016[a]
Gravida	2 (3)	3 (1)	0.169[b]
Parity	1 (2)	1 (1)	0.154[b]
Nulliparous	139 (63.5%)	39 (79.6%)	0.031[c]
In vitro fertilization	1 (6.4%)	2 (4.1%)	0.744[d]
Height (cm)	161±6	162±5.4	0.081[a]
Weight (kg)	81.9±14.7	84.6±12.7	0.254[a]
BMI (kg/m$^{2)}$	31.7±5.6	32±4.3	0.735[a]
Family history of diabetes mellitus	4 (1.8%)	5 (10.2%)	0.012[d]
Hemoglobin (g/dl)	11.80 (1.5)	12 (1.6)	0.130[b]
White blood cell count (10^9/L)	9.81 (3.05)	10.17 (3.16)	0.014[b]
Lymphocyte count (10^9/L)	1.86 (0.72)	2.02 (0.79)	0.031[b]
Neutrophil count (10^9/L)	7.24 (2.54)	7.23 (2.72)	0.077[b]
Monocyte count (10^9/L)	0.59 (0.25)	0.62 (0.27)	0.112[b]
Platelet count (10^9/L)	234.5 (78)	252.00 (83)	0.013[b]
TSH (mU/ml)	1.79 (1.67)	1.71 (1.15)	0.792[b]
AST (IU/L)	15 (6)	15 (5)	0.376[b]
ALT (IU/L)	11 (5.5)	11 (8)	0.132[b]
Albumin (g/dl)	35.65 (4.15)	37.75 (2.7)	<0.001[b]
Fibrinogen (mg/dl)	465 (116)	485 (141)	0.730[b]
HgbA1c (%)	5.3 (0.8)	5 (0.6)	0.009[b]

Data are expressed as n (%), mean±standard deviation or median (interquartile range) where appropriate. A p-value of <0.05 indicates a significant difference and statistically significant p-values are in bold. GDM: Gestational diabetes mellitus, OGTT: Oral glucose tolerance test, BMI: Body-mass index, TSH: Thyroid stimulating hormone, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HgbA1c: Hemoglobin A1c, [a]: Student T test, [b]: Mann-Whitney U test, [c]: Pearson chi-square, [d]: Fisher's exact test

Analysis of birth outcomes revealed that the delivery week occurred sooner in the insulin therapy cohort (p=0.001). A notable disparity was seen between the groups regarding infant gender; it was established that the offspring of patients undergoing insulin therapy were predominantly male (p=0.011). In addition, no statistical significance was observed between the rates of NICU admission and other neonatal complication rates in this group (Table 2).

Table 2. Characteristics and laboratory results of patients diagnosed with GDM with 100 g OGTT according to need for insulin treatment

	GDM-regulated with insulin n: 120 (87%)	GDM-regulated with diet n: 18 (13%)	p-value
Maternal age (year)	32.3±5.6	32.1±6.8	0.925[a]
Gravida	2 (2)	3 (2)	0.894[b]
Parity	1 (2)	1 (2)	0.513[b]
Nulliparous	87 (72.5%)	10 (55.6%)	0.142[c]
In vitro fertilization	6 (5%)	1 (5.6%)	1[d]
Height (cm)	161±6.1	161.1±5.6	0.914[a]
Weight (kg)	83.3±13.9	87.7±11.9	0.209[a]
BMI (kg/m^2)	32.1±4.9	33.7±4.3	0.188[a]
Family history of diabetes mellitus	2 (1.7%)	3 (16.7%)	0.016[d]
Hemoglobin (g/dl)	12 (0.8)	11.85 (1.5)	0.495[b]
White blood cell count (10^9/L)	9.73 (2.01)	10.19 (3.11)	0.951[b]
Lymphocyte count (10^9/L)	1.91 (0.52)	1.77 (0.52)	0.466[b]
Neutrophil count (10^9/L)	7.27 (1.44)	7.50 (2.7)	0.792[b]
Monocyte count (10^9/L)	0.61 (0.18)	0.59 (0.28)	0.371[b]
Platelet count (10^9/L)	241 (63)	239 (75)	0.493[b]
TSH (mU/ml)	1.34 (0.88)	1.63 (1.07)	0.441[b]
AST (IU/L)	16 (5)	16 (7)	0.544[b]
ALT (IU/L)	10 (4)	11 (8)	0.631[b]
Albumin (g/dl)	36.30 (2.6)	36.80 (4.5)	0.680[b]
Fibrinogen (mg/dl)	458.5 (123)	470 (145.5)	0.919[b]
HgbA1c (%)	5.10 (0.7)	5.05 (0.8)	0.572[b]

Data are expressed as n (%), mean±standard deviation or median (interquartile range) where appropriate. A p-value of <0.05 indicates a significant difference and statistically significant p-values are in bold. GDM: Gestational diabetes mellitus, OGTT: Oral glucose tolerance test, BMI: Body-mass index, TSH: Thyroid stimulating hormone, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HgbA1c: Hemoglobin A1c, [a]: Student T test, [b]: Mann-Whitney U test, [c]: Pearson chi-square, [d]: Fisher's exact test

No significant differences were seen between the insulin-regulated group and the diet-regulated group regarding maternal age, gravida, parity, BMI, and other laboratory parameters in patients assessed with a 100 g OGTT. Nonetheless, family history of diabetes was found to be higher in the insulin-treated group (p=0.016). No significant difference was seen between the groups regarding serum HgbA1c levels and glucose measurements (Table 3). Birth outcomes indicated that birth week and birth weights were comparable in both groups, with no statistical significance observed in neonatal results (Table 4).

In the comparison of serum glucose levels between insulin-regulated and diet-regulated GDM patients diagnosed via the 75 g OGTT (Table 5), fasting, 1st-hour, and 2nd hour glucose levels were significantly higher in the insulin-requiring group

Table 3. Birth characteristics and neonatal outcomes of newborns of patients diagnosed with GDM by 75 g OGTT

	GDM-regulated with insulin n: 49 (18.3%)	GDM-regulated with diet n: 219 (81.7%)	p-value
Gestational age at delivery (week)	38 (1)	38 (2)	0.001[a]
Cesarean section	34 (69.4%)	134 (61.2%)	0.283[b]
Birth weight (gram)	3239±609	3238±407	0.989[c]
Gender			0.011[b]
Female	20 (40.8%)	133 (60.7%)	
Male	29 (59.2%)	86 (39.3%)	
Apgar score at 1st minute	9 (0)	9 (0)	0.270[a]
Apgar score at 5th minute	10 (0)	10 (0)	0.752[a]
CAPO	12 (24.5%)	36 (16.4%)	0.184[b]
NICU admission	4 (8.2%)	5 (2.3%)	0.061[d]
Umbilical cord pH	7.38 (0.06)	7.36 (0.08)	0.180[a]
Preterm birth	7 (14.3%)	20 (9.1%)	0.279[d]
Transient tachypnea of the newborn	5 (10.2%)	12 (5.5%)	0.220[d]
Neonatal sepsis	0 (0%)	0 (0%)	NA
Fetal distress	2 (4.1%)	19 (8.7%)	0.385[d]
Respiratory distress syndrome	2 (4.1%)	4 (1.8%)	0.302[d]
Continues positive airway pressure	4 (8.2%)	14 (6.4%)	0.751[d]
Mechanical ventilation	3 (6.1%)	14 (6.4%)	1[d]
Phototherapy for neonates	2 (4.1%)	11 (5%)	1[d]
Neonatal hypoglycemia	9 (18.4%)	22 (10%)	0.135[b]
Interventricular hemorrhage	0 (0%)	0 (0%)	NA
Necrotizing enterocolitis	0 (0%)	0 (0%)	NA

Composite adverse perinatal outcomes include the presence of at least one of the following adverse outcomes: 5th-minute APGAR score <7, transient tachypnea of the newborn, respiratory distress syndrome, need for continuous positive airway pressure, need for mechanical ventilation, neonatal intensive care unit admission, preterm birth, neonatal hypoglycemia, need for phototherapy, intraventricular hemorrhage and neonatal sepsis. Data are expressed as n (%), mean±standard deviation or median (interquartile range) where appropriate. A p-value of <0.05 indicates a significant difference and statistically significant p-values are in bold. GDM: Gestational diabetes mellitus, OGTT: Oral glucose tolerance test, CAPO: Composite adverse perinatal outcome, NICU: Neonatal intensive care unit, NA: Not applicable, [a]: Mann-Whitney U test, [b]: Pearson chi-square, [c]: Student T test, [d]: Fisher's exact test

Table 4. Birth characteristics and neonatal outcomes of newborns of patients diagnosed with GDM by 100 g OGTT

	GDM-regulated with insulin n: 18 (13%)	GDM-regulated with diet n: 120 (87%)	p-value
Gestational age at delivery (week)	38 (2)	38 (2)	0.869[a]
Cesarean section	13 (72.2%)	77 (64.2%)	0.503[b]
Birth weight (gram)	3186±514	3232±587	0.752[c]
Gender			0.125[d]
Female	14 (77.8%)	69 (57.5%)	
Male	4 (22.2%)	51 (42.5%)	
Apgar score at 1st minute	9 (1)	9 (1)	0.243[a]
Apgar score at 5th minute	10 (1)	10 (1)	0.752[a]
CAPO	3 (16.7%)	36 (30%)	0.241[b]
NICU admission	0 (0%)	6 (5%)	1[d]
Umbilical cord pH	7.39 (0.1)	7.36 (0.09)	0.450[a]
Preterm birth	2 (11.1%)	26 (21.6%)	0.529[d]
Transient tachypnea of the newborn	1 (5.6%)	12 (10%)	1[d]
Neonatal sepsis	0 (0%)	0 (0%)	NA
Fetal distress	1 (5.6%)	9 (7.5%)	1[d]
Respiratory distress syndrome	0 (0%)	3 (2.5%)	1[d]
Continues positive airway pressure	1 (5.6%)	10 (8.3%)	1[d]
Mechanical ventilation	0 (0%)	7 (5.8%)	0.594[d]
Phototherapy for neonates	1 (5.6%)	5 (4.2%)	0.575[d]
Neonatal hypoglycemia	1 (5.6%)	15 (12.5%)	0.694[d]
Interventricular hemorrhage	0 (0%)	0 (0%)	NA
Necrotizing enterocolitis	0 (0%)	0 (0%)	NA

Data are expressed as n (%), mean±standard deviation or median (interquartile range) where appropriate. A p-value of <0.05 indicates a significant difference and statistically significant p-values are in bold. GDM: Gestational diabetes mellitus, OGTT: Oral glucose tolerance test, CAPO: Composite adverse perinatal outcome, NICU: Neonatal intensive care unit, NA: Not applicable, [a]: Mann-Whitney U test, [b]: Pearson chi-square test, [c]: Student T test, [d]: Fisher's exact test

Table 5. Comparison of serum glucose levels in patients diagnosed with GDM by 75 g OGTT

	GDM-regulated with insulin n: 49 (18.3%)	GDM-regulated with diet n: 219 (81.7%)	p-value
Fasting	97 (25)	89 (19)	<0.001[a]
1st hour	203 (37)	187 (35)	<0.001[a]
2nd hour	163 (58)	139 (48)	0.001[a]

Data are expressed as n (%) or median (interquartile range) where appropriate. A p-value of <0.05 indicates a significant difference and statistically significant p-values are in bold. GDM: Gestational diabetes mellitus, OGTT: Oral glucose tolerance test, [a]: Mann-Whitney U test

Table 6. Comparison of serum glucose levels in patients diagnosed with GDM by 100 g OGTT

	GDM-regulated with insulin n: 18 (13%)	GDM-regulated with diet n: 120 (87%)	p-value
Fasting	90 (23)	83 (17.5)	0.090[a]
1st hour	200 (39)	193 (27)	0.164[a]
2nd hour	189 (39)	162 (36)	0.032[a]
3rd hour	140 (25)	125 (41)	0.141[a]

Data are expressed as n (%) or median (interquartile range) where appropriate. A p-value of <0.05 indicates a significant difference and statistically significant p-values are in bold. GDM: Gestational diabetes mellitus, OGTT: Oral glucose tolerance test, [a]: Mann-Whitney U test

(p<0.001, p<0.001, and p=0.001, respectively). Similarly, in patients diagnosed with GDM using the 100 g OGTT (Table 6), the 2nd hour glucose level was significantly higher in the insulin-requiring group (p=0.032), while fasting, 1st hour, and 3rd hour glucose levels did not show statistically significant differences.

ROC analysis evaluating the ability of serum glucose levels to predict insulin requirements (Table 7) demonstrated that fasting glucose >92 mg/dl in all patients (AUC=0.657, p<0.001), >94 mg/dl in 75 g OGTT patients (AUC=0.669, p<0.001), 1st-hour glucose >196 mg/dl (AUC=0.667, p<0.001), and 2nd hour glucose >160 mg/dl (AUC=0.656, p=0.001) were predictive of insulin requirement. Among 100 g OGTT patients, a 2nd hour glucose level >169 mg/dl was associated with insulin use (AUC=0.661, p=0.032).

Table 7. Evaluation of serum glucose levels to predict insulin requirements in patients diagnosed with GDM by using ROC analysis

	LR+	LR-	Cut-off*	Sensitivity	Specificity	AUC	95% CI	p-value
Fasting (with all patients)	1.52	0.68	>92	58.2%	61.7%	0.657	0.58-0.73	<0.001
Fasting (for 75 g OGTT)	1.58	0.67	>94	57.1%	63.8%	0.669	0.58-0.76	<0.001
1st hour (for 75 g OGTT)	2.09	0.50	>196	65.3%	68.8%	0.667	0.58-0.76	<0.001
2nd hour (for 75 g OGTT)	2.27	0.59	>160	55.1%	75.7%	0.656	0.57-0.75	0.001
2nd hour (for 100 g OGTT)	1.72	0.57	>169	64.7%	62.4%	0.661	0.51-0.81	0.032

*Cut-off values were found according to Youden Index, GDM: Gestational diabetes mellitus, ROC: Receiver operating characteristic, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, AUC: Area under the curve, CI: Confidence interval, OGTT: Oral glucose tolerance test

Evaluation of HbA1c for predicting insulin requirement in 75 g OGTT-diagnosed GDM patients (Table 8) revealed that an HbA1c cutoff of >5.25% had an AUC of 0.633 (p=0.009), with a sensitivity of 53.5% and specificity of 71.4%. However, in patients diagnosed with the 100 g OGTT, HbA1c was not predictive of insulin need (AUC=0.544, p=0.573).

Finally, the ability of HbA1c to predict composite adverse perinatal outcomes (Table 9) was significant in 75 g OGTT patients, with an AUC of 0.662 (p=0.003) at a cutoff of >5.25%. However, in patients diagnosed with the 100 g OGTT, HbA1c did not significantly predict adverse outcomes (AUC=0.475, p=0.704). Serum glucose levels and insulin requirements; ROC analysis indicated that fasting blood glucose levels obtained during the 75 g OGTT, namely at the 1st and 2nd hour, were significant predictors of insulin requirements (p<0.001). The threshold value established for the 2nd hour glucose level (>160 mg/dl) exhibited 55.1% sensitivity and 75.7% specificity in forecasting insulin necessity (Figure 1). The study of HgbA1c revealed that a threshold value over 5.25 significantly predicted insulin demand (p=0.009), however statistical significance was not attained for the 100 g OGTT group (Figure 2).

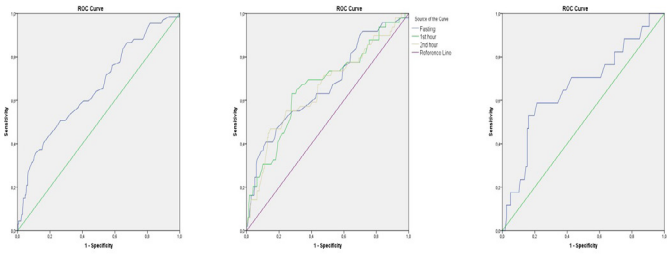

Figure 1. ROC curves of fasting, 1st hour and 2nd hour serum glucose levels to predict insulin requirements in patients diagnosed with gestational diabetes mellitus

ROC: Receiver operating characteristic

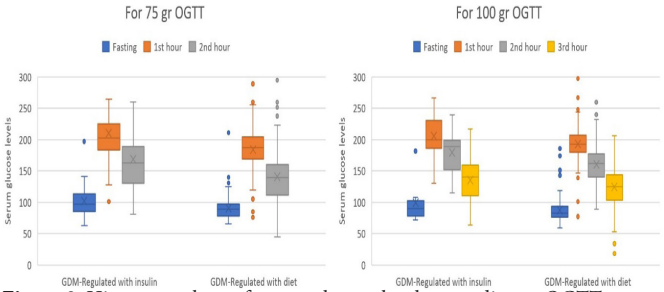

Figure 2. Histogram chart of serum glucose levels according to OGTT

OGTT: Oral glucose tolerance test

DISCUSSION

The primary conclusions of our study indicate that glucose measurements and HbA1c levels derived from a 75 g OGTT can effectively predict the necessity for insulin in pregnancies diagnosed with GDM. The data in the 100 g OGTT results lack statistical significance in forecasting insulin utilization. Despite the elevated incidence of preterm delivery in the insulin-treated cohort suggesting worse prenatal outcomes, dismal neonatal outcomes did not exhibit a statistically significant difference in this group. Maternal age, familial diabetes history, and specific hematological and biochemical indicators can predict insulin utilization.

In the demographic data of our investigation, contrary to existing literature, maternal age was lower and the nulliparity rate was considerably elevated among insulin users, specifically within the group diagnosed with the 75 g OGTT. Certain research have identified a correlation between youth, nulliparity, and gestational diabetes. This study contradicts the prevailing trend in the literature and indicates that several factors may influence the onset of gestational diabetes. Genetic predisposition, lifestyle, and environmental variables may elevate the risk of gestational diabetes in young

Table 8. Evaluation of HgbA1c to predict insulin requirements in patients diagnosed with GDM by 75 g OGTT using ROC analysis

	LR+	LR-	Cut-off*	Sensitivity	Specificity	AUC	95% CI	p-value
HgbA1c	1.87	0.65	>5.25	53.5%	71.4%	0.633	0.53-0.74	0.009

*Cut-off values were found according to Youden Index, HgbA1c: Hemoglobin A1c, GDM: Gestational diabetes mellitus, OGTT: Oral glucose tolerance test, ROC: Receiver operating characteristic, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, AUC: Area under the curve, CI: Confidence interval

Table 9. Evaluation of HgbA1c to predict composite adverse perinatal outcome in patients diagnosed with GDM by 75 g OGTT using ROC analysis

	LR+	LR-	Cut-off*	Sensitivity	Specificity	AUC	95% CI	p-value
HgbA1c	1.76	0.68	>5.25	52.8%	69.9%	0.662	0.57-0.76	0.003

*Cut-off values were found according to Youden Index, HgbA1c: Hemoglobin A1c, GDM: Gestational diabetes mellitus, OGTT: Oral glucose tolerance test, ROC: Receiver operating characteristic, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, AUC: Area under the curve, CI: Confidence interval

nulliparous women. Consequently, it is essential to evaluate individual risk factors instead of concentrating exclusively on demographic variables like age and parity in the assessment of gestational diabetes risk. Every pregnant woman must undergo an assessment of her individual and familial medical history, lifestyle, and other possible risk factors.[22,23]

Research indicates that elevated levels of white blood cells, platelets, and hematocrit are prevalent among non-pregnant individuals with diabetes who experience high complication rates, suggesting a potential correlation with the chronic inflammatory processes associated with diabetes.[24,25] Jindal et al.[26] indicated in their research that elevated platelet counts may correlate with microvascular problems. Consistent with these findings, HgbA1c levels were markedly elevated in diabetes patients with problems and in those utilizing insulin. Research on GDM mostly focused on predicting hematological markers only. Markovic et al.[27] assessed various hematological and biochemical markers in women with GDM compared to control groups. Alanine aminotransferase (ALT), fibrinogen, sedimentation rate, granulocyte count, and leukocyte count were correlated with adverse neonatal outcomes in patients with GDM. Another study revealed that HgbA1c and platelet distribution width were considerably elevated in GDM.[28] These investigations indicate that certain hematological and biochemical markers may forecast GDM, although they are not pertinent for anticipating insulin requires. In our investigation, women who took a 75 g OGTT and required insulin exhibited significantly elevated lymphocyte count, platelet count, albumin levels, and HbA1c levels. Consequently, to our knowledge, this study is the inaugural investigation in the literature that substantiates the potential of hematological and biochemical markers to predict insulin utilization, warranting further extensive studies on this topic.

Numerous studies have examined factors that retroactively predict diagnosis in GDM patients identified using the 100 g and 75 g OGTTs. These studies corroborate that the risk factors for GDM are identical for both screening techniques.[16,29,30] Helseth et al.[31] conducted a study indicating that the diagnosis of GDM is more prevalent with the 75 g OGTT, and that the risk variables differ between the two diagnoses. The primary risk variables found were maternal age, BMI prior to and during pregnancy, familial history of type 2 diabetes, and weight gain during pregnancy. Nevertheless, the quantity of studies aimed at predicting insulin requirements or identifying risk factors for insulin utilization in patients with GDM is very restricted. Research is mostly focused on identifying risk factors for GDM to facilitate the use of screening tests. Tamagawa et al. assessed the predictive factors for insulin utilization by comparing the insulin requirement risk factors in pregnant women diagnosed with early GDM based on positive OGTT in the first trimester, and those identified with late GDM based on positive OGTT in the second trimester. It was determined that blood sugar measurements during the 1st and 2nd hours, excluding fasting blood sugar, were considerably elevated in the insulin-dependent group. They also indicated that among pregnant women with early GDM, a pre-pregnancy BMI of ≥25 kg/m^2, a family history of diabetes, and 75 g OGTT scores were all significantly elevated in those requiring insulin. The evaluation of unfavorable neonatal outcomes between the two groups revealed no statistically significant difference between the insulin-using group and the non-using group. Furthermore, this study found no statistically significant difference in HbA1c values between the insulin-administering group and the non-insulin-administering group.[13] Consistent with these observations, prior research indicate that insulin requirements in pregnant women identified with 75 g OGTT correlate with elevated BMI and a familial history of diabetes.[32,33] Our investigation revealed that insulin utilization in patients diagnosed via the 75 g OGTT correlated with maternal age, elevated HbA1c levels, and a familial history of diabetes; however, its association with BMI was not statistically significant. In individuals diagnosed with 100 g OGTT, only a family history of diabetes was correlated with the insulin-using cohort. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) project is among the greatest investigations on hyperglycemia and negative neonatal outcomes. This study unequivocally shown that maternal hyperglycemia is directly linked to negative neonatal outcomes.[15,34] Moreover, given that GDM is predominantly diagnosed using the 75 g OGTT, our study, alongside other research, suggests that predictive factors for insulin therapy may assist clinicians in managing hyperglycemia. This can be achieved by enhancing lifestyle modifications, such as dietary adjustments and physical activity, or by assessing the patient for the early initiation of insulin treatment.

In our investigation, individuals who received a 75 g OGTT had significantly elevated mean fasting, 1st hour, and 2nd hour blood sugar levels in the insulin-dependent group. In the 100 g OGTT, only the blood glucose level recorded at the second hour was substantially elevated in the insulin-using group. The primary findings of our investigation indicated that additional parameters could predict insulin utilization with the 75 g OGTT. The two-step diagnostic test may be less advantageous than the single-step diagnostic test for application and cost, and prior research have assessed the suggestion of the single-step method.[35,36] Furthermore, numerous studies have indicated that the treatment of GDM yields superior newborn outcomes relative to the expectant management method, underscoring the significance of hyperglycemia regulation.[13,34,37] We contend that our research could assist doctors in implementing OGTT during the initial weeks of pregnancy, with a preference for a single-step diagnosis approach, particularly for patients exhibiting risk indicators for GDM.

Limitations

A principal strength of this study is its thorough retrospective analysis of a substantial cohort of patients, facilitating an in-depth assessment of several OGTT methods and their predictive significance for insulin requirements in GDM. The research offers significant insights into the practical applicability of diverse diagnostic techniques and prospective biomarkers for informing early intervention tactics. Nevertheless, specific limits must also be recognized. The retrospective methodology obviously poses a risk of selection and information bias, as data were sourced from existing medical records, potentially resulting in incomplete or

absent information. The study is conducted on a single-center population, perhaps restricting the generalizability of the findings to wider, more heterogeneous populations. Future prospective, multi-center research employing standardized data collection methods would be advantageous for validating and reinforcing these findings.

CONCLUSION

This study assessed the impact of several OGTT procedures on the diagnosis and management of GDM and analyzed the factors influencing insulin need. The results indicate that the selection of OGTT procedures may influence clinical outcomes and that specific criteria should be considered when predicting the necessity for insulin therapy. In the management of GDM, it may be possible to predict insulin requirements using glucose levels based on the 75 g OGTT and this could support early interventions. The advancement of personalized strategies for managing gestational diabetes may enhance mother and newborn health.

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: 25.12.2024, Decision No: AEŞH-BADEK–2024-1199).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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The relationship between neutrophil percentage-to-albumin ratio and infarct related artery patency in patients with acute coronary syndrome

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ABSTRACT

Aims: One of the leading causes of death and disease burden globally is coronary heart disease (CHD). The primary cause of acute coronary syndrome (ACS) is atherosclerotic plaque rupture and thrombus development. The prognosis of ACS patients is also linked to atherosclerotic plaques, inflammatory cell infiltration (lymphocytes, monocytes, and neutrophils), and inflammation indicators. Low serum albumin (SA) levels have been linked to death in ACS patients in earlier research. In our study, we aimed to investigate the association of neutrophil percentage-to-albumin ratio (NPAR) with infarct-related adverse cardiac events (MACE) and infarct-related coronary artery patency (IRA).

Methods: The NPAR ratio was calculated based on the past laboratory findings of patients admitted with ACS who underwent coronary angiography (CAG), which were registered in the data system at the time of admission. A total of 87 patients were included in the study. Of these patients, 62 (71%) were non-patent and 25 (29%) were patent IRA patients.

Results: NPAR was significantly higher in the non-patent group (19.22±3.14 and 17.14±2.78 p=0.004). In multivariable logistic regression analysis, NPAR [p=0.027, odds ratio (OR): 0.787, 95% confidence intervals (CIs): 0.637-0.974] levels were found to be independent predictors of patent IRA. As revealed by the ROC curve analysis, the cut-off value of 17.88 for NPAR predicted the non-patent IRA with a sensitivity of 64% and specificity of 64% (AUC: 0.681; CIs: 0.588-0.809; p=0.008) NPAR was significantly higher in the MACE group (22.83±3.85 and 17.95±2.49 p<0.001).

Conclusion: In conclusion, inflammatory markers have been and are being used as predictive parameters for cardiovascular diseases in many studies. In our study, we focused on neutrophils and albumin. These findings revealed that NPAR is a independent predictor of IRA patency and long term mortality. We also indicated that NPAR may have a predictive role for mortality in the long-term follow-up of ACS patients.

Keywords: Neutrophil, albumin, infarct related artery, acute coronary syndrome

INTRODUCTION

One of the leading causes of death and disease burden globally is coronary heart disease (CHD). One severe form of CHD with a high morbidity and mortality rate is ACS. The primary cause of ACS is atherosclerotic plaque rupture and thrombus development. The prognosis of ACS patients is also linked to atherosclerotic plaques, inflammatory cell infiltration (lymphocytes, monocytes, and neutrophils), and inflammation indicators. In recent years, neutrophil/lymphocyte ratio (NLR) is one of the most important and widely used inflammatory markers in the prognosis of ACS. A prognostic biomarker for cardiovascular, viral, and cancer conditions, NLR is an indication of inflammation.[1,2] It has been demonstrated that NLR, an indicator of inflammation, can forecast in-hospital death in patients with ACS.[3]

Serum albumin (SA) is linked to both acute and chronic inflammatory reactions, and elevated inflammation lowers SA levels in addition to suggesting nutritional status.[4] Low SA levels have been linked to death in ACS patients in earlier research.[5]

Neutrophil percentage-to-albumin (NPAR), calculated as neutrophil percentage numerator divided by serum albumin concentration, can amplify the changes of these two accessible evaluation parameters. According to one study, the NPAR at admission was an independent predictor of in-hospital mortality for patients with acute ST segment elevation myocardial infarction (STEMI).[6] In critically sick patients with coronary artery disease (CAD), a higher NPAR level was strongly associated with higher 30-day, 90-day, and 365-day all-cause death, according to another study.[7]

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In our study, we aimed to investigate the association of NPAR with infarct-related adverse cardiac events (MACE) and infarct-related coronary artery patency (IRA) in patients aged <65 years.

METHODS

Ethics

The study was carried out with the permission of Bandırma Onyedi Eylül University Health Sciences Non-interventional Researches Ethics Committee (Date: 22.04.2024, Decision No: 2024-4). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Population

We retrospectively evaluated patients with ACS from Bandırma Research and Training Hospital database who were admitted to the department of cardiology. STEMI was defined as typical symptoms (chest pain >30 minutes) and ST elevation (greater than or equal to 1 mm in at least consecutive 2 leads on ECG) and NSTEMI was defined patients with chest pain, high cardiac troponin (cTn) levels and ST changes on ECG. Exclusion criteria were active infectious disease, active carcinoma, hematologic proliferative diseases, chronic inflammatory disease, coronary artery bypass graft (CABG), ACS and ischemic stroke in the last 3 months, active hepatobiliary diseases, steroid treatment for autoimmune disease, pulmonary embolism, pulmonary hypertension, malignancy, age >65 years and patients with inaccessible laboratory parameters. Finally, a total of 87 patients were included in the study (Table 1).

Laboratory Analysis and NPAR Calculation

Peripheral blood samples obtained from patients at the time of admission were used. These data were obtained retrospectively from the hospital automation system. NPAR was calculated by dividing the neutrophil percentage share (i.e. 66% was recorded 66) by albumin using the same blood samples taken at admission. Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and high-sensitivity C-reactivity protein levels were obtained from fasting blood samples taken the morning after admission. Serum levels of cardiac markers such as cTn and creatinine kinase-MB (CK-MB) were measured at admission and every 24 hours until peaks occurred, but values taken at the time of admission were used. Demographic, clinical and laboratory data of the patients were obtained from the hospital registry system.

Data Collection and Definition

Demographic information and cardiovascular risk factors such as previous CHD, hyper blood pressure, diabetic mellitus, dyslipidemia and smoking history were retrospectively collected from medical records. Systemic blood pressure, diastolic blood pressure, heart rate and Killip class were defined as the initial data recorded at admission. Simpson's method was used to calculate left ventricular ejection fraction (LVEF) for quantitative assessment of left ventricular systolic function before discharge. On 365-days, major adverse cardiac events (MACE) were defined as mortality due to reinfarction, stroke, malignant arrhythmia and heart failure.

Table 1. Characteristics of study patients according to the IRA

Variables	All (87)	IRA non-patent (62)	IRA patent (25)	p
Age	61.1±11.6	61.2±11.0	60.9±13.1	0.907
Male gender, n (%)	65 (74.7)	46 (74.2)	19 (76.0)	0.861
Hypertension, n (%)	46 (52.9)	30 (48.4)	16 (64.0)	0.187
Diabetes mellitus, n (%)	20 (23.0)	16 (25.8)	4 (16.0)	0.325
HL	39 (44.8)	29 (46.8)	10 (40.0)	0.565
CAD	30 (34.5)	21 (33.9)	9 (36.0)	0.850
LVEF	45.0 (40.0-55.0)	45.0 (35.0-55.0)	50 (45.0-55.0)	0.168
WBC	10.9 (9.0-13.4)	10.9 (9.3-14.2)	9.9 (7.3-11.9)	0.024
Hgb	13.7±2.1	13.7±2.0	13.8±2.3	0.881
Neutrophil count, x1000/ul	8.09 (5.98-10.18)	8.71 (6.62-10.70)	6.61 (4.75-8.80)	0.009
Lymphocyte count, x1000/ul	1.93 (1.42-2.57)	1.98 (1.44-2.62)	1.64 (1.26-2.53)	0.558
PLT	244.5 (204.0-279.0)	245.0 (201.0-280.0)	241.5 (212.0-268.0)	0.488
Albumin	4.03 (3.81-4.30)	4.00 (3.70-4.30)	4.10 (4.00-4.40)	0.131
CRP	0.75 (0.20-2.01)	1.05 (0.30-2.80)	0.30 (0.10-0.70)	0.001
Creatinine, mg/dl	0.94 (0.85-1.08)	0.95 (0.85-1.10)	0.92 (0.87-1.05)	0.666
Total cholesterol	189.0 (158.5-224.0)	198.5 (165.0-227.0)	176.0 (141.0-190.0)	0.028
Trigliserid	125.5 (104.0-176.0)	125.5 (104.0-216.0)	127.0 (105.0-163.0)	0.498
LDL	116.1±39.3	120.3±39.5	104.7±37.2	0.105
Troponin	6750.11	9059.69	1022.35	0.000
NPAR	18.62±3.17	19.22±3.14	17.14±2.78	0.004

IRA: Infarct-related coronary artery patency, HL: Hodgkin lymphoma, CAD: Coronary artery disease, LVEF: Left ventricular ejection fraction, WBC: White blood cell, Hgb: Hemoglobin, PLT: Thrombocyte, CRP: C-reactive protein, LDL: Low-density lipoprotein, NPAR: Neutrophil percentage-to-albumin ratio

Revascularization Procedure and Medications

Prior to percutaneous coronary intervention (PCI), a loading dose of antiplatelet drugs (aspirin 300 mg, clopidogrel 300 to 600 mg or ticagrelor 180 mg) was used according to established guidelines. PCI was performed via the femoral or radial route at the discretion of the attending physician, using standard techniques and appropriate strategies according to guidelines. No thrombolytic therapy was administered in the study population. During hospitalization and after discharge, antiplatelets, statins, b-blockers and angiotensin-converting enzyme inhibitors were administered to all patients according to guidelines unless contraindicated.

Statistical Analysis

IBM SPSS Statistics 23 package was used for statistical analysis. Categorical variables are presented as percentages, continuous variables are presented as mean±standard deviation if normally distributed and median interquartile range (IQR) if not. Two independent groups with normal distribution were compared using student's T test, while those without normal distribution were compared using Mann Whitney U test. The chi-square test will be used to compare categorical variables. Receiver operating characteristic curve (ROC) analysis was used to define the area under the curve to estimate the optimal cutoff level of NPAR and IRA patency. Regression analysis was performed for possible parameters in predicting IRA patency, evaluated in univariable analysis, and those with p-value <0.05 were evaluated in multivariable analysis. Statistical significance is defined as p-values less than 0.05.

G-power (version 3.1.9.7) was used to determine the minimum sample size. Accordingly, T tests, means: difference between two independent means (matched pairs), a priori: compute required sample size-given a, power, and effect size were selected. Accordingly, when α err prob=0.05, power (1-β err prob)=0.80, and effect size=0.6, it was determined that at least 86 participants should participate in the study for each group (actual power=80.3%).

RESULTS

A total of 87 patients with 62 non-patent and 25 patent IRA were included in the study. The responsible artery was the left anterior descending artery (LAD) in 29 patients, right coronary artery (RCA) in 29, circumflex artery (CX) in 12, saphenous grafts in 2, and diagonal artery or obtuse marginal artery in the rest. 65 (74%) of the patients were male and 22 (26%) were female (Table 1). NPAR was also significantly higher in the non-patent group (19.22±3.14 and 17.14±2.78 p=0.004). Troponin values were also significantly higher in the non-patent group (9059.69 and 1022.35 p<0.001). NPAR was also significantly higher in the MACE group (22.83±3.85 and 17.95±2.49 p<0.001). Albumin was also significantly higher in the MACE group (4.07 ± 0.35 and 3.50 ± 0.65 p<0.001). WBC values were compared between the two groups, the non-patent group was found to be significantly higher (10.9 and 9.9 p=0.02). CRP values were significantly higher in the non-patent group (1.05 and 0.3 p=0.001) (Table 2).

In multivariable logistic regression analysis, NPAR [p=0.027, odds ratio (OR): 0.787, 95% confidence intervals (CIs): 0.637-0.974] levels were found to be independent predictors of patent IRA. WBC (p= 0.049, OR: 0.848, 95% CIs: 0.717-0.999) levels were found to be independent predictors of patent IRA. But CRP (p=0.049, OR: 0.656, 95% CIs: 0.414-1.040). Univariable and multivariable regression analyses of potential predictive factors in determining IRA patency are shown in Table 3.

Table 2. Characteristics of study patients according to the MACE

Variables	Non-MACE (75)	MACE (12)	p
Hypertension, n (%)	38 (50.6)	8 (66.6)	0.308
Diabetes mellitus, n (%)	16 (21.3)	4 (33.3)	0.100
HL	34 (45.3)	5 (41.6)	0.815
CAD	26 (34.6)	4 (33.3)	0.929
LVEF	46.84±9.91	43.33±11.34	0.268
WBC	11.97±4.21	10.77±3.29	0.350
Hgb	14±1.86	12±2.68	0.002
Neutrophil count, x1000/ul	8.78 (6.62-10.70)	8.59 (4.75-8.80)	0.859
Lymphocyte count, x1000/ul	2.14 (1.44-2.62)	1.51 (1.26-2.53)	0.048
PLT	257.2 (201.0-280.0)	216.0 (212.0-268.0)	0.101
Albumin	4.07±0.35	3.50±0.65	0.000
CRP	3.10	2.70	0.114
Total kolesterol	190.64 (165.0-227.0)	189.75 (141.0-190.0)	0.949
Trigliserid	146.98 (104.0-216.0)	190.25 (105.0-202.0)	0.093
LDL	116.34±39.5	114.62±41.6	0.889
Troponin	5661.23	13555.70	0.083
NPAR	17.95±2.49	22.83±3.85	0.000

MACE: Major adverse cardiovascular events, HL: Hodgkin lymphoma, CAD: Coronary artery disease, LVEF: Left ventricular ejection fraction, WBC: White blood cell, Hgb: Hemoglobin, PLT: Thrombocyte, CRP: C-reactive protein, LDL: Low-density lipoprotein, NPAR: Neutrophil percentage-to-albumin ratio

Table 3. Univariate and multivariate logistic regression analysis for the risk factors in predicting the IRA patency

	Univariate	Multivariate
	OR (95% confidence interval)	OR (95% confidence interval)
NPAR	0.771 (0.637-0.934, p=0.008)	0.787 (0.637-0.974, p=0.027)
WBC	0.822 (0.698-0.969, p=0.019)	0.848 (0.717-0.999, p=0.049)
CRP	0.590 (0.360-0.968, p=0.037)	0.656 (0.414-1.040, p=0.073)

IRA: Infarct-related coronary artery patency, OR: Odds ratio, NPAR: Neutrophil percentage-to-albumin ratio, WBC: White blood cell, CRP: C-reactive protein

As revealed by the ROC curve analysis, the cut-off value of 17.88 for NPAR predicted the non-patent IRA with a sensitivity of 64% and specificity of 64% (AUC: 0.681; CIs: 0.588-0.809; p=0.008 (Figure).

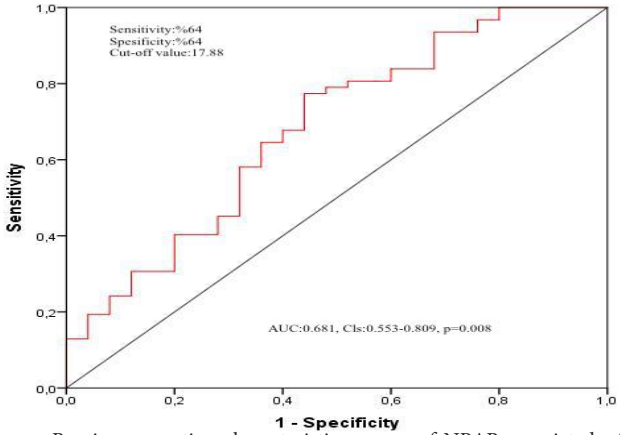

Figure. Receiver operating characteristics curves of NPAR associated with IRA patency

NPAR: Neutrophil percentage-to-albumin ratio, IRA: Infarct-related coronary artery patency

DISCUSSION

In our study, we investigated the relationship between NPAR and IRA patency and the group with MACE in ACS patients. The main finding of our study was that significantly higher NPAR levels were associated with non-patent IRA patients and MACE group and were independent predictors.

Coronary artery disease is one of the leading causes of death in the world and in our country. In recent years, the role of inflammation and biomarkers reflecting inflammatory status in CAD and its relationship with adverse events have been investigated in many studies. Numerous indicators of inflammation have been investigated. The condition and degree of stimulation of the inflammatory response in our bodies have been examined using a variety of biomarkers, including cytokines, adhesion molecules, white blood cells, and acute phase reactants. White blood cell (WBC) count, one of the most basic cells of inflammation, and its subtypes have been investigated in adverse events in cardiovascular diseases and used as a marker of inflammatory status. One study showed that increased neutrophil levels in ACS were associated with the extent of myocardial damage and short-term prognosis.[8]

Inflammation, the atherosclerotic process and the occurrence of CAD are tightly linked through several complex pathophysiological pathways. Neutrophils, an important member of the WBC, together with cytokines and phospholipids, play an important role in triggering the inflammatory reaction, coronary atherosclerosis and acute myocardial infarction (AMI).[9]

It has long been believed that albumin is a sign of nutritional well. According to the majority of data, alterations in acute phase proteins such SA and prealbumin may be linked to inflammation and the severity of the illness rather than reflecting inadequate nutritional condition.[10] In patients with ACS, low SA levels have been shown to be an independent predictor of both in-hospital mortality.[11] Reduced SA levels, or hypoalbuminemia, also raise blood viscosity and impair endothelium. Ischemic heart disease incidence is inversely correlated with SA levels.[12] Additionally, a significant correlation between low SA levels and long-term mortality was shown in STEMI patients undergoing PCI, as well as in patients with unstable angina pectoris (USAP) and NSTEMI.[13] In our study, albumin levels were significantly lower in the group with MACE. This suggests that low SA levels may be a predictive factor for long-term mortality after ACS, as in previous studies.

The ratio of neutrophil percentage to albumin count is expressed using a new metric called NPAR. In cases of severe sepsis or other clinical events such septic shock, acute renal injury, and cardiogenic shock, prior research has shown the predictive usefulness of NPAR.[14-16] In a study by Cai et al.[17] NPAR was found to be an independent predictor of 365-day mortality in patients followed in the coronary intensive care unit. Another study by Cui et al.[18] showed that NPAR was an independent predictor of in-hospital mortality after STEMI. In our study, the NPAR was significantly higher in the group with MACE compared to the group without MACE. This suggests that higher NPAR on admission may be independently associated with death from causes such as 365-day reinfarction, stroke, malignant arrhythmia and heart failure in patients with ACS. Furthermore, in our analysis, the NPAR was significantly higher in the group with non-patent IRA compared to the group patent IRA. This implies that NPAR may also serve as a predictor of IRA patency.

Preserving the IRA patent at an early stage is the primary objective of treatment for patients with AMI. Poor clinical results have been linked to off-patent IRA at presentation. Particularly in patients with STEMI, early IRA patency is crucial to maintaining cardiac function and lowering the likelihood of mechanical and lethal arrhythmias.[19] The TIMI flow rate is used to determine IRA patency. Good clinical results have been linked to monitoring the TIMI-3 flow rate at admission.[20] Another crucial sign of post-procedural patency is IRA patency at admission. For all of these reasons, the prognosis depends on the early assessment and restoration of IRA patency. The function of various indicators in forecasting IRA patency at presentation has been examined in earlier study. Doğan et al.[21] reported IRA patency in STEMI patients was predicted by the neutrophil-to-lymphocyte (N/L) ratio, another inflammatory marker. In another study, hematologic parameters were analyzed in STEMI patients undergoing primary angioplasty, and WBC count, which plays a vital role in inflammation, was associated with IRA patency.[22] In our study, WBC levels were significantly higher in patients with non-patent IRA compared to patent IRA group, which was similar to previous studies. It showed that the WBC values during hospitalization can be used as an indicator of IRA patency.

Troponin is the most commonly used biochemical parameter in the diagnosis of AMI. In previous studies, troponin values were found to be significantly higher in patients with non-patent IRA compared to patients with patent IRA.[23] In our study, similar to these studies, troponin values were found to be significantly higher in patients with non-patent IRA. Troponin was considered as a method that can be used for both diagnosis and patent IRA.

In everyday practice, it is simple to determine inflammation parameters. Their use for practitioners is expanded because they will be obtained using blood biomarkers that should be regularly observed in patients undergoing or planned CAG. The murky regions in this regard are still being clarified by several studies conducted in recent years. ACS continues to rank among the world's major causes of death. Our task will be made easier if there are more parameters available for usage, particularly in the follow-up of ACS patients. Thus, metrics that may make predictions without wasting a lot of time, like inflammatory parameters, come to the fore. We believe that our study demonstrates the importance of NPAR, simply calculated using neutrophils and albumin, for mortality prediction. Additionally, we discovered that NPAR was important in demonstrating IRA patency. One computation technique that is simple to apply in day-to-day work is NPAR.

Limitations

Since our study was single-center and retrospective, not all patients had albumin values and this led to a limitation in the number of patients. In addition, since inflammation parameters may be affected in patients older than 65 years of age, the age of the patients included in the study was limited to 65 years of age, considering that this would not lead to incorrect results.

CONCLUSION

In conclusion, inflammatory markers have been and are being used as predictive parameters for cardiovascular diseases in many studies. In our study, we focused on neutrophils and albumin. We have shown that NPAR may be pathway markers for IRA. We also indicated that NPAR may have a predictive role for mortality in the long-term follow-up of ACS patients. In addition, we think that easily calculable markers such as WBC and troponin may be instructive for IRA patency. According to the results of multivariate regression analysis, we think that CRP can also be used, albeit weakly.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Bandırma Onyedi Eylül University Health Sciences Non-interventional Researches Ethics Committee (Date: 22.04.2024, Decision No: 2024-4).

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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Oxidative stress in the cerebellum of pinealectomized rats and its correlation with GFAP expression

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ABSTRACT

Aims: This study aims to investigate the results of the lack of melatonin in the cerebellar tissue of pinealectomized Wistar albino rats using immunohistochemistry and biochemistry.

Methods: Control, pinealectomy, and sham pinealectomy groups were designed for the experiment (n=8). Pinealectomy and sham pinealectomy surgery were employed. At the end of 30 days, cerebellum tissue was used for histopathological, glial fibrillary acidic protein (GFAP) immunostaining, and biochemical (oxidative stress markers) analyses. Purkinje cell counts and cerebellar layer thickness in the cerebellum were also measured within the scope of histometrical analyses.

Results: The study revealed that melatonin deficiency (pinealectomy) adversely impacts the overall histological structure of the cerebellum, leading to heightened immunoreactivity to GFAP antibody, elevated malondialdehyde levels, and reduced glutathione and superoxide dismutase levels in comparison to control and sham pinealectomy groups ($p<0.05$). This study has, for the first time, elucidated the amounts of oxidants and antioxidants, GFAP immunoreactivity, Purkinje cell counts, and cerebellar layers thicknesses in the cerebellum of a pinealectomized rat model. This study is the inaugural investigation to elucidate the association between melatonin and the cerebellum, a topic hitherto overlooked in the literature, thereby establishing a significant foundation.

Conclusion: Lack of melatonin can be a reason for neurodegeneration and oxidative stress in the cerebellum. Pinealectomy surgery was found to be a reason for the elevation of oxidative stress, deterioration of the histological architecture, and increase of GFAP expression in the cerebellar tissue of the Wistar albino rats.

Keywords: Cerebellum, GFAP, oxidative stress, pinealectomy

INTRODUCTION

The circadian rhythm, governed by the pacemaker in the hypothalamic suprachiasmatic nucleus (SCN), governs daily physiological processes and behaviors to sustain melatonin production by the pineal gland and ensure optimal performance.[1,2] Melatonin, synthesized by the pineal gland at night, is integral to the circadian rhythm and serves as a neurohormone that significantly regulates physiological systems and aids in adapting to environmental changes.[3] Disruption of the circadian rhythm exacerbates stress in the brain and several bodily systems, influencing the onset and progression of numerous diseases that induce oxidative damage to cellular components due to the overproduction of free radicals.[4]

Free radicals, perpetually generated as metabolic wastes,[5] oxidize unsaturated fatty acids in membranes via lipid peroxidation. The elevation of free radicals results in the excessive synthesis of malondialdehyde (MDA), a byproduct of lipid peroxidation and an indicator of oxidative stress.[6] Nevertheless, several antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH), are molecules capable of stabilizing or neutralizing free radicals prior to cellular harm.[7,8] Numerous studies demonstrate melatonin's preventive role against free radical-induced oxidative alterations in brain tissue by enhancing antioxidant enzyme activity and diminishing lipid peroxidation.[9-11] Conversely, research involving experimental melatonin deprivation (pinealectomy) indicates that pinealectomy exacerbates tissue damage induced by reactive oxygen species and cerebral damage resulting from localized ischemia and excitotoxic convulsions.[12] Pinealectomy concurrently disrupts the antioxidant system by elevating SOD activity in the frontal brain and hippocampus while diminishing GSH levels. Numerous studies indicate a substantial rise in oxidative and structural alterations in the

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tissues and organs, including the liver, kidneys, testes, uterus, and lungs of rats following pinealectomy, which also results in a notable elevation of MDA levels and a reduction in GSH levels.[13]

Glial fibrillary acidic protein (GFAP) is an intracellular protein exclusive to central nervous system astrocytes and serves as a marker for astrocyte activation.[14] Alterations in GFAP expression and/or phosphorylation in brain injury or various neurological disorders may indicate aberrant synaptogenesis and neurotransmission, potentially correlating with neurodegenerative diseases.[15,16] The reactive alterations in astrocytes inside the hippocampus and cerebellum correlate with neuronal degeneration.[17] Research indicates that GSH levels are markedly diminished in the brains of rats subjected to continuous light, while total and degraded GFAP content is elevated; also, melatonin treatment results in reduced degraded GFAP content. Moreover, melatonin markedly diminishes lipid peroxidation in neural tissue, whereas prolonged light exposure substantially enhances lipid degradation in the brain.[18]

The cerebellum exhibits unique binding sites for melatonin,[19] however, the impact of pinealectomy on cerebellar tissue remains inadequately established. This investigation was predicated on the deficiency of melatonin and its potential impact on cerebellar tissue, considering the underlying causes of oxidative stress, given the possible antioxidant and therapeutic properties of melatonin. In our study, oxidative and structural changes in the cerebellum after pinealectomy were demonstrated by SOD, GSH, and MDA levels, and data supporting their relationship with GFAP were presented.

METHODS

Ethics Statement and Animal Care

Approval from the Karabük University Rectorate Animal Experiments Local Ethics Committee for Animal Experiments was secured for the study (Date: 26.12.2024, Decision No: 2024/12/32) and conducted following its requirements. All procedures were carried out in accordance with the ethical rules and the principles. Twenty-four male Wistar Albino rats, each weighing at least 150 g, were obtained from the Experimental Medicine Research and Application Center of Karabük University. The rats were housed in rooms with constant temperature and humidity, maintained at 22±1°C, and subjected to a 12-hour light-dark cycle, with unrestricted access to water and food.

Experimental Design and Group Allocation

The rats were randomly separated into three groups 8 rats each. Groups were named as follows:

Control (Co): The rats in this group received no treatment.

Pinealectomy (PNX): The rats in this group underwent pinealectomy surgery.

Sham pinealectomy (PNX-sham): The rats in this group underwent sham pinealectomy surgery. All the procedure for PNX surgery was applied (as described in the "2.3. surgical pinealectomy" title) except that the pineal gland was not removed.

Surgical pinealectomy

The PNX procedure was carried out as the authors mentioned before.[20]

Experiment Termination and Tissue Sample Collection

On the 30th day post-PNX and PNX-sham surgery, rats from all groups were sedated, and beheaded, and the excised cerebellum tissues were taken. Half of the cerebellum tissue was resected and immersed in 10% formalin for histological examination. The remaining portion was employed for biochemical research.

Histometric Analysis of Cerebellar Cortex Layers and Purkinje Cell Quantification

The thicknesses of the molecular layer, granular layer, and total cortex were measured from a minimum of 10 distinct regions across 3 serial sections obtained from the midline of the cerebellar tissue of each animal; Purkinje cell counts were similarly conducted in various regions across 3 serial sections, each with a total length of 1 mm. Serial sections were obtained at roughly 30 µm intervals, omitting 5 sections with each extraction. Sections were evaluated semiquantitatively over 10 distinct fields at 40X magnification.

Histopathological and Immunohistochemical Analysis

Following their removal, cerebellar tissues were submerged in 10% neutral buffered formalin. Following fixation, the tissues were washed in running tap water for 24 hours. The tissues were subsequently dehydrated in ascending alcohol concentrations (from 70% to 100%), clarified with xylene, and embedded in paraffin. Five-micrometer sections were cut from the paraffin-embedded specimens for light microscopic examination. The overall histological architecture was analyzed utilizing hematoxylin-eosin (H&E) staining, while cresyl-violet (C-V) staining was employed to visualize the Purkinje Cells. Leica® DM2500 LED microscope was used to investigate all the slices stained. For immunohistochemical analyses, serial paraffin sections, each 5 µm thick, were placed on positively charged glass slides. Sections were subjected to deparaffinization and hydration. Ten percent hydrogen peroxide was employed to inhibit endogenous peroxidase activity for 10 minutes. Sections were subjected to 0.01 mol/l citrate buffer (pH=6) in the microwave for 5 minutes to expose the antigenic sites. To prevent nonspecific background staining, the slides were initially rinsed in phosphate-buffered saline (PBS) at pH 7.4 for 5 minutes, followed by incubation in 1% bovine serum albumin (BSA) in PBS for 30 minutes at 37°C. Except for negative controls, the sections were treated with two drops of a ready-to-use primary antibody of GFAP (GeneTex-GTX108711) at room temperature overnight. After a PBS rinse, several drops of biotinylated goat polyvalent secondary antibody were applied to the slides and incubated for 10 minutes. The slides were dried, cleaned, and mounted with dibutylphthalate polystyrene xylene (DPX) mounting medium following a 15-minute incubation in 3,3-diaminobenzidine (DAB) to assess the reaction.

All the histological results were obtained using the LAS V4.8 image analysis program on a Leica® DM2500 LED brand research microscope with an MC170 HD model camera attachment.

Levels of MDA, SOD, and GSH in the Cerebellum as Markers of Antioxidants and Oxidants

The cerebellum tissues were homogenized in a 10% phosphate buffer, thereafter centrifuged for 4 minutes at 8,000 rpm and 4°C, and the supernatants were collected to assess oxidative stress indicators. The activities of MDA, GSH, and SOD in the cerebellum were assessed utilizing commercial kits (Rel Assay Diagnostics, Turkiye).

Statistical Analysis

Statistical data analysis was conducted using IBM SPSS Statistics version 25.0 for Windows software. The Kolmogorov-Simirnov test indicated a normal distribution of the data (p>0.05). Multiple comparisons were evaluated using a One-Way ANOVA test with Tukey HSD correction. Results are expressed as mean±standard deviation (SD), with p<0.05 being statistically significant.

RESULTS

Results of Histometrical Measurements of Cerebellar Cortex Layers and Purkinje Cell Quantification

The assessment of molecular, granular, and total cerebellar cortex thickness revealed a substantial reduction in these layers in the PNX group compared to the control and PNX-sham groups (p<0.05). No statistically significant difference was seen between the control and PNX-sham groups for the thickness of the cerebellar cortex layers (p>0.05) (Figure 1).

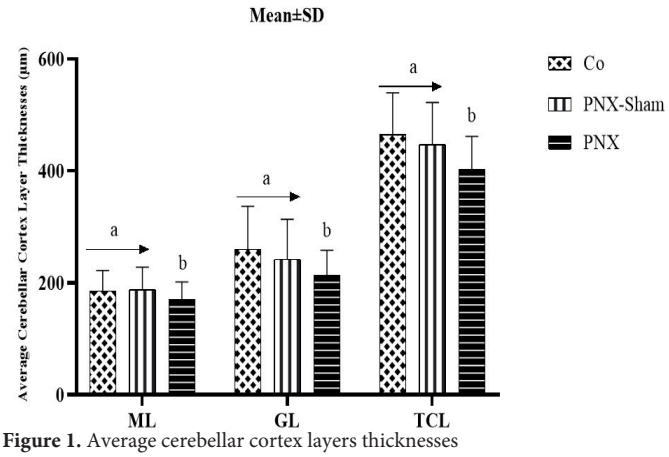

Figure 1. Average cerebellar cortex layers thicknesses

Substantial reduction in the PNX group compared to the control and PNX-sham groups (p<0.05). ML: Molecular layer thickness, GL: Granular layr thickness, TCL: Total cerebellar cortex thickness, Co: Control group, PNX: Pinealectomy surgery group, PNX-sham: Sham-Pinealectomy group. a and b presenting the statistical difference between the groups of the study (p<0.05)

According to the analysis of Purkinje cell counts that revealed the layout in the cerebellar cortex's ganglionary cell layer, the PNX group had a significantly lower number of Purkinje cells than the control and PNX-sham groups (p>0.05). No statistically significant difference was seen between the control and PNX-sham groups for the number of Purkinje cells (p>0.05) (Figure 2).

Histological Results

The H&E and C-V staining results: The H&E and C-V stainings from the control and PNX sham groups revealed distinguishable layers of the cerebellum, which displayed a normal histological appearance (Figure 3 A-D). In the PNX group, pyknotic nuclei, necrosis, and perineuronal vacuolated regions were identified in the Purkinje cells within the ganglion cell layer. Demyelinated and vacuolated regions were particularly observed in the white matter layer (Figure 3 E, F).

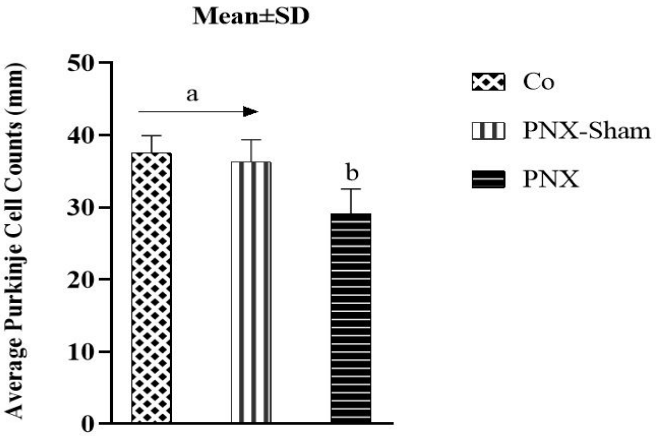

Figure 2. Average Purkinje cell counts

PNX group had a significantly lower number of Purkinje cells than the control and PNX-sham groups (p>0.05). PNX: Pinealectomy surgery group, PNX-sham: Sham-pinealectomy group. a and b presenting the statistical difference between the groups of the study (p<0.05)

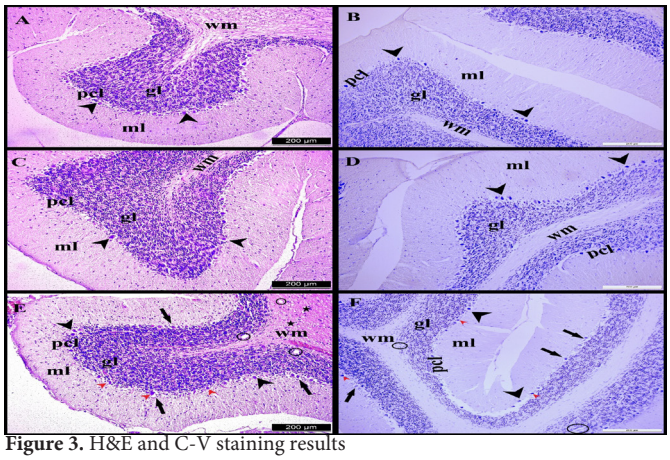

Figure 3. H&E and C-V staining results

ml: Molecular layer, pcl: Purkinje cell layer, gl: Granular layer, wm: White matter, Arrowheads: Purkinje cells, Black circle: Vacuolized areas in the white mater and granular layer, Arrows: Perineuronal vacuolization, Asterisks: Demyelinated areas, Red arrowhead: Necrotic Purkinje cells and pyknotic nuclei, A: H&E stain of the control group, C: H&E stain of the PNX-sham group, E: H&E stain of the PNX- group, B: C-V stain of the control group, D: C-V stain of the PNX-sham group, F: C-V stain of the PNX group, H&E: Hematoxylin-eosin, C-V: Cresyl-violet, PNX: Pinealectomy surgery group

The GFAP Immunohistochemical Staining Results

Immunohistochemical staining with GFAP antibody revealed that the immune response and staining intensity were comparable in the control and PNX-sham groups; however, the PNX group exhibited a significant presence of GFAP (+) astrocytes, characterized by intense staining in the granular layer of the cerebellar cortex and the area of substantia alba. The cytoplasmic extensions of astrocytes in the PNX group had a pronounced trajectory in the molecular layer. Cytoplasmic extensions of astrocytes were shown to be interwoven. Histoscore (H-score) was calculated by a semi-quantitative assessment of both the intensity of staining (graded as: 0, non-staining; 1, weak; 2, median; or 3, strong using adjacent normal cells as the median) and the percentage of positive cells. The H-score for GFAP immunoreaction is given in Figure 4, 5.

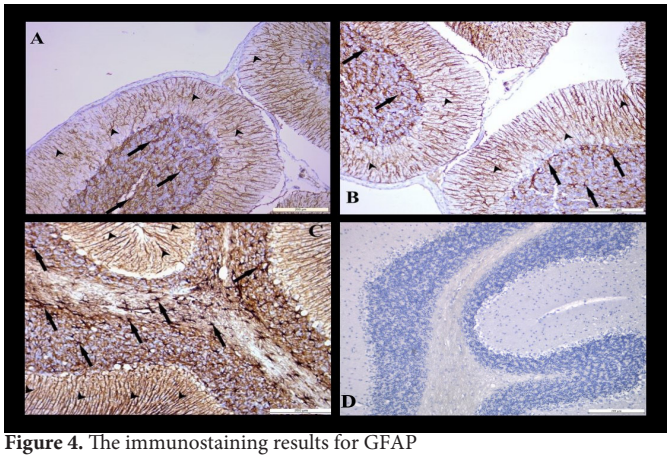

Figure 4. The immunostaining results for GFAP

Arrowheads: The immunoreaction in the cytoplasmic processes of the astrocytes located in the molecular layer, Arrows: Immunoreactive astrocytes located in the granular layer and white matter, A: GFAP immunohistochemistry stain of the control group, B: GFAP immunohistochemistry stain of the PNX-sham group, C: GFAP immunohistochemistry stain of the PNX group, D: Negative control for GFAP immunstain, GFAP: Glial fibrillary acidic protein, PNX: Pinealectomy surgery group

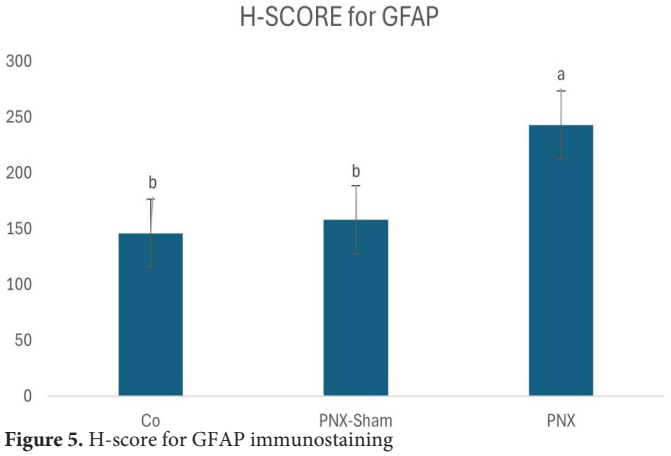

Figure 5. H-score for GFAP immunostaining

PNX group had a significantly higher number of immunoreactive cells than the control and PNX-sham groups (p>0.05). H-score: Histoscore, GFAP: Glial fibrillary acidic protein, PNX: Pinealectomy surgery group, PNX-sham: Sham-pinealectomy group. a and b presenting the statistical difference between the groups of the study (p<0.05)

Biochemical Results

Biochemical analyses of cerebellar tissue revealed that pinealectomy resulted in elevated MDA levels and reduced GSH and SOD levels. The elevation of MDA levels in the pinealectomy group was statistically significant when compared to the Co and PNX-sham groups (p>0.05), although no significant difference was observed between the Co and PNX-sham groups (p<0.05). The reduction in GSH and SOD levels was statistically significant when compared to the Co and PNX-sham groups (p>0.05), although no significant change was observed between the Co and PNX-sham groups (p<0.05). The biochemical results are summarized in **Figure 6**.

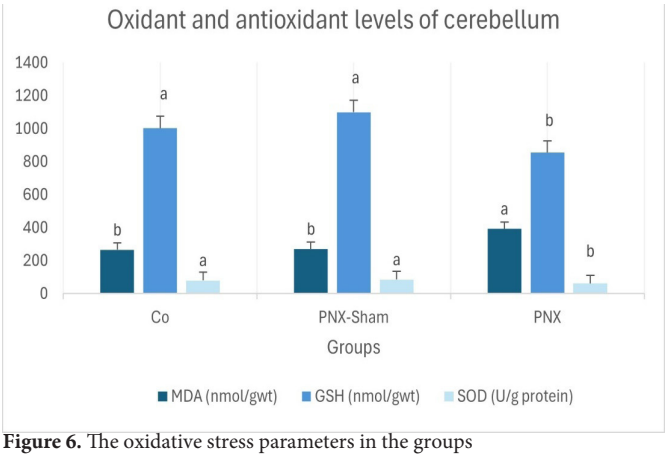

Figure 6. The oxidative stress parameters in the groups

Data are expressed as mean±standard deviation (n=8). MDA: Malondialdehyde, GSH: Reduced glutathione, gwt: Gram wet tissue, SOD: Superoxide dismutase. Superscripts represent the statistically significant difference MDA; [a]p<0.05 vs Co and PNX-sham, [b]p>0.05 Co vs PNX-sham; GSH and SOD; [a]p>0.05 Co vs PNX-Sham, [b]p<0.05 vs Co and PNX-sham

DISCUSSION

In this study, the cerebellar oxidant and antioxidant status were revealed using MDA, SOD, and CAT, and the GFAP immunoreaction in cerebellar tissue was shown in control, Pinealectomy and sham-pinealectomy performed rat groups. The histomorphometric measurements for granular, molecular, and total cortex thickness were also employed as well as the Purkinje cell counts. The findings indicated that the lack of melatonin resulted in elevated MDA levels in the cerebellum and a statistically significant reduction in GSH and SOD levels relative to the control and PNX-sham groups (p<0.05). A statistically significant increase in GFAP immunoreactivity in the cerebellum coincided with a statistically significant reduction in Purkinje cell count, as well as in the thickness of the molecular, granular, and total cortex (p<0.05).

In animals, including humans, the circadian system is structured hierarchically, with a central pacemaker located in the SCN.[21] The SCN coordinates circadian physiological and behavioral rhythms, such as sleep and wakefulness, temperature, eating, neuroendocrine, and autonomic functions, with a 24-hour cycle to align with the ambient light-dark cycle, thus establishing an optimum internal temporal order. Light serves as the principal stimulus for synchronizing the SCN rhythm period and phase with the external environment.[22] In humans and other diurnal organisms, melatonin functions in the SCN to diminish the wake-promoting signals of the circadian clock.[23] Although melatonin was discovered over fifty years ago and several papers addressing its neuroprotective properties,[24] shockingly little is understood about the effects of melatonin on the cerebellum. The majority of research investigating the consequences of melatonin deficiency has predominantly focused on specific tissues.[25] The cerebellum performs numerous essential activities, including motor coordination, learning, motivational processes, regulation of feeding and food anticipation, language, attention, and working memory.[26] Many of these tasks rely on a functional cellular clock and a stable circadian structure.[27] Even the cerebellum was found to have specific binding areas for melatonin,[19] yet the effect of the pinealectomy surgery on the cerebellar tissue has not been well-documented. Antioxidant and anti-inflammatory properties of melatonin have gained prominence in recent years,[28] whereas melatonin has a multifaceted impact by modulating factors in oxidative and inflammatory pathways, including the regulation of fundamental physiological and biological activities.[29] Moreover, melatonin metabolites significantly mitigate oxidative stress and inhibit inflammatory responses.[30] Melatonin is an effective free radical scavenger, and besides models of neurodegenerative illnesses, CNS

trauma, and ischemia-reperfusion injury, melatonin safeguards the brain from hyperoxia, excitotoxicity, ionizing radiation, and DNA damage.[31] Melatonin administration was shown to affect levels of MDA, GSH, SOD, and GPx of cerebellar tissue compared to the control groups, on behalf of the antioxidants.[32] The optimal operation of the endogenous molecular clock relies on cellular redox equilibrium and an antioxidant milieu.[33] The equilibrium between oxidants and antioxidants in healthy tissues is sustained by a preponderance of antioxidants. Diverse factors that may cause tissue damage disturb the oxidant/antioxidant equilibrium, favoring oxidants.[34] One contributing factor is the reduction in circulating hormone levels. In the literature, some studies explain how oxidative stress levels of the cerebellum are related to hormone levels.[35,36] Nevertheless, while the therapeutic or protective effects of melatonin on the cerebellum against various substances have been examined, no research has specifically addressed the harm resulting from melatonin shortage. The existence of hormone-specific receptors in an organ indicates that its function will be regulated by that hormone,[37] such as in the case of cerebellum and melatonin. While not explicitly detailed, it is evident that melatonin contributes to the maintenance of cerebellar function.[38] Although data suggest that exogenous melatonin, leveraging its antioxidant characteristics, mitigates oxidative damage in cerebellar tissue,[29,32,39] the deficiency of melatonin and its recognized antioxidant properties on cerebellar tissue merit thorough investigation. In this study, the lack of melatonin in the PNX group caused an increase in the levels of MDA which was statistically significant ($p<0.05$) compared to the control and PNX-sham groups, but a decrease in the levels of GSH and SOD which was statistically significant ($p<0.05$) compared to the control and PNX-sham groups. These results are attributed to the anti-oxidant property of melatonin. We believe that even sham pinealectomy operation caused little difference in the oxidative levels of the cerebellum, it did not affect the situation statistically so all the changes seen in the PNX group are related to the lack of melatonin synthise from the pineal gland.

Neurons have traditionally been seen as the fundamental functional units of the central nervous system, whereas glial cells were perceived only as supportive components. This idea has recently undergone rapid transformation; it has been claimed that the proper functioning of the neuron-microglia-astrocyte "trio" is essential to the functional organization of the central nervous system (CNS).[40,41] Astrocytes, a kind of glial cell, are recognized for their critical functional role in the development and maturation of the CNS. They participate in the regulation of brain extracellular ionic homeostasis, the migration and maturation of neurons, the synthesis and reuptake of specific neurotransmitters, and possess the capability to store energy as glycogen.[42] Astrocytes possess two varieties of cytoskeletal intermediate filaments: glial fibrillary acidic protein (GFAP) which is a type II intermediary filament and vimentin.[43] GFAP, mostly located in fibrous astrocytes and to a lesser degree in protoplasmic astrocytes serves as a dependable and extensively utilized marker for astroglia.[44] GFAP is also regarded as a key immunohistochemistry marker for astrocytes.[45] The body of work about GFAP transcription is extensive, as nearly any alteration or disruption of homeostasis in the CNS results in modifications to GFAP expression.[46] GFAP expression elevates in reaction to oxidative damage, aging, and environmental toxin exposure.[47] On the other hand, melatonin, the primary secretion of the pineal gland during the dark phase of the photoperiod, can influence the organization of microfilaments, microtubules, and intermediate filaments by functioning as a cytoskeletal modulator.[48] According to our results, an elevation of GFAP immunoreactivity in the pinealectomized rat group was seen. We speculate that this can be attributed to the loss of melatonin's cytoskeletal modulatory function for the organism. Moreover, we plan to further examine the potential that the lobes of the cerebellum, recognized for their distinct functions, may likewise serve varying roles for GFAP. We hypothesized that increased astrocyte activity serves as a compensatory response to neuronal damage and correlated the increase in astrocyte activity with increased GFAP expression.

Pinealectomy triggers apoptosis in Purkinje cells.[49] According to the results of our study, there was a significant decrease ($p>0.05$) in the number of Purkinje cells in the cerebellum. In our study even if the cascade of apoptosis was not explained, the Purkinje cell loss might be related to the apoptosis caused by the lack of melatonin. There is not a lot of literature planned to observe the effects of pinealectomy on the cerebellum, nonetheless, it is stated that pineal melatonin did not promote the survival of Purkinje cells during the developmental phase.[50] We believe in adult rats the contribution of melatonin for the survival of the Purkinje cells is more essential since the loss of the Purkinje cells in the PNX group is statistically significant compared to other groups of the study.

In the literature, some studies focused on the effects of pinealectomy on the Purkinje cells, but all these studies put forward the importance of melatonin for the normal development of cerebellar layers. However, there are no studies that focused on the effect of melatonin on the cerebellum in adult rats. Conversely, certain studies in the literature indicate the beneficial effects of specific antioxidant compounds on the overall structure of the cerebellum. In our study, a lack of melatonin not only resulted in the loss of Purkinje cells, but also revealed a substantial reduction in molecular, granular, and total cerebellar cortex thicknesses. These results underscore the necessity for comprehensive study, including volume calculation of the cerebellum in the pinealectomy model.

Limitations

This work elucidates the levels of oxidants and antioxidants, GFAP immunoreactivity, Purkinje cell counts, and cerebellar layer thickness in the cerebellum of a pinealectomized rat model for the first time; nonetheless, it possesses several limitations. The primary issue is that the impact of exogenous melatonin on the cerebellum could not be assessed with the existing parameters. This is attributable to financial limitations. It may be advantageous to design new studies addressing this problem.

CONCLUSION

This study has, for the first time, elucidated the amounts of oxidants and antioxidants, GFAP immunoreactivity, Purkinje cell counts, and cerebellar layer thickness in the cerebellum of a pinealectomized rat model. This study is the inaugural investigation to elucidate the association between melatonin and the cerebellum, a topic hitherto overlooked in the literature, thereby establishing a significant foundation. The contribution of more studies on the topic is essential.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Karabük University Rectorate Animal Experiments Local Ethics Committee (Date: 26.12.2024, Decision No: 2024/12/32).

Informed Consent

Since this study was conducted with experimental animals, a written consent form was 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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Predictors of no-reflow after coronary stenting in patients with high thrombus burden

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ABSTRACT

Aims: In this study, we aimed to reveal the predictors of no-reflow after coronary stenting in patients with high thrombus burden.

Methods: Patients with acute myocardial infarction who underwent stenting of a coronary lesion with high thrombus burden in the same session between February 2020 and July 2022 in our center were included in this retrospective study. High thrombus burden was accepted as Thrombolysis in Myocardial Infarction (TIMI) grade 4 or 5 thrombus. No-reflow was accepted as TIMI grade ≤2 flow at the end of the procedure. Multivariate logistic regression analysis was executed to ascertain the predictors of no-reflow.

Results: Of the 485 patients included in the study, 407 (83.9%) did not develop no-reflow. Of the 78 (16.1%) patients who developed no-reflow at the end of the procedure, 61 had TIMI 2, 10 had TIMI 1, and 7 had TIMI 0 flow. Age [odds ratio (OR) 1.051; 95% confidence interval (CI) 1.021-1.082; p=.001], accumulated thrombus proximal to the occlusion (OR 3.318; 95% CI 1.176-9.365; p=.023), reference vessel diameter (RVD) greater than 4 mm (OR 2.569; 95% CI 1.005-6.565; p=.049), and TIMI flow grade after wiring or small balloon dilation (OR 0.108; 95% CI 0.065-0.181; p<.001) were the independent predictors of no-reflow.

Conclusion: Older age, accumulated thrombus proximal to the occlusion, RVD greater than 4 mm, and the absence of TIMI grade 3 flow after wiring or small balloon dilation may be associated with an increased risk of no-reflow after coronary stenting in patients with high thrombus burden.

Keywords: No-reflow, coronary stenting, high thrombus burden

INTRODUCTION

Despite the considerable advancements in interventional cardiology, coronary lesions with high thrombus burden remain challenging for operators. High thrombus burden may complicate percutaneous coronary intervention (PCI) in several ways, one of which is no-reflow. No-reflow is characterized by inadequate myocardial perfusion despite the relief of mechanical vessel obstruction.[1] This complication may lead to a variety of unfavorable consequences, including arrhythmias, early infarct-associated pericarditis, acute heart failure (HF), adverse cardiac remodeling and chronic HF.[2-5] Predicting the potential for no-reflow, which may even result in mortality, may enable interventional cardiologists to select a more appropriate PCI strategy in order to avoid this complication. In this study, we aimed to reveal the predictors of no-reflow after coronary stenting in patients with high thrombus burden.

METHODS

The study was approved by the Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 28.11.2024, Decision No: KAEK 2024/547) and conducted in accordance with the Declaration of Helsinki.

Patients with acute myocardial infarction (MI) who underwent stenting of a coronary lesion with high thrombus burden in the same session between February 2020 and July 2022 in our center were included in this retrospective study. High thrombus burden was accepted as thrombolysis in myocardial infarction (TIMI) grade 4 [thrombus length greater than 2 times the reference vessel diameter (RVD)] or 5 thrombus [totally occluded infarct-related artery (IRA)].[6] Chronic total occlusion as the IRA, intracoronary (IC) fibrinolytic therapy, thrombectomy, and deferred stenting strategy rather than immediate stenting were the exclusion criteria. Two groups were formed as those who developed no-reflow and those who

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did not. No-reflow was accepted as TIMI grade ≤2 flow at the end of the procedure.

The demographic and clinical characteristics of the study population were obtained from the hospital database. Age and gender were recorded. History of hypertension, diabetes, prior MI, prior PCI, and prior coronary artery bypass grafting were noted. Patients exhibiting a glomerular filtration rate of less than 60 ml/min/1.73 m^2 for a minimum of 3 months were deemed to have chronic kidney disease (CKD).[7] Patients on maintenance dialysis were also recorded. The diagnosis at admission and P2Y12 inhibitor choice were noted. Time from first medical contact (FMC) to stenting was documented. FMC was accepted as the patient's arrival time at our hospital.

The procedural characteristics of the study population were assessed by the same interventional cardiologist. IRA and native or in-stent lesion were recorded. Two-dimensional quantitative coronary angiography analysis was used to estimate the diameter stenosis, lesion length, and thrombus length. The RVD was accepted as the diameter reached by the stent or postdilation balloon if used, whichever was higher. The features of high thrombus burden defined by Yip et al.[8] including cutoff occlusion, accumulated thrombus greater than 5 mm proximal to the occlusion, floating thrombus, sustained dye stasis distal to the obstruction, RVD greater than 4 mm, and thrombus length greater than 3 times the RVD were also reviewed. Initial TIMI thrombus grade and initial TIMI flow grade were documented. In patients with an initial lack of antegrade flow, TIMI thrombus grade and TIMI flow grade were reclassified after wiring or small (≤2 mm in diameter) balloon dilation for the purpose of restoring antegrade flow. Predilation, number of stents per lesion, total stent length per lesion, and postdilation were also noted.

Statistical Analysis

The statistical package for social sciences (SPSS) version 25 was used to upload and analyze the research data. The chi-square test was employed to compare categorical variables, which were presented in terms of frequencies and percentages. The Kolmogorov-Smirnov test was implemented to determine the normality of the distribution of continuous variables. An independent samples T test was applied to compare continuous variables with a normal distribution, which were expressed as mean±standard deviation. The Mann-Whitney U test was utilized to compare continuous variables without a normal distribution, which were given as median (minimum-maximum). Multivariate logistic regression analysis was executed to ascertain the predictors of no-reflow, and also TIMI 0 or 1 flow at the end of the procedure. All clinical and procedural characteristics assessed in the study were initially examined through univariate analysis, and variables with p≤0.1 in the univariate analysis were then put under multivariate analysis. p≤0.05 was considered statistically significant.

RESULTS

Of the 485 patients included in the study, 407 (83.9%) did not develop no-reflow. Of the 78 (16.1%) patients who developed no-reflow at the end of the procedure, 61 had TIMI 2, 10 had TIMI 1, and 7 had TIMI 0 flow.

When comparing patients with and without no-reflow (**Table 1**), patients with no-reflow had older age and higher prevalence of CKD (p<.001 and p=.010, respectively). The diameter stenosis, lesion length, and thrombus length were greater in patients with no-reflow (p=.022, p=.002, and p=.021, respectively). Accumulated thrombus proximal to the occlusion was more common in patients with no-reflow (p<.001). Initial TIMI thrombus grade and TIMI thrombus grade after wiring or small balloon dilation were higher (p=.022 and p<.001, respectively), initial TIMI flow grade and TIMI flow grade after wiring or small balloon dilation were lower in patients with no-reflow (p=.050 and p<.001, respectively). The number of stents per lesion and total stent length per lesion were also greater in patients with no-reflow (p=.006 and p=.001, respectively).

Age [odds ratio (OR) 1.051; 95% confidence interval (CI) 1.021-1.082; p=.001], accumulated thrombus proximal to the occlusion (OR 3.318; 95% CI 1.176-9.365; p=.023), RVD greater than 4 mm (OR 2.569; 95% CI 1.005-6.565; p=.049), and TIMI flow grade after wiring or small balloon dilation (OR 0.108; 95% CI 0.065-0.181; p<.001) were the independent predictors of no-reflow (**Table 2**). The only independent predictor of TIMI 0 or 1 flow at the end of the procedure was TIMI flow grade after wiring or small balloon dilation (OR 0.118; 95% CI 0.053-0.262; p<.001) (**Table 3**).

DISCUSSION

In the present study, older age, accumulated thrombus proximal to the occlusion, RVD greater than 4 mm, and TIMI flow grade after wiring or small balloon dilation were found to be independently associated with no-reflow after coronary stenting in patients with high thrombus burden. The absence of TIMI grade 3 flow after wiring or small balloon dilation was the only independent predictor of TIMI 0 or 1 flow at the end of the procedure, which could be considered severe no-reflow.

Consistent with the literature, older age was associated with an increased risk of no-reflow in our study.[9-15] Increased number of comorbidities, higher plaque burden, and delayed hospital admission in the elderly may contribute to an increased susceptibility to no-reflow.[13,16] In addition, aging causes progressive endothelial dysfunction and impaired coronary flow reserve, which may act in the pathogenesis of no-reflow.[17]

In our study, high thrombus burden was accepted as TIMI grade 4 or 5 thrombus. However, the features of high thrombus burden defined by Yip et al.[8] were also reviewed in the study. Among these features, accumulated thrombus proximal to the occlusion and RVD greater than 4 mm were found to be independently associated with no-reflow. These features may indicate higher thrombus burden and increased likelihood of distal embolization, which may contribute to the pathogenesis of no-reflow. It is evident that the presence of an IRA with an RVD greater than 4 mm suggests the existence of a substantial thrombus and/or plaque burden. It is also noteworthy that distal embolization of thrombotic remnants typically manifests following stent implantation in large coronary arteries, as opposed to small ones where the thrombus is mostly trapped between the stent and the

Table 1. Clinical and procedural characteristics of patients with and without no-reflow				
Variable		**No-reflow (+) (n=78)**	**No-reflow (-) (n=407)**	**p**
Age (year)		66.0 ± 11.7	60.6 ± 11.4	<.001
Male (%*)		68 (87.2)	336 (82.6)	.316
Hypertension (%*)		37 (47.4)	195 (47.9)	.939
Diabetes (%*)		23 (29.5)	135 (33.2)	.525
Chronic kidney disease (%*)		19 (24.4)	53 (13.0)	.010
Dialysis (%*)		0	3 (0.7)	.447
Prior MI (%*)		12 (15.4)	78 (19.2)	.431
Prior PCI (%*)		10 (12.8)	73 (17.9)	.272
Prior CABG (%*)		3 (3.8)	20 (4.9)	.684
Diagnosis at admission	STEMI (%*)	57 (73.1)	265 (65.1)	.172
	NSTEMI (%*)	21 (26.9)	142 (34.9)	
Time from FMC to stenting (h)		1.0 (0.5-37.0)	1.0 (0.5-74.0)	.519
IRA	LM (%*)	0	2 (0.5)	.324
	LAD (%*)	35 (44.9)	144 (35.4)	
	LCX (%*)	11 (14.1)	88 (21.6)	
	RCA (%*)	29 (37.2)	164 (40.3)	
	SVG (%*)	3 (3.8)	9 (2.2)	
Native/in-stent	Native (%*)	76 (97.4)	391 (96.1)	.558
	In-stent (%*)	2 (2.6)	16 (3.9)	
Diameter stenosis (%)		100 (90-100)	100 (70-100)	.022
P2Y12 inhibitor	Prasugrel (%*)	9 (11.5)	85 (20.9)	.155
	Ticagrelor (%*)	28 (35.9)	136 (33.4)	
	Clopidogrel (%*)	41 (52.6)	186 (45.7)	
RVD (mm)		3.0 (2.3-5.0)	3.0 (2.3-5.0)	.777
Lesion length (mm)		32 (14-84)	26 (8-70)	.002
Thrombus length (mm)		8 (0-30)	5 (0-42)	.021
Cutoff occlusion (%*)		8 (10.3)	22 (5.4)	.103
Accumulated thrombus proximal to the occlusion (%*)		16 (20.5)	22 (5.4)	<.001
Floating thrombus (%*)		0	6 (1.5)	.281
Sustained dye stasis distal to the obstruction (%*)		6 (7.7)	45 (11.1)	.375
RVD greater than 4 mm (%*)		13 (16.7)	38 (9.3)	.053
Thrombus length greater than 3 times RVD (%*)		3 (3.8)	30 (7.4)	.257
Initial TIMI thrombus grade	4 (%*)	7 (9.0)	81 (19.9)	.022
	5 (%*)	71 (91.0)	326 (80.1)	
TIMI thrombus grade after wiring or small balloon dilation	0 (%*)	11 (14.1)	71 (17.4)	<.001
	1 (%*)	11 (14.1)	78 (19.2)	
	2 (%*)	1 (1.3)	14 (3.4)	
	3 (%*)	12 (15.4)	80 (19.7)	
	4 (%*)	36 (46.2)	161 (39.6)	
	5 (%*)	7 (9.0)	3 (0.7)	
Initial TIMI flow grade	0 (%*)	71 (91.0)	320 (78.6)	.050
	1 (%*)	0	6 (1.5)	
	2 (%*)	4 (5.1)	25 (6.1)	
	3 (%*)	3 (3.8)	56 (13.8)	
TIMI flow grade after wiring or small balloon dilation	0 (%*)	3 (3.8)	0	<.001
	1 (%*)	17 (21.8)	11 (2.7)	
	2 (%*)	44 (56.4)	66 (16.2)	
	3 (%*)	14 (17.9)	330 (81.1)	
Predilation (%*)		72 (92.3)	363 (89.2)	.407
Number of stents per lesion		1.3 ± 0.5	1.1 ± 0.4	.006
Total stent length per lesion (mm)		38 (16-96)	32 (15-96)	.001
Postdilation (%*)		35 (44.9)	206 (50.6)	.353

*Column percentage, MI: Myocardial infarction, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass grafting, STEMI: ST-segment elevation myocardial infarction, NSTEMI: Non-ST-segment elevation myocardial infarction, FMC: First medical contact, IRA: Infarct-related artery, LM: Left main coronary artery, LAD: Left anterior descending artery, LCX: Left circumflex artery, RCA: Right coronary artery, SVG: Saphenous vein graft, RVD: Reference vessel diameter, TIMI: Thrombolysis in Myocardial Infarction

Table 2. Predictors of no-reflow in multivariate logistic regression analysis

Variable	OR (95% CI)	p
Age	1.051 (1.021-1.082)	.001
Chronic kidney disease	1.664 (0.742-3.733)	.217
Lesion length	1.032 (0.992-1.073)	.118
Thrombus length	0.972 (0.915-1.034)	.371
Accumulated thrombus proximal to the occlusion	3.318 (1.176-9.365)	.023
RVD greater than 4 mm	2.569 (1.005-6.565)	.049
Initial TIMI thrombus grade	1.553 (0.553-4.362)	.404
TIMI thrombus grade after wiring or small balloon dilation	0.921 (0.696-1.218)	.563
TIMI flow grade after wiring or small balloon dilation	0.108 (0.065-0.181)	<.001
Number of stents per lesion	0.553 (0.193-1.587)	.271

OR: Odds ratio, CI: Confidence interval, RVD: Reference vessel diameter, TIMI: Thrombolysis in myocardial infarction

Table 3. Predictors of TIMI 0 or 1 flow in multivariate logistic regression analysis

Variable	OR (95% CI)	p
Chronic kidney disease	2.507 (0.700-8.976)	.158
Accumulated thrombus proximal to the occlusion	1.267 (0.265-6.060)	.767
RVD greater than 4 mm	2.515 (0.607-10.420)	.204
TIMI thrombus grade after wiring or small balloon dilation	0.920 (0.620-1.366)	.679
TIMI flow grade after wiring or small balloon dilation	0.118 (0.053-0.262)	<.001
Number of stents per lesion	0.874 (0.261-2.929)	.827

OR: Odds ratio, CI: Confidence interval, RVD: Reference vessel diameter, TIMI: Thrombolysis in myocardial infarction

vessel wall. Furthermore, an IRA with a larger RVD may be associated with larger infarct size and greater extent of ischemia, which may also contribute to the pathogenesis of no-reflow.[18]

Initial TIMI thrombus grade and initial TIMI flow grade are inadequate for predicting the occurrence of no-reflow after coronary stenting. Therefore, we also evaluated TIMI thrombus grade and TIMI flow grade after wiring or small (≤2 mm in diameter) balloon dilation in the present study. Multivariate logistic regression analyses demonstrated that TIMI flow grade after wiring or small balloon dilation was an independent predictor of no-reflow, as well as TIMI 0 or 1 flow at the end of the procedure. This finding may be suggestive of potential clinical implications. In patients with the absence of TIMI grade 3 flow after wiring or small balloon dilation, deferred stenting may be reasonable in selected cases. This is particularly applicable for patients with TIMI grade 2 flow after wiring or small balloon dilation, in the absence of ongoing ischemic symptoms. Antithrombotic management with repeat coronary angiography in 48 hours may be considered for these patients.[19] TIMI 0 or 1 flow after wiring or small balloon dilation represents a much more challenging scenario in patients with high thrombus burden. IC administration of fibrinolytic agents and glycoprotein (GP) IIb/IIIa inhibitors, thrombectomy, or deferred stenting in the absence of ongoing ischemia may be viable options. However, the optimal management strategy remains unclear in these patients.

Diabetes has been associated with impaired microvascular reperfusion in patients undergoing primary PCI.[20] However, a review of the extant literature reveals conflicting results regarding the impact of diabetes on the development of no-reflow. While certain clinical studies have identified diabetes as an independent predictor of no-reflow after PCI,[10,21] contradictory findings have also been reported in other studies.[8,11-15] In the present study, the prevalence of diabetes was found to be similar in patients with and without no-reflow. The observed inconsistency among clinical studies in this regard may be related to variations in patient enrollment criteria and the definition of no-reflow.

Limitations

Our study had several limitations. It was a retrospective, single-center study with a relatively small sample size. We did not have data on time from symptom onset to stenting, Killip class, left ventricular ejection fraction and troponin level at admission, as well as pre-PCI GP IIb/IIIa inhibitor use. Data regarding the management of no-reflow were also missing. Coronary artery flow was assessed visually using the TIMI flow grade, which is limited by interobserver variability and the need for a more objective quantification of the different degrees of complete perfusion in a coronary artery. Finally, myocardial blush grade was not incorporated into the definition of no-reflow, as the majority of angiographic movies were not sufficiently long to visualize the myocardial blush.

CONCLUSION

Older age, accumulated thrombus proximal to the occlusion, RVD greater than 4 mm, and the absence of TIMI grade 3 flow after wiring or small balloon dilation may be associated with an increased risk of no-reflow after coronary stenting in patients with high thrombus burden.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 28.11.2024, Decision No: KAEK 2024/547).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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The effect of supportive nursing care during labor on maternity blues and birth satisfaction: randomised controlled trial

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ABSTRACT

Aims: The purpose of this study is to determine the effect of supportive nursing care given to pregnant women in labor on maternity blues and birth satisfaction.

Methods: The type of research was randomised controlled trial. A total of 47 women with healthy fetuses, 23 in the intervention group and 24 in the control group, were included in the study. Pregnant women in the control group received standard hospital care. Pregnant women in the intervention group received supportive nursing care including physical, emotional, informational and advocating elements during labor. Data were collected with The Gratification from Labor and Delivery Questionnaire (Turkish version), Stein's Maternity Blues Scale (Turkish version) and Pregnant Information Form.

Results: Sociodemographic and pregnancy characteristics of women in both groups were similar. Birth satisfaction in the intervention group was found to be higher than in the control group ($p<0.001$). In the intervention group, the duration of the second stage of labor and maternity blues scores on days 4 and 15 were lower ($p<0.001$). A significant correlation was determined between maternity blues and birth satisfaction ($r=0.611$; $p<0.001$).

Conclusion: Supportive care given to pregnant women during labor was found to shorten the second stage of labor, increase mothers' birth satisfaction, and decrease maternity blues. It was found that as birth satisfaction increased, the level of maternity blues decreased.

Keywords: Maternity blues, supportive care, labor, birth satisfaction

INTRODUCTION

Background and Significance

Maternity blues, which is well known among postpartum mental disorders and one of postpartum depression, is commonly seen.[1-3] The maternity blues, defined by Moloney in 1952 for the first time, has not been able to get the standard diagnostic criteria even today. Therefore, although its prevalence varies, it is expressed between 26% and 85% or between 40% and 60% in different studies.[3-5] Being a temporary mental disorder, maternity blues starts within the first few days of the postpartum period and reaches the highest level at the fourth and fifth days. Symptoms usually disappear spontaneously within two weeks. Its characteristic features include mood change, crying, anxiety, insomnia, loss of appetite, irritability, poor concentration, and sadness, as well as feelings of isolation, restlessness, and tension. Although this group of complaints seems to be specific to the postpartum period, it can be distinguished from other reactions by characteristic symptoms against stress. If symptoms do not regress, it can cause disorders leading to postpartum depression and it is a disorder that needs to be examined with care.[3,6-8]

In studies conducted on the supportive care given in the first stage of labor, it was emphasized that women's negative feelings about birth and the need for intervention also decreased Pregnant women who do not receive adequate prenatal care are at higher risk of postpartum depression and instrumental birth. Additionally, women's birth satisfaction has decreased.[9,10] We know that births with reduced need for intervention positively affect postpartum mood.[7] Therefore, it is conceivable that the supportive care that is provided affects satisfaction positively and reduces maternity blues. When we look at the supportive care studies in the literature mentioned above, it is seen that most of them focus on disorders such as postpartum depression and dysphoria. In addition, when supportive care procedures were examined, variations were found.[6,9] To the best of our knowledge, many other studies on maternity blues have not addressed birth experience.[9,10] In our opinion, there is an information gap regarding the relationship

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between maternity blues and supportive care. The importance of non-invasive and spontaneous labor is obvious for a healthy postpartum process.[11] It has become necessary to investigate the possible effects of the birth process on maternity blues. Based on this reason, the aim of this study was to evaluate the effect of supportive nursing care given to pregnant women during labour on maternity blues and birth satisfaction.

Research Hypotheses

H1: Supportive nursing care during labor affects satisfaction with birth.

H2: Supportive nursing care during labor affects maternal blues score.

METHODS

Ethics

The study was carried out with the permission of the Erciyes University Clinical Researches Ethics Committee and Kayseri Training and Research Hospital (Date: 03.02.2017, Decision No: 2017/70). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants by the researchers.

Research Design

This randomized controlled experimental study was conducted to determine the effect of supportive nursing care during labour on maternity blues and birth satisfaction. The study was carried out in the obstetric service of a training and research hospital between January and May 2018.

Population and Sampling

The population of the study calculated a total of 1726 deliveries including 732 vaginal deliveries, 3 instrumental delivery, and 991 caesarean sections performed in the hospital in 2017. Because the large effect level was expected between the intervention and control groups for the variables in the study, the sample size was calculated as a total of 52 including 26 in each group with power of 80%, significance level of 5%, and an effect size of 0.8 for each group. 26 pairs of written opaque envelopes were used for randomization. In order to reach the sample size, a total of 98 mothers were included in the study, 45 in the intervention group and 53 in the control group. Of these, 22 pregnant women in the intervention group and 29 pregnant women in the control group were excluded from the sample due to prolonged labor pains and fetal distress. A total of 47 patients were reached in the study, 23 intervention and 24 control. With the post-power analysis conducted with 47 patients, 99% power was reached and data collection was terminated (Figure 1).

Inclusion Criteria

The inclusion criteria for pregnant women included being aged between 19 and 35, speaking Turkish, residence in the city center, having a healthy single fetus of 37-41 weeks, not having any obstacle for vaginal delivery, being in the early latent phase of labor (dilatation max 0-1 cm), and being healthy (no chronic physical and psychological diseases).

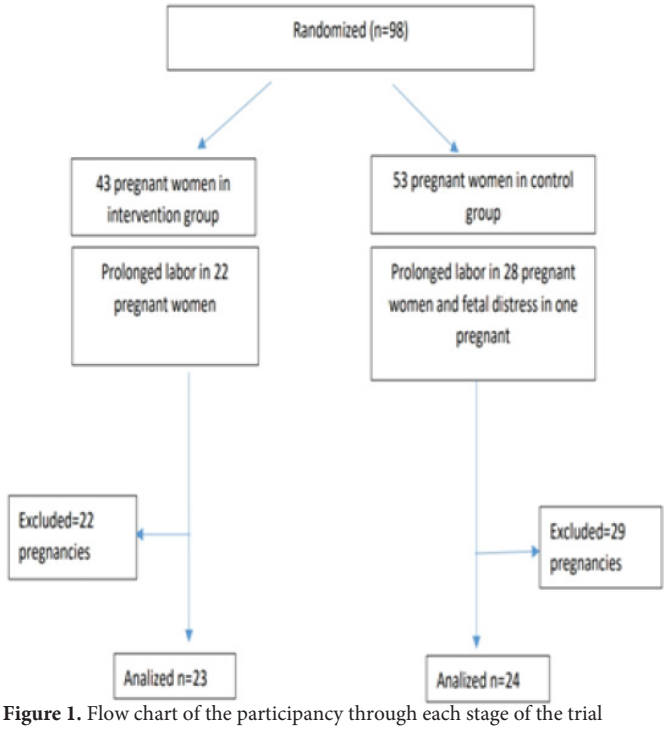

Figure 1. Flow chart of the participancy through each stage of the trial

Study Process

Control group: During the study, the pregnant women in the control group received standard hospital care. In the hospital where the study was conducted, the pregnant women were admitted to the obstetrics ward. Oral intake is restricted, and intravenous isotonic fluid is given to pregnant women in the latent phase with regular contractions. Dilation, non-stress test (NST) and vital signs are monitored by the clinical nurse/midwife according to the frequency of pain. When contractions increase and cervical dilation reaches 3-4 cm, pregnant women determined to be in the active phase are taken to the delivery room. Dilation, vital monitoring and NST are performed more frequently in the delivery room. The pregnant woman is restricted from standing up and walking. No pharmacological or non-pharmacological intervention is performed regarding pain management.

Intervention group: In addition to standard care, pregnant women in the intervention group were given information about breathing techniques and effective pushing during labor. Other supportive nursing care given to pregnant women is shown in Figure 2 according to their categories.

Open epiglottis type pushing was taught to the pregnant woman in the early latent phase when she was open to communication. In this type of pushing, when the woman inevitably feels the urge to push, she pushes forcefully 3-5 times starting from the peak of the contraction without taking a deep breath.[12]

It is taught as a breathing technique in stages;

First stage (normal breathing): The pregnant woman breathes in through her nose and exhales by pursing her lips as if blowing out a candle. Only the chest wall moves during this time. The respiratory rate should be set to 2 times in 15 seconds.[13,14]

Care practices	Type of supportive care			
	Physical	Emotional	Informational	Advocative
Accepting the pregnant woman warm-heartedly to the service		✓		
Explaining the hospital routines			✓	
Answering the potential requests of the pregnant woman correctly/clearly			✓	✓
Giving information about the frequency of contraction and breathing techniques during delivery			✓	
Supporting the position with objects such as pillows during contraction	✓			
Circular rubbing massage to the sacral area during contraction	✓			
Asking the pregnant to empty her bladder and explaining its importance	✓		✓	
Giving information about effective straining			✓	
Supporting her to take the position she wants	✓			
Explaining the reasons of possible interventions to pregnant women (enema, parenteral fluid support, NST results)			✓	
Explaining the reason to the pregnant woman whose oral intake is restricted and providing relief by soaking her lips and mouth rinsing	✓		✓	
Paying attention to personal privacy.				✓
Supporting and praising words		✓		
Empathic interventions such as hand holding or patting the shoulder		✓		
Expressing positive/negative opinions about the interventions				✓

NST: Non-stress test

Figure 2. Supportive care practices given to the pregnant women

Second stage (slow or deep chest breathing): Normal breathing is done at the beginning of each contraction. Then, 4-5 seconds of inspiration is followed by 4-5 seconds of expiration and a breath that can be heard from the outside is made. Breath is taken through the nose and exhaled through the mouth.[13,14]

Third level (rapid-shallow chest breathing): This type of breathing is also called audible breathing. It is also effective in dealing with waves, but it is an example of breathing that requires concentration. It has a great effect in diverting attention and preventing energy loss. The exhalation may be accompanied by "hii" or "hoo" sounds. Breathing should be done only with the chest muscles without using the abdominal muscles. Each wave begins with normal breathing. As the wave intensifies, the respiratory rate gradually increases. When the wave begins to calm down, the respiratory rate also slows down. Normal breathing is continued between two contractions. It is very important to change the air equally to prevent hyperventilation. Breathing is taken in and out through the mouth.[13,14]

In the early latent phase, normal breathing was followed by slow and deep chest breathing during the contraction period; in the late latent phase and active phase, rapid - shallow chest breathing was applied.

Massage was applied to the sacral region of the pregnant woman under the supervision of a midwife or obstetrician during the contractions. Circular rubbing massage was applied on the sacral vertebrae during the contraction period while the pregnant woman was sitting or lying down, as desired. The duration of the massage application was not standard. Because the frequency and duration of contractions of pregnant women varied.[15]

Data Collection

The Pregnancy Information Form was administered to pregnant women in both the intervention and control groups face-to-face when they first arrived at the clinic. After vaginal delivery, the women were administered the 10-question "Labor and Delivery Satisfaction Questionnaire" on the first postpartum day. After discharge, the mother was visited twice at home, on the 4-5th postpartum day when maternity blues were most intense, and on the 14-15th day when maternity blues should have subsided. During these visits, the mother was administered the "Stein's Maternity Blues Scale."

Measures

Three instruments were used for data collection.

Pregnant Information Form: It was prepared by the researcher upon the related literature review.[3,16-18] It consists of a total of 27 questions prepared to determine sociodemographic (age, education level, working status, economic status, etc.) and obstetric characteristics (gestational age, pregnancy intention status, gravidity, sex of the infant, etc.), information about the process of delivery, social support status and delivery duration, presence of episiotomy, and birth weight of the baby

Stein's Maternity Blues Scale (Turkish version): The scale developed by Stein in 1980 consists of 13 items. The total score of the scale ranges between 0 and 26. If the daily score is between 0-2, it is defined as no maternity blues, the scores between 3 and 8 points are defined as mild to moderate maternity blues and scores of 9 points and more are defined as severe maternity blues. For the use of the scale, Dr. George Stein was contacted for permission. The original English version of the scale was translated by 3 experts specialized in their fields. Thirteen items of the scale which was adapted into Turkish were presented to the opinions of 10 experts. Polit and Back Content Validity Index (CVI) were used to evaluate the expert opinion. After the expert evaluation, all items in the scale were evaluated above 0.78 and the Content Validity Index of the scale was found to be 0.975. In accordance with the analyses and recommendations, it was determined that the content validity of the scale was achieved.[19]

The Gratification from Labour and Delivery Questionnaire (Turkish version): The Gratification from Labour and Delivery Questionnaire is a subscale of the Postpartum Self-Evaluation Questionnaire developed by Lederman and Weingarten in 1981. Its Turkish adaptation was carried out by Tasci and Mete in 2007. The Gratification from Labour And Delivery Questionnaire is used to determine the birth satisfaction of mothers. The Cronbach's alpha coefficient, which is the Gratification from Labour and Delivery Questionnaire, was calculated as 0.88. It is composed of the items 6,9,28,47,48,58,67,68,73, and 79. The evaluation of the scale is a four-point Likert type. The lowest score is 10 and the highest score is 40. Low scores indicate good postpartum adjustment.[20]

Statistical Analysis

The data were assessed using IBM SPSS Statistics 25.0 statistical software. Descriptive statistics were given as number of units (n), percentage (%), mean±standard deviation (x±SD),

median, minimum value (min), the maximum value (max), and average rank score values. The normal distribution of the data of the numerical variables was evaluated by the Shapiro Wilk normality test and Q-Q graphs. In normally distributed variables, two independent samples t-test was used to compare two groups. On the other hand, the Mann-Whitney U test was applied in variables not showing a normal distribution. Within-group comparisons of variables not showing normal distribution were performed by Wilcoxon analysis. The correlation between categorical variables was examined by Fisher's exact test in 2x2 and rxc tables. The value of $p<0.05$ was accepted as statistically significant.

RESULTS

It was observed that the mean age, median gravida, median age of marriage, education, employment, family and income levels of the pregnant women in the intervention and control groups in the study were similar (Table 1) ($p>0.05$).

Table 1. Sociodemographic characteristics of mothers

Characteristics	Intervention group (n=23) n	%	Control group (n=24) n	%	p
Education					
Primery school	3	13	5	20.8	0.914
Middle school	2	21.7	6	25.0	
High school	10	43.6	10	41.6	
University and above	5	21.5	3	12.6	
Working status					
Employee	4	17.4	3	12.5	0.701
Unemployed	19	82.6	21	87.5	
Family type					
Nuclear family	17	73.9	15	62.5	0.534
Extended family	6	26.1	9	37.5	
Income status					
Good	7	30.4	5	20.8	0.775
Medium	13	56.5	15	62.5	
Poor	3	13.1	4	16.7	
Age X±SD (min-max)	27.0±4.4 (19-35)		26.6±5.1 (19-36)		0.812
Gravida [median (min-max)]	2 (1-5)		2 (1-5)		0.216
Married age [median (min-max)]	4 (1-17)		4.5 (1-18)		0.210
Age of previous child X±SD (min-max)	4.1±1.9 (1-11)		(2-8) 4.3±2.8		0.792

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

No significant correlation was found between the data of the participating mothers regarding the infant's gender, birth weight of the infant, induction, episiotomy, and duration of the first stage of labour. However, the duration of the second stage of labour was significantly different between the groups (Table 2) ($p<0.001$).

Table 3 shows the difference between the SMBS scores between the two groups. It was found that the SMBS median score was 2 in the intervention group and 6 in the control group on the postpartum 4th day. There was a statistically highly significant difference between the groups in terms of maternity blues scores on the postpartum 4th day ($p<0.001$). On the other hand, on the postpartum 15th day, the SMBS median score was 0 in the intervention group and 0 in the control group. There was no statistically significant difference between the groups in terms of maternity blues scores on the postpartum 15th day ($p<0.05$). Satisfaction of the group receiving supportive nursing care was higher than the control group and the difference between them was statistically significant ($p<0.001$).

Distribution of the mean scores obtained by women from the Gratification from Labour and Delivery Questionnaire ise 15.3±3.1 in intervention group and 21.8±6.1 in control group (Table 4).

Table 2. Some data on neonatal, situmulation of labour, and labor duration

Characteristics	Intervention group n	%	Control group n	%	p
Gender of the infant					
Female	8	34.8	8	33.3	0.580
Male	15	65.2	16	66.7	
Birth weight of the infant					
<3000 g	6	26.1	5	20.8	0.740
3000-4000 g	17	73.9	19	79.2	
Situmulation					
Oxytocin	12	80.0	9	60.0	0.427
Cervical prostaglandin	3	20.0	6	40.0	
Episiotomy					
Yes	20	87.0	19	79.2	0.701
No	3	13.0	5	20.8	
	X±SD (min-max)		X±SD (min-max)		p
Duration of the first stage (hours) X±SD (min-max)	7.1±3.2 (3-12)		8.4±3.5 (3-15)		0.195
Duration of the second stage (min) X±SD (min-max)	16.1±7.4 (5-30)		27.1±11.2 (10-50)		<0.001*

*Statistically significant, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 3. The distribution of SMBS median scores of the women

SMBS score	Intervention group	Control group	p
Postpartum 4th day [median (min-max)]	2 (0-5)	6 (0-21)	<0.001*
Postpartum 15th day [median (min-max)]	0 (0-1)	0 (0-7)	0.011*
Difference (4th day- 15th day) [median (min-max)]	1 [(-1) - (5)]	5 (0-14)	<0.001*

*Statistically significant, SMBS: Stein's Maternity Blues Scale, Min: Minimum, Max: Maximum

Table 4. Distribution of the mean scores obtained by women from the Gratification from Labour and Delivery Questionnaire

	Intervention group	Control group	p
Gratification from labour and delivery scores X±SD (min-max)	15.3±3.1 (10-21)	21.8±6.1 (13-32)	<0.001*

*Statistically significant, SD: Standard deviation, Min: Minimum, Max: Maximum

The correlation coefficient between the Gratification from Labour and Delivery Questionnaire and SMBS scores of women was determined 0.611 [Correlation is significant at the level of 0.01 (2-tailed)]. There is a strong positive relationship between women's satisfaction with their birth experience and their SMBS scores (Table 5).

Table 5. The relationship between satisfaction with the birth experience and SMBS scores of women

	SMBS	
	r	p
Satisfaction with the birth experience	0.611**	0.000
Correlation is significant at the 0.01 level (2-tailed)		

SMBS: Stein's Maternity Blues Scale

DISCUSSION

A positive outcome of labor is important for both the newborn and the mother's health. Supporting the mother with nursing care during labor provides a positive birth experience. Mothers with increased birth satisfaction have a healthier postpartum period. In this section, the findings regarding the effects of supportive nursing care during labor on birth satisfaction and maternity blues will be discussed.[6,10-12]

When examining the satisfaction scores of the intervention group and the control group, it was found that the intervention group was more satisfied with the birth experience than the control group (Table 4). In related studies, it is known that supportive care at birth change positively women's birth outcomes.[21,22] Some studies have proved that supportive nursing care yielded the positive results in physiological parameters such as pain, bleeding and perineal laceration in addition to psychological parameters related to supportive nursing care such as fear of birth, anxiety, and concern.[23-25] Moreover, in some studies, it was found that supportive care given at birth shortened the delivery duration of women.[25-28] In the study conducted by İşbir and Serçekuş, the supportive care given at birth and routine hospital care groups were compared and it was determined that the duration of birth was shorter in the intervention group.[11] In this study, the length of the first stage of labour was similar between the groups but similar to the literature, the second stage of labour was shorter in the intervention group than the control group (Table 2). Regarding this, it can be thought that the decrease in the delivery duration and therefore the decrease in the contraction time bring about maternal satisfaction. There are features highlighting the latent phase concerning supportive care applied in different phases. For example, since long-term intrapartum pain is associated with birth satisfaction, the latent phase is reported to be the best time for women to share their opinions about their birth requests and analgesia.[29,30] Therefore, in this study, the information we provided in the latent phase, in which the pregnant woman is open to communicate and can use her focusing ability well, was likely related to the result of the birth satisfaction.

When examining the maternity blues scores on the postpartum 4th day, it was found that the SMBS median scores of the intervention group was lower than the control group (Table 3). In some of studies on maternity blues, the maternity blues scores of the women who received nursing care for a longer period were not different than those who do not receive nursing care, but they emphasised the importance of supportive nursing care in women since the maternity blues were experienced more in primiparous ones.[3] As cited by Smith et al.,[24] in their study Field et al., determined that supportive care given at birth to women in the latent phase (dilatation of 3-5 cm) reduced their postpartum depression and reduced their stress levels. In this study, it was thought that in addition to supportive interventions to provide physical comfort related to supportive care, empathic behaviours such as sacral massage and hand-holding shoulder patting were effective in maternity blues. In studies related to massage and therapeutic touch among studies on supportive care, it has been reported that maternity blues, postpartum depression, and similar psychological disorders decrease.[15,31]

In this study, it was determined that the supportive care increased satisfaction by helping to provide a positive birth experience (Table 4). In addition, a strong positive correlation was found between satisfaction with the birth experience and SMBS scores (Table 5). Maternity blues studies related to positive birth experience are not available in the literature, but studies involving women suffering from postpartum depression shed light on this issue. When we look at the studies related to postpartum depression, it is seen that negative or adverse birth experience affects mothers with depression.[6,32,33]

Limitations

In this study, the researchers were not blinded. Most of the pregnant women who applied to the clinic for delivery were in the active or transitional stages, which made it difficult to reach the sample size. The cesarean rate was very high. Therefore, it took longer than planned to reach the determined sample size. Another limitation of this study is that some routines in the hospital had to be included in this study.

CONCLUSION

Supportive care given to pregnant women in labor was found to shorten the second stage of labor, increase mothers' birth satisfaction, and reduce maternity blues. In the fourth and fifteenth day follow-ups of mothers in the intervention group, maternity blues scores were significantly lower compared to the control group. It has been found that maternity blues level decreases with increasing birth satisfaction.It may be recommended that similar studies be conducted to support the effects of nursing care on maternity blues.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Erciyes University Clinical Researches Ethics Committee (Date: 03.02.2017, Decision No: 2017/70).

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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The relationship between QT dispersion, fragmented QRS, and collateral circulation in patients with chronic total coronary artery occlusion

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ABSTRACT

Aims: Corrected QT dispersion (QTcD), prolonged QT dispersion (QTD), and fragmented QRS (fQRS) are known as indicators of high risk for cardiac arrhythmias. Within this context, our research was conducted to assess the role of coronary collateral circulation (CCC) on QTD and fQRS in participants with chronic total coronary artery occlusion.

Methods: This study examined 131 participants with CCC in total. The participants were divided into two groups based on the Rentrop classification: group 1 (Rentrop 0 and 1) and group 2 (rentrop 2 and 3). Demographic data, laboratory results, and electrocardiogram findings were analyzed retrospectively.

Results: Significantly, variability was observed between the poor and good collateral groups in terms of QTcD (91.3±21.6 vs 57.2±26.2, p<0.001), QTD (87.6±21.3 vs. 55.2±26.2, p<0.001), and the presence of fQRS (139.5±8.0 vs. 128.1±13.1, p<0.001). Correlation analysis indicated a significant connection between the Rentrop classification and diabetes mellitus, creatinine levels, QTD, QTcD, and the existence of fQRS.

Conclusion: Poorly developed CCC was associated with increased QTcD, QTD, and the presence of fQRS. These parameters QTD, QTcD, and fQRS may serve as important, easily accessible, and effective tools in predicting the quality of CCC in individuals with coronary artery disorder. Nevertheless, these outcomes should be investigated through further research.

Keywords: Fragmented QRS, coronary collateral circulation, QT dispersion

INTRODUCTION

The prevalence of coronary artery disease (CAD) is widely considered a leading cause of death globally, with death mainly caused by arrhythmias, especially sudden cardiac arrest.[1] The presence of scar tissue in the ventricle, along with viable myocardial tissue that survives, is believed to significantly contribute to the heterogeneity of ventricular repolarization and the subsequent arrhythmias observed in CAD.[2] It is proposed that the variation in impulse formation and conduction between normal, ischemic, and necrotic tissues is a basic reason in the emergence of ventricular arrhythmias in CAD.[3] The severity of CAD and left ventricular dysfunction are associated with the prevalence of arrhythmias.[3]

Chronic total coronary occlusion (CTO) refers to the complete blockage of a coronary artery, which occurs as a result of thrombosis following a myocardial infarction (MI) and is marked by TIMI 0 flow that persists for at least three months.[4] CTO is observed in approximately 16% of individuals undergoing coronary imaging.[5] Coronary collateral circulation (CCC) is made up of potential vessels that are usually undetectable with conventional coronary angiography but become visible when coronary arteries are occluded, as collateral vessels expand to supply blood due to pressure differences.[6]

Various ECG markers, including QT dispersion (QTD) and fragmented QRS (fQRS), are used to clarify participants at increased risk for ventricular arrhythmias, and their relationship with collateral circulation has been studied in CTO participants.[7-9] QTD, which is described as the distinction between the minimum and maximum QT intervals, is a non-invasive method to assess irregularities in myocardial repolarization. Differences in the QT interval between leads indicate regional disparities in cardiac repolarization, and increased dispersion of ventricular recovery time is considered a substrate for serious arrhythmias and sudden cardiac death.[10] fQRS complexes are characterized by abnormal patterns or Q waves in consecutive leads that correspond to a primary coronary artery region, without a classic bundle branch block.[11] They are classified into two types based on their duration: narrow fQRS complexes (QRS <120 ms) and wide fQRS complexes (QRS ≥120 ms), which can appear in

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various QRS morphologies. Occasionally, fQRS is the single ECG indicator of myocardial destruction in individuals with non-Q myocardial infarctions or those with a resolved Q wave.[11]

Our research purposed to find out whether the presence of collateral CCC in individuals with coronary CTO influences QTD, corrected QT dispersion (QTcD), and fQRS, which are markers used to predict ventricular arrhythmias.

METHODS

Ethics

The study protocol was approved by Yozgat Bozok University Rectorate Non-interventional Clinical Researches Ethics Committee (Date: 04.12.2024, Decision No: 2024-GOKAEK-2414_2024.12.04_204). All procedures were conducted in line with ethical guidelines and the principles outlined in the Declaration of Helsinki. Participants' formal informed permission was not acquired because the work was a retrospective plan.

Patient Population and Study Protocol

Between January 2018 and June 2024, we examined 131 patients with stable coronary artery disorder subsequent to performing coronary angiography at our hospital and documenting total occlusion in one of their major coronary arteries. Demographic characteristics, laboratory results, and ECG data were collected retrospectively. CTO was characterized as a fully blocked lesion with TIMI 0 flow persisting for over three months, as defined by the Euro CTO Club.[12] Collateral circulation was assessed using the Rentrop classification: grade 0 (no collateral filling), grade 1 (collateral vessels supply side branches of the CTO artery, excluding epicardial segments), grade 2 (collateral vessels partially fill epicardial arteries), and grade 3 (collateral vessels fill epicardial vessel).[13] Participants were separated into two groups based on the Rentrop classification: group 1 (Rentrop 0 and 1) and group 2 (Rentrop 2 and 3). Exclusion criteria included recent myocardial infarction (within three months), arrhythmias other than atrial fibrillation, sinus rhythm, any level of atrioventricular or bundle branch block, diseases related to valve disorders, patients who have undergone bypass surgery, abnormal serum electrolyte concentrations, use of antiarrhythmic medications, or having a permanent pacemaker.

ECG Parameters

A standard 12-lead resting ECG was recorded via the Nihon Kohden recorder (Tokyo, Japan) with a 10 mm/mV amplitude and a 25 mm/s paper speed. Two expert cardiologists reviewed all ECGs without knowing the patient's clinical condition or angiographic results. The QT interval was calculated from the onset of the first negative deflection of the QRS complex to the end of the T wave, considering the TP isoelectric line. The heart ratio QTc interval was calculated via Bazett's formula. QTD was defined as the distinction between the maximum and minimum QT calculations from the precordial leads.[10] fQRS was detected as the emergence of an extra R wave (R'), interruption of the R or S wave, or the occurrence of several R waves (R') in sequential leads correlating with a major coronary artery territory.[11]

Statistical Analysis

As SPSS software, version 26.0 (SPSS Inc., Chicago, IL, USA) was carried out to conduct statistical analyses, the Kolmogorov-Smirnov test was applied to examine variable distribution patterns. While continuous variants were shown as mean±standard deviations or medians with interquartile range (IQR), considering the level of distribution, categorical variables were presented as ratios and percentages. Nonparametric continuous variables were determined via the Mann-Whitney U test, as categorical variants were analyzed via Fisher's exact test or Pearson's chi-square test. The correlation between clinical parameters and Rentrop classification was determined using Spearman's correlation examination. The Hosmer-Lemeshow test was used to evaluate model fit. We also used receiver operating characteristic (ROC) curve analysis to determine optimal cut-off values for QTcD and fQRS in predicting collateral circulation and to assess specificity and sensitivity. A p-value <0.05 was regarded as statistically significant.

RESULTS

131 participants overall were encompassed within the research, with general patient characteristics shown in **Table 1**. Sixty-four patients were allocated to collateral group 1, and 67 patients to collateral group 2. Laboratory analysis revealed that the population of individuals with diabetes mellitus (DM) was remarkably higher in group 1 compared to group 2 [39 (60.9%) vs. 29 (43.3%), p=0.043]. ECG parameters related to the good and poor collateral groups were assessed as presented in **Table 2**. Remarkable distinctions were detected between the groups with respect to QTcD (91.3±21.6 vs. 57.2±26.2, p<0.001), QTD (87.6±21.3 vs. 55.2±26.2, p<0.001), and the existence of fQRS (139.5±8.0 vs. 128.1±13.1, p<0.001).

Correlation analysis revealed substantial relationships between the Rentrop classification and QTcD (r=-0.659, p<0.001), QTD (r=-0.648, p<0.001), fQRS (r=-0.557, p<0.001), DM (r=-0.176, p=0.044), and creatinine (r=0.185, p=0.034), (**Table 3**).

ROC curve tests indicated that a QTcD cut-off rate above 75.5 predicted the Rentrop classification with 84.4% sensitivity and 85.1% specificity (AUC:0.885; 95% CI:0.822-0.949; p<0.001). For fQRS, a cut-off rate above 133.5 estimated the Rentrop classification with 78.1% sensitivity and 79.1% specificity AUC:0.840; 95% CI:0.769-0.912; p<0.001, (**Figure 1, 2**).

DISCUSSION

Our research purposed to detect the connection between the condition of CCC, QTcD, QTD, and fQRS in individuals with CTO. The improvement of CCC can affect the prognosis of CTO individuals. CCC is a response to occlusive damage in the coronary arteries. CTO individuals often have collateral vessels in the distal arteries, and these collaterals may help alleviate ischemic and anginal symptoms, as well as preserve ventricular function.[14] Former works have proved that good collateral circulation is correlated with fewer infarctions,

Table 1. Baseline characteristics and laboratory parameters of the study groups

Variables	Good collateral (n: 67)	Poor collateral (n: 64)	p-value
Baseline characteristics			
Age, years	67.3±11.9	68.0±11.7	0.885
Male gender, n (%)	47 (70.1)	46 (71.9)	0.828
Diabetes mellitus, n (%)	29 (43.3)	39 (60.9)	0.043
Hypertension, n (%)	44 (65.7)	46 (71.9)	0.444
Dyslipidemia, n (%)	20 (29.9)	20 (31.2)	0.862
Smoking status, n (%)	32 (47.8)	31 (48.4)	0.938
History of CAD, n (%)	26 (38.8)	21 (32.8)	0.475
Laboratory parameters			
Glucose, mg/dl	115 (99-171)	134 (106-167)	0.098
Creatinine, mg/dl	1.26±0.96	1.09±0.83	0.064
Sodium, mmol/L	138 (137-140)	138 (135-140)	0.387
Potassium, mmol/L	4.2 (4.0-4.4)	4.1 (3.9-4.5)	0.991
Uric acid, mh/dl	6.3±1.7	6.9±5.6	0.809
Total cholesterol, mg/dl	180±37	181±48	0.885
HDL-C, mg/dl	41 (35-46)	43 (36-47)	0.197
LDL-C, mg/dl	110±35	110±42	0.718
Triglycerides, mg/dl	129 (86-176)	117 (84-177)	0.385
WBC count, x10^3/µl	9.4 (7.1-12.5)	9.5 (6.9-11.8)	0.985
Neutrophil count, x10^3/µl	6.3 (4.2-8.0)	6.0 (4.4-8.4)	0.883
Lymphocyte count, x10^3/µl	1.5 (1.0-2.6)	1.7 (1.1-2.5)	0.471
Monocyte count, x10^3/µl	0.7 (0.4-0.9)	0.7 (0.5-0.9)	0.195
Hemoglobin, g/dl	13.2±1.9	13.1±1.9	0.816
Platelet count, x10^3/µl	222 (184-282)	230 (175-294)	0.950

Data are given as mean± standard deviation, n (%), or median (interquartile range). CAD: Coronary artery disease, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, WBC: White blood cell

Table 2. Electrocardiographic and angiographic findings of the study population

Variables	Good collateral (n: 67)	Poor collateral (n: 64)	p-value
QTc dispersion (ms)	57.2±26.2	91.3±21.6	<0.001
QT dispersion (ms)	55.2±26.2	87.6±21.3	<0.001
Fragmante QRS (ms)	128.1±13.1	139.5±8.0	<0.001
Occluded artery, n (%)			
LAD	7 (10.4)	12 (18.8)	0.177
LCX	13 (19.4)	10 (15.6)	0.570
RCA	49 (73.1)	45 (70.3)	0.720

Data are given as mean±standard deviation or n (%), QT: The time from the beginning of the Q wave to the end of the T wave, QRS: Electrical activity of ventricular muscles, LAD: Left anterior descending artery, LCx: Left circumflex artery, RCA: Right coronary artery

Table 3. Correlation between the Rentrop classification and clinical variables

Parameters	r-value	p-value
Diabetes mellitus	-0.176	0.044
Creatinin	0.185	0.034
QT dispersion	-0.648	<0.001
QTc dispersion	-0.659	<0.001
Fragmented QRS	-0.557	<0.001

QT: The time from the beginning of the Q wave to the end of the T wave, QRS: Electrical activity of ventricular muscles

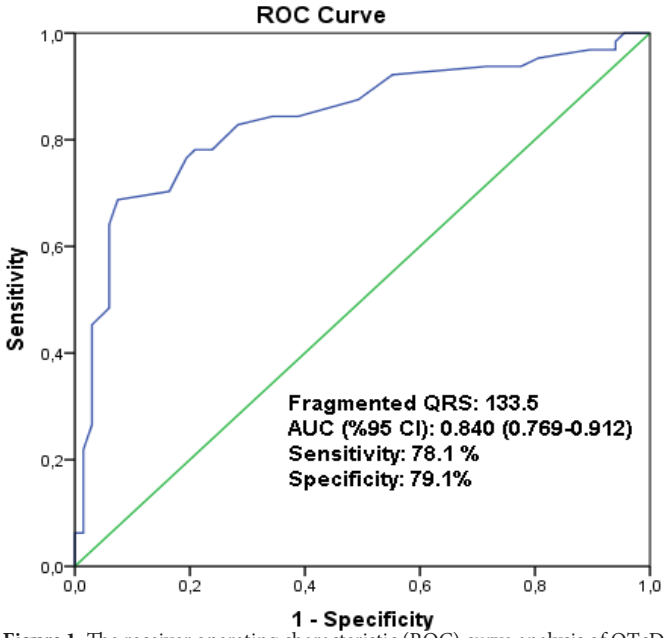

Figure 1. The receiver operating characteristic (ROC) curve analysis of QTcD for the Rentrop classification

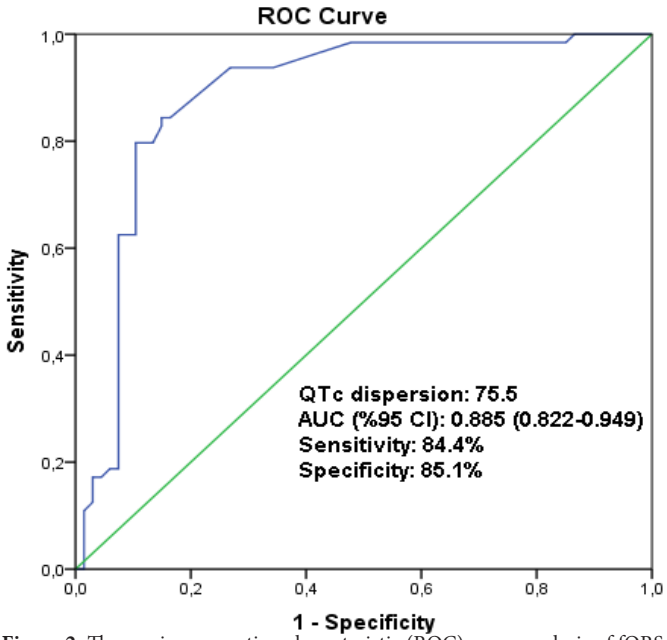

Figure 2. The receiver operating characteristic (ROC) curve analysis of fQRS for the Rentrop classification

fewer ventricular aneurysms, enhanced cardiac function, fewer future cardiac incidents, and better survival.[15] Enhanced repolarization dispersion is regarded as a contributing factor to the development of lethal ventricular arrhythmias.[16]

The intervals measured during the QT period reflect the duration from the start of the Q wave to the end of the T wave on an ECG, reflecting the duration of the activation wave's depolarization and the electrical recovery or repolarization of the cells. The shortest QT interval on a standard ECG represents the early repolarization region, while the lead showing the longest QT interval corresponds to the region of the ventricular myocardium that repolarizes last. The difference between these intervals is defined as QTD, which is considered an indicator of ventricular repolarization

variability and electrical instability.[17] Thus, as the QTD gets larger, the variability in the timing of electrical recovery in the heart becomes greater, which features a clinical significance, especially in the case of cardiac ischemia, as experimental studies have revealed that larger dispersion of repolarization is a crucial agent underlying severe and, fatal arrhythmias.[18] Various works have suggested that QTD also increases extraordinarily in conditions such as heart failure and ventricular hypertrophy, beyond coronary artery stenosis.[19,20]

In individuals with CAD, regional differences in repolarization, particularly in determining QTD, are prominent. The increased dispersion of ventricular repolarization at rest in CAD individuals may result in regional myocardial ischemia since ventricular repolarization can act more sensitively compared to other myocardial functions. Therefore, ischemic regions and/or fibrosis that may develop due to chronic ischemia can lead to electrical instability and heterogeneous repolarization in the myocardium, contributing to the high level of QTD.[21] It is believed that the increased QTD seen in CAD individuals is parallel to the severity of ischemia, partially caused by impaired responses to catecholamines or abnormal calcium ion flux in the ischemic myocardium.[22]

It has been stated in different works that ECG changes are often seen after stroke and that intracardiac sympathetic activity increases after intracranial ischemia and this triggers cardiac arrhythmias.[23] This situation is one of the cardiac causes of death in stroke individuals in the long term.[23] High troponin values and ECG changes can be seen in patients with acute ischemic stroke even if structural and ischemic heart diseases are excluded.[24]

Another parameter related to inflammation and ischemic changes is fQRS. fQRS is characterized by unpredicted deviations in the QRS morphology, but the exact reason of fragmentation in surface ECGs is not yet wholly understood. It has been argued that fQRS can prognosticate cardiac incidents in various cases. From a pathophysiological perspective, fQRS is usually considered to result from cardiac fibrosis, scarring, and ischemia, which lead to inhomogeneous cardiac electrical activation.[25] It has been demonstrated that fQRS is connected with cardiac fibrosis in individuals with ischemic or non-ischemic left ventricular dysfunction.[26] In previous studies that used gadolinium-enhanced delayed contrast cardiac magnetic resonance imaging to assess myocardial structure, fQRS was detected to be related to large cardiac scars.[27] fQRS complexes can be highly sensitive with a negative predictive rate than the Q wave in predicting prior myocardial infarction, as shown by scintigraphic assessments of regional perfusion abnormalities.[11] Regional fQRS complexes indicate the presence of larger regional myocardial scars, as demonstrated by stress myocardial perfusion imaging.[28] A work by Çetin et al.[29] identified a relationship between coronary atherosclerotic burden, CAD prevalence, and fQRS.

Another study suggested that fQRS may be present even if myocardial fibrosis cannot be detected with any technique. They stated that this could be due to the technique being inadequate to show low-grade fibrosis, depolarization abnormality, or a normal variant.[30] Çetin et al.[29] reported that fQRS may be associated with ventricular systolic functions in individuals with stable CAD or normal coronary arteries. In the same study, they reported that fQRS is causally related to inflammation.[29] It has also been proposed that both prolonged or shortened QRS duration and left ventricular systolic dysfunction serve as independent predictors of fQRS complexes on an ECG.[29]

The specified ECG parameters will provide useful information about CCC in CTO patients. Thus, we will have the opportunity to evaluate the treatment strategy in CTO patients more accurately.

Limitations

Some major limitations encountered during the study were the insufficient sample size, the use of manual measurements instead of computer software for calculating ECG parameters, and the inability to obtain evidence of ischemia. Other limitations include the complexity of local ischemia models and the fact that their contribution to the overall distribution of repolarization in patients has not been systematically investigated. The fact that the JT interval, which truly reflects ventricular repolarization, has not been evaluated.

CONCLUSION

This study suggests that increased QTcD, QTD, and the presence of fQRS are correlated with poor coronary collateral circulation in CAD individuals. Additional research should be conveyed to explain the connection between ECG parameters and collateral recovery.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Yozgat Bozok University Rectorate Non-interventional Clinical Researches Ethics Committee (Date: 04.12.2024, Decision No: 2024-GOKAEK-2414_2024.12.04_204).

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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Factors affecting health expenditures: the case of MINT countries

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ABSTRACT

Aims: Per capita income, carbon dioxide emissions and urbanization are factors that have significant effects on health expenditures, and the interaction between these variables shapes the level of health and access to services in societies. The objective of this study is to analyse the impact of economic growth, air pollution and urbanisation on health expenditures in MINT (Mexico, Indonesia, Nigeria and Turkiye) countries.

Methods: The environmental factors affecting health expenditures are investigated with DHausman and LM Bootstrap cointegration tests among panel data analysis methods. After determining that the series are cointegrated, the coefficients of the variables are investigated with the help of AMG and CCEMG coefficient tests.

Results: According to the cointegration test results, it is proved that there is a long-run relationship between the series. With reference to results of AMG and CCEMG coefficient estimation, the coefficient of carbon dioxide emission variable is statistically significant at 1% significance level, while the effects of other variables on health expenditures are not statistically significant. However, a 1% increase in carbon dioxide emissions in the MINT country group increases health expenditures (per capita) by 0.20-0.25%.

Conclusion: The MINT country groupshould implement policies to prevent air pollution in order to reduce the increasing effect of CO_2 emissions on health expenditures. JEL classification: E10, H10, O44.

Keywords: Economic growth, air pollution, health expenditures

INTRODUCTION

Economic growth, a primary macroeconomic objective of developing countries, has been demonstrated to result in an enhancement in overall welfare. However, this phenomenon is concomitant with the emergence of environmental concerns, including air, water, and soil pollution. Especially in developing countries, when economic development efforts proceed by compromising environmental regulations, the negative impacts on the environment become more pronounced. These impacts increase the demand for health services and lead to an increase in health expenditures (HE). According to OECD,[1] countries with high per capita income levels also have high health expenditures. This relationship between HE and income level was first addressed with the Grosman hypothesis. Grosman's[1] seminal work established the foundation for the study of traditional demand theory. This theory posits that each consumer possesses a utility function, defined by the goods and services procured within the market. The theory further stipulates that expenditures on these market goods and services must remain constrained by the individual's income. But the demand for health services is not like this. This is because when consumers demand health services, they do not actually aim to obtain the service itself, but to achieve a "better state of health". From this perspective, health is considered as an investment good rather than a consumption good. Individuals aim for a longer and more productive life with their investments in health, which shows that health services are economic capital. For this reason, Grosman[2] stated that health is a capital stock, that people are born with this capital stock, but that this stock loses value over time, and that the capital stock can be increased through investments in health.

Developing economies trying to achieve economic growth with disadvantages such as insufficient capital stock, unplanned industrialization and unplanned urbanization pave the way for increasing environmental problems. This situation creates negative impacts on public health by increasing environmental degradation such as air, water and soil pollution. Environmental problems trigger respiratory diseases, infectious diseases and other health problems, increasing the demand for health services and leading to increased health expenditures. In particular, environmental risks arising from unplanned urbanization, inadequate infrastructure and uncontrolled industrialization threaten public health and create additional cost pressure on health systems. Developing countries increase their health expenditures by having to make more health investments to solve these problems. Thus, the process of economic growth brings with it both environmental degradation and increased health expenditures.

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Air pollution, the most important type of environmental problem, has become the most binding type of pollution that requires mutual responsibility between countries.[3] Air pollution, which poses the greatest danger compared to other types of pollution, has reached dangerous dimensions with the increase in human activities today, although it emerged with natural events such as forest fires and volcanic eruptions before industrialization. Air pollution, which varies depending on industrialization, urbanization and population growth, is more common in regions with dense populations and high levels of industrialization and urbanization. On the other hand, air pollution is observed to be less in areas with low population and limited industrialization and urbanization.[4] In this study, the impact of environmental pollution on health expenditures in Mexico, Indonesia, Nigeria and Turkiye (MINT) countries representing developing countries is tried to be explained by using urbanization, CO_2 emissions and per capita income variables. While urbanization and carbon dioxide emission variables are included in the study to explain environmental pollution, per capita income variable is used to represent economic growth.

The MINT countries have become prominent among emerging economies after 2000, thanks to their rapid economic growth, young populations and vast natural resources. In addition to economic growth and socioeconomic development, these countries have also experienced environmental, social and political challenges. Table 1 presents the main macroeconomic data for MINT.

Table 1. Key economic indicators in MINT economies (2023)[5]

Countries	World nominal GDP ranking	GDP ($ billion)	GDP per capita ($)	Population (thousand)
Mexico	13	1.788	13.923	129.739
Indonesia	16	1.371	4.940	281.190
Nigeria	56	362	1.621	227.882
Turkiye	17	1.108	12.985	85.372

MINT: Mexico, Indonesia, Nigeria and Turkiye, GDP: Gross domestic product

When Table 1 is analyzed, it is seen that the other three economies in the MINT country group, except Nigeria, are among the top 20 countries in the world nominal income ranking. However, when we look at the per capita income values as a welfare indicator, Mexico and Turkiye are in the upper middle income countries category, while Nigeria and Indonesia are in the lower middle income countries group with their per capita income. In this respect, it is not possible to say that the MINT country group exhibits a completely homogeneous structure. These differences, which can be observed in terms of major macroeconomic indicators, are also similar in terms of health expenditures. The development of health expenditures in MINT countries between 2000 and 2020 is shown in Table 2.

When Table 2 is analyzed, the country with the highest increase in health expenditures (per capita) between 2000 and 2020 is Indonesia. Indonesia was followed by Nigeria, Mexico and Turkiye, respectively.

The objective of this study is to analyse the environmental factors that exert an influence on health expenditures in the group of MINT countries for the period 2000-2020. The

Table 2. Health expenditures in MINT countries (per capita, USD)[5]

Years	Mexico	Indonesia	Nigeria	Turkiye
2000	273,1238	63,67851	49,85982	167,4208
2001	304,6524	67,12623	54,40167	146,541
2002	327,6472	71,3113	51,94444	141,0708
2003	393,2214	82,32534	118,7912	138,4138
2004	409,2666	83,14131	104,9848	150,7891
2005	428,9849	118,3174	110,8055	187,2508
2006	449,4225	126,5394	117,1218	217,6965
2007	466,8952	136,8011	116,7614	241,9372
2008	464,7726	135,3181	123,4492	227,6472
2009	481,6357	141,3308	134,8287	165,0358
2010	441,709	177,5219	124,2778	191,472
2011	436,1232	203,8243	126,1334	190,3858
2012	462,1742	204,3824	124,5118	190,6942
2013	472,9	202,1473	128,713	210,5444
2014	486,98	195,6156	134,9253	230,7062
2015	507,743	179,0354	140,9066	228,5881
2016	530,6382	170,8631	144,2839	241,2877
2017	540,7903	167,8927	150,0332	256,9776
2018	554,5211	170,4108	123,6057	259,3069
2019	560,8407	181,3332	114,55	261,2099
2020	561,7481	184,3907	130,8993	266,7091

MINT: Mexico, Indonesia, Nigeria and Turkiye

variables used in the study are per capita income, urbanization, HE and CO_2 emissions. It is aimed to contribute to the literature by analyzing the long-run relationship between variables with the help of up-to-date econometric tests. Unlike other studies, the effects of environmental factors such as air pollution on HE are analyzed in detail. In line with the findings, the study aims to make a practical contribution by making concrete suggestions for the development of health and environmental policies specific to MINT countries.

LITERATURE REVIEW

In the studies conducted in the literature, authors have obtained different results depending on the periods considered, the diversity of country groups and the variables used. When the studies in the literature are examined, variables such as economic growth, health expenditures, foreign trade deficit, population, foreign direct investments, research and development expenditures, renewable energy consumption, Human Development Index, carbon dioxide, particulate matter, non-renewable energy consumption, exports, urbanization, CO_2 emission, sulfur dioxide are some of the variables used for panel data analysis. Jaunky,[6] Arouri et al.[7] and Apergis et al.[8] concluded that the effect of the GDP variable on the CO_2 emission variable representing environmental pollution is positively related in the long run, that is, an increase in GDP increases CO_2. Ozcan,[9] on the other hand, found that the effect of GDP on environmental pollution is negative in the long run. When the results in the literature are evaluated in terms of health expenditures, among the studies that consider CO_2 emission as the dependent variable representing environmental pollution in the long run, Apergis et al. found that the effect of health expenditures on CO_2 emission is negative. Nasreen,[10] Haseeb et al.[11] and Yahaya et al.[12] found that the effect of CO_2 emissions on HE is positive in the long run. Among the studies that investigated the

relationship between GDP and HE in the long run, Nasreen, Haseeb et al. and Yahaya et al. proved that there is a positive relationship between the variables.

In the literature, Doğan and Aslan[13] and Wang et al.[14] find bidirectional causality between CO_2 emissions and GDP. Ozcan[9] argues that there is no causality between CO_2 emissions and GDP. In addition, Hossain[15] Jaunky,[6] Arouri et al.,[7] Anastacio[16] Gövdeli[17] Bekun et al.[18] found that there is a unidirectional causality from GDP to CO_2 emission and Apergis et al.[8] found that there is a unidirectional causality from CO_2 emission to GDP.

According to causality analyses between HE and CO_2 emissions, Zaidi and Saidi[19] Wang et al.,[14] Akbar et al.[20] found that there is bidirectional causality. Gövdeli,[17] Haseeb et al.,[11] Keyifli and Recepoğlu,[21] Mujtaba and Shahzad[22] Nasreen[10] found a unidirectional causality from CO_2 emissions to HE.

When the causality analysis results between HE and GDP are evaluated, Elmi and Sadeghi[23] Gövdeli[17] and Nasreen[10] found bidirectional causality between HE and GDP, while Keyifli and Recepoğlu[21] could not find any causality relationship between these two variables. Zaidi and Saidi[19] and Haseeb et al.[11] proved unilateral causality from the GDP variable to the health expenditure variable. In addition, Şen et al.[24] proved the unilateral causality from health expenditure variable to GDP variable in his study. A summary of the literature is shown in **Table 3**.

Table 3. Literature summary

Author(s)	Region	Period	Variables	Method	Conclusion
Hossain[15]	NIC countries	1971-2007	CO_2, GDP, ET, DTA, URBAN	Granger causality	GDP→CO_2, DTA→CO_2, GDP→ET, URBAN→GDP, DTA→GDP, DTA→CITY
Jaunky[6]	36 countries	1980-2005	CO_2, GDP	GMM, VECM	In the short and long run, CO_2; GDP (+). According to the causality result; GDP→CO_2
Arouri et al.[7]	MENA countries	1981-2005	CO_2, GDP, ET	Panel cointegration test, granger causality	CO_2; ET (+) in the long run GDP (+) According to the causality result; GDP→CO_2
Elmi and Sadeghi[23]	Developing countries	1990-2009	HE, GDP	Granger causality	HE←→GDP
Omri[25]	MENA countries	1990-2011	CO_2, GDP, ET	Granger causality	ET←→GDP, ET→CO_2
Ozcan[9]	Middle east countries	1990-2008	CO_2, GDP, ET	FMOLS, granger causality	In the long run CO_2; GDP (-), ET (+) According to the causality result; ET≠CO_2, GDP≠CO_2
Şen et al.[24]	8 developed countries	1995-2012	HE, GDP, EH	Granger causality	For Brazil and Mexico, HE→GDP, for other countries except Indonesia, EH→GDP, HE→GDP
Li and Lin[26]	73 countries	1971-2010	CO_2, GDP, ET, URBAN, SAN	Panel threshold analysis	Low income group; URBAN; CO_2 (+), ET (-), Medium low and high income group; SAN; CO_2 (+), ET (-), Middle high income group; SAN; CO_2≠ET≠.
Yahaya et al.[12]	125 developing countries	1995-2012	HE, GDP, NO_2, SO_2, CO_2, CO	OLS, DOLS	In the long run HE; GDP(+), NO_2 (+), SO_2 (+), CO_2 (+), CO (+)
Anastacio[16]	3 North American countries	1980-2018	CO_2, GDP, ET, ELT	Granger causality	GDP→CO_2, ET→ CO_2, ELT→CO_2
Dogan and Aslan[13]	EU member and candidate countries	1995-2011	CO_2, GDP, ET, T	Panel causality	T→ CO_2, CO_2←→GDP, CO_2←→T
Yazdi and Khanalizadeh[27]	MENA countries	1995-2014	GDP, HE, CO_2, PM10	ARDL	In the long term, HE; GDP (+), CO_2 (+), PM10(+)
Apergis et al.[8]	42 sub-Saharan African countries	1995-2011	CO_2, GDP, YET, HE	FMOLS, DOLS, granger causality	In the long run CO_2; GDP (+) YET (-), HE (-) According to the causality result; YET←→CO_2, CO_2→GDP, HE ≠CO_2
Zaidi and Saidi[19]	Sub-Saharan African countries	1990-2015	HE, CO_2, GDP, NO_2	ARDL, PMG, VECM granger causality	In the long run HE; GDP (+), CO_2 (-), NO_2 (-), HE←→CO_2, GDP→HE, NO_2→HE
Gövdeli[17]	26 OECD countries	1992-2014	CO_2, GDP, HE	VECM granger causality	CO_2→HE, GDP→ CO_2, GDP←→HE
Haseeb et al.[11]	ASEAN countries	2009-2018	HE, CO_2, GDP, ET	ARDL, panel causality	In the long run HE; GDP (+), CO_2 (+), ET (-) According to the causality result; GDP→HE, CO_2→HE, ET→HE
Wang et al.[14]	18 OECD countries	1975-2017	HE, CO_2, GDP	ARDL, panel causality	In the short term, HE in Ireland, the Netherlands, the US, New Zealand and Norway; CO_2 (+), GDP (+) According to the causality result; for Germany and the US, GDP←→HE, Canada for Germany and for the USA, CO_2←→GDP, for New Zealand and Norway, HE←→CO_2
Keyifli and Recepoglu[21]	E7 countries	2000-2016	HE, CO_2, GDP, YET	Granger causality	For Turkiye, HE←→CO_2, for Brazil and Indonesia, HE→CO_2 for India and Russia, CO_2→HE, HE≠GDP, HE≠YET.
Bekun et al.[18]	EU countries	1990-2017	CO_2, GDP, EY	Dumitrescu hurlin causality	GDP→ CO_2, EY→ CO_2
Akbar et al.[20]	OECD	2006-2016	HE, CO_2, N, R&D, IG	Granger causality	CO_2←→HE, IG←→HE, R&D≠HE
Mujtaba and Shahzad[22]	OECD	2002-2018	CO_2, GDP, HE, YET	FMOLS, VECM	Long-term HE; YET (+), according to the causality result; CO_2→HE, YET→HE
Nasreen[10]	20 Asian countries	1995-2017	HE, CO_2, GDP	CEMG, AMG, Dumitrescu hurlin causality	In the long term, HE; GDP (+), CO_2 (+), according to the causality result; GDP←→HE, CO_2→HE

CO_2: Carbon dioxide, SO_2: Sulfur dioxide, GDP: Gross domestic product, ET: Energy consumption, ELT: Electricity consumption, HE: Health expenditures, DTA: Foreign trade deficit, T: Tourism, NF: Population, FDI: Foreign direct investments, R&D: Research and development expenditures, HDI: Human Development Index, PM: Particulate matter, E: Education expenditures, EY: Energy intensity, RE: Renewable energy consumption, SAN: Industry, EXP: Exports, URBAN: Urbanization, +: Positive relationship, -: There is a negative relationship, →: There is unidirectional causality, ←→: There is bidirectional causality, ≠: There is no causality relationship

METHODOLOGICAL FRAMEWORK

The model developed to ascertain the factors influencing health expenditures in the MINT country group between 2000 and 2020 is presented in Equation 1. In the literature, the first model in which HE (per capita) are used as the dependent variable and per capita income as the independent variable was constructed by Newhouse (1977). With the development of new test techniques in the following processes, different independent variables other than per capita income have been included in the models in the studies on the subject. The variables used in the model are consistent with the models of Samadi and Homaie Rad,[28] Zaidi and Saidi[19] and Yazdi and Khanalizadeh.[27]

$$HE_{it} = \alpha_i + \beta PGDP_{it} + \delta CO2_{it} + \partial URBAN_{it} + \varepsilon_{it} \quad \text{(Equation 1)}$$

i (country)=4 and

t (year)=1....21.

β, δ, ∂ are the parameters representing the coefficients of GDP per capita, CO_2 emissions per capita and urbanization rate, respectively. In order to avoid the problem of variance, natural logarithms of all variables were taken and included in the model. As illustrated in Table 4, the data for all the variables employed is derived from the World Bank database.

Table 4. Variable abbreviations and definitions used in the model

Variable abbreviation	Variable	Description	Source
HE	Health expenditures	Health expenditures per capita ($ in 2015 constant prices)	WB
PGDP	Per capita income	Gross domestic product per capita ($ in 2015 constant prices)	WB
CO_2	Carbon dioxide emission	Carbon dioxide emissions, in metric tons per capita	WB
URBAN	Urbanization	Urbanization rate	WB

The descriptive statistics of the variables employed in the panel data analysis are displayed in Table 5.

When the p-values of the Jarque-Bera normality test in Table 5 are analyzed, it is possible to say that the variables have a normal distribution. In this case, there is no drawback in using tests based on the assumption of normality.

Table 5. Descriptive statistics of variables

Variables	Number of observations	Min	Max	SD	Normality Jarque-Bera test
PGDP	84	7.28	9.40	0.28	3.97 (0.137)
CO_2	84	-0.71	1.64	0.78	9.52 (0.28)
URBAN	84	3.55	4.39	0.25	7.57 (0.210)
HE	84	3.90	6.33	0.60	1.03 (0.595)

Values in square brackets indicate p-values for the Jarque-Bera test, Min: Minimum, Max: Maximum, SD: Standard deviation, PGDP: Per capita income, CO_2: Carbon dioxide, URBAN: Urbanization

ECONOMETRIC ANALYSIS AND RESULTS

In this study, firstly, cross-section (CS) dependence and homogeneity tests will be applied to the data of the countries that make up the panel. Pursuant to the findings of the CS dependence and homogeneity test, the unit root test will be implemented to ascertain the stationarity of the series. When conducting panel data analysis, it is very important for the reliability of the analysis that the series do not have a unit root, that is, they are stationary. At this juncture, however, the utilization of first-generation unit root tests is recommended when CS dependence is absent. Conversely, in instances where CS dependence is present, the employment of second-generation unit root tests is advised. The selection of the most suitable unit root test is contingent upon the determination of CS dependence. In this study, CDLM1 and CDLM2 tests are applied if T>N, that is, if the time dimension is larger than the horizontal dimension. In the opposite case (N>T), the CDLM test is preferred in the analysis. In the context of MINT countries, the Breusch-Pagan[29] LM test is the preferred analytical approach due to the predominance of the time dimension over the horizontal dimension (T>N). A secondary rationale for this preference is the capacity of the test to function in data sets that exhibit unit roots in the presence of structural breaks. The hypotheses underlying the Breusch-Pagan[29] LM test are as follows:

- H0: There is no dependence between cross-sections.
- H1: There is dependence between cross-sections.

As can be seen in Table 6, when the test statistics and p-values of all variables are considered, it is seen that there is CS dependence both for individual variables and for the all panel. Therefore, it is possible to say that the variables of the

Table 6. CS dependence test results

	HE	Ol. value	CO_2	Ol. value	PGDP	Ol. value	URBAN	Ol. value
	Ist.		Ist.		Ist.		Ist	
CD_{LM1}[29]	101.05	0.000	45.837	0.000	78.296	0.000	125.86	0.000
CD_{LM2}[32]	27.440	0.000	11.500	0.000	20.870	0.000	34.603	0.000
CD_{LM}[32]	9.9928	0.000	-2.2690	0.0233	8.6536	0.000	11.219	0.000
LM_{adj}[31]	27.340	0.000	11.400	0.000	20.770	0.000	34.503	0.000
CS dependence test results for equation 1								
			Statistic value			**p-value**		
CD_{LM1}[29]			50.6323			0.000		
CD_{LM2}[32]			17.8541			0.000		
CD_{LM}[32]			5.71391			0.000		
LM_{adj}[31]			12.8842			0.000		

CS: Cross-section, HE: Health expenditures, CO_2: Carbon dioxide, CD: Candela, LM: Lumen

countries in the MINT country group that make up the panel are mutually influenced by each other.

On the other hand, testing the similarity of the slope coefficients of the variables together with the CS dependence test is important for the efficiency of the study and the significance of the estimation results. The homogeneity test by Hsiao[29] is used to check if the slope coefficients of the countries are the same. This homogeneity test assumes three different hypotheses. If H0 is rejected, H1, H2 (alternative hypothesis of heterogeneity) and H3 (alternative hypothesis of partial heterogeneity) are concluded.

According to the homogeneity test results shown in **Table 7**, the hypothesis H0, which accepts homogeneity at 1% significance level, is rejected for all three hypotheses H1, H2 and H3. Accordingly, it is accepted that the coefficients are heterogeneous for hypotheses H1 and H2 and partially heterogeneous for hypothesis H3. Consequently, the decision was taken to utilise the CADF test, a second-generation unit root test that incorporates both cointegration and heterogeneity.

Table 7. Homogeneity test results

Hypothesis	F-statistic	p-value
H1	17.35270	0.0000
H2	15.76751	0.0000
H3	8.109944	0.0000

The presence of a genuine relationship between variables is indicated when the variables do not possess unit roots, that is, when stationarity is a subject of inquiry. Consequently, tests conducted without stationarity analysis can yield erroneous results. In the model delineated for MINT countries, the CADF unit root test developed by Pesaran[32] is employed. This test is a second-generation unit root test that incorporates heterogeneity and CS dependence. The CADF test operates under the assumption that the series possess a unit root, while the alternative hypothesis posits that the series are stationary. The determination of the appropriate lag length is achieved through the employment of the t statistic, with a maximum lag length of 3 established for the dependent variable and 2 for the independent variables, as per the Akaike information criterion (AIC).

According to the unit root test results shown in **Table 8**, when the CIPS test statistics, which test the entire panel, are compared with Pesaran[32] table values, it is understood that the series of all variables are non-stationary at level values. Conversely, it has been demonstrated that all series become stationary when the initial difference is taken. Following the testing of the stationarity of the series, it was determined that the Durbin-Hausman (D-H) test and the LM Bootstrap tests would be utilised. These tests permit cointegration at varying levels of stationarity, on the condition that the dependent variable is stationary at first difference, in order to investigate the long-run relationship between the variables.

Table 8. CADF unit root test results

Countries	Variables (level)	Lag	CADF t-ist	Variables (1st difference)	Lag	CADF t-ist.
Mexico	PGDP	2	-1.818	ΔPGDP	1	-1.495
Indonesia		1	-2.797		1	-3.159
Nigeria		2	-0.348		1	-3.128
Turkiye		1	-2.483		1	-2.821
CIPS t-ist.			-1.861			-2.651***
Mexico	CO_2	1	0.762	ΔCO_2	1	-1.085
Indonesia		1	-0.594		1	-1.831
Nigeria		1	-1.378		1	-2.455
Turkiye		1	-1.430		1	-3.114
CIPS t-ist.			-0.660			-2.221*
Mexico	URBAN	1	0.627	ΔURBAN	1	0.788
Indonesia		2	-1.114		1	-5.246
Nigeria		1	-1.092		1	-3.222
Turkiye		2	0.265		2	-5.270
CIPS t-ist.			-0.328			-3.238***
Mexico	HE	1	-1.573	ΔHE	1	-2.604
Indonesia		1	-2.626		1	-2.561
Nigeria		2	-3.205		1	-4.385
Turkiye		1	-1.719		1	-2.731
CIPS t-ist.			-2.201			-3.070***

***, **, * denote significance at 1%, 5% and 10% levels, respectively. Lag refers to lag length. CADF test is conducted for the model with constant. CADF critical values are -4.11%, -3.36%, -2.97% at 1%, 5% and 10% levels, respectively. CIPS critical values are -2.57, -2.33, -2.21. Critical values are taken from Pesaran.[32] CADF: Cross-sectionally augmented dickey-fuller, PGDP: Per capita income, CIPS: Chartered Institute of Purchasing and Supply, CO_2: Carbon dioxide, URBAN: Urbanization, HE: Health expenditures

The D-H test has been shown to produce reliable results when the independent variables are I (0), that is to say, stationary at level, and/or I (1), stationary at first difference, on the condition that the dependent variable is stationary at first difference I (1).[31] The hypotheses of the Durbin Hausman test are as follows.

- H0: There is no cointegration relationship between the series.
- H1: There is a cointegration relationship between the series.

This test developed by Westerlund[31] produces two different test statistics, panel and group. The D-H panel test statistics calculated when the autoregressive parameters are homogeneous is as follows.

$$DH_p = \hat{S}_n(\tilde{\phi} - \hat{\phi})^2 \sum_{i=1}^{n}\sum_{t=2}^{T} \hat{e}_{it-1}^2 \quad \text{(Equation 2)}$$

If the panel test statistic is significant, the existence of a cointegration relationship for the entire panel is accepted. The other test statistic, the D-H group test statistic, is calculated when the autoregressive parameters, i.e. slope parameters, are heterogeneous. The D-H group test statistic is calculated as follows.

$$DH_g = \sum_{i=1}^{n} \hat{S}_i(\tilde{\phi}_i - \hat{\phi}_i)^2 \sum_{t=2}^{T} \hat{e}_{it-1}^2 \quad \text{(Equation 3)}$$

The D-H test is used to test the cointegration relationship between the variables in Equation 1. The results are in Table 9.

Table 9. DH co-integration test results

Model	Calculation method	Test statistic	p-value
Equation 1	DH group statistic	-1.575	0.058
	DH panel statistics	-1.284	0.100

DH: Durbin-Hausman

Given the heterogeneity of the slope coefficients of the variables in Equation 1, the D-H test statistic (Table 9) indicates a cointegration relationship between the variables at the 10% significance level.

Another cointegration test used in the study is the panel LM boostrap test developed by Westerlund and Edgerton.[34] This test, like the D-H test, allows for heterogeneity and CS dependence. On the other hand, the LM Bootstrap panel cointegration test of Westerlund and Edgerton. allows for autocorrelation and heteroscedasticity in the cointegration equation, thus providing efficient results.[35] It is also observed that this test gives good results in small samples.[36] This test is calculated as follows;

$$LM_n^+ = \frac{1}{nT^2}\sum_{i=1}^{n}\sum_{t=1}^{T} \partial_i^{-2}\ell_{it}^2 \quad \text{(Equation 4)}$$

ℓ_{it} represents the partial sum process and ∂_i^{-2} represents the long-run variance. The null hypothesis of the test tests the existence of cointegration in all horizontal sections, while the alternative hypothesis tests the absence of cointegration for some horizontal sections.[33] The results of the test are presented in Table 10.

Table 10. LM boostrap panel cointegration test results

	Test statistic	Boostrap p-value
LM_n^+	7.352	0.328

LM: Lagrange multiplier

Table 10 shows that the null hypothesis testing the existence of cointegration relationship is accepted (p>0.005). Since there is cross-sectional dependence in the countries forming the panel, only boostrap values are reported.

It is evident that both the D-H test and the LM Boostrap test offer robust evidence for the existence of a cointegration relationship between the variables incorporated within the model. However, it should be noted that these tests do not provide insight into the coefficients of the variables. Therefore, in the following part of the study, the long-run coefficients of the variables are investigated with the AMG method and CCEMG coefficient estimation developed by Pesaran[33] which are used under CS dependence and also allow the slope coefficients to be heterogeneous. With AMG and CCEMG methods, both coefficient results for the entire panel and separate results for each country in the panel can be obtained.

The Panel AMG method is an estimation method that can obtain effective results even in unbalanced panels by taking into account common factors and dynamic effects in the series. On the other hand, this method can be easily applied when there is endogeneity problem in the error term. The calculation of the coefficients according to this method is as follows.

i=1,.....,n and t=1,.....,T

$$y_{it} = \beta_i' x_{it} + u_{it}$$

$$u_{it} = \alpha_i + \lambda_i' f_t + \varepsilon_{it}$$

$$x_{mit} = \pi_{mi} + \delta_{mi}' g_{mt} + \rho_{1mi} f_{1mt} + ... + \rho_{nmi} f_{nmt} + \nu_{mit}$$

Assuming that *m=1,.....,k;* and $f_{.mt} \subset f_t$

$$f_t = o' f_{t-1} + \varepsilon_t \text{ and } g_t = k' g_{t-1} + \varepsilon_t \quad \text{(Equation 5)}$$

In the above equations, x_{it} is the vector of observed variables, α_i is the panel's truncation parameter, f_t is the set of common factors, λ_i' is the set of country-specific factors, and g_t is the country-specific factor loadings.

The CCEMG method used for estimating the long-run coefficients in this study is based on the least squares method. In this method, the multifactor error model for coefficient estimates is calculated as follows.

$$X_{it} = a_{1i} + \varphi_i f_t + \gamma_i g_t + \lambda_{it}$$

$$\mu_{it} = a_{2i} + \eta_i f_t + \varepsilon_{it} \quad \text{(Equation 6)}$$

Here f_t and g_t are unobservable time-varying common factors with country-specific factor loadings φ_i and γ_i . λ_{it} and ε_{it} are country-specific individual errors that are assumed to be independent of the common factors and distributed across panel units.

Table 11 presents the results of the AMG method developed by Eberhard[37] and the CCEMG coefficient test developed by Pesaran.[33]

According to the results of the AMG coefficient estimation for the entire panel, the coefficient of the CO_2 emission variable is statistically significant at the 1% level of significance, while the coefficient of the per capita income variable is statistically significant at the 10% level. The coefficient of the urbanization variable, however, is not statistically significant. From this perspective, a 1% increase in CO_2 emission in the MINT country group increases health expenditures (per capita) by 0.25%. Conversely, a 1% rise in per capita income in these countries results in a 0.07% reduction in HE.

One of the most important features of the AMG method developed by Eberhard[37] is that it can produce coefficient estimates both for the entire panel and for each country in the panel separately. When the country-by-country results are analyzed; a 1% increase in CO_2 emissions in Mexico

Table 11. Estimation of cointegration coefficients (AMG)

Results for the full panel							
Variable		**Coeff.**			**z-stat**		**p-value**
CO_2		0.257510			4.05		0.000
URBAN		1.055681			1.44		0.150
PGDP		-0.074473			-1.77		0.078
Const.		-1.725881			-0,66		0.510
Ol. >Chi-squared test=0.000					**Wald Chi-squared test= 48.08**		
Results by country							
Mexico					**Indonesia**		
Variable	**Coeff.**	**z-stat**	**p-value**	**Variable**	**Coeff.**	**z-stat**	**p-value**
CO_2	0.125737	2.38	0.017	CO_2	0.1718	1.30	0.192
URBAN	2.323991	5.20	0.000	URBAN	1.2887	0.98	0.327
PGDP	-0.05257	-0.59	0.558	PGDP	-.14243	-0.36	0.719
Const.	-7.00253	-4.68	0.000	Const.	-1.8252	-0.87	0.385
Nigeria					**Turkiye**		
Variable	**Coeff.**	**z-stat**	**p-value**	**Variable**	**Coeff.**	**z-stat**	**p-value**
CO_2	0.373834	4.05	0.000	CO_2	0.3586	3.31	0.001
URBAN	-1.05088	-6.67	0.000	URBAN	1.6608	3.05	0.002
PGDP	0.035737	0.29	0.773	PGDP	-0.1386	-1.19	0.234
Const.	5.435483	5.87	0.000	Const.	3.5112	-2.20	0.028
Results for the full panel (CCEMG)							
Variable		**Coeff.**			**z-stat**		**p-value**
CO_2		0.209626			7.58		0.000
URBAN		-12.94971			-0.57		0.568
PGDP		0.0239303			0.36		0.719
Const.		41.85906			1.40		0.160
Results by country							
Mexico					**Indonesia**		
Variable	**Coeff.**	**z-stat**	**p-value**	**Variable**	**Coeff.**	**z-stat**	**p-value**
CO_2	0.135913	0.95	0.343	CO_2	0.26997	1.09	0.277
URBAN	5.64293	0.52	0.600	URBAN	3.74380	0.58	0.560
PGDP	-0.171784	-0.82	0.413	PGDP	0.11160	0.15	0.877
Const.	-16.47543	-0.52	0.603	Const.	2.36804	0.27	0.790
Nigeria					**Turkiye**		
Variable	**Coeff.**	**z-stat**	**p-value**	**Variable**	**Coeff.**	**z-stat**	**p-value**
CO_2	0.219452	1.37	0.172	CO_2	0.21316	2.52	0.012
URBAN	18.96803	0.78	0.433	URBAN	1.51362	-3.11	0.002
PGDP	0.052206	0.29	0.774	PGDP	0.10369	0.72	0.470
Const.	69.37945	0.88	0.378	Const.	112.164	3.03	0.002

AMG: Augmented mean group, CO2: Carbon dioxide, URBAN: Urbanization, PGDP: Per capita income, CCEMG: Common correlated effects mean group

increases HE (per capita) by 0.12%, while a 1% increase in the urbanization rate increases HE (per capita) by 2.32% in Mexico. The effect of per capita income on HE is statistically insignificant. According to the results of the AMG coefficient test calculated with the data of Indonesia for the years 2000-2020, the coefficients of the variables in Equation 1 are statistically insignificant.

When Table 11 is analyzed in terms of probablity values, a 1% increase in CO_2 emissions in Nigeria increases HE (per capita) by 0.37%. On the other hand, a 1% increase in urbanization rate decreases HE (per capita) by 1.05%. The coefficient of the income per capita variable is statistically insignificant. Finally, in case of a 1% increase in CO_2 emissions in Turkiye, HE per capita will increase by 0.35%. A 1% increase in the urbanization rate increases HE per capita by 1.66%.

The CCEMG coefficient estimation results for the all panel indicate that the coefficient of the emission variable is statistically significant at the 1% level of significance. Conversely, the coefficients of the other variables are statistically insignificant. Consequently, a 1% increase in CO_2 emissions in the MINT country group is associated with a 0.20% increase in HE (per capita).

When the results by country are analyzed; according to the results of the CCEMG coefficient test calculated with the data for the years 2000-2020, the effect of all variables on HE is statistically insignificant for Mexico, Indonesia and Nigeria.

In Turkiye, a 1% increase in CO_2 emissions has been shown to result in a 0.21% rise in HE (per capita). Similarly, a 1% rise in the urbanization rate has been demonstrated to lead to a 1.51% increase in HE (per capita).

Given the heterogeneous slope coefficients of the variables, an analysis of the results considering the D-H group test statistic (-1.575*) in Table 9 reveals a cointegration relationship between the variables at the 10% significance level. The LM bootstrap panel cointegration test, as presented in Table 10, indicates a 5% significance level (p>0.005) for the existence of a cointegration relationship between the variables. While the D-H and LM bootstrap tests offer a robust test for the presence of cointegration among the variables within the model, they do not provide insight into the coefficients of these variables. Consequently, the long-run coefficients are investigated with the AMG and CCEMG methods, which are used under CS dependence and also allow the slope coefficients to be heterogeneous. According to the AMG and CCEMG coefficient estimation results for the entire panel, the coefficient of the carbon dioxide emission variable is significant at the 1%. This outcome aligns with the findings reported by Yahaya et al.,[11] Haseeb et al.,[10] and Nasreen.[9]

CONCLUSION

HE are a critical indicator, providing valuable insights into a society's health status and quality of life. This study investigates the impact of urbanization rate, income (per capita), and CO_2 emission variables on HE (per capita) within the MINT country group. To this end, Durbin Hausman and LM Bootstrap cointegration tests are employed. Initially, the study undertakes a thorough investigation into CS dependence and homogeneity of slope coefficients through the implementation of appropriate tests. The analysis revealed that both CS dependence and slope coefficients exhibited heterogeneity within the MINT country group. Consequently, the decision was made to employ the CADF test, a second-generation unit root test that incorporates both CS dependence and heterogeneity. The determination of the appropriate lag length was conducted by examining the t statistics, and the maximum lag length was established as 3 for the dependent variable and 2 for the independent variables according to the AIC. The outcomes of the unit root test revealed that the series of all variables are non-stationary at the level value, but become stationary when the first difference is taken. Subsequent to the stationarity assessment of the series, the D-H test was employed to ascertain the presence of cointegration across disparate stationarity levels, contingent upon the stationarity of the dependent variable at the first difference. This approach was undertaken to investigate the long-run relationship between the variables. Thereafter, the LM Bootstrap panel cointegration test was implemented, a method that accounts for both CS dependence and heterogeneity. The coefficient of the per capita income variable is statistically significant at the 10% level of significance, as determined by the AMG coefficient test. However, the CCEMG coefficient test result indicates that the coefficient is insignificant. The coefficient of urbanization variable does not attain statistical significance, according to both tests. The MINT country group, as analyzed in the study, should implement policies to prevent air pollution in order to reduce the increasing effect of CO_2 emissions on HE. Carbon tax systems should be implemented to reduce fossil fuel use, as rapid industrialization in developing countries increases air pollution by increasing energy consumption. Tax revenues from carbon tax systems can also be used for the development of clean energy technologies. Furthermore, the transition to clean energy technologies in industrial production can be facilitated by offering tax incentives to private companies investing in renewable energy sources. These measures, when implemented, should naturally absorb CO_2 emissions into the atmosphere through afforestation projects. Countries within the MINT group that are deficient in developing clean energy technologies can collaborate with international organizations to facilitate the transfer of clean technologies. Additionally, the development of public health programs to prevent health problems related to air pollution is crucial. Screening and preventive health services should be expanded to combat lung diseases, respiratory infections, and chronic diseases. Increasing green areas in cities and developing clean transportation systems are critical for improving air quality. Electric public transportation systems should be expanded, and urban policies that reduce carbon emissions should be established.

ETHICAL DECLARATIONS

Referee Evaluation Process

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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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Erratum

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Relationship between Triglyceride Glucose Index and intravenous thrombolysis outcomes for acute ischemic stroke

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Dear Editor,

We are writing about the article published under the title ''Relationship between triglyceride-glucose index and intravenous thrombolysis outcomes for acute ischemic stroke'' (2025;8(1):52-56) published in the first issue of your journal in 2025.

In the Result section of the abstract, the sentence was mistakenly written as follows:

The incidence of intracerebral hemorrhage was recorded at 9.6%, while the occurrence of END was noted in 39.6% of cases.

The corrected version of the sentence is as follows:

The incidence of intracerebral hemorrhage was recorded at 9.9%, while the occurrence of END was noted in 26.7% of cases.

In the Result section, the sentence in the first paragraph was mistakenly written as follows:

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 corrected version of the sentence is as follows:

The incidence of intracerebral hemorrhage was 9.9%, while END occurred in 26.7% of cases, and the 30-day mortality rate was 28.2%.

The sentence in Table 1 was mistakenly written as follows:

Intracerebral hemorrhage 7 (9.6)

The corrected version of the sentence is as follows:

Intracerebral hemorrhage 7 (9.9)

The sentence in the third paragraph of the Discussion section was mistakenly written as follows:

Our study identified an intracerebral hemorrhage rate of 8.5%.

The corrected version of the sentence is as follows:

Our study identified an intracerebral hemorrhage rate of 9.6%.

We deeply regret this oversight and sincerely apologize for any inconvenience caused.

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 (9.9)
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
Triglyceride Glucose Index	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

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