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Research

The Relationship Between Cognitive Functions and Pain Intensity in Patients with Fibromyalgia

Fibromiyalji Hastalarında Kognitif Bozuklukların Ağrı Şiddeti ile İlişkisi

Sevda Bağ

University of Health Sciences Turkey, Istanbul Training and Research Hospital, Clinic of Psychiatry, Istanbul, Turkey

ABSTRACT

Objective: This study aimed to determine the cognitive functions in patients with fibromyalgia and healthy control group and compare the relationship of cognitive dysfunction with pain severity.

Methods: This study evaluated the cognitive functions and pain severity of 93 patients and 93 healthy controls who were diagnosed with fibromyalgia in the physical medicine and rehabilitation clinic and referred to our outpatient psychiatry clinic for consultation. Sociodemographic data form, Montreal Cognitive Assessment (MOCA) scale for cognitive functions, Mini-Mental test, Hamilton Depression scale, and visual analogue scale (VAS) for pain severity were applied to the patients. Consent was obtained from the patient and the control groups.

Results: The total points of MOCA, attention, visuospatial, naming, language, abstraction, orientation, and delayed memory subscores of the fibromyalgia group were significantly lower than the healthy control group. This result revealed a significant level of mild deterioration in cognitive functions in the fibromyalgia group ($p<0.005$). Additionally, the VAS pain score was significantly higher in patients with fibromyalgia having cognitive impairment ($p<0.005$).

Conclusion: Pain and psychiatric symptoms are quite frequently seen in patients with fibromyalgia; however, they are accompanied by cognitive dysfunction. Dysfunction in attention, visualization, naming, language, abstraction, orientation, and delayed memory increase the severity of pain. Therefore, we think that it will also affect the functionality in the future. Additionally, cognitive dysfunction identification and cognitive-behavioral treatments should be added to the current fibromyalgia treatment.

Keywords: Cognitive functions, fibromyalgia, attention, pain intensity

ÖZ

Amaç: Amacımız fibromiyaljisi olan hastalarda ve sağlıklı kontrol grubunda bilişsel fonksiyonları tanımlamak ve bilişsel fonksiyonlardaki bozukluğun ağrı şiddeti ile olan ilişkisini incelemektir.

Gereç ve Yöntem: Fizik tedavi kliniğinde fibromiyalji tanısı konularak konsültasyon amacı ile ayaktan psikiyatri polikliniğimize gönderilen toplam 93 hasta ve 93 sağlıklı kontrol hastasının bilişsel fonksiyonları ve ağrı şiddetleri değerlendirildi. Bu amaçla hastalara sosyodemografik veri formu kognitif fonksiyonlar için Montreal Kognitif Değerlendirme (MOBİD) ölçeği, Mini-Mental test, Hamilton Depresyon ölçeği ve ağrı şiddeti için vizüel analog skala (VAS) uygulanmıştır. Hasta ve kontrol grubundan onam alınmıştır.

Bulgular: Fibromiyalji grubunun MOBİD toplam, dikkat, vizyospasiyal, adlandırma, dil, soyutlama, oryantasyon ve gecikmeli hafıza skorları sağlıklı kontrol grubuna göre anlamlı düzeyde daha düşük bulunmuştur. Bu sonuç fibromiyalji grubunda anlamlı düzeyde kognitif fonksiyonlarda hafif bozulma olduğunu göstermiştir ($p<0,005$). Ayrıca kognitif bozukluk saptanan fibromiyalji hastalarında VAS ağrı skorunda anlamlı oranda yüksek bulunmuştur ($p<0,005$).

Sonuç: Fibromiyaljili hastalarda ağrı ve psikiyatrik belirtiler oldukça sık oranda görülmekle beraber kognitif bozukluklarda eşlik etmektedir. Dikkat, vizyospasiyal, adlandırma, dil, soyutlama, oryantasyon ve gecikmeli hafıza alanındaki bozukluklar ağrı şiddetini artırmaktadır. Sonuç olarak olarak ileride işlevselliği de etkileyeceğini düşünmekteyiz. Bu sebeple kognitif bozuklukların belirlenmesi ve bilişsel davranışsal tedaviler fibromiyaljinin güncel tedavisine eklenmelidir.

Anahtar Kelimeler: Kognitif bozukluk, fibromiyalji, dikkat, ağrı yoğunluğu

Address for Correspondence: Sevda Bağ, University of Health Sciences Turkey, Istanbul Training and Research Hospital, Clinic of Psychiatry, Istanbul, Turkey
Phone: +90 505 384 25 29 E-mail: sevdabag@yahoo.com ORCID ID: orcid.org/0000-0001-8041-3611

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INTRODUCTION

Fibromyalgia syndrome is a chronic disease that is accompanied by many psychiatric symptoms, such as sleep disorder, cognitive dysfunction, and depression, as well as severe pain and fatigue (1). The population prevalence of fibromyalgia ranges from 2% to 8%, and the prevalence increases with increasing age. Studies revealed that female gender, socioeconomic status, and low educational level increase the risk of disease (2). It is common in women aged 40-60 years. Its etiology and pathogenesis are still unknown but are thought to be multifactorial. Neural activity changes in the central nervous system, abnormality of metabolism in some biogenic amines, and immunological events may lead to disease development. Fibromyalgia syndrome complaints are mostly subjective. Distinguishing the disease from psychosomatic diseases is difficult (3).

Fibromyalgia is defined as a disease, in which chronic widespread muscle pains that cannot be explained by another disease are accompanied by fatigue, sleep disturbance, and various somatic symptoms. Psychiatric disorders that occur in patients with fibromyalgia are among the factors that seriously affect the quality of life of the person. These patients have a high rate of lifelong psychiatric disorders and psychiatric disorders even before the disease onset (4). Psychiatric disorders often accompany fibromyalgia. The most common accompanying psychiatric disorder is depression, which is seen in approximately 20-80% of patients with fibromyalgia. This is followed by psychiatric disorders, such as anxiety, somatization, and obsessive-compulsive (4).

Two factors are considered in the development of high rates of depression in patients with fibromyalgia. Common genetic predispositions and triggering factors increase the risk of depression (5). Studies of patients with depression level and pain severity reported not only the common pathophysiological processes between pain and depression but also the low pain threshold, which is shaped by structure deformation, such as the amygdala and hippocampus, is important (6). Factors that increase the pain of people should be considered to understand the nature of depression that occurs in patients with fibromyalgia. One of them is cognitive processes. According to the latest obtained data, as the level of pain perceived by the person increases, the level of depression also increases. Based on this connection, the reason for intense negative orientation towards painful stimuli is cognitive distortions defined as catastrophizing (6).

In recent years, especially in developed countries, fibromyalgia has emerged as a serious functionality problem by reducing the workforce and quality of life. Cognitive dysfunction seen in fibromyalgia is now considered a separate clinical condition. Thus, cognitive dysfunctions can cause depression, anxiety, sleep disorders, and an increased pain level. Previous studies revealed an inverse relationship between obesity and cognitive dysfunction (7).

Despite all the obtained information, the treatment of choice for fibromyalgia was not achieved. Cognitive complaints are seen up to 95% in fibromyalgia; however, they are not adequately recognized by clinicians, and patients are left untreated. Subjective cognitive complaints are quite high in fibromyalgia patients, but the number of studies that use objective tests is very few. Therefore, this study aimed to examine the cognitive functions and the relationship between these functions and pain intensity in patients with fibromyalgia.

METHODS

This study evaluated the cognitive functions and pain severity of 93 patients and 93 healthy control who were diagnosed with fibromyalgia in the physical therapy clinic and referred to our outpatient psychiatry clinic for consultation. Sociodemographic data form, Montreal Cognitive Assessment (MOCA) scale for cognitive functions, Mini-Mental test (MMT), Hamilton Depression scale (HAM-D), and visual analogue scale (VAS) for pain severity were applied to patients and healthy control group. Consent was obtained from the patient and the control groups. Approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Istanbul Training and Research Hospital for our study (decision no: 2936, date: 08.10.2021).

The sociodemographic data form included patients' gender, age, educational status, functionality, marital status, number of children, and duration of a fibromyalgia diagnosis.

VAS was used to measure the pain severity on the scale, which is prepared to convert some values that cannot be numerically measured. Patients are requested to mark the pain severity by showing a line with the words "0 (no pain)" at one end and "10 (severe pain)" at the other end (8).

The MMT is used to detect severe cognitive impairment and monitor treatment responses. The total score is calculated out of 30. The threshold value is accepted as 23/24 (23 and below points of cognitive dysfunction) (9).

The MOCA was developed to distinguish healthy individuals from those with mild cognitive impairment. It consists

of questions that assess attention and concentration, executive functions, memory, language, visuospatial skills, abstract thinking, calculation, and orientation. It can be applied in 10 minutes. The total score is calculated out of 30. The threshold value is 21 (20 and below points of cognitive dysfunction). Turkish validity and reliability study was made by Selekler et al. (10). The MOCA scale can detect cognitive impairment in milder stages, whereas the MMT is useful in more advanced stages (10).

Statistical Analysis

Statistical analyses were carried out using the Statistical Package for the Social Sciences version 17.0 program. The suitability of variables to the normal distribution was examined with histogram graphs and the Kolmogorov-Smirnov test. Average, standard deviation, and median values were used to present descriptive analyses. Categorical variables were compared with the Pearson Square test. The Mann-Whitney U test was used to evaluate nonparametric groups that did not show normal distribution. Spearman correlation test was used in the analysis of measuring data with each other. P-values of <0.05 were evaluated as statistically significant results.

RESULTS

A total of 186 people participated in the study, including 93 with fibromyalgia and 93 healthy controls. Of the participants, 64 (68.82%) were females and 29 (31.18%) were males; 32 (34.41%) are in primary education, 36 (38.71%) in high school, and 25 at university (26.88%); 58 (62.37%) are single and 8% (8.60%) are widows; 38 (40.86%) are working and 55 (59.14%) are not. The mean age of the participants was 38.33±8.23 years. The mean duration of fibromyalgia diagnosis of the fibromyalgia group is 3.40±1.71 years. No significant difference was found between the control group and the sociodemographic data of the fibromyalgia group (Table 1).

The mean MMT was 26.46±1.57 (median: 27.00) of the fibromyalgia group. According to this result, severe cognitive impairment was not detected in patients with fibromyalgia.

The average HAM-D results in the fibromyalgia group were 5.15±1.02 (median: 5.00), whereas 5.10±0.72 (median: 5.00) in the healthy control group (p=0.201). Thus, depression was not detected in both groups.

The total MOCA, attention, visuospatial, naming, language, abstraction, orientation, and delayed memory scores of the fibromyalgia and control groups were compared. MOCA total, attention, visuospatial, naming, language, abstraction, orientation, and delayed week scores of the control group were significantly higher than the fibromyalgia group. This result showed significant mild cognitive impairment in the fibromyalgia group (p<0.005) (Table 2).

For the cognitive impairment status in the fibromyalgia group, the MOCA scale and VAS scores were compared, which revealed significance (p<0.005). This result revealed that pain score was significantly higher in patients with fibromyalgia with cognitive impairment (Table 3).

DISCUSSION

This study aimed to evaluate the cognitive functions in patients with fibromyalgia without depression and the relationship between pain severity and mild cognitive impairment. Our study used the MOCA scales for cognitive functions, which revealed a statistically significant cognitive impairment compared to the healthy controls. The decreased visuospatial area, attention, naming, language orientation, and delayed memory areas were statistically significant, but the decreased abstraction area was not statistically significant. Pain intensity was also significantly higher in the group with mild cognitive retardation. This result shows that mild cognitive impairment in fibromyalgia causes pain to be felt more severely.

Fibromyalgia syndrome is a long-term syndrome that is characterized by pain, severe fatigue, sleep disturbances, and cognitive and emotional disturbances. The main symptom of fibromyalgia includes chronic and widespread pain accompanied by light sensitivity, as well as secondary complaints, such as decreased concentration and memory (11). Most reported is mild cognitive impairment. Especially in patients with occupations that require high concentration, cognitive impairments are likely to affect their performance. This condition is often included under the terms "cognitive dysfunction" and "fibrofog" in the medical literature and is being diagnosed with increasing frequency (12).

Cognitive problems are frequently encountered in studies that conducted objective tests (conceptual memory, daily attention, and selective attention) in patients with fibromyalgia. These patients experience serious memory problems in complex and demanding tasks (13). Studies revealed that cognitive impairment is experienced by 95% of patients with fibromyalgia (14). Further, depression is a disease that causes cognitive impairment. Thus, patients with fibromyalgia with depression were excluded from our study, as well as cognitive impairment due to depression.

Table 1. Sociodemographic variables

		Fibromyalgia		Controls		p-value
		n	%	n	%	
Sex	Female	64	(68.82)	60	(66.66)	0.250
	Male	29	(31.18)	33	(36.66)	
Education	Primary school	32	(34.41)	34	(36.56)	0.580
	High school	36	(38.71)	40	(43.01)	
	University	25	(26.88)	19	(20.43)	
Marital status	Married	58	(62.37)	41	(44.09)	0.036
	Single	27	(29.03)	43	(46.24)	
	Divorced	8	(8.60)	9	(9.68)	
Occupation	Worked	38	(40.86)	46	(49.46)	0.239
	No work	55	(59.14)	47	(50.54)	
Age		38.33±8.23		40.33±8.43		
Ki-kare test	-	-	-	-	-	-

Table 2. MOCA scores in the fibromyalgia and control groups

	Fibromyalgia			Controls			p-value
	Average	SD	Median	Average	SD	Median	
MOCA total	19.45	±1.91	19.00	27.08	±2.14	27.00	<0.001
Attention	3.84	±1.35	4.00	5.37	±0.67	5.00	<0.001
Visuospatial	4.18	±0.61	4.00	4.82	±0.44	5.00	<0.001
Naming	1.86	±0.62	2.00	2.65	±0.50	3.00	<0.001
Language	1.73	±0.51	2.00	2.52	±0.54	3.00	<0.001
Abstrational	1.26	±0.44	1.00	1.45	±0.50	1.00	0.006
Orientation	3.38	±1.20	4.00	5.45	±0.76	6.00	<0.001
Delayed recall	3.06	±1.25	3.00	4.81	±0.40	5.00	<0.001
Mann-Whitney U test							

SD: Standard deviation, MOCA: Montreal Cognitive Assessment

Table 3. The relationship between cognitive dysfunctions and pain scales

Fibromyalgia groups	Cognitive dysfunctions (MOCA scores 20 and below points)						p-value
	No			Yes			
	Average	SD	Median	Average	SD	Median	
VAS scale	4.04	±0.81	4.00	9.78	±0.94	9.00	<0.001
Mann-Whitney U test	-	-	-	-	-	-	-

SD: Standard deviation, MOCA: Montreal Cognitive Assessment, VAS: Visual analogue scale

Cognitive dysfunction is thought to be associated with an increased intensity of fibromyalgia symptoms, mental health deterioration, and reluctance (15). Making the differential diagnosis of cognitive dysfunction from real brain damage, such as organic origin, is necessary for patients with fibromyalgia.

Todd has argued that pain in patients with fibromyalgia may be related to patient phobias. The response to the onset or increased intensity of pain and the weak effort on neuropsychological tasks translates into a concept they call "overthinking and causing pain." This theory is called

"kinesophobia," this results in patients with pain being overly anxious about re-experiencing or exacerbating the pain and avoiding physical activities. Thus, the concept of cognitive phobia has received little attention but is a topic that will take place in future studies, which more likely supports this hypothesis (16,17).

CONCLUSION

Fibromyalgia is one of the most important health problems in developed countries, especially in recent years, which causes serious loss of workforce and a decreased quality of life. In these patients, difficulty in performing daily activities, widespread musculoskeletal pain, stiffness, and other symptoms, such as fatigue, sleep disorders, cognitive dysfunction, and mood disorders, are frequently encountered. Cognitive complaints are seen in functions, such as tasks that require attention, short-term memory, and decision-making functions, which are often neglected by clinicians. Standardized tests are insufficient to diagnose the cognitive dysfunction and determine the treatment strategy, thus most patients remain untreated.

Our study recommends including cognitive-behavioral treatments in addition to pharmacological treatment. The concept of kinesophobia will take place more in future studies. There, the functionality of patients will increase due to a multidisciplinary approach.

ETHICS

Ethics Committee Approval: Approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Istanbul Training and Research Hospital for our study (decision no: 2936, date: 08.10.2021).

Informed Consent: Consent was obtained from the patient and the control groups.

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Research

Assessment of Tpe/QT Ratio, Tpe/QTc Ratio, and Tpe Interval in Patients with an Ulcerative Colitis

Ülseratif Kolitli Hastalarda Tpe/QT Oranı, Tpe/QTc Oranı ve Tpe Mesafesinin Değerlendirilmesi

Erdinç Gülümsek[1], Hilmi Erdem Sümbül[1], Begüm Şeyda Avcı[1], Muhammed Zübeyir Aslan[1], Yahya Kemal İçen[2], Akkan Avcı[3], Mevlüt Koç[2]

[1]University of Health Sciences Turkey, Adana City Training and Research Hospital, Clinic of Internal Medicine, Adana, Turkey
[2]University of Health Sciences Turkey, Adana City Training and Research Hospital, Clinic of Cardiology, Adana, Turkey
[3]University of Health Sciences Turkey, Adana City Training and Research Hospital, Clinic of Emergency Medicine, Adana, Turkey

ABSTRACT

Objective: In this study, our aim was to investigate the change in Tpe/QTc, Tpe/QT ratios, and Tpe interval in patients with ulcerative colitis (UC).

Methods: Our cross-sectional study included 40-patients followed-up with a UC diagnosis and 40 healthy controls. All the patients underwent 12-lead electrocardiography (ECG). In addition to the routine ECG measurements, Tpe/QT and Tpe/QTc ratios and Tpe interval were measured.

Results: Resting heart rate and serum high-sensitive C-reactive protein (hs-CRP) levels were higher with UC patients ($p<0.05$). Tpe interval and Tpe/QTc ratio values were higher in patients with UC ($p<0.05$). QT and QTc measurements were similar in the UC patients and healthy controls. Ratio of Tpe to QT and QTc, and Tpe distance measurements positively correlated with the heart rate, UC disease duration, and hs-CRP ($p<0.05$ for each-one). Tpe/QT, Tpe/QTc ratios, and Tpe interval were found to be independently associated with the heart rate and UC disease duration in a linear regression analyze.

Conclusion: In patients with UC; Tpe/QT, Tpe/QTc ratios, and Tpe interval are increased and are independently associated with a disease duration in these patients. This may be associated with the increased inflammation in the UC patients and its cardiac effects.

Keywords: Ulcerative colitis, Tpe/QT, Tpe/QTc ratios and Tpe interval

ÖZ

Amaç: Bu çalışmada amacımız ülseratif kolitli (ÜK) hastalarda Tpe/QTc, Tpe/QT oranları ve Tpe mesafesindeki değişimi incelemektir.

Gereç ve Yöntem: Kesitsel çalışmamıza ÜK tanısı ile takip edilen 40 hasta ve 40 sağlıklı kontrol dahil edildi. Tüm hastalara on iki derivasyonlu elektrokardiyografi (EKG) çekildi. Rutin EKG ölçümlerine ek olarak Tpe/QT ve Tpe/QTc oranları ve Tpe mesafesi ölçüldü.

Bulgular: ÜK hastalarında istirahat kalp hızı ve serum yüksek duyarlılıklı C-reaktif protein (hs-CRP) düzeyleri daha yüksekti ($p<0,05$). ÜK'li hastalarda Tpe aralığı ve Tpe/QTc oranı değerleri daha yüksekti ($p<0,05$). ÜK hastalarında ve sağlıklı kontrollerde QT ve QTc ölçümleri benzerdi. Tpe/QT oranı, Tpe/QTc oranı ve Tpe interval ölçümleri kalp hızı, ÜK hastalık süresi ve hs-CRP ile pozitif korelasyon gösterdi (her biri için $p<0,05$). Lineer regresyon analizinde Tpe/QT, Tpe/QTc oranları ve Tpe aralığı kalp hızı ve ÜK hastalık süresi ile bağımsız olarak ilişkili bulundu.

Sonuç: ÜK'li hastalarda, Tpe/QT, Tpe/QTc oranları ve Tpe aralığı artar ve bu hastalarda hastalık süresi ile bağımsız olarak ilişkilidir. Bu, ÜK hastalarında artan enflamasyon ve bunun kardiyak etkileri ile ilişkili olabilir.

Anahtar Kelimeler: Ülseratif kolit, Tpe/QT, Tpe/QTc oranları ve Tpe mesafesi

Address for Correspondence: Akkan Avcı, University of Health Sciences Turkey, Adana City Training and Research Hospital, Clinic of Emergency Medicine, Adana, Turkey
Phone: +90 533 423 03 69 E-mail: drakkanavci@gmail.com ORCID ID: orcid.org/0000-0002-4627-0909

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INTRODUCTION

The most common extra-intestinal involvement in the patients with an ulcerative colitis (UC) is the skin, eye, and live. Although the cardiac involvement is much rarer, it is associated with the increased mortality and morbidity of the UC patients (1-3). Cardiac involvement usually occurs as myocarditis, pericarditis, valvular involvement, cardiac arrhythmia, and venous thrombosis (1,2).

Twelve lead electrocardiographic (ECG) changes are associated with a serious ventricular arrhythmia. These ECG parameters are interval of QT-QTc, dispersion of QT-QTc, and T wave-peak and end-distance (Tpe interval). QT-QTc are related to a ventricular repolarization and depolarization. Tpe is mostly a sign of a ventricular repolarization and could be more meaningful in evaluating especially the repolarization. During the repolarization ventricular transmural dispersion is associated with the ratio of Tpe to QT and QTc (4). Increased Tpe interval is associated with an increased risk of a ventricular arrhythmia and shows abnormality in a ventricular repolarization (5). As far as we have investigated, although it has been shown that the QTc and QTc dispersion has increased in the patients with UC (6-9), there is no study about the ratio of Tpe to QT and QTc and distance of Tpe used in a ventricular repolarization assessment in the recent years.

In this study, our aim was to investigate the change in the Tpe/QT ratio, Tpe/QTc ratio, and Tpe interval in patients with the UC.

METHODS

Between January 2019 and January 2020, a total of 59 UK patients who were followed-up in the Gastroenterology Clinic in University of Health Sciences, Adana City Research and Training Hospital were scanned. Written informed consent was not necessary for those who did not include any patients' data in the study. After the exclusion criteria, a total of 40 patients diagnosed with the UC and 40 healthy controls that were similar in the age and gender were included. Taking a medical treatment known to affect the QT-QTc interval, history of sudden cardiac arrest or syncope, persons with under 18 years-old, failure to obtain the QTc and Tpe measurements, mild-advanced valvular disease, known ischemic heart disease (IHD), or major risk factors for IHD such as: hypertension, diabetes mellitus, and systolic and diastolic heart failure were the exclusion criterion.

Local Ethics Committee approved our study (Cukurova University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee, decision number: 72, date: 14.02.2020). The demographic data were recorded from the UC patients and healthy controls. Active disease duration of the patients with the UC was noted. Glucose, creatinine, sodium, aspartate aminotransferase, blood urea nitrogen, alanine aminotransferase, potassium, calcium, triglyceride, high-sensitive C-reactive protein (hs-CRP), and low-density lipoprotein cholesterol levels were measured (Abbott Aeroset, MN, USA).

Twelve-lead Electrocardiographic Evaluation

Twelve-lead ECGs carried out by an ECG Device of MAC 2000 (GE-medical, Inc, WI-USA) in a sinus rhythm, 1 mv/10 mm and 25 mm/sec speed, and standard calibration was obtained from all the individuals. QT-interval was measured (the time from where QRS started to the point where the T wave merges with the isoelectric line was calculated). Bazett Formula was used for QTc measurement ($QTc=QT/\sqrt{R\text{-}R}$). It was evaluated whether there was a supraventricular extrasystole and ventricular extrasystole along with the cardiac axis. Tpe is defined as the distance from the peak of the T wave to the end of the T wave. V_5 was used for measurements (10). The ratio of the Tpe to QT-QTc were calculated.

Statistical Analysis

All the analyses were conducted using SPSS-24.0 (Chicago, IL, USA). The Kolmogorov-Smirnov test was used. The data are expressed as the means ± the standard deviations and as percentages and numbers for the categorical variables. Student-t test and Mann-Whitney U test was used. The categorical variables were compared by the chi-square (χ^2) test. We use kappa coefficient to examine the inter-intra observer variability of the ECG parameters. Parameters associated with a Tpe distance, Tpe/QTc, and Tpe/QTc were determined with an univariate Spearman's or Pearson's correlation analyses.

RESULTS

ECG measurement was successfully obtained. Cohen kappa values were >90% that evaluate the interobserver variability for all the ECG evaluation ($p<0.001$ for all the comparisons). The study population was divided into two groups (UC patients and healthy controls).

Gender and age were similar between both the groups. The resting heart rate, one of the clinical parameters, was higher in the UC patients. Among the laboratory parameters, hs-CRP level was significantly higher in the UC patients. Other ECG and laboratory measurements were same for each group (Table 1).

Table 1. Comparison of demographic and laboratory findings patients with ulcerative colitis and control group

	Ulcerative colitis (+) n=40	Control group n=40	p
Age (year)	38.5±4.8	37.8±5.9	0.536
Male % (n)	50 (15)	50 (15)	1.000
Smoking % (n)	50 (15)	50 (15)	1.000
Disease duration (years)	4.15±2.19	-	-
Blood pressure for systolic (mmHg)	120±17	124±13	0.271
Blood pressure diastolic (mmHg)	70±9.6	72±8.3	0.327
Heart rate (pulse/minute)	71±14	62±4.4	<0.001
Body mass index (kg/m^2)	27.5±1.7	27.9±1.5	0.365
Glucose (mg/dL)	93±8.2	90±12	0.153
Urea (mg/dL)	25.5±7.6	27.1±8.2	0.350
Creatinine (mg/dL)	0.65±0.19	0.60±0.08	0.871
Sodium (mEq/L)	139±6.5	140±3.7	0.457
Potassium (mEq/L)	4.36±0.60	4.34±0.32	0.871
Aspartate aminotransferase (u/L)	20.1±5.9	18.2±2.8	0.063
Alanine aminotransferase (u/L)	17.4±5.1	17.5±2.4	0.877
Calcium (mg/dL)	9.74±0.66	9.45±0.52	0.869
Low-density lipoprotein cholesterol (mg/dL)	92±24	101±24	0.091
Triglycerides (mg/dL)	115±34	118±39	0.745
hs-CRP (mg/dL)	2.74±1.12	1.15±0.20	<0.001

hs-CRP: High-sensitive C-reactive protein

QTc and QT measurements were similar between both the groups. Ratio of Tpe to QT and QTc, and Tpe distance were significantly higher in the patients with UC (Table 2). Tpe distance, the ratio of Tpe to QT, and QTc positively related with the hs-CRP and UC disease duration (Table 3). Tpe/QT, Tpe/QTc ratios, and Tpe interval were found to be independently associated with the hs-CRP and UC disease duration in a linear regression analysis (Table 4). Most significant relation was found hs-CRP-UC disease duration and Tpe-interval.

DISCUSSION

Most important evidence of this investigation was that without the QT and QTc prolongation, Tpe distance, Tpe/QTc ratio, and Tpe/QT ratio were higher in the patients with UC in contrast to healthy controls. As we observed, this is the first study to show the increase of the ventricular repolarization parameters such as: Tpe distance, ratio of Tpe to QTc, and QT in patients with UC. We also found that the hs-CRP and UC disease duration have a close and positive relationship with a Tpe distance, ratio of Tpe to QTc, and QT.

Ventricular depolarization starts from the endocardium to the epicardium. During the ventricular repolarization, dispersion between the endocardial and the epicardial region occurs. Tpe distance, which is associated with a transmural ventricular repolarization, is between the T wave peak and the end distance and this interval (4,11). In the literature, there are studies about the Tpe distance and the ratios of the Tpe to QT are associated with the arrhythmic situations and sudden cardiac death (5,12-14). Increased Tpe distance, ratio of Tpe to QT are associated with a normal arrhythmia and a sudden cardiac death. The dispersion in the repolarization between the endocardial and the epicardial region in the ventricular myocardium causes slow conduction in the endocardium and epicardium. It may especially be increasing the re-entry-related arrhythmias.

Although there are studies evaluating the QT and QTc distance and QT dispersion, which are among the ventricular repolarization parameters, there is no study investigating the Tpe distance, ratio of Tpe to QTc, and QT in patients with UC (6-9). In most of the studies, the findings indicate that the QTc and QTc dispersion are markedly elongated in the

Table 2. Comparison of ventricular repolarization parameters patients with ulcerative colitis and control group

	Ulcerative colitis (+) n=40	Control group n=40	p
QT distance (msn)	403±38	401±23	0.889
QTc distance (msn)	431±35	427±27	0.372
Tpe distance (msn)	87.8±9.1	72.7±7.4	0.002
The ratio of Tpe to QT	0.227±0.048	0.191±0.025	0.010
The ratio of Tpe to QTc	0.203±0.028	0.185±0.023	0.002

Table 3. Correlation of Tpe distance, the ratio of Tpe to QT, and QTc with the clinical and laboratory parameters

	Tpe distance		The ratio of Tpe to QT		The ratio of Tpe to QTc	
	r	p	r	p	r	p
Pulse (per min)	0.380	<0.001	0.068	0.463	0.100	0.278
Disease duration (years)	0.560	<0.001	0.190	0.021	0.290	0.009
hs-CRP	0.474	<0.001	0.217	0.017	0.310	0.001

hs-CRP: High-sensitive C-reactive protein

Table 4. A linear regression analysis for parameters significantly correlated with Tpe distance, the ratio of Tpe to QT and QTc

	Tpe distance		The ratio of Tpe to QT		The ratio of Tpe to QTc	
	β	p	β	p	β	p
Heart rate	0.187	0.054	-	-	-	-
Disease duration (years)	0.487	<0.001	0.264	0.023	0.290	0.009
hs-CRP	0.240	0.014	0.123	0.045	0.334	<0.001

R square for Tpe-interval, Tpe/QT and Tpe/QTc as 401-290-361, respectively, hs-CRP: High-sensitive C-reactive protein

patients with UC (6-8). However, in the study conducted by Dogan et al. (9), there was no significant difference in the QTc and QT dispersion (the longest and shortest QTc difference) in the UC patients compared to the healthy controls. In the same study, these parameters were also not associated with a disease duration and the activity (9). Yorulmaz et al. (8) reported that the QT dispersion was higher in the UC patients than the healthy controls. While QTc dispersion was associated with a systolic blood pressure and patient's age, no relationship was found between a disease duration and the QTc dispersion (8). In our study, the QT and QTc intervals obtained supported the study where the QT and QTc prolongation were not detected from the previous articles. However, the increase in the Tpe distance, ratio of Tpe to QTc, and QT, in patients with UC was markedly more important than the QTc distances. Increased QT and QTc dispersion, QTc duration, Tpe/QTc, Tpe distance have been shown to be risk factors for the ventricular arrhythmia and sudden death (4,5). In our study, Tpe interval, Tpe/QT, and Tpe/QTc were shown to be increased for the first time in patients with UC. So, it is important.

In our study and in the previous studies, it has been shown that there may be prolonged ventricular repolarization parameters without the cardiac involvement and cardiovascular disease (6-8). In these studies, and in our study, serum electrolytes were normal, and there are no drugs that prolongs the ventricular repolarization. It was thought that the prolongation in the repolarization among UC patients from our previous study, and previous studies resulted from a myocardial repolarization of an electrical remodeling caused by the increased intra-cardiac inflammation, because of the increased systemic inflammatory process. The increased inflammatory process also does endothelial damage and dysfunction in the intra-cardiac vascular system, as in the entire vascular endothelium. This leads to depolarization/repolarization abnormality in the cardiac myocytes (15,16). Although this physiopathology is not clearly shown in our study, indirectly supporting findings were obtained. The

most important parameter was increased serum hs-CRP, which is an important indicator of the systemic inflammation in the UC patients, and the duration of the disease was related to the Tpe interval, Tpe/QT, and Tpe/QTc.

In our study there are some important limitations. The most important limitation is the cross-sectional design of the study, and another limitation is the number of the patients enrolled in the study. In our study, the number of patients were limited to 40. Therefore, in the regression analysis, ventricular repolarization parameters were found to be associated only with the hs-CRP and UC disease duration. In addition, arrhythmic event and clinical follow-up parameters could not be evaluated due to the low number of the patients and no clinical follow-up.

In our study, taking medication and medical treatment that may cause QT prolongation was accepted as an exclusion criterion. In the patients with UC, the risk of atrial and ventricular arrhythmia increases (2,17,18), but in our study, although no arrhythmia symptoms were observed, more significant results could be obtained, if 48 hours Holter examination was performed.

CONCLUSION

Tpe distance and the ratio of Tpe to QTc are increased in the UC patients. This may be due to a neuroendocrine system activity and serum electrolytes in the UC patients. Also, QTc evaluation, which was routine in patients diagnosed with UC, it was thought that the Tpe-interval and Tpe/QT ratios should be measured and monitored more closely in terms of a hypopotassemia and hypomagnesemia.

ETHICS

Ethics Committee Approval: This study approved by Cukurova University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (decision no: 72, date: 14.02.2020).

Informed Consent: Written informed consent was not necessary for those who did not include any patients' data in the study.

Authorship Contributions

Surgical and Medical Practices: E.G., H.E.S., M.K., Concept: E.G., H.E.S., M.K., Design: E.G., H.E.S., B.Ş.A., A.A., M.K., Data Collection or Processing: B.Ş.A., M.Z.A., Y.K.İ., Analysis or Interpretation: B.Ş.A., M.Z.A., Y.K.İ., A.A., Literature Search: H.E.S., B.Ş.A., M.Z.A., Y.K.İ., M.K., Writing: E.G., H.E.S., A.A., M.K.

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Research

Mental Health Problems in Renal Nurses During Novel Coronavirus Disease of 2019 Pandemic

Koronavirüs Hastalığı-2019 Pandemisinde Diyaliz Hemşirelerinin Ruh Sağlığı Sorunları

Şennur Köse[1], Barış Sancak[2], Çağatay Karşıdağ[2]

[1]University of Health Sciences Turkey, Istanbul Training and Research Hospital, Clinic of Nephrology, Istanbul, Turkey
[2]Acibadem Mehmet Ali Aydinlar University Atakent Hospital, Clinic of Psychiatry, Istanbul, Turkey

ABSTRACT

Objective: The most important factor in facing the pandemic is to ensure the physical and mental health status of the healthcare workers. Studies have found serious stressors experienced by the hemodialysis incharge-nurses but report less burnout than the other nurses. Determining the mental distress of the hemodialysis incharge-nurses during the pandemic is important in determining the necessary precautions. The objective of this study is to determine the psychological complaints of the hemodialysis incharge-nurses during the pandemic.

Methods: The participants of the study are hemodialysis incharge-nurses who work in different provinces of Turkey. The data of the study were collected from April to June 2020. Beck Anxiety Inventory was used to measure the frequency of anxiety symptoms experienced by the individuals. Beck Depression Inventory was used to measure the behavioral manifestations of depression. Maslach Burnout Inventory was used to measure burnout in the workplace. The Perceived Trauma Coping Scale was used to evaluate the perception of coping-up with a traumatic life.

Results: In our study, we found Beck Anxiety Inventory mean score was 13.42±11.28, Beck Depression Inventory mean score was 11.88±9.57, Maslach emotional exhaustion mean score was 15.74±8.19, Maslach depersonalization mean score was 4.96±3.70, and Maslach personal failure mean score was 8.95±4.50, respectively. Finally, the mean Perceived Trauma Coping Scale trauma score was 63.05±12.78, the mean Perceived Trauma Coping Scale future score was 36.34±8.65, and the mean Perceived Trauma Coping Scale elasticity score was 71.94±17.67, respectively.

Conclusion: The findings of the study show the importance of the improvements to be made in reducing the depression and burnout levels of the nurses.

Keywords: Renal, COVID-19, nurse psychology, mental health

ÖZ

Amaç: Pandemi ile mücadelede en önemli faktör sağlık çalışanlarının beden ve ruh sağlığının sağlanmasıdır. Araştırmalar, diyaliz hemşirelerinin yaşadığı ciddi stresörler bulmuş, ancak diyaliz hemşirelerinde diğer hemşirelerden daha az tükenmişlik görülmüştür. Hemodiyaliz hemşirelerinin pandemi sırasında yaşadığı ruhsal sıkıntıların belirlenmesi, alınması gereken önlemlerin belirlenmesi açısından önemlidir. Bu çalışmanın amacı, diyaliz hemşirelerinin pandemi sürecindeki psikolojik şikayetlerini belirlemektir.

Gereç ve Yöntem: Araştırmanın katılımcıları Türkiye'nin farklı illerinde çalışan diyaliz hemşireleridir. Araştırmanın verileri Nisan-Haziran 2020 tarihleri arasında toplanmıştır. Bireyin yaşadığı anksiyete belirtilerinin sıklığını ölçmek için Beck Anksiyete Envanteri kullanıldı. Depresyonun davranışsal belirtilerini ölçmek için Beck Depresyon Envanteri kullanıldı. İşyerinde tükenmişliği ölçmek için Maslach Tükenmişlik Envanteri kullanıldı. Travmatik yaşamla başa çıkma algısını değerlendirmek için Algılanan Travmayla Başa Çıkma Ölçeği kullanıldı.

Bulgular: Çalışmada Beck Anksiyete Envanteri puan ortalaması 13,42±11,28, Beck Depresyon Envanteri puan ortalaması 11,88±9,57, Maslach duygusal tükenme puan ortalaması 15,74±8,19, Maslach Duyarsızlaşma ölçeği puan ortalaması 4,96±3,70 ve Maslach Kişisel Başarısızlık ölçeği puan ortalaması 8,95±4,50 idi. Son olarak, Algılanan Travmayla Başa Çıkma Ölçeği travma odağı puanı ortalaması 63,05±12,78, Algılanan Travmayla Başa Çıkma Ölçeği gelecek odağı puanı ortalaması 36,34±8,65 ve Algılanan Travmayla Başa Çıkma Ölçeği esneklik puanı ortalaması 71,94±17,67 idi.

Sonuç: Araştırmanın bulguları, hemşirelerin depresyon ve tükenmişlik düzeylerinin azaltılmasında yapılacak iyileştirmelerin önemini göstermektedir.

Anahtar Kelimeler: Böbrek hastalıkları, COVID-19, hemşire psikolojisi, ruh sağlığı

Address for Correspondence: Şennur Köse, University of Health Sciences Turkey, Istanbul Training and Research Hospital, Clinic of Nephrology, Istanbul, Turkey
Phone: +90 212 459 64 00 E-mail: drsennurkose@gmail.com ORCID ID: orcid.org/0000-0002-1920-5159

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INTRODUCTION

Healthcare workers who have been working on the frontline since the outbreak of the pandemic are at a great pressure, and risk of an infection is more among the population. Factors such as lack of knowledge about the coronavirus disease-2019 (COVID-19), high education level, having an infected family member or a friend, especially the fear of being infected with the virus to themselves and their colleagues, were found to be associated with the increased anxiety levels (1). Factors such as "infection stigma" toward the healthcare workers, difficult Ethical and moral decisions are made for patients due to the insufficient resources, and fatigue because of long hours spent wearing the personal protective equipment (PPE) cause nurses to experience the serious internal conflicts during this period (2). In these regard, it is underlined that one of the most important factors in fighting this pandemic is to ensure the physical and mental health of the healthcare workers stable (3).

Hemodialysis incharge-nurses are actively involved in the treatment of patients receiving a regular dialysis treatment due to the kidney failure. Hemodialysis nursing, which requires special training and experience, is generally carried out in the hemodialysis units which are very busy and crowded (4). After the pandemic, the functioning of the hemodialysis units has also been greatly affected. Patients with the kidney failure, defined as a risk group in terms of COVID-19, need to be physically present in the hemodialysis units to maintain their body functions (5). It is very difficult to create the social distance environment required to avoid the spread of COVID-19 virus in hemodialysis units, so 35-84% infection rates have been reported among the dialysis unit workers. Also, COVID-19 infection was less common in the patients who were on dialysis at home (6). In this pandemic conditions, it is difficult to maintain a balance between providing a good nursing service and keeping patients receiving the dialysis treatment safely.

High levels of depression and anxiety were detected in nurses working in the different countries of the world (7,8). For this reason, interventions to protect the mental health of healthcare professionals are marked (9). It has been shown that improving the working conditions of the nurses, mindfulness-based meditations, online group therapies, and training psychiatric nurses in this regard have been beneficial (10). Studies on healthcare workers are useful for determining the appropriate policies and identifying the necessary psychological well-being interventions (2). It is known that the mortality of the patients that the hemodialysis incharge-nurses are responsible for is high, in terms of the COVID-19 (11). For this reason, we think that they work in a stressful environment in terms of their own health and the patient group they work with, and therefore they face the risk of experiencing the serious mental problems. Studies have found that the serious stressors experienced by the hemodialysis incharge-nurses, but renal nurses report less burnout than the other nurses. Therefore, it is known that the hemodialysis incharge-nurses are generally good at coping-up with the workplace stressors (12).

In our study, we aimed to determine the psychological complaints associated with a COVID-19 in the hemodialysis incharge-nurses. We investigate the hypothesis that anxiety, depression, and burnout levels are high in the hemodialysis incharge-nurses, and there is a negative relationship between the perception of coping-up with a trauma and the psychological parameters. In addition, we aim to determine whether the social and physical conditions are effective in psychological complaints in the hemodialysis incharge-nurses.

METHODS

Participants and Study Design

The authors have attempted to reach the hemodialysis incharge-nurses who work in the different provinces of Turkey. A study form (questionnaire) was sent to the hemodialysis incharge-nurses thru social media and mail groups. The data of the participants who volunteered to participate in the study were collected in 3 months between April 2020 and June 2020. At the beginning of the study, participants' online consent was obtained through a consent form containing information about the study.

Measurement Tools

Sociodemographic data form was used for questioning basic information, such as age, gender, marital status, medical history, smoking, and alcohol use. In addition to these, we aimed to question the mental status after the COVID-19, and its relation to several parameters such as maintaining a healthcare service, approval from the society, fear of infection, and spread among the community.

Beck Anxiety Inventory (BAI) was used to measure the frequency of anxiety symptoms experienced by the individuals (13). It is a Likert-type self-rating scale scored between 0 and 3, consisting of 21 items. The higher the total score, higher the anxiety experienced by the person. The results are evaluated as follows: 8-15 points: mild anxiety, 16-25 points: moderate anxiety, 26-63 points: severe anxiety.

Beck Depression Inventory (BDI) was used to measure the behavioral manifestations of depression (14). It is designed

to measure the severity of the depression and to monitor changes with a treatment. Depression-specific behaviors and symptoms were described, and each sentence was scored between 0 and 3. It consists of 21 items and the items are listed from mild to severe. Patients are asked to mark the statements best describe their current condition, and the result is obtained by the sum of these scores. The result of the scale is interpreted as: 0-9: minimal, 10-16: mild, 17-29: moderate, 30-63: severe.

The Maslach Burnout Inventory (MBI) was used to measure the workplace burnout (15). MBI is a seven-point Likert-type scale. This measurement tool comprises of 22 items and three subscales. Subscales such as: 1. emotional exhaustion: This subdimension of the scale expresses the feelings of being consumed by the one's job or occupation and being overburdened, 2. depersonalization: This subdimension of the scale defines the deprivation of emotion toward the people to whom the person serves, without considering that the people concerned are peculiar beings, 3. personal failure: This subdimension of the scale expresses the feelings of a person working with the people to overcome the situation with a sufficient success (16).

The Perceived Ability to Cope with Trauma (PACT) scale was used to evaluate the perception of coping-up with the traumatic life (17). The scale is composed of 20 items that ask participants to rate their ability to use the different coping strategies on a seven-point scale (1= not at all able, 7= extremely able). Factor analysis that has been made by the Bonanno et al. (17) indicated the presence of the two subscales: Forward Focus and Trauma Focus. Forward Focus (12 items, α=0.91) was explained as the component that defines the coping abilities related to maintaining plans and goals, attending to the needs of others, being optimistic, staying calm, reducing the painful emotions, and being able to laugh. The Trauma Focus subscale (eight items, α=0.79) examines the ability to experience the emotional and cognitive significance of a possible traumatic event. These subscales were independently related to better the adjustment, and each scale moderated the effect of a trauma exposure. Last, flexibility is another subdimension of the PACT, which is calculated by the difference between the sum and polarity of the other two subscales.

Statistical Analysis

The compliance of the variables to a normal distribution was examined using the histogram graphics and the Kolmogorov-Smirnov test. Mean, standard deviation, and median values were used while presenting the descriptive analyzes. Categorical variables were compared using the Pearson's chi-squared test. In cases where the data did not show a normal distribution, groups of two were evaluated with the Mann-Whitney U test, and groups >2 were evaluated with the Kruskal-Wallis test. Spearman correlation test was used in analyzing the measurement data with each other. The situations where the p-value was <0.05 were evaluated as statistically significant.

Ethical Considerations

The study was performed in accordance with the Declaration of Helsinki, and approval for this study was obtained from the Clinical Research Ethics Board of University of Health Sciences Turkey, Istanbul Training and Research Hospital (decision no: 2454, date: 26.06.2020). The board decided that the need for informed consent was not necessary.

RESULTS

Out of 129 people, a total of 111 females (86.05%) and 18 males (13.5%) participated in the study. The average age of the participants was determined as 27.80 (±7.48) years. The average number of the children owned was 0.3 (±0.7), the average number of people living in the same household was 4.12 (±2.88), and the average length of the professional experience was 69.58 (±212.47) months. The sociodemographic characteristics of the participants are detailed in Table 1.

A total of 16 of the participants (12.4%) had a history of psychiatric disorders, whereas 113 people (87.60%) did not. Considering the diagnoses of the psychiatric disorders in the medical history, six people had anxiety disorder, five people had major depression, one person had obsessive compulsive disorder, and one person had bipolar disorder. Eleven people had a family history of psychiatric disorders. While four people had a history of suicide before the COVID-19 became pandemic, two people had attempted suicide after the COVID-19 pandemic. While 60 people (46.51%) said that they were given enough information about the COVID-19, 63 people (48.84%) said that they were partially given, and 6 people (4.65%) stated insufficient information. While they said that they could reach enough materials while working with the 62 people, 58 people stated that they could partially reach, and 9 people stated that they could not reach enough materials. Also, 28 people had physical illnesses. Access to the PPE was found to be 62 (4.65%), 58 (44.96%), and 9 (6.98%), respectively as, sufficient, partially sufficient, and insufficient.

When examining whether there were people with a COVID-19 in the family of the participants, it was found that eight people (6.2%) had COVID-19 in their family, four of them were followed up on an outpatient clinic, three were

treated in the inpatient service, and one person was treated in intensive care unit. In addition, eight of its participants stated that a relative died due to the COVID-19. During the pandemic process, some participants limited their contact with their families and could not be in close contact with them for a while. A total of 11 people (8.53%) did not fully isolate themselves, 40 people (31.01%) said that they lived in the same environment but had a reduced contact, 20 people (15.50%) lived in a different environment, but they met their family, and 58 people (44.96%) completely isolated themselves.

During this pandemic period, 94 (72.87%) of the participants were actively continuing to provide the healthcare services. The results of the psychological factors such as: fear of getting sick, fear of infecting someone else, being affected by the appreciation of the society, the possibility of seeking a psychological help, and the effect of the pandemic on their personal development are given in Table 2.

The BAI mean score was 13.42±11.28, BDI mean score was 11.88±9.57, Maslach emotional exhaustion mean score was 15.74±8.19, Maslach depersonalization mean score was 4.96±3.70, and Maslach personal failure mean score was 8.95±4.50, respectively. Finally, the mean PACT trauma score was 63.05±12.78, the mean PACT future score was 36.34±8.65, and the mean PACT elasticity score was 71.94±17.67, respectively. The mean BAI scores, mean BDI scores, mean scores of the MBI and its subscales, and the mean scores of the PACT and its subscales were compared with the nonparametric variables. In the comparison made by the gender, the mean BAI mean scores were found to be higher in women (14.52) than the men (6.61) (p=0.002). In the comparison made according to smoking, the mean BAI scores of nonsmokers (14.75) were found to be higher than those of the smokers (11.68) (p=0.002). BDI mean scores of those who provide healthcare services (12.76) were found to be higher than those who did not (9.51) (p=0.034). The average BDI score was found to be higher in patients with a family history of the psychiatric disorders (20.00) than those without (11.12) (p=0.006), again, the average BAI score was

Table 1. Sociodemographic characteristics of participants

		Number (n)	Percentage (%)
Gender	Female	111	(86.05)
	Male	18	(13.95)
Marital status	Single	87	(67.44)
	Married	33	(25.58)
	Divorced	5	(3.88)
	Other	4	(3.10)
Living with	Alone	10	(7.75)
	Nuclear family	70	(54.26)
	Extended family	5	(3.88)
	Housemate	25	(19.38)
	Other	19	(14.73)
Smoking	No	73	(56.59)
	Yes	56	(43.41)
Change in the amount of smoking after COVID-19	Decrease	10	(7.75)
	Same	97	(75.19)
	Increase	22	(17.05)
Alcohol consumption	No	125	(96.90)
	Yes	4	(3.10)

COVID-19: Coronavirus disease-2019

Table 2. Factors that mentally affecting the participants

		Number (n)	Percentage (%)
Providing health care	No	35	(27.13)
	Yes	94	(72.87)
Mental difficulty during health service	No	30	(23.26)
	Partially	52	(40.31)
	Reasonable	32	(24.81)
	High	15	(11.63)
Fear of infection	No	17	(13.18)
	Partially	62	(48.06)
	Yes	50	(38.76)
Community appreciation	No	51	(39.53)
	Partially	45	(34.88)
	Yes	33	(25.58)
Being affected by the lack of appreciation	No	50	(38.76)
	Partially	42	(32.56)
	Yes	37	(28.68)
Fear of infecting someone	No	23	(17.83)
	Partially	59	(45.74)
	Yes	47	(36.43)
Psychological consultation or help	No	35	(27.13)
	Partially	47	(36.43)
	Yes	47	(36.43)
Personal development	Negative	37	(28.68)
	Same	45	(34.88)
	Positive	47	(36.43)

found in those with a family history of the psychological disorders (20.64) compared to those without (12.75) was higher (p=0.058). The mean PACT future score was higher in those with a medical illness history (39.29) compared to those without a medical illness (35.52) (p=0.051).

In the comparison made according to marital status, the mean PACT future score was found to be higher in the divorced patients (44.20) than in those who were married (33.85) (p=0.047). The PACT flexibility mean scores were found to be higher in the divorced patients (88.40) than the married ones (66.61) (p=0.038). In the comparison made according to whom they live with, the Maslach personal failure mean score was found to be lower in those living alone (9.50) than those living with a nuclear family (9.03), and those living with others (10.00) (p=0.030).

The BDI mean score was higher (p=0.004) in those with insufficient PPE (17.11) than those having partially (13.28) and sufficient PPE (9.81). The mean BAI score was found to be lower in those who think they have no mental difficulty in providing the health services (8.60) than those who think they have partial (13.04), reasonable (17.75), and high difficulties (15.13) in providing the health services (p=0.002). Similar results have been obtained from the BDI scores: the mean BDI score was found to be lower in those who think that there is no mental difficulty (8.63), those who think it is partially (10.54), those who think they have a reasonable difficulty (16.19), and those who think they always have difficulty (13.80) (p=0.007). The comparison of the groups affected by the feeling of not being appreciated enough by the society, and those who were not affected are given in Table 3. The mean BDI scores of those who had the fear of transmitting the disease to their relatives (10.79) were lower than those who partially survived (11.42), and those who did not (15.26) (p=0.0046).

When it was investigated whether there was a person or a center that participant could consult or get a psychological help, it was seen that there was a statistical significance between yes (7.60), partially (13.09), and no (16.00) answers in terms of the BDI scores (p=0.008). Also, the MBI score was lower in those who said "yes" (17.16) than those who said "partially" (13.96), and "no" (15.63) (p=0.008). The relationship of impact of the pandemic on a personal development with the psychological factors is shown in Table 4. The mean PACT future scores of those who had the fear of transmitting the disease to their relatives (34.45) were lower than those who had a moderate fear (37.81), and those who had no fear (36.43) (p=0.005).

A highly significant negative correlation was found between the MBI scores and PACT trauma scores (r: -0.388, p<0.001), a significant negative relationship was found between the MBI depersonalization scores and PACT scores (r: -0.217, p=0.013), a highly significant negative correlation was found between the MBI personal failure scores and PACT scores (r: -0.373, p<0.001). There was a significant positive relationship between the MBI depersonalization scores and PACT future scores (r: 0.175, p=0.048). Details of the correlations between the scales have been presented in Table 5.

Table 3. Comparison of groups according to the state of being affected by the appreciation of the society

	The feeling of not being appreciated enough from the society									p
	No			Partially			Yes			
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	
BAI score	11.44	±11.93	7.00	11.95	±8.75	10.50	17.76	±12.02	14.00	0.009
BDI score	10.36	±10.65	8.50	12.38	±8.23	11.00	13.35	±9.42	13.00	0.136
MBI-EE	16.12	±8.43	17.50	13.62	±7.77	13.00	17.62	±8.02	19.00	0.085
MBI-D	5.24	±3.36	5.00	4.05	±3.67	2.50	5.62	±4.07	5.00	0.067
MBI-PF	8.50	±3.66	8.00	9.60	±5.84	9.00	8.81	±3.75	9.00	0.639
PACT-TF	65.36	±13.24	68.00	61.26	±14.00	65.00	61.97	±10.33	63.00	0.172
PACT-FF	37.76	±10.07	37.00	36.02	±7.71	33.50	34.78	±7.39	35.00	0.277
PACT-F	74.44	±20.50	74.00	71.05	±16.35	66.00	69.57	±14.78	70.00	0.434

Kruskal-Wallis test, SD: Standard deviation, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, MBI-EE: Maslach Burnout Inventory-Emotional Exhaustion, MBI-D: Maslach Burnout Inventory Depersonalization, MBI-PF: Maslach Burnout Inventory-Personal Failure, PACT-FF: Perceived Ability to Cope with Trauma scale-Forward Focus, PACT-TF: Perceived Ability to Cope with Trauma scale-Trauma Focus, PACT-F: Perceived Ability to Cope with Trauma scale-Flexibility

DISCUSSION

Burnout syndrome is a complex phenomenon associated with a stressful work environment. It was first described by the Freudenberger for healthcare workers, and it is defined as a condition that results from working for a long time in the environments with the intense emotional demands, accompanied by the symptoms such as: physical wear, negative attitudes toward employees, and different parts of the life (18). The most prominent features of burnout, along with a physical, emotional, and mental signs and symptoms include fatigue, lack of motivation, helplessness and hopelessness, negative attitude toward others, and active withdrawal from the immediate environment (19). Many stress factors may cause burnout in the hemodialysis incharge-nurses: Providing care for patients with an end-stage renal disease, working in a technical environment that requires frequent physical effort, coping-up with the increasing expectations of the patients, complex dialysis techniques, complex modern dialysis machines, intensive activities during the initiation and termination of dialysis sessions, life-threatening complications, implementation of infection control policies and procedures, Emergency interventions, an increasing number of the patients and job demands, verbal and/or physical conflicts (20).

In a study conducted in Turkey, when the scores of the MBI subdimensions of the hemodialysis incharge-nurses were evaluated, the emotional exhaustion score was found to be

Table 4. Comparison of groups according to the status of the pandemic affecting personal development

	Personal development									p
	Negative			Same			Positive			
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	
BAI score	16.38	±12.80	12.00	11.22	±9.60	9.00	13.19	±11.23	12.00	0.169
BDI score	16.76	±10.74	16.00	10.20	±8.47	9.00	9.64	±8.32	8.00	0.002
MBI-EE	16.22	±8.99	17.00	16.00	±7.95	17.00	15.11	±7.90	15.00	0.748
MBI-D	4.49	±3.54	4.00	5.20	±3.71	5.00	5.11	±3.86	5.00	0.637
MBI-PF	9.51	±5.38	8.00	8.64	±4.30	9.00	8.79	±3.94	9.00	0.995
PACT-TF	63.54	±13.43	65.00	63.42	±12.49	66.00	62.32	±12.78	65.00	0.837
PACT-FF	35.68	±9.30	35.00	37.24	±8.66	34.00	36.00	±8.21	36.00	0.725
PACT-F	70.38	±19.59	70.00	73.29	±17.70	66.00	71.87	±16.28	72.00	0.727

Kruskal-Wallis test, SD: Standard deviation, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, MBI-EE: Maslach Burnout Inventory-Emotional Exhaustion, MBI-D: Maslach Burnout Inventory-Depersonalization, MBI-PF: Maslach Burnout Inventory-Personal Failure, PACT-FF: Perceived Ability to Cope with Trauma scale-Forward Focus, PACT-TF: Perceived Ability to Cope with Trauma scale-Trauma Focus, PACT-F: Perceived Ability to Cope with Trauma scale-Flexibility

Table 5. Correlation analysis of Beck Anxiety Inventory, Beck Depression Inventory, Maslach Burnout Inventory, and Perceived Ability to Cope with Trauma

	BAI	BDI	MBI-EE	MBI-D	MBI-PF	PACT-FF	PACT-TF	PACT-F
BAI	1							
BDI	0.725**	1						
MBI-EE	-0.031	-0.064	1					
MBI-D	-0.019	-0.043	0.733**	1				
MBI-PF	0.073	0.059	0.292**	0.304**	1			
PACT-FF	0.106	0.077	-0.388*	-0.217**	-0.373*	1		
PACT-TF	0.158	0.089	0.096	0.175**	-0.047	0.207*	1	
PACT-F	0.143	0.099	0.047	0.146	-0.102	0.271**	0.959**	1

Spearman Correlation test, *<0.01, **<0.05, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, MBI-EE: Maslach Burnout Inventory-Emotional Exhaustion, MBI-D: Maslach Burnout Inventory-Depersonalization, MBI-PF: Maslach Burnout Inventory-Personal Failure, PACT-FF: Perceived Ability to Cope with Trauma scale-Forward Focus, PACT-TF: Perceived Ability to Cope with Trauma scale-Trauma Focus, PACT-F: Perceived Ability to Cope with Trauma scale-Flexibility

25.08±6.65 (medium), depersonalization score 9.63±3.19 (low), and personal success score 30.29±3.60 (high), respectively (21). In another study, the mean emotional exhaustion score was 16.25, the mean depersonalization score was 4.67, and the mean personal achievement score was 22.83, respectively (22). When the results of these studies are evaluated together, it could be said that the burnout status of the hemodialysis incharge-nurses is like those working in the other clinics. In another study, it was reported that there was no significant relationship between the working unit and burnouts (23). The reason for different results between the unit and burnouts may be related to the working conditions in the specific unit, staff's morale levels, and the lack of clear and understandable job descriptions (24). Negative factors such as the increasing number of the elderly patients, increasing care demands, extra responsibilities, staff shortage, and overworking, may affect the nurses physically and mentally, but also leads to burnout (25). Most of our participants are women, as the nursing profession is generally preferred by the women. In addition, it is known that the psychological problems related to COVID-19 are more common in the female healthcare workers (26). However, it is not possible to explain the high rates we obtained in our study only with this data.

Hemodialysis incharge-nurses are a group of healthcare workers that deal with the treatment of patients receiving a dialysis and have received training in this field. Patients receiving the hemodialysis are connected to dialysis machines for at least four hours for three days a week due to a chronic disease process and are followed up by the same nurse group for years. In addition, they also serve distressed patients with an acute kidney failure. In the study conducted by Klersy et al. (27), the relationship between the burnout and the quality of life of physicians and nurses working in the hemodialysis unit was examined, and it was generally found to be lower in both the groups. However, it has been observed that the nurses experience more burnouts than the doctors. Karkar et al. (28) aimed to determine the type and level of the stress, stress management skills, work performance, and the amount of burnout of hemodialysis incharge-nurses. They found mild stress and moderate burnouts in most hemodialysis incharge-nurses in their study. Malfunction in the dialysis machines, needle sticks, challenging patient groups, and long working hours are among the stressful reasons (28). After the COVID-19 pandemic, this workload increased exponentially, and they had to serve patients with the COVID-19 in close contact with a PPE, and more frequent complications, and the need for an intensive intervention emerged in these patients with the poor hemodynamics. Despite the increase in the workload, the lack of educated new staff to help them significantly increased their anxiety risk of infecting themselves, their friends, and their families. It is known that the nurses are on the verge of exhaustion during the COVID-19 pandemic (29). A study conducted in the early days of the epidemic found a relationship between the higher anxiety levels and the lack of knowledge about COVID-19 among the healthcare workers, higher education level, and having infected family members or friends. Also, this study highlights how vulnerable health workers working in the front line are going through a stress and depression (1).

In a study by Karataş et al. (30), a significant amount of anxiety and depression were observed in healthcare workers serving in the hemodialysis units during the COVID-19 pandemic. It was determined that the gender, occupation, type of hospital, frequency of encountering with a COVID-19 infected patient, and their status of serving these patients affected their anxiety and depression levels (30). In addition, the anxiety of the patients' group in which the hemodialysis incharge-nurses work has increased compared to before. This patient group, to whom they provide an emotional support most of the time, has a fear of getting sick and knows that the risk of death is higher than the general population. Furthermore, due to the more complex course of the COVID-19 symptoms in this group, the diagnosis may be delayed, the risk of transmission increases, and the dialysis centers have been defined as the risky areas. The fact that the patients whom hemodialysis incharge-nurses have followed for years became infected with COVID-19, and sometimes the death of the patient significantly increases anxiety, and the feeling of losing people they know creates depression among the healthcare workers. The decrease in the social activities and support, uncertainties about the pandemic, and being away from the family elders and children increase the risk of physical and mental burnout syndrome in this process. The fact that we found a significant decrease in the depression and burnout levels of the nurses who knew that they could receive a psychological support shows the importance of interventions on this issue.

This study included the nurses working in as many dialysis centers as possible. The most important limitation of our study is that the data is obtained online. The study was carried out during the period of partial quarantine due to the COVID-19 pandemic. For this reason, an online questionnaire with a volunteer sample was applied to collect the data quickly. However, the use of an online questionnaire with a volunteer sample results in the biased

responses and limits the generalizability of the findings.

This study is limited in scope. Most respondents are from Istanbul, limiting the generalization of our findings to regions less affected by this pandemic. In addition, the dialysis centers are not separated in terms of a patient density with a COVID-19 infection. All the hemodialysis incharge-nurses in the dialysis centers within the scope of the research were reached. Therefore, the sample of the study increases the representativeness of the findings.

As with all the survey studies, social desirability and recall bias are potential limitations of this study. Also, the study was cross-sectional, lacking a longitudinal follow-up. Therefore, further research will be required for the long-term impact of these symptoms. It is unclear whether the findings are a direct result of the COVID-19, as other factors have been neglected. However, this study was done with the many different healthcare professionals. Therefore, the results are likely to be valid internally, and the relationships among common variables are likely to be reliable.

CONCLUSION

During the COVID-19 pandemic, the healthcare workers made an extraordinary effort and performed critical tasks. Therefore, in the fight against this pandemic, the protection of the physical and mental health of the healthcare workers has become extremely important.

Hemodialysis incharge-nurses are actively involved in the treatment of the patients undergoing a regular dialysis treatment due to a renal failure. Therefore, hemodialysis incharge-nurses are in close contact with the patients for a long time, and they establish the emotional bonds with them during the treatment process and observe them throughout the treatment process. Although working under the conditions of the COVID-19 pandemic further increases the anxiety and burnout symptoms of the healthcare workers, it was seen in this study that the hemodialysis incharge-nurses were successful in coping-up with these problems. However, the hemodialysis incharge-nurse group, who works hard, needs to be supported due to this troublesome process and the uncertain conditions caused after it. To provide better health care to the patients receiving a dialysis, it is extremely important to keep the mental health and motivation of the healthcare workers at the highest level, and to manage their feelings of exhaustion and anxiety throughout the period.

ETHICS

Ethics Committee Approval: The study was performed in accordance with the Declaration of Helsinki, and approval for this study was obtained from the Clinical Research Ethics Board of University of Health Sciences Turkey, Istanbul Training and Research Hospital (decision no: 2454, date: 26.06.2020).

Informed Consent: The board decided that the need for informed consent was not necessary.

Authorship Contributions

Concept: Ş.K., B.S., Ç.K., Design: Ş.K., B.S., Ç.K., Data Collection or Processing: Ş.K., B.S., Ç.K., Analysis or Interpretation: Ş.K., B.S., Ç.K., Literature Search: Ş.K., B.S., Ç.K., Writing: Ş.K., B.S., Ç.K.

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Research

Acute Appendicitis in Istanbul: An 8-year Retrospective Cohort Study

İstanbul'da Akut Apandisit İnsidansı: 8 Yıllık Retrospektif Kohort Çalışması

Ülkü Nur Kırman[1], Betül Nur Keser[1], Hüseyin Akten[2], Nuray Çolapkulu[3], Ahmet Sürek[4], Candaş Erçetin[5], Hasan Fehmi Küçük[6], Acar Aren[7], İnanç Şamil Sarıcı[8], Fikret Ezberci[9], Berk Gökçek[10], Fazilet Erözgen[11], Ali Fuat Kaan Gök[12], Osman Şimşek[13], Orhan Alimoğlu[3]

[1]Istanbul Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Turkey
[2]Istanbul Medeniyet University Faculty of Medicine, Istanbul, Turkey
[3]Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Clinic of General Surgery, Istanbul, Turkey
[4]University of Health Sciences Turkey, Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Clinic of General Surgery, Istanbul, Turkey
[5]University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital, Clinic of General Surgery, Istanbul, Turkey
[6]Istanbul Kartal Dr. Lutfi Kirdar City Hospital, Clinic of General Surgery, Istanbul, Turkey
[7]Istanbul Kent University Vocational School of Health Services, Department of Operating Room Services, Istanbul, Turkey
[8]University of Health Sciences Turkey, Istanbul Kanuni Sultan Suleyman Training and Research Hospital, Clinic of General Surgery, Istanbul, Turkey
[9]University of Health Sciences Turkey, Istanbul Umraniye Training and Research Hospital, Clinic of General Surgery, Istanbul, Turkey
[10]University of Health Sciences Turkey, Istanbul Prof. Dr. Cemil Tascioglu City Hospital, Clinic of General Surgery, Istanbul, Turkey
[11]University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of General Surgery, Istanbul, Turkey
[12]Istanbul University, Istanbul Faculty of Medicine, Department of General Surgery, Istanbul, Turkey
[13]Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of General Surgery, Istanbul, Turkey

ABSTRACT

Objective: Acute appendicitis (AA) is the most common cause of acute abdominal and emergency surgery worldwide. Over the past decades, the incidence of AA has been increasing, and with minimally invasive technology, treatment modalities are changing. This study aimed to examine the incidence of AA in Istanbul, Turkey over the years and seasons and investigate the rates of open and laparoscopic appendectomy (LA).

Methods: This retrospective cohort study reviewed the archives of the Turkish Association of Trauma and Emergency Surgery between January 2012 and December 2019. Data from 11 tertiary hospitals with heavy patient flow from Istanbul were included. Descriptive statistics and univariate analysis of variance tests were performed. Statistical significance was defined as p-values of <0.05.

Results: A total of 39,932 AA cases were evaluated. The cumulative incidence of AA in Istanbul was 123/100,000 between 2012 and 2019, with increasing incidence over the years (p=0.01). LA rates have increased, and 68.5% of the cases were laparoscopically managed in 2019. AA rates were slightly higher in spring than in other seasons (p>0.05).

Conclusion: The incidence rate of AA and its laparoscopic management are significantly increasing in Istanbul.

Keywords: Acute appendicitis, epidemiology, incidence, incidence rate, laparoscopic appendectomy

ÖZ

Amaç: Akut apandisit (AA), tüm dünyada en sık görülen akut karın ve acil cerrahi nedenidir. Son yıllarda, AA insidansı artmakta ve gelişen minimal invaziv teknolojiyle birlikte tedavi şekli değişmektedir. Bu çalışmada, İstanbul'daki AA olgularının yıllara ve mevsimlere göre insidansını belirlemeyi, ve açık ve laparoskopik apendektomi (LA) oranlarını incelemeyi amaçladık.

Address for Correspondence: Ülkü Nur Kırman,Istanbul Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Turkey
Phone: +90 506 124 52 96 E-mail: ulkunurkirman@gmail.com ORCID ID: orcid.org/0000-0001-8275-7047

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Gereç ve Yöntem: Bu retrospektif çalışmada, Ulusal Travma ve Acil Cerrahi Derneği'nin arşivinde yer alan Ocak 2012-Aralık 2019 tarihleri arasındaki veriler incelendi. İstanbul'un en fazla hasta yoğunluğuna sahip 11 üçüncü basamak hastane çalışmaya dahil edildi. Tanımlayıcı istatistik testleri ve tek değişkenli varyans analizi (UNIANOVA) uygulandı. İstatistiksel anlamlılık p<0,05 olarak kabul edildi.

Bulgular: Bu çalışmada 39.932 AA olgusu değerlendirildi. İstanbul'da 2012-2019 yılları arasında AA'nın kümülatif insidansı 123/100.000 idi ve AA'nın insidans hızı yıllar içinde artış gösterdi (p=0,01). LA oranı artmaktadır ve bu oran 2019 yılında %68,5'e ulaşmıştır. AA'nın görülme oranı ilkbaharda diğer mevsimlere göre hafif yüksektir (p>0,05).

Sonuç: İstanbul'da AA insidans hızı ve LA uygulanma sıklığı artmaktadır.

Anahtar Kelimeler: Akut apandisit, epidemiyoloji, insidans, insidans hızı, laparoskopik apendektomi

INTRODUCTION

Acute appendicitis (AA) is the most common cause of acute abdominal and emergency surgery worldwide, and the lifetime risk of developing AA is 8.6% in males and 6.9% in females (1). The global incidence of AA is 100-206 per 100,000 person-years annually and increasing, especially in newly industrialized populations (2).

AA develops more frequently in the second and third decades of life, and better socioeconomic status is associated with its lower incidence rates (3). AA can occur throughout the year. No consensus was achieved on the seasonal variation of AA; however, the majority of the epidemiological studies reported that the seasons with their highest and lowest incidence are summer and winter, respectively (4-7).

Minimally invasive AA management was first described and performed in the early 80s and gained popularity over the decades (8,9). With increasing experience, laparoscopic appendectomy (LA) has significantly lowered morbidity and complication rates (9).

To the best of our knowledge, this is the first epidemiologic study that examined AA in Istanbul, which is the most densely populated city in Turkey. This study aimed to determine the incidence and incidence rate of AA in Istanbul over the years and seasons and investigate the rates of LA.

METHODS

Participants and Data Collection

This retrospective cohort study reviewed the archive of the Turkish Association of Trauma and Emergency Surgery, and the data of the Monthly Marmara Region Trauma and Emergency Surgery Meetings between January 2012 and December 2019 were enrolled. Data from 11 tertiary hospitals with heavy patient flow from Istanbul was evaluated for selection and patients older than 18 years who underwent surgery for AA were included. The number of AA cases and surgical approaches were identified.

Ethical Considerations

This study was approved by the Ethics Committee of Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research (decision no: 2019/0308, date: 18.09.2019), and permissions were received from the included hospitals in the study.

Statistical Analysis

International Business Machines Statistical Package for the Social Sciences version 20 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Missing data were managed using the mean imputation method. Incidence, incidence rate, and percentage calculations were performed. For incidence rate calculations, census data of the districts of the hospitals were reached in the determined time interval. The Shapiro-Wilk test was performed to test normality. Univariate analysis of variance was accordingly implemented. A two-tailed p-value of <0.05 was considered statistically significant.

RESULTS

A total of 39,932 AA cases were evaluated. In 2012-2019, the average incidence rate of AA was 123 per 100,000 person-years, which was significantly increasing (p=0.01) (Figure 1, 2). The total LA rate was 43.77%, and the rate increased from 31.8% up to 68.5% in 8 years (Figure 3).

The incidence of AA was the highest in spring and the lowest in winter (Table 1). However, no significant association was detected between the incidence and seasons (p>0.05). Of the total cases, 1.8% (n=712) were perforated AA, which tended to decrease (Figure 4). The highest incidence of perforated AA was seen during winter and lowest in the fall, though this was statistically insignificant (p>0.05).

Table 1. Seasonal distribution of AA and perforated AA in Istanbul

	AA [n (%)]	Perforated AA [n (%)]	p
Spring	10,327 (25.9%)	166 (23.3%)	>0.05
Summer	10,066 (25.2%)	166 (23.3%)	>0.05
Fall	10,050 (25.2%)	163 (22.9%)	>0.05
Winter	9,489 (23.8%)	217 (30.5%)	>0.05
Total	39,932 (100.0%)	712 (100.0%)	>0.05

AA: Acute appendicitis

DISCUSSION

The present study, with its large sample size, comprehensively overviews the AA incidence and LA rates in Istanbul for 8 years. In Istanbul, the cumulative incidence rate of AA in Istanbul is 123/100,000 in 2012-2019 and the incidence rate increased over the years. The presence of a gap in the literature on population-based studies in our country prohibits the conclusion of epidemiological assumptions for AA incidence in Turkey. A study that included 1,871 AA cases in Kars (an eastern city of Turkey) between 2004 and 2007 revealed that the average incidence rate of AA was 150/100,000 (10). Ferris et al. (2) conducted the largest meta-analysis for global incidence of AA between 1950 and 2015. The incidence of AA has been remaining constant in North America and Europe during the 21st century, while the rate is increasing in the Middle East, Asia, and South America. In the study, the pooled incidence was 160/100,000 in Turkey.

LA rates are significantly rising in Istanbul. The average was 43.77% between 2012 and 2019. The rate increased from 31.81% in 2012 to 68.51% in 2019. A comprehensive study that examined the 66,990 AA cases in New York between 2009 and 2014 revealed a 77.7% LA rate (11). Another study from Ireland that included 23,684 appendectomies between 2014 and 2017 revealed a 77.6% LA rate (12). After gaining experience on laparoscopic procedures with improved infrastructures, increased LA rates may be predicted for the future.

The majority of studies revealed that the highest and lowest incidence of AA is in summer and winter, respectively (4-7). Environmental factors, such as gastrointestinal infections, air pollution exposure, excess alcohol consumption, and a high carbohydrate diet with low fibers may lead to AA in summer (13). Our study revealed the highest incidence rate of AA in spring, unlike most studies that reported summer with the highest incidence. During summer, majority of the residents leave Istanbul for their home cities or vacation, which may be the reason for the decreased rates of AA in these months. The incidence rate of perforated AA varies between 8.3% and 46% in the literature, and the perforated AA incidence has not been precisely linked to seasonal variations (5,6,14). Reinisch et al. (15) reported the association between non-ambient temperature and complicated AA. Our study revealed a 1.8% perforated AA rate, and cases mostly occurred in winter; however, no significant association was found between the seasons and perforated AA incidence (p>0.05).

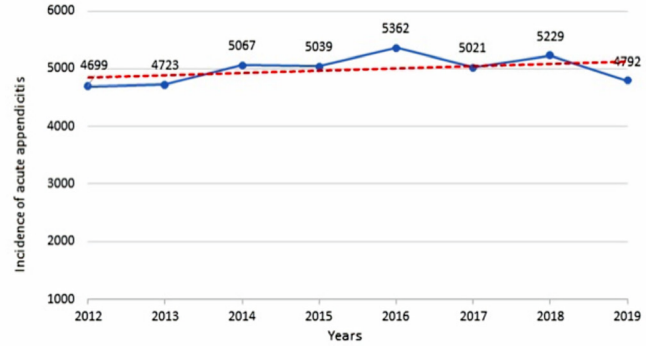

Figure 1. Incidence of acute appendicitis cases in Istanbul between 2012 and 2019

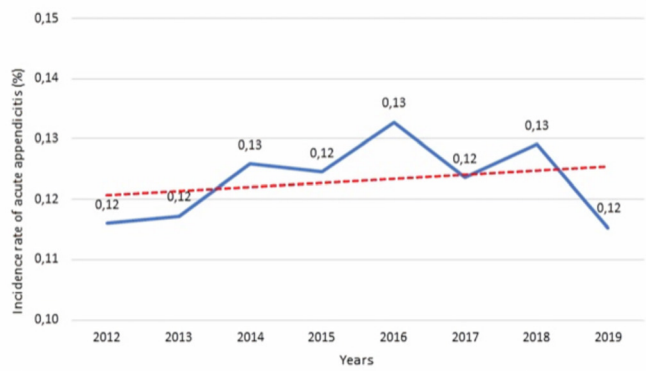

Figure 2. The incidence rate of acute appendicitis cases in Istanbul between 2012 and 2019

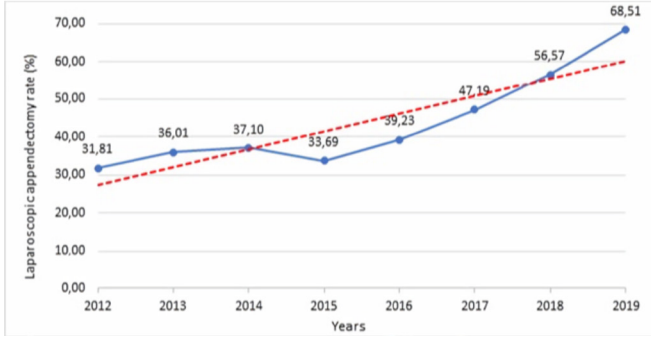

Figure 3. Laparoscopic appendectomy rate in Istanbul between 2012 and 2019

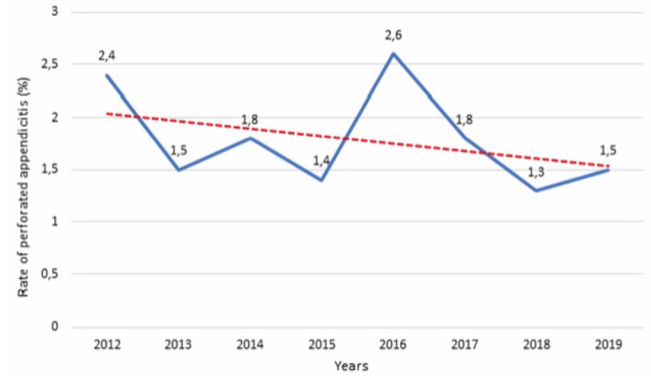

Figure 4. Rate of perforated appendicitis in Istanbul between 2012 and 2019

The limitation of our study includes the missing demographic data of patients in the medical records obtained from the archives. The strengths of our study include its multi-centric and population-based design with a large sample study.

CONCLUSION

Our study is the first and most comprehensive epidemiologic study on AA in Istanbul. The incidence rate of AA in Istanbul is compatible with the western regions of the globe. Rapidly increasing rates of LA revealed improvements in the treatment modalities and experiences.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research (decision no: 2019/0308, date: 18.09.2019), and permissions were received from the included hospitals in the study.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medikal Practices: Ü.N.K., B.N.K., H.A., N.Ç., A.S., C.E., H.F.K., A.A., İ.Ş.S., F.E., B.G., Fa.E., A.F.K.G., O.Ş., O.A., Concept: Ü.N.K., B.N.K., N.Ç., Design: Ü.N.K., B.N.K., N.Ç., Data Collection or Processing: Ü.N.K., B.N.K., H.A., N.Ç., A.S., C.E., H.F.K., A.A., İ.Ş.S., F.E., B.G., Fa.E., A.F.K.G., O.Ş., O.A., Analysis or Interpretation: Ü.N.K., B.N.K., N.Ç., Literature Search: Ü.N.K., B.N.K., H.A., N.Ç., Writing: Ü.N.K., B.N.K., H.A., N.Ç., A.S., C.E., H.F.K., A.A., İ.Ş.S., F.E., B.G., Fa.E., A.F.K.G., O.Ş., O.A.

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Research

Peritoneal Dialysis-related Peritonitis: Microbiological Profile and Outcome

Periton Diyalizi İlişkili Peritonit: Mikrobiyolojik Etkenler ve Klinik Sonlanım

Arzu Özdemir, Sibel Yücel Koçak

University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Nephrology, Istanbul, Turkey

ABSTRACT

Objective: Peritonitis is a major complication of peritoneal dialysis (PD) and leads to significant mortality and technical failure. Understanding local peritonitis rates and microbiologic profiles are important for the prevention and appropriate management of PD-related peritonitis. We investigated the incidence rate, causative agents, and outcomes of PD-related peritonitis episodes.

Methods: This retrospective study enrolled all patients who were receiving PD and have been treated for PD-related peritonitis between February 2005 and November 2021 in our PD unit. Data of the patients included demographic characteristics, causes of primary renal disease, microbiology, and outcomes (resolution, catheter loss, and death) of peritonitis episodes.

Results: During the study period, 143 PD-related peritonitis episodes were identified in 69 patients. The peritonitis rate was 0.56 episodes per patient-year. Overall, 62.9% of the episodes were due to Gram-positive organisms, 32.1% were due to Gram-negative organisms, 3.4% were culture negative and 1.3% were candida. Coagulase-negative *staphylococci* were isolated in half of the Gram-positive episodes. *Acinetobacter* and *Pseudomonas* were the most frequently observed microorganisms among Gram-negative episodes. Overall, 81.1% of cases improved completely with medical treatment. The PD catheter was removed in 27 (18.8%) patients, and two patients died from sepsis. Gram-negative organisms resulted in a significantly higher rate of catheter removals and a lower rate of resolution than Gram-positive organisms ($p<0.001$).

Conclusion: Reducing the incidence of PD-related peritonitis could be possible by knowledge of prevalent microbial agents in each center, adjusting empirical treatment accordingly, and taking the necessary measures to prevent peritonitis attacks.

Keywords: Peritoneal dialysis, peritonitis, microbiology, outcome

ÖZ

Amaç: Peritonit, periton diyalizinin (PD) önemli bir komplikasyonudur, teknik yetersizliğe ve morbiditeye yol açabilir. Lokal peritonit oranlarını ve mikrobiyolojik etkenleri anlamak PD ile ilişkili enfeksiyonların önlenmesi ve uygun yönetimi için önemlidir. Bu çalışmada, PD ilişkili peritonitlerin sıklığının, etken mikroorganizmaların ve klinik sonlanımlarının belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Hastanemiz PD ünitesinde Şubat 2005 ve Kasım 2021 tarihleri arasında PD ile ilişkili peritonit tanısıyla tedavi edilen hastalar çalışmaya alındı. Hastaların demografik verileri, primer böbrek hastalığı nedenleri, peritonit etkenleri ve atakların klinik sonuçları (düzelme, kateter kaybı ve ölüm) kaydedildi.

Bulgular: Çalışma sürecinde, PD uygulayan 69 hastada 143 peritonit atağı saptandı. Peritonit atak sıklığı 0,56 atak/hasta yılı idi. Atakların %62,9'unda Gram-pozitif etkenler, %32,1'inde Gram-negatif etkenler, %1,3'ünde mantarlar saptanırken, %3,4'ünde kültür negatifti. Gram-pozitif atakların yarısında koagülaz negatif *stafilokoklar* izole edildi. En sık saptanan Gram-negatif mikroorganizmalar *Pseudomonas* ve enterokoktu. Tıbbi tedavi ile olguların %81,1'i tam düzeldi. Yirmi yedi (%18,8) hastada PD kateteri çıkarılmak zorunda kalındı ve iki hasta sepsis nedeniyle hayatını kaybetti. Gram-pozitif etkenlerle karşılaştırıldığında; Gram-negatif etkenlere bağlı peritonitlerde iyileşme oranının düşük ve PD kateter çıkarılma oranının daha fazla olduğu görüldü ($p<0,001$).

Sonuç: PD ilişkili peritonit insidansının azaltılması, her merkezin kendi etken mikroorganizma profilini bilmesi, ampirik tedavi seçenekleri belirlemesi ve peritonit ataklarını önlemek için gerekli tedbirleri alması ile mümkün olabilir.

Anahtar Kelimeler: Periton diyalizi, peritonit, mikrobiyoloji, sonlanım

Address for Correspondence: Arzu Özdemir, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Nephrology, Istanbul, Turkey
Phone: +90 532 695 79 62 E-mail: arzukayalar@yahoo.com ORCID ID: orcid.org/0000-0001-7651-7282

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INTRODUCTION

Peritoneal dialysis (PD) is one of two principal modalities of renal replacement therapy and an alternative to hemodialysis. Despite the advances in technology and antibiotic therapy, PD-related infections, including peritonitis, tunnel infections, and exit-site infections, remain common and serious complications of PD (1). Peritonitis is associated with significant morbidity, structural and functional alterations of the peritoneal membrane, transient loss of ultrafiltration, eventually permanent membrane damage, catheter loss, transfer to hemodialysis, and occasionally death (2-5). Therefore, knowledge of the causative agent, course, and predisposing factors of peritonitis is important for the appropriate management and prevention of PD-related peritonitis. We determined the incidence rate, microbiological characteristics, and outcomes of PD-related peritonitis.

METHODS

This single-center study was conducted through retrospective examination of all patients who were treated for PD-related peritonitis in our PD unit between February 2005 and December 2021. Standard Tenckhoff catheter was placed in all patients with PD. All episodes of PD-related peritonitis were reviewed. Peritonitis was diagnosed if at least two of the following criteria were present: (a) Presence of symptoms and signs related to peritonitis, i.e. a cloudy peritoneal effluent or abdominal pain, (b) peritoneal effluent white blood cell count higher than 100/μL, with at least 50% polymorphonuclear cells, and (c) positive culture of peritoneal effluent. The exclusion criteria was incomplete clinical data. Empirical antibiotic therapy was initiated after appropriate microbiological specimens have been obtained. First, all episodes were treated with ciprofloxacin and intraperitoneal vancomycin, based on the center-specific treatment protocol, unless the patient had features of systemic sepsis. Antibiotic therapy was adjusted as soon as the culture results were obtained. The duration of antibiotic therapy was 14-21 days based on the causative organism.

Demographic and clinical characteristics for all patients, including age, sex, the underlying cause of end-stage renal disease (ESRD), PD modality (continuous ambulatory PD or automated PD), duration of PD, episodes, etiology, and outcomes (resolution, catheter removal, and death) of peritonitis, and presence of concomitant tunnel or exit site infection were recorded. The resolution was defined as the disappearance of signs and symptoms within 96 h after the beginning of antibiotic therapy and a negative peritoneal fluid culture at least 28 days after treatment completion. Death related to peritonitis was defined as the death of the patient with active peritonitis or admitted with peritonitis or death within 30 days of a peritonitis episode. Catheter removal was indicated for refractory or relapsing peritonitis and peritonitis of fungal etiology. Peritonitis rate was calculated as the number of peritonitis episodes per number of patients-years at risk. The time at risk of peritonitis was counted from the first day of training till the occurrence of peritonitis.

This study was approved by the University of Health Sciences Turkey, Hamidiye Clinical Research Ethics Committee (decision no: 5/53, date: 05.02.2021) and adhered to the principles of the Declaration of Helsinki. Patient consent was not obtained due to the retrospective design of the study.

Statistical Analysis

Study results were expressed as numbers and percentages for categorical variables, and means ± standard deviations or data ranges for continuous variables. Variables were compared using the chi-square test. P-values of ≤0.05 were thought to be significant. Data were analyzed using SPSS Statistics version 24 for Windows (IBM, New York, U.S.).

RESULTS

During the study period, 69 (27.9%) of 247 chronic patients with PD developed 143 episodes of PD-related peritonitis over 3,028 patient months, with an overall peritonitis rate of 0.56 episodes/patient year. The demographic data of the patients with PD-related peritonitis are shown in Table 1. Thirty five (50.8%) were female, and 49 (71%) received continuous ambulatory PD. ESRD was most commonly caused by hypertension (40.5%) and diabetic nephropathy (27.5%).

Among the patients with PD-related peritonitis, 35 (50.7%) experienced one episode, 14 (20.2%) had two and the rest of the patients (28.9%) had ≥3 episodes. None of the patients had polymicrobial peritonitis. The distribution of organisms is shown in Figure 1. Gram-positive organisms were identified in 90 (62.9%) of peritonitis episodes. Among Gram-positive organisms, coagulase-negative *staphylococci* (CNS) was the most common Gram-positive species, accounting for 30.7% of total episodes and 48.8% of Gram-positive episodes. Gram-negative organisms were isolated in 32.1% of episodes. Among Gram-negative organisms, *Acinetobacter* and *Pseudomonas* contributed equally, followed by *Escherichia coli* and *enterobacter*. Fungal infections were observed in 1.3% of episodes and

culture-negative peritonitis was seen in 3.4% of episodes.

Organism-specific outcomes are shown in Table 2. Overall, Gram-positive infections were characterized by greater resolution with therapy and lesser need for catheter removal than Gram-negative organisms (88.8% vs 58.7%, and 10% vs 39%, p≤0.001, respectively). Among Gram-positive organisms, methicillin-resistant *Staphylococcus aureus* (MRSA) resulted in the highest catheter removal rate (23.8%). *Klebsiella* infections had the worst outcome with a 75% catheter removal rate and 25% of mortality. Fungal infections almost always resulted in catheter removal. The overall catheter removal rate was 18.8%. Two episodes resulted in death, which is caused by MRSA and *Klebsiella*.

DISCUSSION

This study describes the microbiological profiles and outcomes of PD-related peritonitis. Our data showed that Gram-positive organisms are the main etiological agents of peritonitis. Moreover, the results demonstrated that gram-negative organisms are associated with a lower resolution rate and a higher need for catheter removal, and candida infections always resulted in catheter loss.

There is a substantial variation in the incidence of PD-related peritonitis reported by different centers and countries, ranging from 0.06 to 1.66 episodes/patient-year (6). This probably result from different practices in the use of prophylactic antibiotics, in the training of PD staff, and varieties in guidelines (7). In our center, the overall incidence rate of PD-related peritonitis was 0.56 per patient-year at risk, which is higher than the International Society of Peritoneal Dialysis (ISPD) limit of 0.5 episodes per patient-year (8).

The present results showed that Gram-positive peritonitis rates exceed Gram-negative rates, similar to the previous studies in which Gram-positive bacteria accounted for approximately two-thirds of the peritonitis episodes (9-

Table 1. Patients demographics

Characteristics	Patients (n=69)
Male (%)	34 (49.2)
Age (years)	56.3±16.2
PD duration (months)	43.8±29.7 (3-149)
PD type	
CAPD	49 (71)
APD	12 (17.3)
CAPD/APD	8 (11.5)
Primary renal disease	
Hypertension	28 (40.5)
Polycystic kidney disease	3 (4.3)
Diabetic nephropathy	19 (27.5)
VUR	3 (4.3)
Glomerulonephritis	4 (5.7)
Unknown	12 (17.3)

Data are shown as mean ± standard deviation, number, and percentages.
APD: Automated peritoneal dialysis, CAPD: Continuous ambulatory peritoneal dialysis, VUR: Vesicoureteric reflux

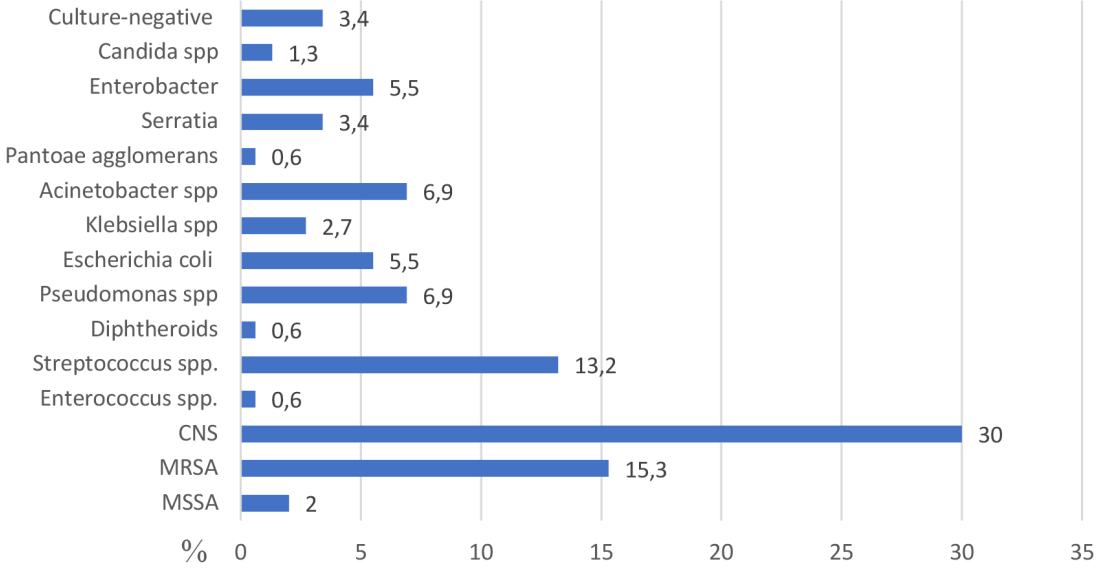

Figure 1. Microbiology of peritonitis
CNS: Coagulase-negative *staphylococci*, MRSA: Methicillin-resistant *Staphylococcus aureus*, MSSA: Methicillin-sensitive *Staphylococcus aureus*

Table 2. Microbiology and outcome of peritonitis episodes

Organism	Episode (n=143)	Resolution (n=112)	Catheter removal (n=29)	Death (n=2)
Gram-positive	90 (62.9)	80 (88.8)	9 (10)	1 (1.1)
Coagulase-negative *staphylococci*	44 (30)	40 (91)	4 (9)	-
Staphylococcus aureus excluding MRSA	3 (2)	-	-	-
MRSA	22 (15.3)	16 (72.7)	5 (22.7)	1 (4.5)
Streptococcus viridans	19 (13.2)	-	-	-
Enterococcus	1 (0.6)	-	-	-
Diphtheroids (Corynebacterium)	1 (0.6)	-	-	-
Gram-negative	46 (32.1)	27 (58.7)	18 (39.1)	1 (2.1)
Escherichia coli	8 (5.5)	7 (87.5)	1 (12.5)	-
Pseudomonas	10 (6.9)	7 (0)	3 (30)	-
Klebsiella	4 (2.7)	-	3 (75)	1 (25)
Enterobacter	8 (5.5)	6 (75)	2 (25)	-
Serratia	5 (3.4)	2 (40)	3 (60)	-
Acinetobacter	10 (6.9)	4 (40)	6 (60)	-
Pantoea agglomerans	1 (0.6)	-	-	-
Fungal (candida)	2 (1.3)	-	2 (100)	-
Culture-negative	5 (3.4)	5 (100)	-	-

Data are expressed as numbers and percentages. MRSA: Methicillin-resistant *Staphylococcus aureus*

11). Among gram-positive peritonitis, CNS was the most common organism isolated in the current study, in line with the literature (12-14). Moreover, *Pseudomonas* and *Acinetobacter* were the most commonly isolated organisms among Gram-negative peritonitis episodes in our study, in contrast with previous studies in which *Escherichia coli* was the most common causative agent (13,15,16). Interestingly, 6 patients developed *Acinetobacter* infection at the same time in our facility and PD catheter was removed in all of them. *Acinetobacter* is rarely reported in association with PD-related peritonitis but it results in serious infection and increases the possibility of drop-out or mortality. In a multicenter study conducted in Australia (17), 253 (2.3%) of 11.122 peritonitis episodes were developed due to Acinetobacter species. One hundred thirty one (74%) out of 176 patients who developed a single episode of *Acinetobacter* peritonitis recovered completely with antibiotic therapy. In contrast to our results, Htay et al. (17) reported that the rates of withdrawal of PD catheter and conversion to hemodialysis were lower with *Acinetobacter* peritonitis than with *Pseudomonas* peritonitis. *Acinetobacter* can be isolated from skin, respiratory tract, and aqueous sources including river waters, humidifiers, and water baths used to warm peritoneal dialysate before administration. The most common causes of *Acinetobacter* peritonitis in patients with PD are a break in exchange sterility, and exit site infection/tunnel infection. None of the participants in our cohort had exit site infection or tunnel infection. We suggested that the development of *Acinetobacter* peritonitis results from the hygiene breaks and contaminated medical equipment. Appropriate measures, such as education of patients, healthcare providers, and caregivers on good hygiene were taken. Additionally, healthcare providers paid attention to infection control practices, including rigorous cleaning of the shared medical equipment and patient rooms to reduce the spread of *Acinetobacter*.

The culture negativity was 3.6% in our study, which is lower than the recommended range by ISPD (8) that should not be more than 20%. Culture negativity may be a result of technical problems with the dialysate cultures, recent antibiotic use, and infection by fastidious organisms. In our center, PD staff takes PD fluid samples for culture in all patients with suspected peritonitis in adherence to international recommendations on diagnostic methods.

Severe and prolonged peritonitis episodes are a major cause of patients discontinuing PD and switching to hemodialysis. Therefore, early and appropriate treatment of peritonitis is important for rapid resolution of inflammation,

preservation of peritoneal membrane function, and patient survival. Our study showed an overall primary cure rate of 81.1%. The catheter was removed in 18.8%, a rate that was similar to previous reports in which the catheter removal rate ranged between 9.8 and 20.4% (12-14,16,18). The closeness of catheter removal rate to the highest level in literature might be explained by a higher rate of Gram-negative peritonitis attacks in our data (32.1%) as numerous studies have reported that Gram-negative peritonitis was associated with a higher rate of antimicrobial resistance, catheter loss, shift of PD to hemodialysis, and death (13,19,20). CNS was accounted for almost half of all Gram-positive episodes. Approximately, 9% of catheters were removed for CNS peritonitis supporting the continued use of empiric vancomycin for Gram-positive cover to control peritonitis attacks. As known, morbidity, and mortality are higher in patients with fungal peritonitis (21). The number of patients with fungal peritonitis in the current study was small but both were switched to hemodialysis.

Peritonitis is rarely associated with a mortal outcome but it is a contributing factor for mortality in 16% of patients with PD related peritonitis (22,23). Two patients died due to *Klebsiella* and MRSA peritonitis septicemia in our cohort.

As we found that the peritonitis rate was higher than the recommended range, we must determine the root cause of each episode, adjust empirical treatments accordingly and take the necessary measures to prevent the peritonitis attacks. Given the most common cause of PD-related peritonitis is Gram-positive microorganism, which is a normal flora of the skin, patient re-education about sterility rules and fluid exchange procedures may prevent peritonitis attacks. Further actions, including developing a home visit protocol to observe patients' home environment are also important in achieving good PD outcomes.

This study has several limitations. First, it has all problems associated with retrospective studies. Second, data of patients with PD without peritonitis were not collected. Therefore, the risk factors associated with peritonitis were not determined. Finally, some results cannot be extrapolated to other centers as the study was conducted at a single center.

CONCLUSION

This study offers insights into the etiology and outcomes of PD-related peritonitis. The incidence of peritonitis was higher than recommended range by ISPD in our population. Gram-positive organisms are the main causative agents of peritonitis and Gram-negative organisms are associated with a lower resolution rate and higher need for catheter removal. Determination of the etiology of each attack, and prevention of next episodes by directing intervention against any reversible risk factors are essential for preserving peritoneal membrane function and patient survival.

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ETHICS

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Hamidiye Clinical Research Ethics Committee (decision no: 5/53, date: 05.02.2021) and adhered to the principles of the Declaration of Helsinki.

Informed Consent: Informed consent was not obtained due to the retrospective design of the study.

Authorship Contributions

Concept: A.Ö., Design: S.Y.K., Data Collection or Processing: A.Ö., S.Y.K., Analysis or Interpretation: S.Y.K., Literature Search: A.Ö., Writing: A.Ö.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Research

Is There an Association Between Initial Clinical Manifestations and the Development of Macrophage Activation Syndrome in Patients with Systemic Juvenile Idiopathic Arthritis?

Sistemik Jüvenil İdiyopatik Artritin Klinik Prezentasyonuyla Makrofaj Aktivasyon Sendromu Gelişimi Arasında İlişki Var Mı?

Oya Köker[1], Nuray Aktay Ayaz[2]

[1]Marmara University Pendik Training and Research Hospital, Clinic of Pediatric Rheumatology, Istanbul, Turkey
[2]Istanbul University, Istanbul Faculty of Medicine, Department of Pediatric Rheumatology, Istanbul, Turkey

ABSTRACT

Objective: Systemic juvenile idiopathic arthritis is deemed as a subtype of the disease complex known as juvenile idiopathic arthritis but differs in the point of its clinical manifestations and pathophysiological features. Besides, macrophage activation syndrome is a potentially fatal complication of systemic juvenile idiopathic arthritis requiring timely management. The study aims to evaluate the presence and recurrence of macrophage activation syndrome according to the initial symptoms and pattern of different phenotypes in systemic juvenile idiopathic arthritis to reveal the comprehensive association of these interrelated disorders.

Methods: The study was conducted at the Department of Pediatric Rheumatology in Istanbul University, Istanbul Faculty of Medicine with a retrospective design, covering the date range 2015 to 2021. Patients, aged 0-18 years, being followed up with a diagnosis of systemic juvenile idiopathic arthritis with or without macrophage activation syndrome were enrolled in the study. The details of demographic data and disease-related clinical and laboratory information were investigated both from their records and the hospital database. The patients with missing or insufficient data and without regular follow-up were excluded from the study.

Results: Seventy-eight patients followed up with the diagnosis of systemic juvenile idiopathic arthritis were included in the study. The gender distribution in the study was equivalent randomly (F/M: 39/39). The median age at the study was 174 (29-229) months. The development and recurrence of macrophage activation syndrome revealed statistical significance between the genders; p=0.01 and p=0.02 respectively. Macrophage activation syndrome was more common in patients with evanescent rash (p=0.00) and those without arthritis (p=0.01). The development of macrophage activation syndrome was statistically higher in patients with predominant systemic symptoms (p=0.02) and polyphasic course (p=0.01). The presence of serositis (p=0.01) correlated with the recurrent macrophage activation syndrome.

Conclusion: The results from our study were consistent in revealing the association between macrophage activation syndrome and the systemic features in systemic juvenile idiopathic arthritis, despite a lack of correlation with arthritis in the initial presentation of the disease. Early clinical indicators and comprehensive studies are required to predict the development of macrophage activation syndrome.

Keywords: Arthritis, child health and disease, emergency medicine, juvenile idiopathic arthritis, macrophage activation syndrome, pediatric rheumatology, systemic juvenile idiopathic arthritis

ÖZ

Amaç: Sistemik jüvenil idiyopatik artrit, jüvenil idiyopatik artrit olarak bilinen hastalık kompleksinin bir alt tipi olarak kabul edilir ancak klinik bulguları ve patofizyolojik özellikleriyle diğer alt tiplerden farklılık gösterir. Ayrıca makrofaj aktivasyon sendromu, sistemik jüvenil idiyopatik artritin zamanında tedavi gerektiren mortalitesi yüksek bir komplikasyonudur. Çalışmanın amacı, sistemik jüvenil idiyopatik artritte karşımıza çıkan farklı fenotiplerin başlangıç semptomlarına ve patternine göre makrofaj aktivasyon sendromunun varlığını ve rekürrensini değerlendirmek ve birbiriyle ilişkili bu bozuklukların kapsamlı birlikteliğini ortaya çıkarmaktır.

Address for Correspondence: Nuray Aktay Ayaz, Istanbul University, Istanbul Faculty of Medicine, Department of Pediatric Rheumatology, Istanbul, Turkey
E-mail: nurayaktay@gmail.com ORCID ID: orcid.org/0000-0003-3594-7387

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Gereç ve Yöntem: Çalışma, İstanbul Üniversitesi, İstanbul Tıp Fakültesi Pediatrik Romatoloji Bilim Dalı'nda 2015-2021 tarih aralığını kapsayacak şekilde retrospektif olarak gerçekleştirildi. Makrofaj aktivasyon sendromu geçirmiş veya geçirmemiş sistemik jüvenil idiyopatik artrit tanısıyla izlenen 0-18 yaş arası hastalar çalışmaya alındı. Demografik verilerin detayları ve hastalıkla ilgili klinik ve laboratuvar bilgileri hem kendi kayıtlarından hem de hastane veri tabanından araştırıldı. Eksik veya yetersiz verisi olan ve düzenli takibi olmayan hastalar çalışma dışı bırakıldı.

Bulgular: Sistemik jüvenil idiyopatik artrit tanısıyla izlenen 78 hasta çalışmaya dahil edildi. Çalışmadaki cinsiyet dağılımı rastgele olarak eşitti (K/E: 39/39). Çalışmadaki ortanca yaş değeri 174 (29-229) ay olarak saptandı. Makrofaj aktivasyon sendromu gelişimi ve rekürrensi cinsiyetler arasında istatistiksel bir anlam göstermekteydi; sırasıyla p=0,01 ve p=0,02. Makrofaj aktivasyon sendromu, geçici döküntüsü olan hastalarda (p=0,00) ve artriti olmayanlarda (p=0,01) daha yaygındı. Sistemik semptomları baskın (p=0,02) ve polifazik seyirli (p=0,01) hastalarda makrofaj aktivasyon sendromu gelişimi istatistiksel olarak daha yüksekti. Serozit varlığı (p=0,01) tekrarlayan makrofaj aktivasyon sendromuyla korelasyon gösterdi.

Sonuç: Makrofaj aktivasyon sendromu sistemik jüvenil idiyopatik artritin geliş tablosunda yer alabilen artrit ile korelasyon göstermezken, sistemik özelliklerle arasındaki ilişki çalışma sonuçlarına göre tutarlıydı. Multidisipliner yaklaşım, yakın klinik izlem ve laboratuvar parametrelerinin seri ölçümü yönlendirici olabilmektedir, ancak göreceli değişiklikleri tespit etmek zordur. Bu nedenle, makrofaj aktivasyon sendromunun gelişimini öngörmek için erken klinik göstergelere ve kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Artrit, çocuk sağlığı ve hastalıkları, acil tıp, jüvenil idiyopatik artrit, makrofaj aktivasyon sendromu, pediatrik romatoloji, sistemik jüvenil idiyopatik artrit

INTRODUCTION

Systemic juvenile idiopathic arthritis (JIA) is deemed as a subtype of the disease complex known as JIA but differs in the point of its clinical manifestations and pathophysiological features (1). Systemic JIA deserves a rigorous distinction from infectious diseases and malignancy beyond the other autoimmune and autoinflammatory systemic disorders (2). However, the clinical picture may remain partial and challenging without a typical presentation. However, macrophage activation syndrome (MAS) is a potentially fatal complication of systemic JIA with a course of coagulopathy, haemodynamic instability, and multiorgan dysfunction, requiring timely management (3). In systemic JIA patients, leukocytosis, thrombocytosis, elevated sedimentation, and fibrinogen may mask the development of MAS (2). Considering the exacerbations of the underlying disease and the overlapping features with sepsis, MAS may render the picture more challenging to recognize.

Systemic JIA represents a heterogeneous portrait in which systemic features are predominant or arthritis is at the forefront, with variations in itself (4-6). It is difficult to foresee the course of the disease as it may display a monophasic, polyphasic, or persistent course (7). Monophasic and polyphasic courses may not always be accompanied by arthritis, and this group of patients may predominantly present with systemic symptoms similar to those seen in MAS, such as fever, rash, organomegaly, and generalized lymphadenopathy. However, MAS, which is estimated to occur in 10% of patients, may emerge at diagnosis, during an exacerbation of systemic JIA, or, conversely, when the disease is in remission (1). Although immune variances and genetic influences in the pathogenesis have been associated with clinical heterogeneity of systemic JIA, mechanistic differences between phenotypes have not been fully demonstrated. Moreover, it is a matter of debate whether MAS is a variant of the disease or a subtype presenting with a noisy clinic or subclinical course (3).

The current study evaluates the presence and recurrence of MAS according to the initial symptoms and pattern of different phenotypes in systemic JIA to reveal the comprehensive association of these two interrelated disorders.

METHODS

Patient Selection

The study was conducted with the patients being followed up with a diagnosis of systemic JIA at the Pediatric Rheumatology Department in Istanbul University, Istanbul Faculty of Medicine. The systemic JIA cohort composed of patients aged 0-16 years, who met the ILAR criteria (8) and who presented with disease features and were eventually diagnosed as systemic JIA after being eliminated from other possible etiologies with a multidisciplinary approach. The cohort included patients with or without MAS, which has been defined according to the 2016 classification criteria set (9). Special attention has been given to include patients who were diagnosed after excluding all existing causes, and without any signs that would raise the diagnostic suspicion during the follow-up and treatment processes.

Data Collection

Medical records covering the date range from September 1, 2015, to September 1, 2021, were retrospectively reviewed. The details of clinical and laboratory characteristics, demographic (age, gender) and disease-related (age at diagnosis, disease duration from the diagnosis to the time of the study, disease pattern, detailed history of symptoms, medication history, current treatment) data were assessed. Baseline laboratory data including leukocyte count, neutrophil percentage, platelet count, C-reactive protein, erythrocyte sedimentation rate, initial, maximum and the latest values of ferritin, alanine transaminase, aspartate transaminase, triglyceride, fibrinogen was investigated both

from their own records and from the hospital database. The patients with missing or insufficient data and without regular follow-up were excluded from the study. Each participant and his/her legal representative have approved the use of their information and informed consent was obtained from the legally authorized representatives of our patients before their inclusion in the study. Approval was obtained from the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine for the study (decision no: 622975, date: 25.11.2021).

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows 21.0 software (Statistical Package for the Social Sciences, Chicago, IL, USA) and Microsoft Excel (Redmond, WA). The visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) were performed to analyze the distribution of the variables. The demographic and clinical data were evaluated using descriptive analysis, and the data are presented as a percentage (%), median with minimum and maximum values. In the comparison and assessment of the data, non-parametric tests, Mann Whitney U and Kruskal-Wallis tests, were performed. Categorical variables were presented as counts or frequencies and Pearson chi-square, Fisher's Exact tests were performed to evaluate the correlations and differences. Statistical significance was defined as p-value <0.05.

RESULTS

Seven patients were excluded from the study because of missing or insufficient data, while 78 patients with a diagnosis of systemic JIA with or without MAS were enrolled. The number of female (F) and male (M) patients who met the inclusion criteria and randomly included in the cohort was equivalent (F/M: 39/39). The median age at the study was 174 (29-229) months. Among the patients in the cohort, 39.7% (n=31) had a history of clinically and laboratory-proven MAS in which 14.1% (n=11) were recurrent. Clinical characteristics of the patients in the cohort are demonstrated in Table 1.

The development and recurrence of MAS revealed statistical significance between the genders; (F/M: 10/21, p=0.01) and (F/M: 2/9, p=0.02) respectively. According to the initial presentation, MAS was more common in patients with evanescent rash (p=0.00) and in those without arthritis (p=0.01). Moreover, it was observed that the development of MAS was statistically higher in patients with systemic type of disease (p=0.02) and polyphasic course (p=0.01). In systemic JIA patients, lymphadenopathy and organomegaly were significant in terms of MAS development, whereas

Table 1. Clinical manifestations of the systemic juvenile idiopathic arthritis cohort

Characteristics med (min-max)/n (%)	Systemic JIA (n=78)
Gender (female)	39 (50)
Age at the study (mo)	174 (29-229)
Disease presentation	
Age at diagnosis (mo)	73 (6-180)
Fever	77 (98.7)
Evanescent erythematous rash	52 (66.7)
Arthralgia (≥2 weeks)	74 (94.9)
Arthritis at diagnosis	59 (75.6)
Type of arthritis	
Monoarthritis	14 (17.9)
Oligoarthritis	26 (33.3)
Polyarthritis	26 (33.3)
Major joint involvement	63 (80.8)
Minor joint involvement	14 (17.9)
Axial involvement	18 (23.1)
Generalized lymphadenopathy	22 (28.2)
Hepatomegaly and/or splenomegaly	32 (41)
Serositis	23 (29.5)
Baseline laboratory data	
WBC (x10^9/L)	17.4 (3.4-29)
Neutrophils	14.4 (2-24.6)
Platelet count (x10^9/L)	494 (110-963)
CRP (mg/L)	130 (28-388)
ESR (mm/h)	76 (12-140)
ALT (units/L)	32 (5-2,356)
AST (units/L)	38 (7-8,754)
Triglyceride (mg/dL)	121 (63-722)
Fibrinogen (mg/dL)	325 (122-822)
Ferritin (initial) (µg/L)	1133 (118-67,873)
Ferritin (maximum) Ferritin (latest)	2340 (310-115,000) 40 (10-235)
Clinical progress	
Disease duration (mo)	66 (25-190)
Disease course	
Monophasic	22 (28.2)
Polyphasic	21 (26.9)
Persistent	35 (44.9)
MAS	31 (39.7)

Table 1. Continiued

Characteristics med (min-max)/n (%)	Systemic JIA (n=78)
Recurrent MAS	11 (14.1)
Organ involvement	
CNS	6 (7.7)
Liver	15 (19.2)
Coronary	1 (1.3)
Kidney	3 (3.8)
ARDS	8 (10.2)
Intensive care unit follow-up	19 (24.4)
Mortality rate	0
Medication history [type, duration (mo)]	
High dose corticosteroid therapy	75 (96.2)
Methotrexate	54 (69.2), 17.5 (4-108)
Cyclosporine	31 (39.7), 3 (1-30)
Anakinra	33 (42.3), 4 (1-20)
Canakinumab	17 (21.8), 16 (3-56)
Tocilizumab	29 (37.2), 20 (1-70)
Etanercept	11 (14.1), 12 (3-36)
Adalimumab	3 (3.8), 6 (6-36)
Current treatment	
Methotrexate	3 (3.8)
Canakinumab	14 (17.9)
Tocilizumab	18 (23.1)
Etanercept	2 (2.6)
Oral corticosteroid	3 (3.8)
Medication-free	43 (55.1)

JIA: Juvenile idiopathic arthritis, WBC: White blood cell, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ALT: Alanine transaminase, AST: Aspartate transaminase, MAS: Macrophage activation syndrome, CNS: Central nervous system, ARDS: Acute respiratory distress syndrome med: Median

the presence of serositis correlated with MAS recurrence (p=0.01). The correlation between the demographic and clinical characteristics of the systemic JIA cohort and the development and recurrence of MAS is detailed in Table 2 with p-values.

Table 2. The correlation between demographic and clinical manifestations of the systemic juvenile idiopathic arthritis cohort and macrophage activation syndrome

Systemic JIA cohort	The development of MAS p-value	Recurrent MAS p-value
Demographic and clinical manifestations		
Gender	**0.01**	**0.02**
Age at diagnosis	0.47	0.9
Fever	1.0	1.0
Evanescent rash	**0.00**	0.08
Arthralgia (≥2 weeks)	0.14	1.0
Arthritis at diagnosis	**0.01**	0.44
Type of arthritis	0.3	0.29
Major joint	**0.01**	0.43
Minor joint	0.79	0.67
Axial involvement	0.93	1.0
Lymphadenopathy	**0.007**	0.27
Organomegaly	**0.001**	0.18
Serositis	0.14	**0.013**
CRP (mg/L)	0.56	0.64
ESR (mm/h)	**0.02**	0.05
Ferritin (initial)	**0.00**	**0.001**
Clinical progress		
Disease duration	**0.02**	0.26
Disease course	**0.01**	0.4
Disease type	**0.02**	0.28

JIA: Juvenile idiopathic arthritis, MAS: Macrophage activation syndrome, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

DISCUSSION

The study aimed to evaluate the presence and recurrence of MAS in systemic JIA and to determine whether the initial symptoms or patterns of different phenotypes demonstrate any association. MAS is known as a rare but life-threatening condition with high mortality (8%) (10). Although the prevalence of MAS in systemic JIA has been reported to be approximately 10% (11), recent data emphasize that it can be detected subclinical in 30-40% of patients (12). In a database study on systemic JIA conducted in Germany, the frequency of MAS was 5% (13). The rate may differ in studies from different centers but from the same geography. In the cohort of Barut et al. (14) consisting of 168 patients, the frequency of MAS was 11.9% with a value close to the expected. According to the results reported by another reference center in Turkey, 36% of the patients had at least one MAS episode during the disease (15). The results of our study in terms of the sample size and the frequency of MAS with many 39.7% were consistent with the aforementioned study. It is crucial to act consciously

and to refer patients to reference centers timely in order to prevent mortality. Hence, it must identify the clinical features and laboratory data that may not be included or may not display major alterations in the presentation.

MAS emerges because of cytolytic pathway defects resulting in sustained activation of CD8+ T-cells and macrophages and uncontrolled production of pro-inflammatory cytokines such as interferon-ɣ (IFN-ɣ) (16,17). IL-18 is principally thought to play a key role in the pathogenesis of systemic JIA, and in MAS by stimulating IFN-ɣ production (3,18). The fact that MAS may display either a subclinical course or recurrent episodes with prompt mortality is a subject of debate open to research. While no mortality was observed in the study cohort, recurrence has been noted in 14.1%. Our patients with recurrent MAS were evaluated for primary hemophagocytic lymphohistiocytosis (HLH) and possible genetic causes. Recent literature has pointed that inflammasome NLR-family CARD domain-containing protein 4 related mutations may lead to persistently elevated IL-18 levels and recurrent episodes of MAS (19,20). Further studies are needed to predict the course of MAS and to elucidate its pathophysiological and genetic aspects.

HLH-2004 diagnostic criteria presented for HLH were formerly used in a treatment study that evaluated the efficacy of etoposide, dexamethasone, and cyclosporine-based induction therapy before hematopoietic stem cell transplantation (21). The histopathological similarity between MAS and HLH suggested that common diagnostic criteria might be applied. However, more sensitive criteria were required to distinguish MAS from certain confounding conditions (22). In 2016, Ravelli et al. (9), and colleagues revealed classification criteria for systemic JIA-related MAS to differentiate MAS, particularly from the disease flare or infection. Of note, it is sufficient to suspect without waiting for all criteria to be met to start treatment. High ferritin levels and a relative decrease in platelet count are noted to be the essential flags for the diagnosis. Moreover, persistent fever, development of cytopenia and decrease in sedimentation value are the significant markers (3). When the initial symptoms and the disease course of systemic JIA were evaluated regarding the development of MAS, the presence of evanescent rash, lymphadenopathy and organomegaly came into prominence. Although the cutaneous signs in systemic JIA and MAS have distinct characteristics, MAS displayed a significant correlation with the evanescent rash of systemic JIA. However, it displayed an inverse correlation with arthritis at disease onset. Consequently, the systemic signs and the polyphasic course of systemic JIA were more associated with the development of MAS.

Unlike other JIA subtypes, no dominance is expected in terms of gender distribution in systemic JIA, and the distribution was equal in our study. However, although there is female predominance in some studies in terms of MAS (10,23,24), both the development and recurrence of MAS was statistically higher in male patients in our study. Patient populations and geographic diversity in different studies may be determinants of the demographic changes. Studies with a large multinational cohort are needed.

One downside regarding our methodology is that the study was conducted retrospectively with a limited sample size and data. As there are individual, ethnic, and temporal determinants, it is not easy to establish a direct correlation and predict the progression. However, the results from our study were consistent in revealing the association of MAS with the systemic shared features of systemic JIA, despite a lack of correlation with arthritis in the initial presentation of the disease.

CONCLUSION

Systemic JIA and MAS are heterogeneous conditions with consecutive and overlapping features. Given that early diagnosis and prompt management are of vital importance to prevent morbidity and mortality, it is crucial to have particular clinical indications that may be noticed early in the disease. The results from our study were consistent in revealing the association between the development and recurrence of MAS and the systemic features, despite a lack of correlation arthritis in systemic JIA. A multidisciplinary approach, close clinical monitorization, and serial measuring of laboratory parameters may be instructive, yet relative alterations may be difficult to detect. Studies on the pathways and triggers associated with cytokine storm will shed light on a deep understanding of the disease and treatment approaches. Besides, there is need for tools or clinical indicators that can be applied in practice, and which may guide clinicians in initial diagnosis and differential diagnosis.

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ETHICS

Ethics Committee Approval: Approval was obtained from the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine for the study (decision no: 622975, date: 25.11.2021).

Informed Consent: Each participant and his/her legal representative have approved the use of their information

and informed consent was obtained from the legally authorized representatives of our patients before their inclusion in the study.

Authorship Contributions

Surgical and Medical Practices: O.K., N.A.A., Concept: O.K., N.A.A., Design: O.K., N.A.A., Data Collection or Processing: O.K., N.A.A., Analysis or Interpretation: O.K., N.A.A., Literature Search: O.K., N.A.A., Writing: O.K., N.A.A.

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Research

Renal Transplantation in Patients with Alport Syndrome

Alport Sendromlu Hastalarda Böbrek Nakli

Abdülhak Hamit Karayağız[1], Ulukan Cenal[2], Gülay Yılmaz[3], Ebru Özdemir[3], Murat Yıldar[3], Ülkem Çakır[3], İbrahim Berber[3]

[1]Esenyurt State Hospital, Clinic of General Surgery, Istanbul, Turkey
[2]Arnavutkoy State Hospital, Clinic of Emergency Medicine, Istanbul, Turkey
[3]Acibadem International Hospital, Organ Transplantation Center, Istanbul, Turkey

ABSTRACT

Objective: Alport syndrome is an inherited disease that occurs in 1/50,000 and is characterized by hematuria, kidney failure, deafness and ocular anomalies. Alport syndrome, which is inherited as X-linked recessive with a rate of 85%, may be inherited also as autosomal dominant or autosomal recessive. Defective type-4 collagen participating in the structure of glomerular basement membrane causes a progressive decline in kidney functions. This research investigates the results of end-stage renal failure in patients with Alport syndrome following kidney transplantation.

Methods: In our Hospital Organ Transplant Center 11 kidney transplantations were performed in 10 patients with Alport syndrome between October 2010 and December 2020. The recipients were analyzed retrospectively for acute rejection, complication rate, graft and patient survival.

Results: Eleven (0.88%) of 1,251 kidney transplants were performed in patients with Alport syndrome. Acute rejection did not occur in any patient after kidney transplantation and no medical or surgical complications were observed in the early postoperative period. One patient died 19 months after surgery because of pneumonia and sepsis while his graft was functional. Graft loss was observed in two patients. In one of these patients, graft loss developed due to drug incompatibility in the 11th month after kidney transplantation. In the other patient, graft loss was observed due to chronic allograft nephropathy in the 63rd month postoperatively. This patient underwent a second kidney transplant surgery from a living donor.

Conclusion: Alport syndrome is a rare cause of chronic kidney failure. Kidney transplantation is an effective and successful treatment method for end-stage renal disease patients with Alport syndrome.

Keywords: Renal transplantation, Alport syndrome, graft survival

ÖZ

Amaç: Alport sendromu 1/50.000'de ortaya çıkan, hematüri, böbrek yetmezliği, işitme kaybı ve oküler anomalilerle karakterize kalıtsal bir hastalıktır. %85 oranında X'e bağlı resesif olarak kalıtılan Alport sendromu, otozomal dominant veya otozomal resesif olarak da kalıtılabilir. Glomerüler bazal membranın yapısına katılan arızalı tip-4 kollajen böbrek fonksiyonlarında ilerleyici bir düşüşe neden olur. Bu araştırma, böbrek nakli sonrası Alport sendromlu son dönem böbrek yetmezliği hastalarının sonuçlarını araştırmaktadır.

Gereç ve Yöntem: Hastanemiz Organ Nakli Merkezi'nde Ekim 2010 ile Aralık 2020 tarihleri arasında Alport sendromlu 10 hastaya 11 böbrek nakli yapıldı. Alıcılar retrospektif olarak akut rejeksiyon, komplikasyon oranı, greft ve hasta sağkalımı açısından incelendi.

Bulgular: Bin iki yüz elli bir böbrek naklinin 11'i (%0,88) Alport sendromlu hasta idi. Böbrek nakli sonrası hiçbir hastada akut rejeksiyon olmadı ve ameliyat sonrası erken dönemde herhangi bir tıbbi veya cerrahi komplikasyon görülmedi. Bir hasta ameliyattan 19 ay sonra greft fonksiyonel iken pnömoni ve sepsis nedeniyle öldü. İki hastada greft kaybı gözlendi. Bu hastalardan birinde böbrek nakli sonrası 11. ayda ilaç uyumsuzluğuna bağlı greft kaybı gelişti. Diğer hastada postoperatif 63. ayda kronik allogreft nefropatisine bağlı greft kaybı gözlendi. Bu hastaya canlı bir donörden ikinci bir böbrek nakli ameliyatı yapıldı.

Sonuç: Alport sendromu, kronik böbrek yetmezliğinin nadir bir nedenidir. Böbrek nakli, Alport sendromlu son dönem böbrek yetmezliği hastalarında etkili ve başarılı bir tedavi yöntemidir.

Anahtar Kelimeler: Böbrek nakli, Alport sendromu, greft sağkalımı

Address for Correspondence: Gülay Yılmaz, Acibadem International Hospital, Organ Transplantation Center, Istanbul, Turkey
Phone: +90 532 548 58 05 E-mail: gulay.yilmaz@acibadem.com ORCID ID: orcid.org/0000-0001-6565-8063

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INTRODUCTION

Alport syndrome (AS) is a rare hereditary disorder that is first described in 1927 and characterized by progressive renal function loss, hematuria, sensorineural deafness and typical ocular anomalies (1,2). Mutations in the *COL4A5* or *COL4A3/COL4A4* genes cause abnormal production of collagen type-IV, which causes lamination in the glomerular basement membrane (GBM) (3). 85% of cases appear X-linked inheritance with the mutations in COL4A5. It can also be seen in autosomal recessive and rarely autosomal dominant resulting from mutations in both gene copies of *COL4A3* and *COL4A4* (4,5). Patients with AS present most commonly hematuria in the first decade and a history of familial renal failure and deafness is diagnostic for AS (5,6). Renal failure before the age of 30 is the most important cause of mortality in AS and renal replacement therapy is the initial type of treatment modality in such patients. Kidney transplant outcomes of patients with AS have been discussed in many studies. Göbel et al. (7) compared survival of kidney transplant patients with AS and patients who are not AS. One- and five-year patient survival was 100 and 91% in AS and 89 and 78% in controls ($p>0.05$, respectively) (7). In another study, Byrne et al. (8) evaluated 41 kidney transplant patients with AS and they revealed that 1-, 5-, and 10-year patient and graft survival rates were 95.1%, 90.2%, and 80.5% and 86.8%, 66%, and 45.3%, respectively.

This study reveals the clinical outcomes of renal transplantation (RTx) in patients with AS.

METHODS

Eleven of 1,251 kidney transplantation was performed in patients with end-stage renal disease (ESRD) due to the AS between October 2010 and December 2020 in our hospital Organ Transplant Center. The data were retrospectively collected from hospital records and expressed as frequencies and percentages. The main outcomes that were assessed in this study were the presence of anti-GBM disease or acute rejection, intraoperative complication rate, renal allograft and patient survival. The study protocol was approved by the Ethic Committee of Acibadem University in December 2021 with the approval number 2021-25/14.

Statistical Analysis

The results were analyzed using the Statistical Package for the Social Sciences, version 22 (SPSS, Chicago, Ill, United States).

RESULTS

A total of 1251 kidney transplants were performed in our hospital Organ Transplant Center between October 2010 and December 2020. Eleven (0.88%) of these transplants were performed in 10 patients with ESRD caused by AS. While only one transplant was carried out from cadavers, 6 of the remaining 10 transplants were performed from 1. degree relatives, 2 from 2. degree relatives and 2 from unrelated donors. 8 of 10 living donor nephrectomies were performed transperitoneal and the remaining 2 with a transvaginal laparoscopic approach. The mean age and follow-up duration of recipients were 25±9.1 years and 46.7 months, respectively. All patients were male in gender. Overall patient survival is 90.9%, only one patient died 19 months after the operation because of pneumonia and sepsis while his graft was functional. The survival of renal allografts in patients with ESRD due to the AS was 81.8%. Two recipients have lost their grafts during the follow-up period; first patient lost his graft 11 months after the kidney transplantation because of the drug incompetence In the second patient graft loss was developed in the 63rd month due to the chronic allograft nephropathy (Chronic active T-cell-mediated rejection) and in this patient the second RTx was performed from the living donor (Table 1). No patient developed the anti-GBM disease, acute rejection, or intra- and postoperative complication.

DISCUSSION

AS is a rare inheritable disorder characterized by renal failure in early ages, hematuria, deafness and ocular anomalies. AS made up quite a low prevalence (0.5-1.6%) in all RTx patients in the literature (2,3). Genetic mutations in collagen type IV result in involvement and dysfunction of multiple organs and the most common cause of mortality in patients with AS are ESRD before 30 years of age (9). This retrospective analysis reports the transplant-related outcomes of 10 patients with AS at our center.

Because of younger age at RTx and fewer episodes of acute rejection have the patients with AS a high twenty-year patient survival rate (70.2%) in compared to RTx patients due to the other renal diseases (44.8%). However, there was no statistically significant difference found in the national case series of Kelly et al. (3) in terms of median graft survival between and non-AS patients with AS.

Yilmaz et al. (10) found no significant difference between 25 AS and 50 non-AS patients in terms of graft and

patient survival at years 1, 3, 5 and 10, requirement for postoperative dialysis, BK virus-associated nephropathy and cytomegalovirus infection. Only lower rates of acute rejection and higher rates of chronic allograft dysfunction were observed in patients with AS compared to the non-AS patient group (10).

The most catastrophic complication in RTx patients with AS is anti-GBM nephritis, which causes rapid allograft loss after the transplantation (3,10). Despite the study by Gumber et al. (9) in 2012, which reported anti-GBM nephritis-related graft loss with an incidence of 12%, the literature manifests lower incidence such as 3-4% of anti-GBM nephritis in RTx with patients with AS (7,11). The more current studies mention the incidence of anti-GBM nephritis 0-0.3%, which can be attributed to the modern and effective usage of immunosuppressive therapy (2,3,10). Also in our study, no allograft rejection was detected due to the anti-GBM nephritis.

Study Limitations

The limitations of this study are the small sample size and lack of long-term follow-up.

Table 1. Main baseline characteristics

	Kidney transplant patients with AS (n=10) Kidney transplantation (11 kidney transplantation to 10 patients)
Recipient gender; n (%)	
Female	0
Male	10 (100%)
Age (years)	25±9.1
Type of transplantation; n (%)	
Cadaveric	1
Living	10
Degree of relationship; n (%)	
1st degree	6
2nd degree	2
Unrelated	2
Overall patient survival (%)	90.9
Overall patient survival (%)	81.8
Cause of graft loss	Drug incompliance Chronic active T-cell-mediated rejection

AS: Alport syndrome

CONCLUSION

This study reveals that RTx is an effective treatment modality in patients with ESRD with AS and shows comparable results with RTx due to the other renal diseases.

ETHICS

Ethics Committee Approval: The study protocol was approved by the Ethic Committee of Acibadem University in December 2021 with the approval number 2021-25/14.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.H.K., E.Ö., İ.B. Concept: A.H.K., G.Y., Ü.Ç., İ.B., Design: A.H.K., G.Y., Ü.Ç., İ.B., Data Collection or Processing: U.C., E.Ö., Analysis or Interpretation: E.Ö., M.Y., Literature Search: G.Y., M.Y., Writing: A.H.K., G.Y.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Research

The Validity of Electromyography and Patient Evaluation Measurement in Evaluating Late-term Satisfaction Level of Patients Undergone Carpal Tunnel Syndrome Decompression Surgery

Karpal Tünel Sendromu Dekompresyon Cerrahisi Geçiren Hastaların Geç Dönem Memnuniyet Düzeylerini Değerlendirmede Elektromiyografi ve Hasta Değerlendirme Ölçümünün Geçerliliği

Ahmet Aybar[1], Mehmet Ümit Çetin[2], Abdulkadir Polat[1], Akif Kurtan[3], Cüneyt May[4], Nihat Acar[5]

[1]University of Health Sciences Turkey, Gaziosmanpasa Training and Research Hospital, Clinic of Orthopaedics and Traumatology, Istanbul, Turkey
[2]Tekirdag Namik Kemal University Faculty of Medicine, Department of Orthopaedics and Traumatology, Tekirdag, Turkey
[3]Bahcelievler Private Nisa Hospital, Clinic of Orthopaedics and Traumatology, Istanbul, Turkey
[4]Kırklareli Training and Research Hospital, Clinic of Orthopaedics and Traumatology, Kırklareli, Turkey
[5]Istanbul Catalca Ilyas Cokay State Hospital, Clinic of Orthopaedics and Traumatology, Istanbul, Turkey

ABSTRACT

Objective: This study investigated whether electromyelography (EMG) evaluation is helpful in the late phase after surgical treatment of carpal tunnel syndrome (CTS).

Methods: This retrospective study included 35 patients who underwent mini-open decompression therapy between 2008 and 2011 with CTS diagnosis. Patients were assessed electrophysiologically and clinically with Patient Evaluation Measurement (PEM) scoring and handgrip, palmar grip, lateral grip, and fingertip grip strength. Additionally, patients' clinical scores and strength values were compared with electrophysiologic values from preoperative and postoperative 4-year controls.

Results: According to the Padua classification, EMG data were classified before and after surgery. One patient had extreme grade, four patients had severe grade, 26 patients had moderate grade, and four had a mild grade before surgery. At the postoperative 4th year EMG follow-up, six patients were classified as minimal and 29 as negative. According to the PEM scale, the mean score before surgery was 58.77±7.89, and in the controls at the 4th year after surgery, the mean score was 13.48±4.01. The strength of the operated hand was significantly weaker than that of the contralateral healthy hand before surgery. However, in the controls at the 4th year after surgery, the strength of the operated hand was significantly increased compared with the preoperative period, and there was no significant difference from the contralateral hand.

Conclusion: Electrophysiological assessment (EMG) in the late phase after surgical treatment of CTS has positive parallels with clinical assessment and strength assessment. Therefore, we conclude that EMG helps follow late surgical outcomes.

Keywords: Carpal tunnel, EMG, PEM

ÖZ

Amaç: Bu çalışmada, karpal tünel sendromunun (KTS) cerrahi tedavisi sonrası geç dönemde elektromyelografi (EMG) değerlendirmesinin yararlı olup olmadığı araştırdık.

Gereç ve Yöntem: Bu retrospektif çalışmaya 2008-2011 yılları arasında KTS tanısı ile mini açık dekompresyon tedavisi uygulanan 35 hasta dahil edildi. Hastalar hem elektrofizyolojik hem de klinik olarak Patient Evaluation Measurement (PEM) skorlaması ve el kavrama, palmar kavrama,

Address for Correspondence: Ahmet Aybar, University of Health Sciences Turkey, Gaziosmanpasa Training and Research Hospital, Clinic of Orthopaedics and Traumatology, Istanbul, Turkey
Phone: +90 532 651 29 58 E-mail: drahmetaybar@yahoo.com ORCID ID: orcid.org/0000-0002-4847-610X

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lateral kavrama ve parmak ucu kavrama güçleri ile değerlendirildik. Ek olarak, hastaların klinik skorları ve güç değerleri, ameliyat öncesi ve ameliyat sonrası 4 yıllık kontrollerden elde edilen elektrofizyolojik değerlerle karşılaştırdık.

Bulgular: Padua sınıflamasına göre EMG verileri ameliyat öncesi ve sonrası olarak sınıflandırıldı. Ameliyat öncesi bir hasta ileri, dört hasta ağır, 26 hasta orta ve dört hasta hafif dereceli olarak sınıflandırıldı. Ameliyat sonrası 4. yıl EMG takibinde altı hasta minimal ve 29 hasta negatif olarak sınıflandırıldı. PEM ölçeğine göre ameliyat öncesi ortalama 58,77±7,89, ameliyat sonrası 4. yılda kontrollerde ortalama puan 13,48±4,01 olarak bulundu. Ameliyat edilen elin gücü, ameliyat öncesi karşı taraftaki sağlıklı elden önemli ölçüde daha zayıf olarak tespit ettik. Ancak ameliyat sonrası 4. yılda yapılan kontrollerde ameliyat edilen elin kuvvetinde ameliyat öncesi döneme göre anlamlı düzeyde artış olduğu ve karşı taraf sağlam elden anlamlı bir fark olmadığı tespit ettik.

Sonuç: KTS'nin cerrahi tedavisinden sonraki geç dönemde elektrofizyolojik değerlendirme (EMG), klinik değerlendirme ve kuvvet değerlendirmeleri ile pozitif yönde paralellik göstermektedir. EMG'nin geç dönem cerrahi sonuçlarının takibinde yardımcı olabilmektedir.

Anahtar Kelimeler: Karpal tünel, EMG, PEM

INTRODUCTION

Carpal tunnel syndrome (CTS) is considered the most common entrapment neuropathy of the median nerve at the level of the wrist region in working-age individuals (1,2). CTS (prevalence was 3-3.4% in men and 0.6-2.7% in women) (2-5). No test alone has sufficient sensitivity for CTS diagnosis. However, patient history, physical examination, and electromyography (EMG) play an essential roles in diagnosis and follow-up (4,5). Several studies have reported that the sensitivity of conventional tests ranges from 49% to 84%, with specificity around 95% (4-6). Various conservative treatment modalities are acceptable in mild-to-moderate cases.

In contrast, surgical decompression procedures are reserved for more severe cases with thenar muscle atrophy or after the failure of conservative treatment (3,4). EMG has been a good method to quantify the severity of median nerve entrapment and correlate closely with the degree of preoperative symptoms compared with physical examination (5). Clinical examination, patient assessment measurements, and EMG are used to evaluate early and long-term postoperative decompression outcomes. However, the literature search revealed few studies comparing symptom resolution and patient satisfaction (6,7).

Recent studies have shown different discrepancies between different methods of postoperative assessment based on complementary tests such as EMG or clinical grading systems in terms of clinical and functional diagnosis and postoperative short- and long-term follow-up CTS decompression surgery (8,9).

Although several studies have shown the close relationship between the clinical presentation of CTS and EMG manifestation outcomes (9,10), many other studies have shown earlier symptomatic clinical improvement than EMG improvement, especially in severe forms of the disease due to the late recovery process of the demyelination nature of the nerve sheath due to the persistent compression-induced ischemic effect on the nerve sheath, which may take several months to return to normal patterns (10,11). Therefore, the degree of postoperative patient satisfaction is considered one of the most important criteria for measuring the success rate of CTS decompression surgery (12,13). Apart from being an invasive and expensive examination method, the validity of EMG for measuring postoperative patient satisfaction has been discussed in several recent studies (14,15).

Our study investigates the effectiveness of physical EMG examination and clinical grading systems in the long-term follow-up of patients undergoing CTS decompression surgery.

METHODS

All the patients were investigated after the Taksim Training and Research Hospital's approval of the Clinical Research Ethics Committee (decision no: 110, date: 16.10.2019). Informed consent was also obtained from the patients. We reviewed the records of eighty-eight patients diagnosed in our orthopedic and traumatology outpatient clinic between 2008 and 2011 CTS who underwent minimal approach CTS decompression surgery.

All patients with metabolic syndromes, rheumatologic diseases, recurrent CTS, pregnancies, and trauma-related diseases were excluded. Simultaneously, patients with no prominent history of medical illness or trauma were included in the study.

Of the eighty-eight patients, 35 were included in this study (7 male and 28 female). Out of the 35 patients, 14 were left-handed CTS (40%), while 21 were right-handed CTS (60%). The mean age was 51.75±5.33 years, while the mean body mass index was 29.82±4.23. The mean time between the onset of symptoms and the time of surgery was 6.51±2.06 months (Table 1).

Surgical Technique: All patients were operated on by a single experienced surgeon using the same technique. Under a pneumatic tourniquet, after the upper limb was properly stained and draped, a 3-4 cm longitudinal incision

Table 1. Demographic, clinical and examination data of the patients

Gender (F/M)	28/7
Age (years)	51.75±5.33
Side (R/L)	21/14
Symptom onset time (months)	6.51±2.06
Numbness	94.55%
Weakness	69.3%
Night pain	85.71%
Tinel test positivity	77.14%
Phalen test positivity	68.57%
BMI (kg/m²)	29.82±4.23

F: Female, M: Male, R: Right, L: Left, BMI: Body mass index

was made over the volar crease. The transverse carpal ligament, which forms the roof of the carpal tunnel, was completely transected, and the superficial palmar fascia was loosened. Only the skin was closed with a nonabsorbable 4/0 suture. A fixation splint was not applied after surgery, but an elastic bandage was applied. After surgery, patients were allowed to use their hands. Two weeks after the operation, the skin sutures were removed.

EMG was performed by the same neurologist using the EMG device. The EMG values of all patients were obtained 2-6 ±3.6 days before the surgical procedure, while the late postoperative term (48±3 months) EMG was performed after the completion of surgical decompression.

The diagnosis CTS was made when a peak velocity of conduction of sensation of the median nerve slower than 41.25 m/s or a velocity of conduction slower than 34 m/s of a mixed nerve on the palmar side of the hand and the volar side of the distal forearm (8 cm) or distal motor latency (DML) of the abductor pollicis brevis muscle longer than 3.6 m/s were recorded (15). The EMG results obtained were graded accordingly using the clinical grading system developed by Padua et al. (10).

Hand grasp strength was measured using a Jamar Dynamometer. In contrast, the power of the digits was measured using the Pinchmetre. All measurements were taken thrice, and the mean values of the three measurements were calculated in kilograms (kg). These measurements were taken one day before surgery and four years after the time of surgery.

The same surgeon assessed Tinnel and Phalen's tests for all patients (16,17).

Patient Evaluation Measurement (PEM) clinical grading system was used for clinical evaluation. Many scoring systems have been developed to evaluate patient satisfaction and functional outcomes after CTS surgery. Studies indicate that the PEM questionnaire is easily applicable, easy to understand, and reliable compared to other evaluations in evaluating patient satisfaction and functional results in the application and outcome stages of the treatment of CTS (17).

Statistical Analysis

Normality control in statistical analysis was performed by the Shapiro-Wilk test, histogram, Q-Q plot, and boxplot diagrams. Preoperative and control comparisons of EMG, PEM, and grip strength variables were performed using Wilcoxon signed-ranks test. The significance threshold was taken as $p<0.05$ and bidirectional. The correlation between EMG, PEM, and grip strengths was evaluated using the Spearman correlation test ($p<0.01$). Analysis were performed using the NCSS 10 software (2015. Kaysville, Utah, USA).

RESULTS

The mean EMG value of DML was 5.09±0.07 m/s in the preoperative period, while it was 3.83±0.12 m/s in the postoperative period. Moreover, a significant statistical difference was found between the DML values in the preoperative and late postoperative periods with a p-value of 0.0023.

According to the Padua evaluation criteria, EMG values, the mean Compound Action Potential (CMAP) of preoperative EMG was 8.49±0.56 m/s, while the mean of postoperative EMG was 20.00±1.14 m/s. Moreover, a significant statistical difference was found between the CMAP values in the preoperative and late postoperative periods with a p-value of 0.0037. As a result, the mean CMAP of preoperative EMG was 8.49±0.56 m/s, while the mean of postoperative EMG was 20.00±1.14 m/s. Additionally, a significant statistical difference was found between the CMAP values in the preoperative and late postoperative periods with a p-value of 0.0037.

The mean sensory nerve conduction velocity (SNCV) was 35.60±3.44 m/s preoperatively and 52.26±3.46 m/s postoperatively. A significant statistical difference was found between SNCV values in the preoperative and late postoperative periods with a p-value of 0.0074.

The sensory nerve action potential (SNAP) preoperative EMG mean was 3.31±0.43 m/s, while the postoperative mean was 13.28±0.61 m/s. Additionally, a significant statistical difference was found between the SNAP values in the preoperative and late postoperative periods with a p-value of 0.0025 (Table 2).

One patient showed advanced CTS in the preoperative period, four patients showed severe CTS, twenty-six

patients showed moderate CTS, and four patients showed mild CTS. However, the postoperative Padua chart showed minimal residual symptoms of entrapment in six patients and complete resolution of symptoms in twenty-nine patients.

Using the PEM criteria and the hand functional status assessment, the preoperative mean score was 58.77±7.89, while four years after surgery, it was 13.48±4.01. A significant statistical difference was found between the two preoperative and late postoperative period scores with a p-value of <0.0001 (Table 2).

Tinnel and Phalen's tests were performed in all patients an average of 1.3 weeks before and four years after surgery. Tinnel sign was positive in 23 patients, while Phalen test was positive in 31 patients before surgery. Whereas Tinnel sign was positive in 4 patients and Phalen test was positive in 2 patients four years after surgery.

The preoperative mean values of handgrip force, Palmer flexion force, lateral deviation force, and distal phalanx flexion force were (34.05±2.98, 14.00±1.47, 9.92±1.72, and 9.54±0.74 kg) respectively. However, the mean values four years after surgery were (41.71±3.25, 16.00±1.26, 12.28±1.63, 12.28±1.63, and 10.04±0.84 kg). Statistical significance was found in all groups with p values of (0.0001, 0.0035. 0.0072, and 0.0022, respectively) (Table 3).

DISCUSSION

There is no standard evaluation algorithm to quantify the success rate in the postoperative period in carpal tunnel surgery (18,19). However, objective evaluation methods such as EMG and handgrip strength measurement and sometimes subjective evaluation methods such as physical examination and satisfaction measurement questionnaires can be used to assess decompression surgery's success or failure rate (20,21).

EMG is considered highly sensitive in the diagnosis of CTS (22). The literature search revealed that many authors prefer EMG examination and physical examination to confirm the diagnosis of CTS. However, the role of EMG in the postoperative period to assess complete recovery and recurrence is still controversial (23).

Table 2. Comparison of EMG measurements before and after surgery

Variable	Preoperative	Postoperative control
Distal motor latency (ms)	5.09±0.07	3.83±0.12
Compound muscle action potential (ms)	8.49±0.56	20.00±1.14
Sensory nerve conduction velocity (ms)	35.60±3.44	52.26±3.46
Sensory nerve action potential (ms)	3.31±0.43	13.28±0.61

EMG: Electromyelography

Table 3. Comparison of handgrip strength, palmar grip, finger lateral grip, fingertip grip strengths preoperatively, postoperatively, and contralateral side

		Preoperative	4th year control	p-value
Grip strength (kg)	Operated hand	34.05±2.98	41.71±3.25	**<0.0001**
	Contrlateral hand	44.08±2.99	42.77±2,65	0.0858
	p-value	**<0.0001**	0.1008	-
Palmar grip (kg)	Operated hand	14.00±1.47	16.00±1.26	**<0.0001**
	Healthy hand	16.51±1.31	16.62±1.47	0.7281
	p-value	**<0.0001**	0.1293	-
Finger lateral grip (kg)	Operated hand	9.02±1.72	12.28±1.63	**<0.0001**
	Healthy hand	13.54±1.54	13.05±1.57	0.2076
	p-value	**<0.0001**	0.0620	-
Fingertip grip (kg)	Operated hand	9.54±0.74	10.04±0.84	**<0.0001**
	Healthy hand	10.85±0.97	10.88±1.49	0.9576
	p-value	**<0.0001**	0.1207	-

Yilmaz et al. (14) Compared EMG results and clinical manifestations of postoperative early CTS decompression surgery. He concluded that clinical healing was faster than EMG healing in the postoperative healing period; therefore, clinical presentation and EMG do not correlate closely, especially in the first three months after surgery (14).

EMG can help detail the syndrome with various differential diagnoses and recurrent cases, but in the classic CTS, ultrasound and magnetic resonance imaging are more useful noninvasive diagnostic measures (22,23).

Uchiyama et al. (15) have demonstrated that improvement in postoperative EMG values is slow and sometimes requires several months to show statistical significance compared with preoperative EMG values.

Louie et al. (16) showed that clinical improvement of patients after CTS decompression surgery improves much faster than EMG results within the first three months. In contrast, after 3-6 months, clinical improvement and EMG results correlate closely. However, six months after surgery, the trends had not evolved in favor of either assessment method (16).

EMG plays an essential role in diagnosing neural ischemia when an entrapped nerve is subjected to prolonged compression; even decompression surgery does not immediately recover neural ischemia, leading to long-term improvement in EMG scores (23,24).

In this study, the long-term results (after four years) of CTS decompression surgery evaluated by EMG improved significantly. Moreover, similar results were shown between the parameters of clinical evaluation variation and EMG results.

However, the improvement in late EMG results is mainly related to the nerve sheath's prolonged compression-induced neural ischemia effect.

This study showed similar results regarding handgrip strength weakness in patients with CTS. Patients diagnosed with moderate to severe CTS-developed weakness in handgrip strength (14-16). However, it was improved that clinical assessment parameters may return to normal values similar to those of the nondiseased limb in the late follow-up periods.

Although various charts have been described to measure postoperative patient satisfaction, the PEM scoring system is a simple, effective, and trustworthy method to assess functional and satisfactory outcomes after CTS decompression surgery (24,25).

This study evaluated functional outcomes and satisfaction levels before and four years after CTS decompression surgery. The PEM scoring technique, physical examination, and EMG study showed similar and correlating results four years after CTS decompression surgery.

The different ages of patients, different gender, and different occupation are considered weak points in this study.

However, the use of the same surgical technique by the same surgeon, EMG, PEM, and clinical evaluation procedures assessed by the same neurologist are study strengths.

CONCLUSION

In late decompression surgery, the evaluation of CTS, PEM, hand measurements, and EMG has shown satisfactorily good and closely correlated results. Therefore, the PEM, hand measurements, and EMG may be reliable methods for evaluating the effects of CTS late decompression surgery.

ETHICS

Ethics Committee Approval: All the patients were investigated after the Taksim Training and Research Hospital's approval of the Clinical Research Ethics Committee (decision no: 110, date: 16.10.2019).

Informed Consent: Informed consent was also obtained from the patients.

Authorship Contributions

Surgical and Medical Practices: A.A., C.M., Concept: A.A., A.P., C.M., Design: A.A., M.Ü.Ç., A.K., N.A., Data Collection or Processing: M.Ü.Ç., A.K., Analysis or Interpretation: A.P., N.A., Literature Search: A.A., A.K., C.M., Writing: A.A., M.Ü.Ç., A.P., N.A.

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Research

Recurrent Coronary Artery Disease Due to Acetylsalicylic Acid Resistance May Be Related to COX-1 and COX-2 Mutations

Asetilsalisilik Asit Direnci Nedeni ile Oluşan Rekürren Koroner Arter Hastalığı, COX-1 ve COX-2 Mutasyonları ile İlişkili Olabilir

Deniz Kıraç[1], Emrah Bayram[2], Tansu Doran[1], Elif Çiğdem Keleş[3]

[1]Yeditepe University Faculty of Medicine, Department of Medical Biology, Istanbul, Turkey
[2]University of Health Sciences Turkey, Umraniye Training and Research Hospital, Clinic of Cardiology, Istanbul, Turkey
[3]Yeditepe University Faculty of Medicine, Department of Biostatistics and Medical Informatics, Istanbul, Turkey

ABSTRACT

Objective: Acetylsalicylic acid (ASA) is a commonly used antiplatelet drug for the treatment of coronary artery disease (CAD). However, in some patients recurrent CAD occurs due to ASA resistance (AR). This condition may be related to some genetic factors. Therefore, this study aims to investigate the effects of cyclooxygenase (COX)-1 and COX-2 mutations on recurrent CAD due to AR.

Methods: Hundred CAD patients taking 100 mg ASA daily for 2 years were enrolled to the study. The patients were divided into two groups according to their recurrent CAD status. Forty-eight patients with recurrent CAD due to AR and 52 patients without recurrent CAD were selected to ASA resistant (AR+) and ASA non-resistant (AR-) group, respectively. AR was confirmed by platelet aggregation testing. Risk factors related to recurrent CAD were also obtained. After DNA was isolated from peripheral blood, rs1330344 variation in *COX-1* and rs20417 variation in *COX-2* were determined using real-time polymerase chain reaction. Results were evaluated statistically.

Results: COX-1 and COX-2 mutations were mostly detected in the AR+ group however these data were not found statistically significant. Nevertheless, C allele of COX-2 was found statistically high in the AR+ group (67.9%) (p=0.023). Additionally statistically significant associations were found between high total cholesterol and low density lipoprotein cholesterol levels with the GC genotype of COX-2.

Conclusion: It was suggested a relation between COX-2 mutations and recurrent CAD due to AR. Similar studies with a large population must explain the mechanisms governing the association of COX-1 and COX-2 genotypes and response to ASA in recurrent CAD patients.

Keywords: ASA resistance, recurrent CAD, COX-1, COX-2

ÖZ

Amaç: Asetilsalisilik asit (ASA), koroner arter hastalığının (KAH) tedavisinde yaygın olarak kullanılan antitrombotik ilaçlardan biridir. Ancak bazı hastalarda ASA direncine (AR) bağlı olarak rekürren KAH oluşur. Bu durum bazı genetik faktörlerle ilişkili olabilir. Bu nedenle bu çalışmanın amacı, siklooksijenaz (COX)-1 ve COX-2 mutasyonlarının AR'ye bağlı rekürren KAH oluşumu üzerine etkilerini araştırmaktır.

Gereç ve Yöntem: İki yıl boyunca günlük 100 mg ASA kullanan 100 KAH hastası çalışmaya alındı. Hastalar tekrarlayan KAH durumlarına göre iki gruba ayrıldı. AR'ye bağlı rekürren KAH gözlenen 48 hasta ASA dirençli (AR+) grubuna, rekküren KAH gelişmeyen 52 hasta ise ASA dirençli olmayan (AR-) grubuna dahil edildi. AR, trombosit agregasyon testi ile ölçüldü. Ayrıca diğer risk faktörleri ile ilgili bilgiler temin edildi. Periferik kandan DNA izole edildikten sonra *COX-1* genindeki rs1330344 ve *COX-2* genindeki rs20417 mutasyonlarının varlığı gerçek zamanlı polimeraz zincir reaksiyonu yöntemi kullanılarak incelendi. Sonuçlar istatistiksel olarak değerlendirildi.

Bulgular: COX-1 ve COX-2 mutasyonları en çok AR+ grubunda tespit edilmiş olmasına rağmen, bu sonuç istatistiksel olarak anlamlı bulunmadı. Bununla birlikte, AR+ grubunda COX-2'nin C alleli istatistiksel olarak anlamlı düzeyde yüksek bulundu (%67,9) (p=0,023). Ek olarak yüksek total kolesterol ve düşük yoğunluklu lipoprotein kolesterol düzeyleri ile COX-2'nin GC genotipi arasında istatistiksel olarak anlamlı ilişkili olduğu belirlendi.

Address for Correspondence: Deniz Kıraç, Yeditepe University Faculty of Medicine, Department of Medical Biology, Istanbul, Turkey
Phone: +90 542 485 52 92 E-mail: denizyat@hotmail.com ORCID ID: orcid.org/0000-0002-3599-7344

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Sonuç: COX-2 mutasyonları ile AR'ye bağlı rekürren KAH arasında bir ilişki olduğu düşünülmektedir. Rekürren KAH gözlenen hastalarda COX-1 ve COX-2 genotiplerinin ilişkisini ve ASA'ya yanıtı etkileyen mekanizmaları açıklamak için daha fazla hasta ile benzer çalışmaların yapılmasına ihtiyaç vardır.

Anahtar Kelimeler: ASA direnci, rekürren KAH, COX-1, COX-2

INTRODUCTION

Coronary artery disease (CAD) is a significant health problem and its complications lead to mortality and disability in the world (1). CAD causes more than 7 million people deaths every year worldwide (2). CAD is a complex disease related to genetic and environmental factors (3).

Acetylsalicylic acid (ASA) is an antiplatelet agent and commonly used for treating cardiovascular disease (4). ASA can decrease mortality and adverse cardiovascular events in patients with CAD (5,6). However, it is thought that approximately half of the patients do not benefit from ASA effectively (7). This condition is known as ASA resistance (AR). AR involves the development of thrombotic vascular events despite aspirin treatment. The heritability of this disorder is thought to be approximately 50% (3). Therefore, investigation of the genetic basis of this disorder due to AR is important for finding new treatment approaches.

Patients who have AR are unable to respond to treatment for CAD as a result of recurrent cardiovascular events are observed in these patients (8-11). ASA irreversibly inhibits platelets by acetylating COX-1 and COX-2 enzymes in platelets (12,13). *COX* genes are related to ischemic stroke (14,15).

The *COX-1* gene contains 10 introns and 11 exons. It is located on chromosomes 9q32-q33.3. COX-1 regulates blood coagulation and platelet function in the body. COX-2 contains 9 introns and 10 exons. It is located on chromosomes 1q25.2-q25.3. COX-2 is found generally in the nuclear membrane and exists in platelets and vascular endothelial cells (16).

Although *COX-1* and *COX-2* genes are related to AR, studies on this subject are insufficient. Therefore in this study the relation between COX-1 and COX-2 variations with AR in recurrent CAD patients were investigated.

The etiology of AR also includes some other factors such as smoking, poor diet, diabetes mellitus, gender, non-compliance with the amount of drug use, hypertension and excessive COX-2 production in platelets (17-19). There may also be some other factors that lead to unsuccessful ASA therapy (17). Therefore in this study the relation between COX-1, COX-2 variations, and other risk factors with recurrent CAD due to AR was also investigated.

METHODS

Patient Characteristics

A hundred patients with CAD who have applied University of Health Sciences Turkey, Umraniye Training and Research Hospital, Cardiology Polyclinic and taking 100 mg ASA daily for 2 years (2018-2020) were enrolled to the study. The patients were divided into two groups according to their recurrent CAD status. Forty-eight patients with recurrent CAD were selected to the AR+ group and 52 patients without recurrent CAD were selected to the AR- group. Patients diagnosed with recurrent CAD were selected from patients who had previously undergone percutaneous coronary intervention (PCI). The recurrent CAD group was determined as those who needed revascularization again with PCI after the first procedure. Patients who used ASA with other antiaggregant or anticoagulants, were allergic to ASA and stopped ASA for any reason for 2 years were excluded from the study. The information regarding the risk factors such as smoking, alcohol consumption was also obtained. This study is an experimental study. This study protocol was approved by the Institutional Ethics Committee of University of Health Sciences Turkey, Umraniye Training and Research Hospital, Istanbul, Turkey (decision no: 139, date: 24.07.2019). Each individual was informed about the study and written informed consent was obtained from each participant. The study was conducted in accordance with the relevant regulations of the Ministry of Health.

Platelet Aggregation Testing

AR was confirmed by platelet aggregation testing. Platelet aggregation studies were conducted in whole blood lumiaggregometer (Chronolog Corporation, Model 560-Ca). AR was defined as a mean aggregation of ≥20% with 0.5 mg/mL arachidonic acid and a mean aggregation of ≥64% with 5 µM adenosine diphosphate (20).

Blood Sampling and Genotyping

DNA samples of 100 patients were isolated from peripheral blood sample using QIAamp DNA Blood Mini kit (Qiagen, GmBH, Hilden, Germany). DNA concentrations were measured using a Nanodrop spectrophotometer (Thermo Scientific, Foster City, CA, USA). Real-time polymerase chain reactions (PCR) for COX-1 (rs1330344) (-1676 T>C) and COX-2 (rs20417) (-765G>C) were performed using 7500 Fast Real-Time PCR System (Applied Biosystems, Foster

City, CA, USA). The reaction was performed according to the manufacturer's instructions.

Statistical Analysis

Statistical Package for the Social Science 23.0 was performed for statistical analysis. Normal distribution assumption was checked with the Kolmogorov-Smirnov test. Two independent samples t-tests was used to compare continuous variables' means between two groups which were normally distributed. Kruskal-Wallis tests were performed to investigate the difference between genotypes and risk factors (which are not normally distributed). If there were statistically significant differences for pairwise comparison, Mann-Whitney U test was performed and Bonferroni correction was applied to p values. P values less than 0.05 ($p<0.05$) were considered statistically significant.

RESULTS

Study Population

Table 1 shows the baseline characteristics of the study population. When the characteristics were compared between groups; gender, fasting blood glucose level, high density lipoprotein (HDL) and hypertension were found statistically significant in AR+ group ($p<0.05$).

COX-1 and COX-2 Genotyping

Table 2 shows the genotype distribution of groups. When groups were compared with each other, however heterozygote and homozygote variations were mostly found in the AR+ group for both COX-1 and COX-2, the relation between groups were not found statistically significant.

Allele Frequencies of COX-1 and COX-2 Variations

Table 3 shows allele frequencies of *COX-1* and *COX-2* genes in study groups. When groups were compared with each other, the presence of C allele of COX-2 was found statistically high in the AR+ group ($p=0.023$).

Relation Between Risk Factors and Polymorphisms

When the relation between risk factors and variations were investigated, it was found that the heterozygote genotype of COX-2 is associated with high total cholesterol and Low density lipoprotein (LDL) levels ($p<0.05$). Table 4 shows the relation between risk factors and mutations.

DISCUSSION

CAD is one of the most known heart disease and leads to death in the world. Considering factors such as unhealthy life, CAD rates are also increasing in low and middle income countries (21). Due to recurrent CAD, adverse outcomes

Table 1. Baseline characteristics of the study population

Baseline characteristics		Groups (number of participants)		p-value
		AR- group (n=52)	AR+ group (n=48)	
Age (years)		59.44±10.52	59.60±10.28	0.938
Height (cm)		169.12±28.45	166.71±7.37	0.414
Weight (kg)		78.09±10.23	80.31±10.94	0.231
Body mass index		28.66±3.79	28.89±3.79	0.6
Gender	Female	29 (55.8%)	15 (31.3%)	0.014*
	Male	23 (44.2%)	33 (68.8%)	
Fasting blood glucose level (mg/dL)		106.62±36.43	117.85±39.01	0.002*
Total cholesterol (mg/dL)		191.04±42.43	203.27±62.25	0.588
LDL (mg/dL)		111.69±41.09	130.39±54.69	0.137
HDL (mg/dL)		51.31±10.91	46.19±8.82	0.012*
Triglyceride (mg/dL)		144.39±92.75	154.67±90.59	0.28
Diabetes mellitus (%)		9 (17.3%)	11 (22.9%)	0.484
Hypertension (%)		24 (46.2%)	34 (70.8%)	0.012*
Smoking (%)		26 (50%)	31 (64.6%)	0.141
Alcohol consumption (%)		3 (5.8%)	5 (10.4%)	0.475

LDL: Low density lipoprotein, HDL: High density lipoprotein, COX: Cyclooxygenase, AR-: ASA non-resistant, AR+: ASA resistant, ASA: Acetylsalicylic acid, *p<0.05

such as death, heart failure, stroke, malignant arrhythmia can be seen more often (22,23). Therefore, it is critical to identify preventable causes of recurrent CAD and to take action against them. The frequency of recurrent cardiovascular events due to AR also varies between countries (24).

A meta-analysis showed a 25% reduction in serious vascular events in high-risk patients with CAD using ASA (10). ASA prevents the conversion of arachidonic acid to thromboxane TXA2 by irreversibly inhibiting COX-1. This inhibition occurs by acetylation of the serin-530 residue located in the active site of COX-1 (25,26). Irreversible enzyme inhibition causes complete COX-1 inhibition with a daily dose of ASA (26). ASA can also reduce the risk of ischemic events by 22% in patients with atherothrombosis (7). However, recurrent cardiovascular events have still seen at a high rate in patients who use ASA (27). Therefore, identification of genetic or environmental factors that may cause recurrent CAD is important for the new therapeutic approaches. Therefore in this study the relation between COX-1, COX-2 variations, and other risk factors related to AR in recurrent CAD patients were investigated.

Table 2. COX-1 and COX-2 genotyping results of groups

Gene names accession number of variations and genotype distributions	Groups (number of participants)		p-value
	AR- group (n=52)	AR+ group (n=48)	
COX-1 (rs1330344) (-1676 T>C)			
TT	42 (80.8%)	32 (66.7%)	0.202
TC	10 (19.2%)	15 (31.3%)	
CC	0 (0%)	1 (2.1%)	
COX-2 (rs20417) (-765G>C)			
GG	44 (84.6%)	32 (66.7%)	0.103
GC	7 (13.5%)	13 (27.1%)	
CC	1 (1.9%)	3 (6.3%)	

*p<0.05, COX: Cyclooxygenase, AR-: ASA non-resistant, AR+: ASA resistant, ASA: Acetylsalicylic acid

Table 3. Allele frequencies of COX-1 and COX-2 in study groups

Gene names accession number of variations and alleles	Groups and allele distributions		p-value
	AR- group (n=52)	AR+ group (n=48)	
COX-1 (rs1330344) (-1676 T>C)			
T	94 (90.4%)	79 (82.3%)	0.094
C	10 (9.6%)	17 (17.7%)	
COX-2 (rs20417) (-765G>C)			
G	95 (91.3%)	77 (80.2%)	**0.023***
C	9 (8.7%)	19* (19.8%)	

*p<0.05, COX: Cyclooxygenase, AR-: ASA non-resistant, AR+: ASA resistant, ASA: Acetylsalicylic acid

Table 4. Relation between risk factors and mutations

Risk factors-variations relationship	Genotype distributions			p-value
	Wild type	Homozygous mutation	Heterozygous mutation	
COX-2 (rs20417)				
Total cholesterol	188.89±50.39*	188.25±43.57	229.1±54.11*	0.01*
LDL	112.13±44.57*	114.5±41.46	154.35±52.75*	0.004*

*p<0.05. LDL: Low density lipoprotein, COX: Cyclooxygenase

COX is an enzyme that is responsible for the synthesis of prostaglandins (PGs) and platelet generation of TXA2. PGs produced by COX-2 can also be synthesized by COX-1 (8). rs1330344 (-1676 T>C) of COX-1 was found to contribute significantly to the occurrence of ischemic stroke. On the one hand, it has been noted that the TT genotype of rs1330344 can reduce ischemic stroke susceptibility and cardioembolic stroke or small vessel occlusion (16). In one study, it was found that the frequency rates of alleles in the COX-1 C50T were 8.6%, therefore this variation may influence the effect of ASA (8). A842G, C22T, G128A, C644A, and C714A are mostly detected variations in the COX-1 and they are related to ASA response (28). In another study, low-dose ASA irreversibly acetylates COX-1 and reduce platelet activity by inhibiting the production of thromboxane A2 (29). In our study, however COX-1 rs1330344 variation was mostly found in the AR+ group, the relation between groups was not found statistically significant (Table 2).

COX-2, induced by cytokines in response to inflammatory stimuli, has been expressed on endothelial cells and macrophages (8). rs20417 SNP is located in the promoter region of COX-2 (-765G>C). This locus mutation in the *COX-2* gene can change the promoter activity and affect the expression of COX-2 (16). In a study, a significant relationship was found between rs20417 polymorphism and CAD (30). In another study it was found that the frequency rate of C allele in the COX-2 rs20417 is 21.3% (8). Therefore, it was suggested that the variation of the *COX-2* gene influences the effect of ASA. Some metabolic factors (reduced absorption or increased metabolism of ASA) may also cause AR. Some studies have suggested that the COX-2 variant increases the risk of AR (8,31). The *COX-2* gene is induced by the activation of the signal transduction pathway and COX-2 protein is covalently acetylated by ASA. ASA activity can be measured using serum TXB2 or urine 11-DH-TXB2 (TXA2 pathway endproducts). Unlike other results, the COX-2 -765G>C variant after ASA treatment causes a high decrease in serum and urine 11-dehydrothromboxane B_2 (11-DH-TXB2) levels (28). In our study, COX-2 (33.3%) variation was mostly detected in the AR+ group, however the relation between groups was not found statistically significant (Table 2). When allel frequencies were compared between groups, C allele of COX-2 was found statistically high in AR+ group ($p<0.05$) (Table 3). Therefore, it was suggested a relation between COX-2 mutations and recurrent CAD due to AR.

One study showed a higher prevalence of AR in patients with acute coronary syndrome than healthy individuals. AR was more prevalent in patients with smokers and low HDL cholesterol. However, no significant difference was found for gender, age and hypertension (11). In other studies any relation was not detected for total cholesterol and LDL cholesterol level with COX-2 variations however in our study, we also found that high total cholesterol and LDL cholesterol levels are related to the GC genotype of COX-2 (Table 4).

CONCLUSION

Similar studies with a large population must explain the mechanisms governing the association of *COX-1* and *COX-2* genotypes and response to ASA in recurrent CAD patients. Detection of AR may be useful in preventing recurrent CAD and reducing mortality and morbidity associated with recurrent CAD.

ETHICS

Ethics Committee Approval: The study, which is compatible with the Helsinki Declaration, was approved by the Institutional Ethics Committee of University of Health Sciences Turkey, Umraniye Training and Research Hospital, Istanbul, Turkey (decision no: 139, date: 24.07.2019).

Informed Consent: All patients and/or legal guardians included in the study provided their written informed consent.

Authorship Contributions

Surgical and Medical Practices: E.B., Concept: D.K., E.B., Design: D.K., E.B., E.Ç.K., Data Collection or Processing: D.K., E.B., T.D., E.Ç.K., Analysis or Interpretation: D.K., E.B., T.D., E.Ç.K., Literature Search: D.K., T.D., Writing: D.K., T.D.

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Research

The Relationship of Elevated Hepatic Fibrosis-4 Index Score with Pneumonia Severity Index and in Hospital Mortality Among COVID-19 Patients Admitted to Intensive Care Unit

Yoğun Bakıma Yatırılan COVID-19 Hastalarında Erken Dönemde Bakılan Yüksek Hepatik Fibrozis-4 Skoru ile Pnömoni Ciddiyet İndeksi ve Hastane İçi Mortalite Arasındaki İlişkinin Araştırılması

Esra Demir[1], Hande Güngör[2], Cem Erdoğan[2], Oktay Olmuşçelik[1], Rümeysa Çakmak[3], Ayşegül Yıldırım[1]

[1]Medipol Mega University Hospital, Clinic of Internal Medicine, Istanbul, Turkey
[2]Medipol Mega University Hospital, Clinic of Anesthesiology and Reanimation, Istanbul, Turkey
[3]Medipol Mega University Hospital, Clinic of Clinical Pharmacy, Istanbul, Turkey

ABSTRACT

Objective: We investigated the relationship hepatic fibrosis-4 (FIB-4) index score calculated in the early period and pneumonia severity index (PSI) and in-hospital mortality in patients hospitalized in the intensive care unit (ICU) due to new severe acute respiratory syndrome coronavirus-2 infection.

Methods: Seventy six consecutive patients diagnosed with coronavirus disease-2019 (COVID-19), hospitalized in the ICU due to hypoxemia, and selected consecutively were included. COVID-19 infection was diagnosed using real-time reverse transcription-polymerase chain reaction (RT-PCR) in nose and throat swab samples. The diagnosis of pneumonia was confirmed by showing typical ground-glass opacities and areas of subsegmental consolidation in lung computed tomography examinations of patients previously diagnosed with COVID-19 by RT-PCR. Hepatic FIB-4 index score and PSI score was calculated separately for each patient. In the statistical method, the independent samples t-test and Mann-Whitney U test were used to compare quantitative data. A chi-square test was used to compare qualitative data.

Results: The FIB-4 value and PSI value were significantly higher ($p<0.05$) in the mortality group than in the non-mortality group. Also, there was no significant statistical difference between the two groups in terms of the other laboratory parameters ($p>0.05$) FIB-4 value was significantly predictive [under the curve 0.835 (0.742-0.929)] in differentiating patients with and without mortality. For a cut-off value of 5.4, FIB-4 had a sensitivity of 60.6%, positive predictive of 95.2%, specificity of 97.6%, and negative predictive value of 75.9%

Conclusion: High FIB-4 index and PSI score detected in the early period in patients admitted to the ICU due to COVID-19 seem to be predictors of in-hospital mortality.

Keywords: Coronavirus infection, liver fibrosis, pneumonia, prognostic factors

ÖZ

Amaç: Yoğun bakım ünitesine (YBÜ) yatırılan, yeni şiddetli akut solunum yolu sendromu koronavirüs-2 enfeksiyonu nedeniyle yatırılan hastalarda erken dönemde hesaplanan hepatik fibrozis-4 (FIB-4) indeks skorunun, pnömoni ciddiyet indeksi (PSI) ve hastane içi mortaliteyle ilişkisinin araştırılması amaçlandı.

Gereç ve Yöntem: Koronavirüs hastalığı-2019 (COVID-19) tanısı konulan, hipoksemi nedeniyle YBÜ'ye yatırılan ve ardışık seçilen 76 hasta dahil edildi. Burun ve boğaz sürüntü örneklerinde gerçek zamanlı ters transkripsiyon-polimeraz zincir reaksiyonu (RT-PCR) kullanılarak COVID-19

Address for Correspondence: Esra Demir, Medipol Mega University Hospital, Clinic of Internal Medicine, Istanbul, Turkey
E-mail: esracokicli@hotmail.com ORCID ID: orcid.org/0000-0002-0427-0900

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enfeksiyonu tanısı konuldu. Daha önce RT-PCR ile COVID-19 tanısı almış hastaların akciğer bilgisayarlı tomografi incelemelerinde tipik buzlu cam opasitelerinin ve subsegmental konsolidasyon alanlarının gösterilmesiyle pnömoni tanısı doğrulandı. Hepatik FIB-4 indeks skoru ve PSI skoru her hasta için ayrı ayrı hesaplandı. İstatistiksel yöntemde, nicel verileri karşılaştırmak için independent samples t-testi ve Mann-Whitney U testi kullanıldı. Niteliksel verilerin karşılaştırılması için ki-kare testi kullanıldı

Bulgular: FIB-4 değeri ve PSI değeri, mortalite olmayan gruba göre mortalite grubunda önemli ölçüde daha yüksekti (p<0,05). Ayrıca diğer laboratuvar parametreleri açısından da iki grup arasında istatistiksel olarak anlamlı fark yoktu (p>0,05) FIB-4 değeri mortalite olan ve olmayan hastaları ayırmada [eğri altında 0,835 (0,742-0,929)] anlamlı olarak prediktifti. 5,4'lük bir eşik değeri için, FIB-4'ün duyarlılığı %60,6, pozitif öngörü değeri %95,2, özgüllüğü %97,6 ve negatif prediktif değeri %75,9 olarak bulundu.

Sonuç: COVID-19 nedeniyle, YBÜ'ye yatırılan hastalarda erken dönemde saptanan yüksek FIB-4 indeksi ve PSI skoru hastane içi mortalitenin prediktörleri olarak gözükmektedir.

Anahtar Kelimeler: Koronavirüs enfeksiyonu, karaciğer fibrozisi, pnömoni, prognostik faktörler

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic continues to threaten public health by being an important cause of mortality due to newly developing mutations and novel variants despite widespread use of vaccination worldwide (1-3). Among patients admitted to intensive care unit for pneumonia and hypoxemia, determining patients at high risk of death early in the infection and treating them more aggressively are particularly important. For this purpose, several risk scores have been developed to predict mortality, which are used in daily practice (4,5). However, some of those scores are too complex, difficult to calculate in daily practice, and time-consuming for clinicians. In this context, there is a need for developing novel risk scores that are relatively simple, inexpensive, and easy-to-calculate that use blood tests routinely studied in daily practice.

Elevation of liver enzymes is common in SARS-CoV-2 infection and has been related to a worse prognosis (6,7). In this regard, some hepatic risk scores predict long-term and short-term prognosis in SARS-CoV-2 infection (8,9). Hepatic fibrosis-4 (FIB-4) index score is one of those hepatic fibrosis scores that can be easily calculated with 4 simple parameters including age, alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels, and platelet (PLT) count (9). Although some of the previous studies have provided important data suggesting that a high FIB-4 score predicts mortality in coronavirus disease-2019 (COVID-19) patients, their overall number is small; moreover, there is a limited number of studies on COVID-19 patients admitted to intensive care unit, necessitating new studies and data on this subject.

In our study, it was investigated the relationship of hepatic FIB-4 index score with pneumonia severity index (PSI) and in-hospital mortality among patients admitted to intensive care unit with SARS-CoV-2 infection.

METHODS

This study included 76 consecutive patients who were diagnosed with COVID-19 and admitted to intensive care unit because of hypoxia. SARS-CoV-2 infection was diagnosed by studying real-time reverse transcription-polymerase chain reaction (RT-PCR) test in nasal and throat swab samples. In COVID-19 patients previously diagnosed by RT-PCR, pneumonia was confirmed by showing the typical ground glass opacities and areas of subsegmentary consolidation in computed tomography (CT).

Among patients who were diagnosed with COVID-19 by showing the typical ground glass opacities and subsegmentary consolidation areas in CT, those with at least a finding given below, which were specified in the R.T. Ministry of Health General Directorate of Public Health, COVID-19 (SARS-CoV-2 infection) Adult Patient Treatment Guideline, were admitted to the intensive care unit (10):

Dyspnea and respiratory difficulty, respiratory rate ≥30/min, PaO_2/FiO_2<300, increased oxygen requirement at follow-up, SpO_2<90% or PaO_2<70 mmHg despite oxygen therapy at a rate of 5 lt/min, hypotension (systolic blood pressure <90 mmHg, and more than 40 mmHg drop in usual blood pressure and mean arterial pressure <65 mmHg, tachycardia >100/min, development of acute organ dysfunction such as acute kidney injury, acute liver dysfunction, confusion, and acute bleeding diathesis, immunosuppression, troponin elevation and arrhythmia, lactate >2 mmol, impaired capillary refill, and skin abnormalities such as cutis marmaratus.

Full blood count, ALT, AST, C-reactive protein, and creatinine levels were studied, and hepatic FIB-4 index score was calculated for each patient individually.

FIB-4 index was calculated using the formula: FIB-4= Age (years)×AST (U/L)/[PLT (10^9/L)×ALT1/2 (U/L) (9).

PSI was calculated by individually assessing and scoring 6 main headings including the demographic data of the patients, comorbidities, physical examination findings, laboratory findings, arterial blood gas analysis results, and radiological pulmonary findings, and 20 subheadings (11,12).

This study complied with the criteria of Helsinki Declaration and approved by Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee (decision no: 91, date: 21.01.2021). Before study entry, written informed consent was obtained from the patients themselves when they could provide it, or their relatives when they were not.

Statistical Analysis

Study data were analyzed using SPSS 27.0 statistical software for Windows (SPSS Inc., Chicago, IL, ABD). Descriptive statistics included mean, standard deviation, median, minimum, maximum, frequency, and percentage. The normality of the distribution of continuous variables was tested using Kolmogorov-Smirnov test. Independent samples t-test and Mann-Whitney U test were used to compare quantitative data. chi-square test was used to compare qualitative data. Receiver operating characteristics curve was used to calculate the cut-off values to discriminate deceased patients with maximum sensitivity and specificity. A p value of less than 0.05 was considered statistically significant.

RESULTS

Demographic data, comorbidities and symptoms of patients are shown in Table 1. The age and gender distribution of the patients did not differ significantly between the groups with and without mortality ($p>0.05$). Cancer, congestive heart failure, stroke, chronic kidney disease, chronic liver disease, diabetes mellitus, chronic obstructive pulmonary disease, asthma, coronary artery disease and extracorporeal membrane oxygenation rates did not differ significantly between groups with and without mortality ($p>0.05$).

Laboratory results of patients are summarized in Table 2. Arterial PH in the mortality group was significantly ($p<0.05$) lower than the non-mortality group. The rate of mechanic ventilator use in the mortality group was significantly ($p<0.05$) higher than the non-mortality group. PaO_2 and SPO_2 values were significantly lower ($p<0.05$) in the mortality group than in the non-mortality group.

The FIB-4 value and PSI value were significantly higher ($p<0.05$) in the mortality group than in the non-mortality group (Table 2, Figure 1). Also, there was no significantly statistical diffence between two groups in terms of the other laboratovary parameters ($p>0.05$) (Table 2).

Additionally, ICU length of stay did not differ significantly ($p>0.05$) between groups with and without mortality.

FIB-4 value was significantly predictive [under the curve 0.835 (0.742-0.929)] in differentiating patients with and without mortality. For a cut-off value of 5.4, FIB-4 had a sensitivity of 60.6%, positive predictive of 95.2%, specificity of 97.6%, and negative predictive value of 75.9% (Figure 2).

DISCUSSION

Our study has two important results. Firstly, a high hepatic FIB-4 score calculated at the time of diagnosis appears to be correlated with in-hospital mortality. Secondly, a high PSI score calculated at the time of diagnosis was higher in a patient with mortality. The reason why mortality was higher in patients with higher FIB-4 score was probably that PSI score was also higher in the same patients.

SARS-CoV-2 infection is a disease characterized by a multi-organ involvement, and mild-to-moderate liver enzyme elevation is frequently encountered during its course (13). Elevated ALT, AST levels combined with mildly elevated bilirubin levels are usually observed (9). The plausible mechanisms for elevating liver enzymes include the direct cytopathic effect of the virus on hepatocytes and cholangiocytes, exaggerated immune response during infection, side effects of some antiviral drugs used to treat the infection, and the occurrence of septicemia during the infection (9,14). However, several studies have also shown that elevated liver enzymes have prognostic significance in SARS-CoV-2 infection (15,16). In this context, it is thought that some hepatic risk scores could be used to determine prognosis. Hepatic FIB-4 index is a useful risk score that can be readily calculated using several laboratory parameters that are widely used to diagnose and monitor COVID-19 patients in daily practice; additionally, many studies have shown that FIB-4 index has prognostic significance in patients with COVID-19 (8,17,18). There are several probable causes of an elevated FIB-4 index in COVID-19 infection. Among these, direct hepatocellular injury caused by the virus, systemic inflammation and cytokine storm, increased pulmonary artery pressure and right chamber pressures are the main ones (17). In a study that included 202 patients admitted to hospital due to COVID-19 infection, a high FIB-4 index was correlated with mortality; there were also positive correlations between a high FIB-4 index and viral load, and monocyte-related cytokines such as interleukin-6 (17). In a more comprehensive, retrospective, multi-center cohort study, Park et al. (18) showed that a high FIB-4 index score was a strong predictor of mortality. Similarly, Xiang et al. (19) demonstrated that FIB-4 index calculated at an early period was an important prognostic marker in patients hospitalized for COVID-19 infection. The authors found that patients with FIB-4 >3.25 had more than 12 times greater need for high-flow oxygen and 11 times greater rate of progression to severe disease, particularly at an early

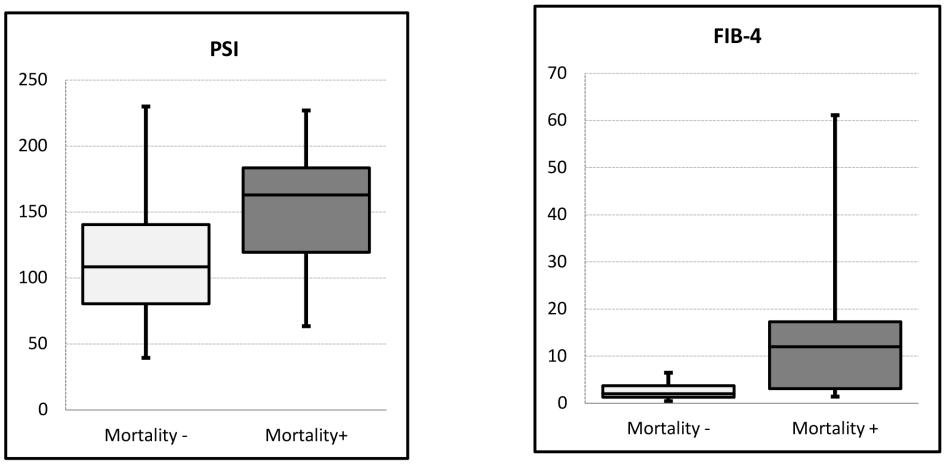

Figure 1. Comparison of FIB-4 index and PSI results between living and deceased patients
FIB-4: Fibrosis-4 index, PSI: Pneumonia severity index

disease period (19). Our results also support those previous observations. Intensive care unit patients who had a higher FIB-4 index early in the disease course suffered a worse prognosis a higher mortality rate.

Another important finding of our study is higher PSI score in patient with mortality. In fact, previous studies have shown that PSI index predicts mortality at the early period of COVID-19 (12,20). For example, Satici et al. (12) found that PSI more effectively predicted 30-day mortality in hospitalized patients than CURB-65, another risk score with proven effectiveness for predicting mortality in community-acquired pneumonia. Similarly, another retrospective study including 1,181 patients showed that PSI was superior than CURB-65 for predicting 30-day mortality (21). However, CURB-65 score was better in predicting patients who needed critical care (21). Hence, patients with a higher PSI score are older and have a higher number of comorbidities, worse vital signs, and a greater rate of multi-organ dysfunction. This makes the finding

	AUC	95% Confidence interval			p
FIB-4	0.835	0.742	-	0.929	**0.000**

ROC CURVE

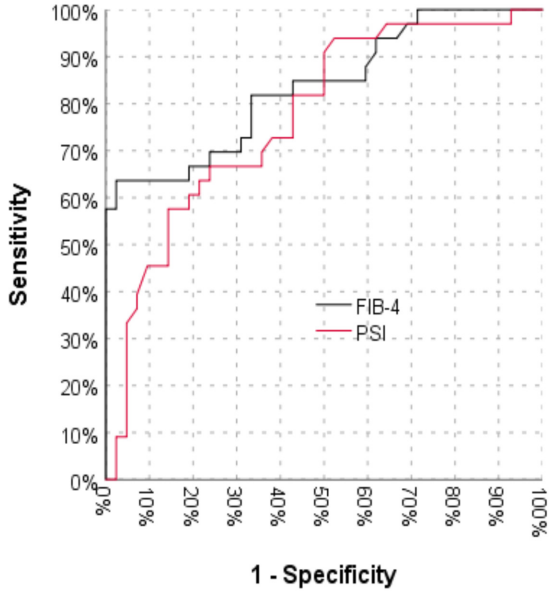

Figure 2. The result of receiver operating characteristic curve
ROC: Receiver operating characteristic, FIB-4: Fibrosis-4 index, PSI: Pneumonia severity index, AUC: Area under the curve

Table 1. Comparison of demographic data, comorbidities and symptoms of patients

		Mortality (-)		Mortality (+)		p
		Mean ± SD/n-%	Median	Mean ± SD/n-%	Median	
Age		62.8±16.2	63.0	65.1±13.2	65.0	0.525[m]
Gender	Female	13/31.0%	-	12/36.4%	-	0.622[X²]
	Male	29/69.0%	-	21/63.6%	-	
Cancer		5/11.9%	-	7/21.2%	-	0.275[X²]
Congestive heart failure		7/16.7%	-	7/21.2%	-	0.616[X²]
Stroke		4/9.5%	-	0/0.0%	-	0.126[X²]
Chronic kidney disease		7/16.7%	-	9/27.3%	-	0.266[X²]
Chronic liver disease		2/4.8%	-	0/0.0%	-	0.501[X²]
Hypertension		21/50.0%	-	15/45.5%	-	0.696[X²]
DM		14/33.3%	-	11/33.3%	-	1.000[X²]
COPD		2/4.8%	-	1/3.0%	-	1.000[X²]
Asthma		3/7.1%	-	4/12.1%	-	0.462[X²]
Coronary artery disease		1/2.4%	-	1/3.0%	-	1.000[X²]
ECMO		0/0.0%	-	2/6.1%	-	0.190[X²]
Symptoms						
High fever		19/45.2%	-	14/42.4%	-	0.807[X²]
Cough		13/31.0%	-	11/33.3%	-	0.826[X²]
Dyspnea		31/73.8%	-	24/72.7%	-	0.916[X²]
Myalgia		4/9.5%	-	5/15.2%	-	0.457[X²]
Headache		1/2.4%	-	4/12.1%	-	0.093[X²]
GIS symtoms		3/7.1%	-	1/3.0%	-	0.626[X²]
Loss of taste and smell		0/0.0%	-	0/0.0%	-	1.000[X²]
Pleural effusion		9/21.4%	-	9/27.3%	-	0.556[X²]
Lung involvement		34/81.0%	-	25/75.8%	-	0.586[X²]

SD: Standard deviation, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, ECMO: Extracorporeal membrane oxygenation, GIS: Gastrointestinal system, [m]Mann-Whitney U test, [X²]chi-square test

of a higher mortality rate among COVID-19 patients with a higher PSI score more understandable. Additionally, one must expect that FIB-4 index, which is calculated using age, PLT count, and basic liver function tests ALT and AST, will be particularly higher in older patients who more commonly have multi-organ failure and liver injury, and a higher PSI score. In conclusion, high FIB-4 index and PSI score calculated early during SARS-CoV-2 infection indicates that these two parameters may independently predict mortality at an early stage. Furthermore, the combined use of these two scores, particularly when both of them are elevated, can allow physicians to diagnose SARS-CoV-2 infection requiring critical care at an early period, and to lower mortality by more aggressively treating such patients.

Study Limitations

Our study has some limitations. A relatively small number of patients is an important limitation. Other important limitations include the lack of having a basal abdominal ultrasonography and not excluding underlying liver diseases that could have increased FIB-4 index. Moreover, the lack of using other hepatic FIB scores such as AST-to-PLT ratio index, aminotransferase

Table 2. Comparison of laboratory findings between living and deceased patients

	Mortality (-)		Mortality (+)		p
	Mean ± SD/n-%	Median	Mean ± SD /n-%	Median	
Heart rate (beats per minute)	98.5±21.7	98.0	99.4±19.7	96.0	0.902[m]
Respiration rate (breaths per minute)	27.0±7.9	26.0	25.4±8.6	24.0	0.330[m]
Systolic blood pressure (mmHg)	136.3±24.7	140.0	124.1±26.2	120.0	**0.034**[m]
Diastolic blood pressure (mmHg)	77.1±15.8	80.0	72.3±14.8	73.0	0.110[m]
Arterial pH	7.4±0.1	7.4	7.3±0.1	7.3	**0.000**[m]
Use of ventilator	13/31.0%	-	31/93.9%	-	**0.000**[X²]
Use of high flow oxygen	36/85.7%	-	14/42.4%	-	**0.000**[X²]
PaO_2 (mmHg)	86.0±19.2	87.5	54.5±8.7	55.0	**0.000**[m]
SPO_2 (%)	95.5±3.4	97.0	79.1±12.5	78.0	**0.000**[m]
FIB-4	2.6±1.6	2.0	14.7±15.9	12.0	**0.000**[m]
PSI	114.2±43.3	108.5	155.2±39.1	163.0	**0.000**[m]
Sodium (mEq/L)	137.0±5.7	137.0	134.9±6.3	136.0	0.096[m]
Glucose (mg/dL)	163.8±81.9	131.1	167.7±93.5	131.8	0.728[m]
Hematocrit (L/L)	34.9±7.3	35.8	33.0±5.6	33.1	0.182[m]
ALT (U/L)	61.3±126.0	37.9	183.9±766.6	23.4	0.144[m]
AST (U/L)	64.4±63.8	47.3	334.0±1510.2	40.6	0.873[m]
Platelet (10^9/L)	245.8±99.8	228.0	250.6±135.3	205.0	0.823[m]
LDH (U/L)	412.8±190.9	359.0	659.5±1230.9	420.0	0.188[m]
CRP (mg/L)	134.1±108.8	92.1	161.3±87.8	163.0	0.147[m]
D-dimer (ng/L)	2900±2870	1852	5173±9897	1992	0.361[m]
Troponin (ng/L)	0.07±0.19	0.01	0.48±1.39	0.01	0.526[m]
Lymphocyte (cells/mm^3)	1.04±0.56	0.84	1.83±5.42	0.82	0.279[m]
Neurophil (cells/mm^3)	8.74±5.25	7.51	9.70±4.89	9.64	0.245[m]
NLR	12.7±13.3	8.2	12.8±9.1	10.6	0.245[m]
PLR	337.8±329.7	288.5	321.3±212.3	276.3	0.777[m]
Ferritin (ng/L)	1335,7±2557,7	596	4382,6±1631,3	946,6	0.036[m]
IL-6 (pg/mL)	227.8±348.2	94.7	763.3±1353.9	151.1	0.097[m]
Time of stay in ICU	8.9±6.5	7.0	9.6±7.9	8.0	0.563[m]

SD: Standard deviation, PaO_2: Partial Pressure of oxygen, SPO_2: Blood oxygen saturation, FIB-4: Fibrosis-4, PSI: Pneumonia severity index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, IL-6: Interleukin-6, ICU: Intensive care unit, [m]Mann-Whitney U test, [X²]chi-square test

ratio to alanine in addition to FIB-4 index may also be considered a limitation. Another important limitation is that other risk scores predicting mortality in COVID-19 infection, such as Severe Community-Acquired Pneumonia, COVID-GRAM score, and CURB-65 score, were not calculated and thus their correlation to FIB-4 was not analyzed (22,23).

CONCLUSION

FIB-4 index, and PSI score calculated at an early period among patients admitted to intensive care unit for COVID-19 appears to be good predictors of in-hospital mortality. More extensive, randomized studies are needed on this subject.

ETHICS

Ethics Committee Approval: This study complied with the criteria of Helsinki Declaration and approved by Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee (decision no: 91, date: 21.01.2021).

Informed Consent: Informed consent form was filled out by all participants.

Authorship Contributions

Surgical and Medical Practices: C.E., H.G., A.Y., Concept: E.D., O.O., Design: E.D., Data Collection or Processing: A.Y., R.Ç., H.G., Analysis or Interpretation: E.D., O.O., H.G., Literature Search: E.D., R.Ç., A.Y., Writing: E.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Research

Increased Neutrophil to Lymphocyte and Platelet to Lymphocyte Ratios in Patients with First Episode Psychosis

İlk Epizod Psikoz Hastalarında Artmış Nötrofil/Lenfosit ve Trombosit/Lenfosit Oranı

Musa Şahpolat[1], Mehmet Akif Karaman[2], Ebru Öztürk Çopur[3], Duygu Ayar[3], Cem Sesliokuyucu[4]

[1]Kilis State Hospital, Clinic of Psychiatry, Kilis, Turkey
[2]American University of The Middle East, Department of Liberal Arts, Agelia, Kuwait
[3]Kilis 7 Aralik University Yusuf Serefoglu Faculty of Health Sciences, Department of Nursing, Kilis, Turkey
[4]Iskenderun State Hospital, Clinic of Psychiatry, Hatay, Turkey

ABSTRACT

Objective: Inflammatory processes have a main role in the etiopathogenesis of psychosis. The aim of current study was to examine differences between the patients with the first episode psychosis's (FEPP) neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) levels with the healthy control groups The NLR and PLR are indicators that may define the existence of systemic inflammatory response.

Methods: The participants of this study included 37 FEPP and 43 healthy individuals who had similar socio-demographic characteristics compared to the patient group. The Positive and Negative Syndrome Scale was conducted to collect data from the patient group. Additionally, participants' complete blood count parameters were analyzed for the study.

Results: The mean NLR and PLR levels of FEPP were significantly higher than the healthy control individuals (p=0.001 and p=0.045). There was no relationship between demographic variables, body mass index, smoking, severity of disease and NLR-PLR.

Conclusion: Based on the literature review and electronic database search, no previous study evaluated PLR in the context of FEP. Therefore, the current study was first examining both NLR and PLR levels in FEP as hematologic inflammatory indicators. Our results indicated that inflammatory processes may play a role in the etiopathogenesis of psychosis.

Keywords: The first episode psychosis, inflammation, lymphocyte, neutrophil, platelet

ÖZ

Amaç: Enflamatuvar süreçler psikozun etiyopatogenezinde anahtar bir role sahiptir. Mevcut çalışmanın amacı, ilk epizod psikoz hastalarında (İEP) nötrofil ile lenfosit oranı (NLO) ve trombosit ile lenfosit oranı (PLO) düzeyleri arasındaki farklılıkları sağlıklı kontrol grubu ile incelemektir. NLO ve PLO sistemik enflamatuvar yanıtın varlığını tanımlayabilecek göstergelerdir.

Gereç ve Yöntem: Bu çalışmaya 37 İEP hastası ve hasta grubu ile benzer sosyodemografik özelliklere sahip 43 sağlıklı gönüllü birey dahil edilmiştir. Hasta grubundan verilerin elde edilebilmesi için Pozitif ve Negatif Sendrom Ölçeği uygulandı. Buna ek olarak, tüm katılımcıların tam kan sayımı parametreleri analiz edildi.

Bulgular: İEP hastalarının ortalama NLO ve PLO düzeyleri sağlıklı kontrol bireylerine göre istatistiksel olarak anlamlı derecede yüksekti (p=0,001 ve p=0,045). Demografik değişkenler, vücut kitle indeksi, sigara kullanımı, hastalık şiddeti ile NLO ve PLO arasında bir ilişki bulunamamıştır.

Sonuç: Literatür taraması ve elektronik veri tabanları aramasına dayanarak, daha önce yapılan hiçbir çalışmada PLO, İEP bağlamında değerlendirilmemiştir. Bu nedenle, mevcut çalışma İEP'de hemaolojik enflamatuvar göstergeler olarak hem NLO hem de PLO düzeylerini inceleyen ilk çalışmadır. Sonuçlarımız, enflamatuvar süreçlerin psikozun etiyopatogenezinde bir rolü olabileceğini göstermiştir.

Anahtar Kelimeler: İlk epizod psikoz, enflamasyon, lenfosit, nötrofil, trombosit

Address for Correspondence: Musa Şahpolat, Kilis State Hospital, Clinic of Psychiatry, Kilis, Turkey
Phone: +90 507 751 76 06 E-mail: drmsahpolat@hotmail.com ORCID ID: orcid.org/0000-0002-0022-2389

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INTRODUCTION

The first episode psychosis (FEP) is the presence of the first psychotic symptoms in an individual. Few previous studies of FEP have examined neutrophil-lymphocyte ratio (NLR) in schizophrenia (SP) (1,2). Psychosis is a progressive, chronic and multifactorial psychiatric disorder affecting approximately 1-2% of people in the world. Studies showed that psychosis is characterized by the positive and negative psychotic symptoms, affective cognitive and psychosocial impairment (3,4). Even though researchers have not fully understood the cause and pathophysiology of psychosis, it has been reported that the immune system affects the brain and behavior through the recognized biological mechanisms (4-6). In the literature, it was known that there was a significant correlation between inflammation and psychosis (4-6). Another finding of the same studies was that the relationship between inflammation and psychosis focused to measure cytokines. As a result, the authors found that assessing cytokines showed increased levels of peripheral proinflamatuar cytokines and indicators (4,6).

Leukocytes can perform different tasks in the immune system (7). For example, it has an important role in mediating inflammation. When examined more carefully, changes in the number of leukocytes may reflect the reaction of the immune system in case of inflammation (7). From here, we can derive the NLR by calculating the number of leukocytes. This is an important indicator of clinical outcomes in neuroimmune disorders (1,8,9). If addressed in terms of applicability and affordability, the NLR, as a new indicator of chronic and low-grade inflammation, is an inexpensive and repeatable test (1,8,9). Platelets are another structure included in proinflammatory secretion along with leukocytes, anti-inflammatory processes and progenitor cells accumulated in the inflammatory regions. The platelet-lymphocyte ratio (PLR) is a commonly used simple indicator that appears to be correlated with inflammation, cardiovascular and chronic diseases (1,8-10). Abnormal platelet counts and mean platelet volume parameters have been determined in some psychiatric disorders including unipolar depression, bipolar disorder and SP (1,11,12). The NLR and PLR have been used recently as an indicator in the diagnosis of various neuropsychiatric disorders. In particular, studies have shown that it has worked correctly in neuropsychiatric disorders, such as Alzheimer's disease, Parkinson's disease, bipolar disorder and SP (8,9,11,12).

A complete blood count test is cheap and can easily be performed in all laboratories that have basic tools. In other words, the NLR, PLR and other all blood counts can be evaluated by clinicians using blood count test, which is a quick and cheap method. For instance, Varsak et al. (2) evaluated the NLR in patients with FEP (FEPP). They found that the NLR was significantly higher in FEPP compared to the control groups However, the NLR was not significantly correlated with the severity based on Brief Psychiatric Rating Scale score. Based on our literature review, previous studies did not focus on the evaluation of the PLR in the context of FEPP. Hence, the main purpose of our study was to investigate whether there were relationships between the FEP and inflammation using the NLR-PLR or not. The second purpose was also to compare the NLR-PLR values of the FEPP with the healthy control groups

METHODS

Participants and Measures

The participants of this study included 37 patients who had the FEP and 43 healthy volunteers who were randomly selected based on the body mass index (BMI). Patients admitted to a public hospital psychiatric outpatient clinic and diagnosed with the FEP by a psychiatric specialist were included in the study. Patients with previous psychiatric diagnoses were excluded from the study. The first group consisted of participants with non-affective drug-naive FEP. The second group included a control group (healthy participants). The FEPP who takes antipsychotics and affective psychosis patient was excluded from the study. Other criteria for exclusion were the presence of substance use disorders, psychiatric disorders other than FEP, other chronic diseases, such as hypertension, diabetes mellitus, dyslipidemia, presence of an organic condition, epilepsy or another severe neurological disorder, presence of infectious disease, pregnancy and women in the menstrual cycle. In total, eight participants with additional exclusion criteria were excluded from the study from 45 patients diagnosed with psychosis.

We collected socio-demographic information including gender, age, smoking, and BMI. All the participants underwent a physical and neurological evaluation. We conducted the study following the principles of the Declaration of Helsinki. The relevant Kilis 7 Aralık University Ethics Committee approved the study protocol (decision no: 5, date: 02.03.2020). The informed consent form was distributed and obtained from all participants. As the measure, the Positive and Negative Syndrome Scale (PANSS) was used to collect data and assess the severity of the psychosis symptoms in the patients (13). Neurological examinations were carried out by the psychiatric specialist who is the first author.

We analyzed complete blood count parameters in all participants. The blood samples were obtained from participants who were fasting between 8 and 10 am using a standard venipuncture technique from antecubital veins. The blood sample was drawn only once, just before the treatment began. The samples were studied at the biochemistry lab on the same day. The accepted reference values were white blood cell (WBC): 4.0-11.0 (/mm^3), red blood cell: 4.0-6.2 (K/uL), platelet: 150-450 (K/uL), lymphocyte: 1.0-4.8 (/mm^3), and neutrophile: 2.0-7.7 (/mm^3).

Statistical Analysis

All the statistical analyses were conducted on Number Cruncher Statistical System (NCSS) version 2007 software (NCSS, Kaysville, UT, USA). The descriptive data included mean, standard deviation, frequency and rate. The Shapiro-Wilk test and graphical examinations were used to assess the normality of the data. The normally distributed quantitative data were compared between two groups using an independent samples t-test. The Pearson's chi-square test was conducted to compare qualitative variables. Pearson's correlation analysis was used to evaluate the relationship among the quantitative variables. Cohen's d values were calculated to measure the degree of effect size of significant differences. Power analysis was performed using the G*Power 3.1 statistical power analysis program to measure the competence of the number of participants in the study in calculating statistical analyses.

RESULTS

The FEPP group consisted of 20 males (54.0%) and 17 females (46.0%). The control group included 23 males (53.4%) and 20 females (46.6%). The results indicated that there was not a significant difference between FEPP's and control groups's age (29.73±11.23 years and 29.32±7.71 respectively, p>0.05). Socio-demographic information of the participants was reported in Table 1.

The NLR value of FEPP was 2.56±0.91 and the control was 1.88±0.78. The NLR value of FEPP was signficantly higher than participants in the control group (p=0.001). PLR value of FEPP was 0.14±0.04 and the controls was 0.12±0.04. The PLR value of FEPP was signficantly higher than the control group (p=0.045). In terms of the relationship between variables, there was no relationship between socio-demographic variables, BMI, smoking, and NLR-PLR (p>0.05). Biochemical characteristics of the participants were summarized in Table 1. Additionally, the results indicated that relationship between the severity of disease and NLR (p=0.940); and PLR (p=0.819) were not significant.

Cohen's d was calculated to understand the magnitude of differences in the variables of neutrophil, lymphocyte, NLR and PLR. The effect sizes for neutrophil (d=0.59) and lymphocyte were medium (d=0.50), for NLR was large (d=0.92) and for PLR was small (d=0.46). The post hoc power analyses were conducted for independent samples t-tests. The results indicated that the power was achieved for neutrophil (0.83) and NLR (0.99). However, lymphocyte (0.72) and PLR (0.65) were under 0.80.

DISCUSSION

Researchers have examined the relationship between psychosis and inflammation for a long time. Results of the previous studies (4-6) supported the hypothetical relationship of SP with proinflammatory cytokine increase, various infectious diseases, metabolic syndrome, cardiovascular diseases and autoimmune diseases (4-6).

The main purpose if this study was to examine the associations between the NLR-PLR and the FEP. The findings of this study were as follows: 1) Increased NLR and PLR were found to be significantly higher in FEPP. 2) There was no relationship between socio-demographic variables, BMI, smoking, and NLR-PLR. 3) There was no relationship between NLR-PLR and severity of disease (PANSS total scores).

Abnormal ultrastructure of blood cell formation and blood cell count in SP was reported in some studies (14). Total WBC count -even inside the normal range- is an indicator of low-grade inflammation, which can encourage vascular injury and atherosclerosis (15). When the relationship between SP and neuroinflammation is evaluated; the results showed differences in serum levels of cytokines such as interleukin-1 (IL-1), IL-2, IL-6, interferon-gamma, and tumor necrosis factor (TNF)-alpha (16,17). A positive relationship between NLR-PLR and inflammatory markers including IL-6 and TNF-alpha was found (18). In addition to inflammation, NLR reflected inflammation in the blood vessel wall, while PLR was indicative of high blood viscosity (19,20). In several studies, the results indicated that schizophrenia patients had higher NLR values than control groups (healthy patients) (1,11,21). Three studies investigated the NLR values in FEPP. Similar to the current study, two of the studies followed similar procedures. A study demonstrated that the experimental group (patients) had higher levels of NLR compared to the control group (2,22). Meanwhile, the other study did not find differences in NLR in patients compared to controls (23).

Researchers stated that the PLR was a more sensitive indicator of inflammation than the NLR (24,25). Platelets display a significant role in atherogenesis, particularly

Table 1. Characteristics of the participants

Variables	FEPP group (n=37)	Control group (n=43)	Significance	p
Age (years)	29.73±11.23	29.32±7.71	0.190*	0.850
Sex (female/male)	17/20	20/23	0.003**	0.960
BMI (kg/m^2)	24.53±4.86	24.15±3.44	0.412*	0.682
Smoking (+/-)	16/21	12/31	2.056**	0.152
PANSS total score	100.64±17.79	-	-	-
WBC count (/mm^3)	8.04±1.84	7.39±1.95	1.505*	0.136
RBC count (K/uL)	4.87±0.51	4.97±0.58	-0.780*	0.438
Platelet (K/uL)	278.10±48.47	271.37±58.76	0.545*	0.587
Lymphocyte (/mm^3)	2.10±0.57	2.40±0.64	**-2.203***	**0.031**
Neutrophil (/mm^3)	5.27±1.62	4.33±1.53	**2.652***	**0.010**
NLR	2.56±0.91	1.88±0.78	**4.068***	**0.001**
PLR	0.14±0.04	0.12±0.04	**2.037***	**0.045**

BMI: Body mass index, NLR: Neutrophil-lymphocyte ratio, PANSS: Positive and Negative Syndrome Scale, PLR: Platelet-lymphocyte ratio, WBC: White blood cell, RBC: Red blood cell, FEPP: Patients with the first episode psychosis, *Independent sample t-test, **Pearson's x^2 test; $p<0.05$

in the progress of inflammation (26,27). Platelets may interplay with several cell types including neutrophils, endothelial cells, T-lymphocytes and mononuclear phagocytes. As stated in the literature, platelets may initiate and exacerbate inflammation on the arterial wall due to its interactions with other cell types especially leukocytes (28,29). It was found higher PLR levels bipolar disorder patients compared to healthy controls in a study (30). Moreover, the results indicated that the NLR and PLR were significantly higher in attention deficit hyperactivity disorder patients than in the control group (31). When the previous studies were reviewed, there was a dearth of studies evaluated the PLR in the context of the FEPP. Hence, this study is the first to demonstrate increased PLR levels in the FEPP. Based on the results of literature and current study's findings, we think that increased NLR-PLR levels may reflect inflammation in SP.

In our study, no significant differences were found between NLR-PLR and severity of disease (PANSS total score). Even though, it was found that NLR at clinical remission decreased compared with the acute psychotic state in a psychotic adolescent group (32), the NLR appeared not to be related to the severity of disease in the FEP and SP (2,11). In another study conducted by Kulaksizoglu and Kulaksizoglu (21) found significant relationship between the severity of disease and NLR. In this study, there was not a significant difference between gender and NLR-PLR in all subjects. However, it was reported that circulating neutrophils, fewer lymphocytes, and higher NLR levels had been found after major surgery in female patients (33). In our study, no significant differences were found between NLR-PLR and severity of disease, we think that it had a relatively small sample size.

Another important finding worth discussion is the differences between NLR-PLR and smoking. The results showed that there was no significant difference between NLR-PLR and smoking. Smoking seems to be associated with increased NLR in the previous studies in general population and increased neutrophil and lymphocyte counts (34-37). However, the PLR was not associated with smoking in the general population (35,37), and similarly no significant difference was found between PLR and smoking in our study. Lack of evidence was reported more frequently that there was a relationship between platelet count and smoking (38,39); even though, lower platelet counts in smokers were also determined (37,40,41).

In this study, the BMI was not significantly correlated with NLR-PLR. However, there are studies claiming the opposite of our findings stating the BMI was related to increased NLR in the general population (34,42) and obesity is often considered to be related to chronic inflammatory conditions (43,44). Hence, dietary habits are considered to influence both leukocyte and platelet counts (45).

Nonetheless, there are some limitations to this study. The first limitation is related to this study's data. This study had cross-sectional data and collected from only one psychiatric clinic. It had a relatively small sample size. Therefore, it affected the power of PLR and lymphocyte; and this prevents the generalization of the findings related to these variables.

We believe that the analysis of inflammatory cytokines, such as cortisol, IL-1, IL-6 as well as NLR, PLR would allow a better understanding of the complex relationship with a higher sample size.

CONCLUSION

Consequently, no previous studies have examined PLR in the context of FEPP. This study was the first to show the NLR-PLR levels (the hematologic inflammatory markers) in the FEPP. Both the NLR and PLR levels in the FEPP were higher than controls among our participants. The NLR and PLR are basic, easy, and inexpensive instruments that should be used for predicting the systemic inflammatory response in the FEPP.

ETHICS

Ethics Committee Approval: We conducted the study following the principles of the Declaration of Helsinki. The relevant Kilis 7 Aralık University Ethics Committee approved the study protocol (decision no: 5, date: 02.03.2020).

Informed Consent: The informed consent form was distributed and obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: M.Ş., C.S., Concept: M.Ş., M.A.K., E.Ö.Ç., D.A., C.S., Design: M.Ş., C.S., Data Collection or Processing: M.Ş., Analysis or Interpretation: M.Ş., M.A.K., E.Ö.Ç., D.A., C.S., Literature Search: M.Ş., M.A.K., E.Ö.Ç., D.A., C.S., Writing: M.Ş., M.A.K., E.Ö.Ç., D.A., C.S.

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Research

SARS-CoV-2 Infection in Patients with Chronic Myeloid Leukemia: A Multicenter Retrospective Study

Kronik Miyeloid Lösemi Hastalarında SARS-CoV-2 Enfeksiyonu: Çok Merkezli Retrospektif Bir Çalışma

Gülden Sincan[1], Yasin Kalpakçı[2], Engin Kelkitli[3], Fuat Erdem[1], Esra Altıntaş Kuşkapan[4], Mete Erdemir[5], Aysu Timuroğlu[1]

[1]Ataturk University Faculty of Medicine, Department of Hematology, Erzurum, Turkey
[2]Sakarya Training and Research Hospital, Clinic of Hematology, Sakarya, Turkey
[3]Ondokuz Mayis University Faculty of Medicine, Department of Hematology, Samsun, Turkey
[4]Ataturk University Faculty of Medicine, Department of Internal Medicine, Erzurum, Turkey
[5]University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital, Clinic of Internal Medicine, Erzurum, Turkey

ABSTRACT

Objective: Coronavirus disease-2019 (COVID-19) infection is more severe and mortality is more common in patients with malignancy.

Methods: We evaluated the clinical course of COVID-19 infection in patients with chronic myeloid leukemia. 327 patients with chronic myeloid leukemia were analyzed and 21 cases with COVID-19 infection were included in this study. The complaints at the time of admission, laboratory and clinical findings, drugs used for treating COVID-19 infection of these patients were examined.

Results: The mean age of 21 patients was 45±15.85 years; 8 (38.1%) of the cases were male and 13 (61.9%) were female. All of these cases had chronic phase chronic myeloid leukemia. The most common complaints at the time of admission to hospital were weakness (66.7%), muscle and/or joint pain (57.1%), sore throat (42.9%). Four (19%) cases had pulmonary involvement and 4 (19%) cases were hospitalized. None of our patients needed intensive care unit admission and mechanical ventilation support. No cases died from COVID-19 infection.

Conclusion: The chronic myeloid leukemia patients with COVID-19 infection had a mild clinical course of COVID-19 infection. This could depend on the normal hematological parameters of chronic myeloid leukemia patients or using tyrosine kinase inhibitors.

Keywords: Chronic myeloid leukemia, COVID-19 infection, tyrosine kinase inhibitors

ÖZ

Amaç: Malignitesi olan hastalarda koronavirüs hastalığı-2019 (COVID-19) enfeksiyonu daha şiddetli ve mortalite daha sıktır. Biz bu çalışmada, kronik miyeloid lösemili hastalarımızda COVID-19 enfeksiyonunun klinik seyrini değerlendirdik.

Gereç ve Yöntem: Kronik miyeloid lösemili 327 hasta analiz edildi ve bu çalışmaya 21 COVID-19 enfeksiyonu olgusu dahil edildi. Bu hastaların başvuru anındaki şikayetleri, laboratuvar ve klinik bulguları, klinik seyirleri, COVID-19 enfeksiyonunun tedavisinde kullanılan ilaçlar incelendi.

Bulgular: Yirmi bir hastanın yaş ortalaması 45±15,85 yıl olup, olguların 8'i (%38,1) erkek, 13'ü (%61,9) kadındı. Bu olguların hepsinde kronik faz kronik miyeloid lösemi vardı. Hastaneye başvuru anında en sık şikayetler güçsüzlük (%66,7), kas ve/veya eklem ağrısı (%57,1), boğaz ağrısı (%42,9) idi. Dört (%19) olguda akciğer tutulumu vardı ve 4 (%19) olgu hastaneye yatırıldı. Hiçbir hastamızın yoğun bakım ünitesine yatış ve mekanik ventilasyon desteğine ihtiyacı olmadı. COVID-19 enfeksiyonu nedeniyle ölen olgu olmadı.

Sonuç: COVID-19 enfeksiyonu olan kronik miyeloid lösemi hastalarında COVID-19 enfeksiyonunun hafif klinik seyri vardı. Bu, kronik miyeloid lösemi hastalarının normal hematolojik parametrelerine veya tirozin kinaz inhibitörlerinin kullanımına bağlı olabilir.

Anahtar Kelimeler: Kronik miyeloid lösemi, COVID-19 enfeksiyonu, tirozin kinaz inhibitörleri

Address for Correspondence: Gülden Sincan, Ataturk University Faculty of Medicine, Department of Hematology, Erzurum, Turkey
Phone: +90 505 272 42 64 E-mail: guldensincan@gmail.com ORCID ID: orcid.org/0000-0002-7671-7628

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a member of the family coronaviridae. It was first reported in Wuhan, Hubei province in December 2019, and the disease it caused was named coronavirus disease-2019 (COVID-19). It is with flu-like symptoms in about 80% of cases. However, severe (dyspnea, respiratory rate ≥30/min, blood oxygen saturation ≤93% and/or 50% increase in lung involvement in 24-48 hours) illness develops in 14% of all cases and critical (respiratory failure, septic shock, multiple organ failure) illness in 5% of all cases (1). The mortality rate is approximately 2%; it causes a higher rate of death by causing severe pneumonia, especially in individuals with chronic diseases such as immunodeficiency, diabetes mellitus, hypertension, cancer, or chronic lung disease (2). The mortality rate associated with COVID-19 infection in cases with solid or hematological cancer is 16.7% (3). In cases with hematologic malignancy, COVID-19 infection causes serious/critical illness in 62% of the cases and the mortality rate is 33% (4). Chronic myeloid leukemia (CML) is a hematological cancer characterized by uncontrolled proliferation of clonal myeloid precursor cells (5). The expected life span of patients with chronic phase CML is longer than that of other hematological malignancies. Tyrosine kinase inhibitors (TKIs) used for treating CML are one of the most important causes of this condition. The expected 10-year survival rate in patients with CML using imatinib mesylate is 80% (6). In the guideline published by the European Leukemia Network group in 2013, the disease-free survival rate was 94% and the overall survival rate was 97% in chronic phase CML (7).

Although COVID-19 infection is more severe and has a high mortality rate in solid and hematological cancer cases, it rarely causes severe and critical disease in cases with CML. Some authors have reported that this is due to the antiviral effect of TKIs on coronavirus. Although the mechanism of action of TKIs in COVID-19 treatment has not been fully determined, Mulgaonkar et al. (8) reported that imatinib mesylate causes inhibition of virus fusion via the cellular kinase pathway, resulting in inhibition of virus replication. In this study, we examined our CML cases who had COVID-19 infection.

METHODS

Ethical approval was obtained from the Ataturk University Faculty of Medicine Clinical Research Ethics Committee for this study (decision no: 9, date: 25.03.2021). In addition written informed consent form was obtained from all participants. This study was designed in accordance with the 1964 Helsinki Declaration. This study was conducted before the start of the vaccination program for COVID-19 infection in our country. For this reason, only the cases who did not receive the COVID-19 vaccine before the COVID-19 infection were included in our study. In our study, the files in the hospital automation system of 327 patients with CML followed in the hematology departments were analyzed retrospectively. In 21 of these cases, SARS-CoV-2 virus was detected by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test in nasopharyngeal and/or oropharyngeal swabs. COVID-19 was diagnosed according to the World Health Organization diagnostic criteria. Age, gender, complaints at the time of admission to hospital, comorbid diseases, laboratory findings, QT interval on electrocardiogram, lung involvement status, drugs used for treating COVID-19 infection, need for oxygen support, hospitalization and intubation was recorded. The name of the TKI used by patients with CML and the continuation of TKI treatment during the COVID-19 infection period was also recorded.

Low-molecular-weight heparin (LMWH) (enoxoparin 0.1 mg/kg/day) was given to all of our cases because the risk of thrombotic complications was high in CML cases. Patients with O_2 saturation <90% in room air were hospitalized. The corrected QT interval >440 ms in men and >460 ms in women was considered a prolonged QT interval. TKI treatment was discontinued in cases with prolonged QT interval. Control RT-PCR test was not performed in our cases after COVID-19 infection treatment.

Statistical Analysis

The IBM SPSS-20 program was used to evaluate the data. Descriptive statistics were used to evaluate the data. Categorical data were presented as numbers and ratios and numerical data as mean ± standard deviation (SD).

RESULTS

COVID-19 was detected in 21 (6.4%) of 327 cases followed up a diagnosis of CML. The mean (SD) age of 21 patients was 45.0 years (14) (range 25 to 74 years); 8 (38.1%) of the cases were male and 13 (61.9%) were female. All the cases had chronic stage CML; 14 (66.7%) patients were treated with imatinib mesylate, 5 (23.8%) patients with dasatinib and 2 (9.5%) patients with nilotinib. Diabetes mellitus, chronic renal failure and Behçet's disease each were in one (4.8%) patient. The body temperature was 37.3±0.6 °C in patients at the time of admission to the hospital. The complaints and laboratory tests of our cases at the time of admission are shown in Table 1. Additionally, the laboratory tests are indicated in Table 2.

O_2 saturation at the time of admission was 93.5±3.7% in patients. Thorax computerized tomography (CT) was performed in 5 (23.8%) cases due to pulmonary symptoms (cough and/or dyspnea), physical examination findings and/or posteroanterior chest radiography findings. Four (19%) cases had pulmonary involvement and 4 (19%) cases were hospitalized. None of our patients needed intensive care unit admission and mechanical ventilation support.

Favipravir treatment was administered to 15 (71.4%) patients [2x1,600 mg (peroral) loading dose on day-1 followed by 1,200 mg maintenance dose (2x600 mg, 2 times daily) on day 2-5]. Favipravir treatment was discontinued at the end of the 5th day in patients. LMWH (enoxoparin 0.1 mg/kg/day) was administered to all cases. Other treatments applied to these cases are shown in Table 3. Imatinib mesylate treatment was discontinued for 14 days because of QT distance (QT interval was: 440 ms) in the electrocardiogram of one patient. None of our cases died from COVID-19 infection.

DISCUSSION

Since December 2019, when the first case of COVID-19 infection was reported, 256,104,097 confirmed COVID-19 infected cases have been reported worldwide, and this number is 3.2% of the world population. The first case with COVID-19 infection in our country was reported on March 11, 2020 and 5,440,368 persons were diagnosed with COVID-19 infection until July 3, 2021. This rate is approximately 6.5% of the country's population. In our study, the rate of COVID-19 infection in CML cases was 6.4%. This rate was higher than the frequency of COVID-19 infection worldwide and it was similar to the rate in our country. 4,336 patients with CML were examined in Brazil and COVID-19 infection was detected in 28 (0.64%) cases (9). 6,883 cases followed up with a diagnosis of CML in Italy were examined and confirmed COVID-19 infection was reported in 12 people (0.17%), two of whom were healthcare workers (10). In our study, the frequency of COVID-19 infection in CML cases was higher than that in Italy and Brazil. This may be due to differences in the number of patients included in the studies and countries have different strategies for testing COVID-19 infection.

5,143,940 (2%) cases died from COVID-19 infection worldwide. In our country, 49,874 (0.9%) cases died from COVID-19 infection since March 11, 2020. Ozturk et al. (11) compared COVID-19 infected cases with and without a history of hemodialysis, chronic renal failure, and renal transplant. They found the mortality rate as 4% in the control group. In our study, In our study, none of our patients with CML needed intensive care and none of them died. The mortality rate in our CML cases was found to be lower than that of the normal population in our country and worldwide. In a study conducted in China, it was reported that COVID-19 infection led to the need for more intensive care and intubation in patients with cancer,

Table 1. Complaints of CML and COVID-19 infection cases at the time of admission

Complaint	n (%)
Sore throat	9 (42.9%)
Weakness	14 (66.7%)
Muscle and/or joint pain	12 (57.1%)
Cough	5 (23.8%)
Dyspnea	3 (14.3%)
Diarrhea	1 (4.8%)
Loss of taste	4 (19%)
Loss of smell	5 (23.8%)

CML: Chronic myeloid leukemia, COVID-19: Coronavirus disease-2019

Table 2. Laboratory tests of CML and COVID-19 infection cases

Laboratory test	Mean ± standard deviation
Hemoglobin (g/dL)	13.92±2.04
Hematocrite (%)	42.03±6.72
Leukocyte (µL)	17385±29899
Neutrophil (µL)	14.51±28.58
Lymphocyte (µL)	2440±1503
Monocyte (µL)	1154±1486
Platelet (µL)	214800±88737
Creatinine (mg/dL)	0.9±0.2
Sodium (mEq/L)	137.22±4.29
Potassium (mEq/L)	4.18±0.31
Calcium (mg/dL)	9.13±0.48
Phosphorus (mEq/L)	4.13±0.32
AST (U/L)	36.1±23.4
ALT (U/L)	29±23
LDH (U/L)	336.11±188.14
CRP (mg/L)	44.8±78.5
Ferritin (ng/mL)	227.56±277.15
D-dimer (ng/mL)	588.29±452.83
Fibrinogen (mg/dL)	336.7±184.1

CML: Chronic myeloid leukemia, COVID-19: Coronavirus disease-2019, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein

Table 3. Drugs given to CML and COVID-19 infection patients in addition to favipravir treatment

Drug	n (%)
Oseltamivir (2x75 mg/day, perorally for 5 days)	5 (23.8%)
Hydroxychlorachine (2x200 mg/day, perorally for 5 days)	6 (28.6%)
Prednisolone (1 mg/kg or pulse steroid)	2 (9.5%)

CML: Chronic myeloid leukemia, COVID-19: Coronavirus disease-2019

and the morbidity and mortality rate was significantly higher than in non-cancer cases (39% and 8%, respectively) (12). In a study conducted in Italy, 355 cases who died from COVID-19 infection were examined and active cancer was detected in 20% of the cases (13). Especially in patients who received chemotherapy and immunotherapy in the 2 weeks before COVID-19 infection, death was observed more (14). In a study in Brazil, 3 of 28 CML cases with COVID-19 infection died (9). A patient who died had advanced age and comorbidity, another case had a newly diagnosed CML disease accompanied by leukocytosis and bacterial infection, and the other case had hematological remission. One case had accelerated phase CML and died 2 months after discharge from the hospital due to pulmonary infection and CML progression. In our study, none of our patients with CML died. This result was less than the mortality rate in COVID-19 infected CML cases in Brazil. The reason for this may be the easy access to the drugs used for treating COVID-19 infection and the free treatment in our country. Additionally, all patients with COVID-19 infection who require hospitalization can be hospitalized because there are enough beds and medical staff in our hospitals. This may have contributed to the absence of COVID-19 related death events in our CML cases.

Yigenoglu et al. (15) reported that 11.5% of cases with COVID-19 infection in our country required follow-up in the intensive care unit. Başcı et al. (16) detected 28 patients with CML with positive SARS-CoV-2 RT-PCR test but they evaluated 16 patients with complete data in Turkey. They compared the clinical and laboratory findings of these cases with the findings of 48 COVID-19 infected cases without cancer. In CML cases compared to the control group, the length of hospitalization stays, mortality rate, the rates of required follow-up in the intensive care unit and mechanical ventilation support was lower than the control group, but no statistical significant difference. In our study, none of our patients with CML required intensive care unit admission and mechanical ventilation support.

Yılmaz et al. (17) examined 243 patients with chronic phase CML and detected COVID-19 infection in 5 patients (2%). Three patients were using imatinib mesylate, one patient was using nilotinib due to imatinib mesylate resistance, and the other patient was using nilotinib due to imatinib mesylate intolerance. None of the patients needed oxygen support in this study. In our study, 2 patients required O_2 support. However, in our study, a patient who required O_2 supplementation had diabetes mellitus and the other case had chronic renal failure. Yılmaz et al. (17) found lung involvement in torax CT in 60% of the cases. In our cases, this rate was 19%. The reason for this may be that our patients with only pulmonary symptoms should undergo torax CT. Asymptomatic lung involvement can also be observed in patients with COVID-19 infection. Yılmaz et al. (17) discontinued nilotinib of 2 patients due to concerns about QT prolongation. In our study, imatinib mesylate was interrupted because the QT distance was in the upper limit of normal in a patient. QT prolongation was not detected in the electrocardiography of our patients whose TKI treatment was continued during the follow-up.

COVID-19 infection causes impaired immune response. Decreased immune response to COVID-19 infection leads to increased viral replication. Increased immune response causes a cytokine storm, increased use of T-cells and lymphopenia. TKIs increase monocyte chemotaxis (18). Baruzzi and Berton (19) reported that abelson (abl) expression is essential for macrophage migration. There are protrusions named podosomes that have abl in their structure on myeloid leukocytes and they are important for the transport of myeloid cells to tissues and cell migration in the interstitium. TKIs prevent cell migration by affecting podosomes. Sisk et al. (20) reported that Imatinib mesylate prevented the entry of coronavirus into the cell (virus-cell and cell-cell) and the viral load of SARS-CoV and Middle East respiratory syndrome coronavirus decreased significantly. Dasatinib contributes to the reactivation of NK cells (18). It has been reported that T-cell activation *in vivo* in leukemia patients with dasatinib (21). It was reported that the very low rate of COVID-19 infection in CML cases was associated with TKI treatment (10). As a result, TKIs have regulatory effects on the immune system. This may contribute to the mild clinical course in patients with COVID-19 who receive TKI treatment. In our study, COVID-19 infection had a mild clinical course, supporting this view.

CONCLUSION

In our study, the mortality rate was lower in our patients who had COVID-19 infection while receiving TKI treatment for

CML compared to the general population in accordance with the literature. The reason for this may be that cases of chronic phase CML have normal hemogram parameters and/or TKIs may reduce the development of SARS by preventing the entry of coronavirus into the cell. Prospective studies with more cases are needed on this subject.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the Ataturk University Faculty of Medicine Clinical Research Ethics Committee for this study (decision no: 9, date: 25.03.2021).

Informed Consent: All patients were informed and written informed consent was obtained.

Authorship Contributions

Surgical and Medical Practices: G.S., Y.K., E.K., F.E., E.A.K., M.E., A.T., Concept: G.S., E.K., F.E., Design: G.S., Y.K., M.E., A.T., Data Collection or Processing: G.S., Y.K., E.A.K., M.E., Analysis or Interpretation: G.S., E.A.K., Literature Search: G.S., E.A.K., A.T., Writing: G.S., E.K., E.A.K.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Research

Impact of COVID-19 Outbreak on Pediatric Trauma Cases in a Tertiary Trauma Center

Üçüncü Seviye Bir Travma Merkezindeki Pediatrik Travma Olgularına COVID-19 Salgınının Etkisi

Buğra İlhan, Göksu Bozdereli Berikol, Halil Doğan

University of Health Sciences Turkey, Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Clinic of Emergency Medicine, Istanbul, Turkey

ABSTRACT

Objective: To evaluate the change in the severity, frequency, and characteristics of pediatric trauma patients presented to the emergency department (ED) during the coronavirus disease-2019 (COVID-19) outbreak.

Methods: A retrospective comparative study was conducted in the ED of a tertiary trauma center in Istanbul, Turkey. Trauma patients aged under 18 years who presented to the ED between May 1st and June 30th, 2020 were included. The same dates of the previous year were included as a control group. Comparison of Manchester Triage Scale (MTS), disposition, injury characteristics, the location of the injury, region of injury, and ED length of stay (LOS) was done.

Results: 2,779 patients were included. There were a 60% reduction in total ED visits and a 50% reduction in daily ED visits. MTS orange code patients (1.1% vs 1.8%) did not change while MTS green code (69.6% vs 41.8%) decreased significantly. Arrival by ambulance (5.8% vs 11.5%) increased (p<0.001). Penetrating (7.2% vs 27.3%), in-home (48.1% vs 65.1%), and upper limb (27.1 vs 34.4%) injuries increased (p<0.001). Fracture (19.0% vs 14.1%) and blunt trauma (90.7% vs 70.9%) frequency, and fall from ground level (64.5% vs 49.3%) injuries decreased significantly. The ward and intensive care unit (ICU) admissions did not change and ED LOS decreased (p<0.001).

Conclusion: We highlighted that there was no change in critical pediatric trauma visits during the COVID-19 pandemic. There is still a need for ward and ICU beds for pediatric trauma patients. The change in injury severity and injury characteristics should be kept in mind while pandemic rearrangements were planned.

Keywords: COVID-19, pandemic, pediatric, trauma, wounds and injuries

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVID-19) salgını sırasında acil servise (AS) başvuran pediatrik travma hastalarının ciddiyet, sıklık ve karakteristiklerindeki değişikliği değerlendirmektir.

Gereç ve Yöntem: Bu geriye dönük karşılaştırmalı çalışma, Türkiye'nin İstanbul şehrindeki üçüncü basamak bir travma merkezinin AS'sinde gerçekleştirildi. 1 Mayıs-30 Haziran 2020 arasında acil servise başvuran 18 yaş altı travma hastaları dahil edildi. Bir önceki yılın aynı tarihleri kontrol grubu olarak dahil edildi. Manchester Triyaj Skalası (MTS), sonlanım, yaralanma karakteristikleri, yaralanmanın yeri, yaralanma bölgesi ve AS kalış süresi karşılaştırıldı.

Bulgular: Çalışmaya toplam 2.779 hasta dahil edildi. Toplam AS başvurularında %60 ve günlük AS başvurularında %50 azalma oldu. MTS turuncu kodlu hastalar (%1,1'e karşı %1,8) değişmezken, MTS yeşil kod (%69,6'ya karşı %41,8) anlamlı olarak azaldı. Ambulansla geliş (%5,8'e karşı %11,5) arttı (p<0,001). Penetran (%7,2'ye karşı %27,3), ev içi (%48,1'e karşı %65,1) ve üst ekstremite (%27,1'e karşı %34,4) yaralanmaları arttı (p<0,001). Kırık (%19,0'a karşı %14,1) ve künt travma (%90,7'ye karşı %70,9) sıklığı ve aynı seviyeden düşme (%64,5'e karşı %49,3) yaralanmaları önemli ölçüde azaldı. Servis ve yoğun bakım ünitesi (YBÜ) yatışları değişmedi ve acilde kalış süresi kısaldı (p<0,001).

Sonuç: Pandemi döneminde kritik pediatrik travma vizitlerinde bir değişiklik olmadığını vurguladık. Pediatrik travma hastaları için hala servis ve YBÜ yataklarına ihtiyaç vardır. Pandemik düzenlemeler planlanırken yaralanma ciddiyeti ve karakteristiklerindeki değişiklikler akılda tutulmalıdır.

Anahtar Kelimeler: COVID-19, pandemi, pediatri, travma, yaralar ve yaralanmalar

Address for Correspondence: Buğra İlhan, University of Health Sciences Turkey, Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Clinic of Emergency Medicine, Istanbul, Turkey
Phone: +90 507 236 86 04 E-mail: bugra_ilhan@yahoo.com ORCID ID: orcid.org/0000-0002-3255-2964

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INTRODUCTION

After atypical pneumonia cases, which first appear in Wuhan, China in December 2019, a different coronavirus subtype [croronavirus disease-2019 (COVID-19)] was detected. Due to its rapid spread, a new pandemic was declared by the World Health Organization (1). So far, above 254 million confirmed cases and more than 5.1 million deaths had been reported (2).

The COVID-19 virus infection brought many undesirable conditions with it. Turkey took some countermeasures to prevent its spread after the first case was detected on March 11th, 2020. These measures include curfews, closing schools and playgrounds, and restrictions in areas where people are crowded.

With the COVID-19 outbreak, healthcare organizations have defined designated areas for COVID-19 suspected patients. Also, there were changes in the frequency and characteristics of patients admitted to healthcare facilities. A decrease in the hospital admissions of patients with life-threatening conditions, acute stroke, and the acute coronary syndrome was detected (3-5). Similarly, the visit frequency of trauma patients and surgical emergencies, and the incidence and characteristics of fractures have changed (6-8).

The pandemic has caused several changes in the lives of children and adults. Similar to adults, pediatric visits to the emergency department (ED) have decreased (9,10). With the closure of schools, daycares, and playgrounds, children started to spend their time at home. These restrictions resulted in changes in pediatric orthopedic trauma admissions (7,11). However, the studies in the literature were focused on a specific region or specific department practices. The studies in the literature evaluating all pediatric trauma patients during the COVID-19 pandemic period were limited.

The current study evaluates the change in the severity, frequency, and characteristics of pediatric trauma patients who presented to the ED during the COVID-19 outbreak.

METHODS

Study Design

This retrospective observational study was done at tertiary training and research hospital. Approval for this study was obtained from the Bakirkoy Dr. Sadi Konuk Training and Research Hospital Institutional Review Board (decision no: 2020-24-06, date: 07.12.2020). The study hospital is a level 3 adult and pediatric trauma center in İstanbul, Turkey. The study ED is accepted approximately 350,000 patients annually. With the first confirmed case in our country on March 11th, 2020, the hospital started to accept COVID-19 patients except for non-COVID-19 patients.

Patient Selection and Groups

Trauma patients aged under 18 years and presented to our ED between May 1st and June 30th, 2020 were included in the study. Patients transferred from another healthcare center and have missing medical information were excluded from the study. The previous year's patients were included as a control group with the same months (May 1st-June 30th 2019) and the same inclusion/exclusion criteria. The informed consent could not be obtained because of the retrospective design. The flow diagram of the study is presented in Figure 1.

Patient data were collected from electronic and written patient files. Patient demographics, trauma type, fracture presence, fracture region, trauma mechanism, trauma location, consultations, and ED length of stay (ED LOS) were recorded and analyzed.

The patients' the first evaluation was done in the triage field by a registered nurse who received the Ministry of Health's triage training. The Manchester Triage Scale (MTS), which is easy to use and achieves successful pediatric patient results, was used to evaluate patients' severity (12). MTS consists of 52 different flowcharts and evaluates patients on a scale of 1 to 5 according to their urgency. Medical care should be given immediately at level 1 (red code), within 10 min at level 2 (orange code), within 60 min at level 3 (yellow code), within 120 min at level 4 (green code), and within 240 min at level 5 (blue code) (13).

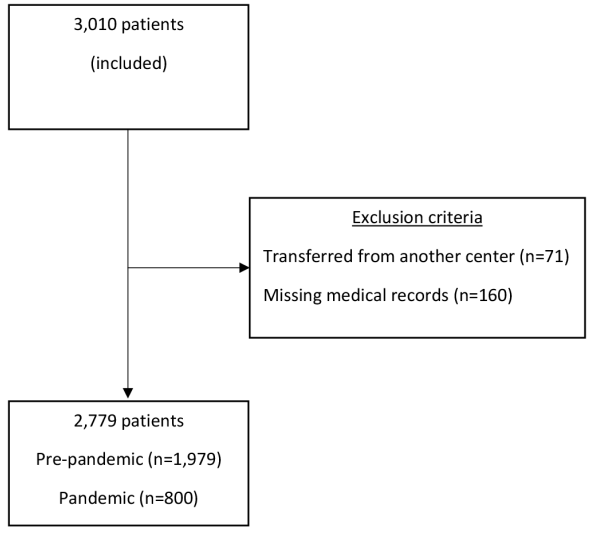

Figure 1. Flow diagram of the study

Outcomes

The primary outcome of the study is the change in the pediatric trauma visits frequency according to their severity levels during the pandemic. The secondary outcomes of the study are the change in injury type, injury region, injury mechanism, and ED LOS of pediatric trauma cases during the COVID-19 outbreak.

Statistical Analysis

Numerical variables were presented with median (interquartile range). Categorical variables were presented with numbers and percentages. The Shapiro-Wilks and Kolmogorov-Smirnov test determined the distribution of the groups. The relationship between numerical variables was evaluated with the Mann-Whitney U test. The relationship between categorical variables was assessed with the chi-square test. Spearman or Pearson test was used in correlation analysis. In univariate analysis, variables with a p-value less than 0.2, sample size greater than 20, and not correlating with each other were included in the logistic regression model. Odds ratios (OR) are presented with a 95% confidence interval (CI). SPSS® for Windows version 23.0 (IBM, Chicago, IL, United States) program was used for statistical analysis. Statistical significance level was set as $p<0.05$.

RESULTS

A total of 2,779 patients (1,979 patients pre-pandemic and 800 patients pandemic period) were included in the study. The mean age of the patients was 7 (range: 3-12) and 1,042 (37.5%) of the patients were girls. Boys presented to the ED more frequently both the pandemic and the pre-pandemic period. The patients who presented in the pandemic period were younger than the pre-pandemic period (Table 1).

An approximately 60% reduction in total ED visits and 50% reduction in daily ED visits were detected. When we evaluate the severity levels, the MTS orange code patients did not change during the pandemic ($p>0.05$). A significant increase in yellow code patients and a significant decrease in green code patients were detected (Table 1). A high negative correlation was found between yellow and green code patients ($p<0.001$, Spearman correlation coefficient: -0.974).

During the pandemic period, patients were presented to the hospital by ambulance at a higher rate [OR: 2.12 (95% CI 1.49-3.02), $p<0.001$)]. A significant decrease was detected in the ED LOS during the pandemic period [OR: 0.997 (95% CI 0.996-0.998), $p<0.001$]. While the proportion of discharged patients decreased significantly during the pandemic period, the ward and intensive care unit (ICU) admissions did not change. The patient characteristics of pre-pandemic and pandemic periods are shown in Table 1.

While the number of penetrating trauma increased during the pandemic period, there was a significant decrease in blunt trauma ($p<0.001$). There was a 70% reduction in fracture frequency ($p=0.002$). There was a significant increase in the number of dislocations ($p=0.045$). When injury locations were evaluated, it was found that while the frequency of in-home injuries increased, there was a decrease in the frequency of injuries in schools, daycares, and sports fields. The frequency of upper limb injuries increased, while other body parts' injuries did not change or decrease during the pandemic period. When we evaluated the mechanisms of injuries, a significant decrease was detected in the fall from ground level. During the pandemic period animal bites increased while sports-related injuries decreased. All other causes of injury remained unchanged. Pre-pandemic and pandemic injury characteristics are presented in Table 2.

Distal forearm fractures were the most common in both pre-pandemic and pandemic periods. The most common fractures are shown in Table 3. Locations of fractures observed pre-pandemic and pandemic periods are shown in Figure 2.

A significant decrease was detected in the total trauma consultations requested from the ED during the pandemic period ($p<0.001$). While there was a significant decrease in the orthopedics department's consultations, there was no significant change in the other trauma consultations. As the number of fractures, there was a significant decrease in the number of orthopedics consultations requested from the ED ($p<0.001$). A moderate correlation was found between the total number of fractures and the total number of consultations and orthopedics consultations ($p<0.001$, $r=0.510$ and $p<0.001$, $r=0.516$, respectively).

In multivariate analysis, MTS green code [OR: 0.24 (95% CI 0.19-0.30), $p<0.001$], blunt trauma [OR: 0.24 (95% CI 0.17-0.34), $p<0.001$], injuries at home [OR: 2.38 (95% CI 1.84-3.08), $p<0.001$], injuries at the street [OR: 2.35 (95% CI 1.73-3.18), $p<0.001$], and upper limb injury [OR: 1.57 (95% CI 1.21-2.03), $p=0.001$] were determined as factors affecting pediatric trauma visits during the pandemic period. Factors affecting pediatric trauma visits during the pandemic period are shown in Table 4.

DISCUSSION

The frequency of total and daily pediatric trauma visits decreased more than 50% in our study. When evaluated in

terms of patient severity, no significant change was detected in critical patient visits, while a significant decrease in the green triage code patients' visits was detected.

Similar to our study, Rotulo et al. (10) found no change in critically ill patients' presentations during the pandemic period. Here, we can say that while there is no change in the critical pediatric trauma patient visits during the pandemic period, non-urgent visits have decreased. We can show country-wide restrictions and the decrease in non-urgent patient visits, which constitute the most patients in the pre-pandemic period, as the reasons for reducing total and daily patient visits. Besides, increased mortality rates and the fear of becoming infected may have decreased non-urgent ED presentations (14). The frequency of pediatric trauma visits decreased, but the critical patients, ward, and ICU admissions did not change in the pandemic period. We still need ward and ICU beds and surgeons to follow up on the pediatric trauma cases. The need for ward/ICU beds and surgeons should be kept in mind while the pandemic rearrangements were planned.

In a study evaluating orthopedic emergencies by Nabian et al. (11), a decrease in orthopedic trauma cases was found similar to our study. Similarly, a decrease of approximately 53% in pediatric trauma patients was found in the study by Greenhalgh et al. (7), and a 64% decrease in the study by Dayananda et al. (15). Unlike other studies, all trauma patients were included in our study. The inclusion of other traumas besides orthopedic traumas in our study may have caused the difference in rates. Although, the reduction in the number of emergency pediatric trauma visits, the critical patient rate did not change. Trauma is still an important cause of pediatric critical visits during the pandemic. Trauma units and staff should continue their duties as a trauma team during a pandemic.

While the hospitalization rates increased in Sugand et al.'s (16) study, there was no change in our study. Besides, a decrease in the rate of discharge from the ED was detected. The reason for this decrease may be the decrease in non-urgent visits. In our study, a significant decrease was found in the ED LOS during the pandemic period. This decrease may be that the patients did not want to wait in the ED with the fear of contamination and left the hospital against medical advice at a higher rate. In a study conducted in Turkey, Demir et al. (17) found that the most frequent reason for discharge against medical advice is the fear of infected by COVID-19 virus.

In our study, while the frequency of penetrating trauma increased, blunt trauma frequency decreased significantly. Similarly, in the study by Nabian et al. (11), an increase in the frequency of penetrating injuries was found, and they stated that this increase might be caused by the rise in the frequency of playing with sharp objects in the home. However, in our study, there was no change in the number of injuries with penetrating objects. The rabies vaccination program started in September 2019 in our ED, and animal bites' presentations began to be accepted afterward. The onset of this vaccination program may elucidate why the increase in the number of penetrating traumas and animal bites during the pandemic period.

In the study by Bram et al. (6), an approximately 2.5-fold decrease in pediatric fracture incidence was found.

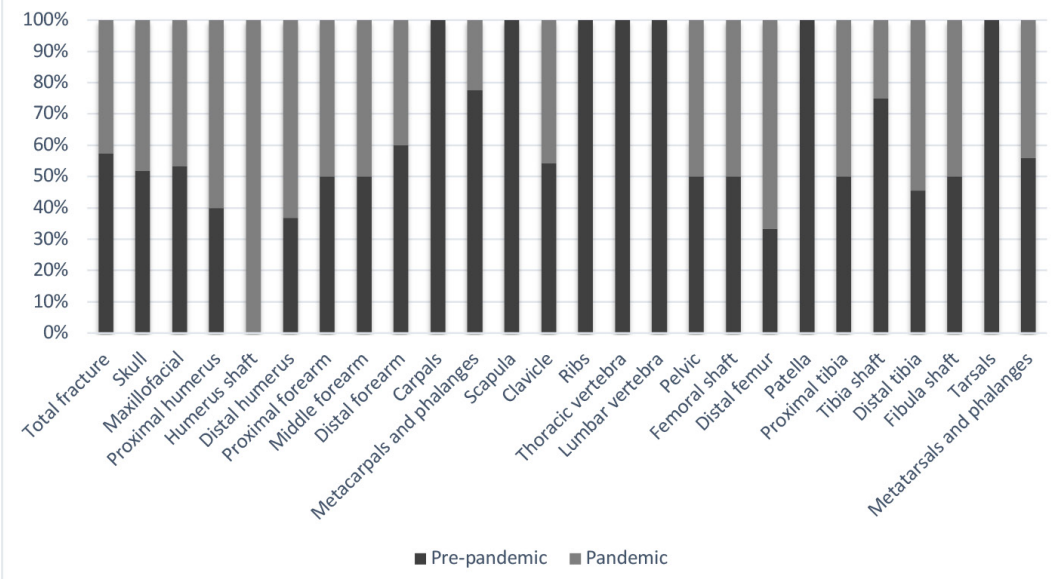

Figure 2. Fracture locations of the patients during pre-pandemic and pandemic period

Similarly, in our study, an about 70% decrease in pediatric fracture frequency was detected. Gumina et al. (18) found a reduction in upper limb injuries during the pandemic period and stated that ground-level falls were frequently caused at home. In our study, while upper limb injuries increased, lower limb and pelvis/genital area injuries decreased. Low energy trauma under parental protection at home compared to schools and playgrounds may have led to reduced fracture frequency. Distal forearm fractures were the most common fractures in our study, similar to Nabian et al.'s (11) study. Parents and caregivers should be aware of the in-home injuries of the pediatric population during the pandemic.

Table 1. Pre-pandemic and pandemic characteristics of the patients

	Pre-pandemic	Pandemic	p-value
Total ED visits, n	1,979	800	-
Daily visits, median (IQR)	24 (21-31.5)	12 (10-15.5)	**<0.001****
Demographics			
Girl, n (%)	719 (36.3)	323 (40.4)	**0.046***
Age (years), median (IQR)	8 (3-13)	5 (2-11)	**<0.001****
Arrival, n (%)			
Ambulatory	1864 (94.2)	708 (88.5)	**<0.001**
EMS, ambulance	115 (5.8)	92 (11.5)	-
Manchester Triage Scale, n (%)			
Red (level 1)	0	0	-
Orange (level 2)	21 (1.1)	14 (1.8)	0.140*
Yellow (level 3)	581 (29.4)	452 (56.5)	**<0.001***
Green (level 4)	1377 (69.6)	334 (41.8)	**<0.001***
Blue (level 5)	0	0	-
Disposition, n (%)			
Discharge	1885 (95.3)	745 (93.1)	**0.024***
Ward admission	52 (2.6)	24 (3.0)	0.586*
ICU admission	2 (0.1)	4 (0.5)	0.061*
Against medical advice	33 (1.7)	20 (2.5)	0.146*
Referral to another hospital	7 (0.4)	7 (0.9)	0.133*
Exitus	0	0	-
ED LOS, median (IQR)	36 (19-80)	31.5 (17-67)	**<0.001****

ED: Emergency department, IQR: Interquartile range, EMS: Emergency medical service, ICU: Intensive care unit, LOS: Length of stay, *Chi-square test; **Mann-Whitney U test, p<0.05 considered significant

Table 2. Pre-pandemic and pandemic injury characteristics of the patients

	Pre-pandemic	Pandemic	p-value*
Injuries, n (%)			
Blunt trauma	1,794 (90.7)	567 (70.9)	**<0.001**
Penetrating trauma	143 (7.2)	218 (27.3)	**<0.001**
Burn	42 (2.1)	15 (1.9)	0.677
Fractures	376 (19.0)	113 (14.1)	**0.002**
Open fractures	5 (0.3)	1 (0.1)	**0.009**
Dislocations	26 (1.3)	19 (2.4)	**0.045**
Location of injury, n (%)			
Home	951 (48.1)	521 (65.1)	**<0.001**
Street	380 (19.2)	174 (21.8)	0.128
School	280 (14.1)	0	**<0.001**
Daycare	33 (1.7)	0	**<0.001**
Playground	263 (13.3)	101 (12.6)	0.683
Sports field	66 (3.3)	3 (0.4)	**<0.001**
Workplace	6 (0.3)	1 (0.1)	0.681
Region of injury, n (%)			
Multiple trauma	152 (7.7)	62 (7.8)	0.950
Head and maxillofacial	772 (39.0)	316 (39.5)	0.810
Cervical	17 (0.9)	8 (1.0)	0.722
Thorax	66 (3.3)	21 (2.6)	0.330
Abdomen	34 (1.7)	6 (0.8)	0.052
Upper limb	537 (27.1)	275 (34.4)	**<0.001**
Lower limb	339 (17.1)	102 (12.8)	**0.004**
Pelvis and genital region	62 (3.1)	10 (1.3)	**0.005**
Mechanism of injury, n (%)			
Fall from ground level	1,276 (64.5)	394 (49.3)	**<0.001**
Fall from height	196 (9.9)	76 (9.5)	0.746
Motor vehicle accident	20 (1.0)	10 (1.3)	0.580
Pedestrian accident	64 (3.2)	28 (3.5)	0.723
Motorcycle accident	19 (1.0)	6 (0.8)	0.595
Bicycle accident	49 (2.5)	23 (2.9)	0.549
Gunshot wounds	3 (0.2)	0	0.562
Penetrating objects related injury	144 (7.3)	69 (8.6)	0.226
Sports related injury	68 (3.4)	3 (0.4)	**<0.001**
Direct blow	88 (4.4)	31 (3.9)	0.500
Animal bites	10 (0.5)	145 (18.1)	**<0.001**
Burns	42 (2.1)	15 (1.9)	0.677

*Chi-square test, p<0.05 considered significant

When the factors affecting pediatric trauma visits during the pandemic period were evaluated, it was mainly associated with home and street injuries. Similarly, Bram et al. (6) found an increase in-home and street injuries. The frequency of in-home injuries has increased in our study due to the curfews' effect and the closure of schools and playgrounds. Besides, burn frequency did not change in our study. Public information should be provided to prevent burns and in-home injuries of the pediatric population.

In our study, the fractures and orthopedics consultation decreased, but other injury mechanisms, injury regions (head, thorax, and abdomen), and trauma consultations did not change. We still need trauma surgeons to follow up the pediatric trauma patients. This situation should be kept in mind while planning the physicians' work areas, especially sending surgeons to COVID-19 wards.

The frequency of ground-level falls decreased during the pandemic period, while sports-related injuries decreased and other mechanisms did not change. Similar to our study, a decrease in sports injuries was found in Sugand et al.'s (16) study. We think that this decrease was caused by schools' closure, daycares, and sports fields during the pandemic period.

Westgard et al. (19) found a decrease in the arrival by emergency medical service (EMS). Still, in our study, the patients prefer to arrive by EMS more frequently during the pandemic period [OR: 2.12 (95% CI 1.49-3.02), p<0.001]. The EMS should be supported with additional personnel and ambulances by the Health Ministries during a pandemic.

Study Limitations

The first limitation of the study was that it was a retrospective study and based on medical records. Some data was missing because of the retrospective design. The second limitation was that there was no mortality in the patients so that no comment could be made on the change in mortality. Besides, the rabies vaccination program did not begin in the pre-pandemic period of the study, which may have affected the distribution imbalance of animal bites between the groups and the results.

Table 3. The most seen fracture locations of the patients

n, (%)	Pre-pandemic	Pandemic
Distal forearm	89 (4.5)	24 (3.0)
Metacarpals and phalanges	76 (3.8)	9 (1.1)
Maxillofacial	47 (2.4)	17 (2.1)
Skull	29 (1.5)	11 (1.4)
Clavicle	26 (1.3)	9 (1.1)
Distal humerus	14 (0.7)	10 (1.2)
Proximal forearm	9 (0.5)	4 (0.5)
Proximal humerus	7 (0.4)	5 (0.6)
Total fractures	376 (19.0)	113 (14.1)

CONCLUSION

There was no change in critical pediatric trauma visits during the outbreak, and there was a decrease in non-urgent visits. The ward and ICU admissions did not change. Trauma is still an important cause of critical emergency visits of the pediatric population during the outbreak. This situation should be kept in mind while personnel and bed managements was done. Patients preferred to arrive ED by ambulance more frequently during the pandemic. EMSs should be supported by the Ministry of Health. In-home and upper limb injuries increased while blunt trauma, ground-level fall, and fracture frequency decreased. Public information should be provided to pay attention to in-home injuries and prevention methods.

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Table 4. Factors affecting the pediatric trauma visits during COVID-19 outbreak

	Odds ratio	95% CI	p-value
Age	0.94	0.92-0.96	**<0.001**
Gender, girl	0.92	0.76-1.11	0.380
Arrival, ambulance	2.12	1.49-3.02	**<0.001**
MTS, green code	0.24	0.19-0.30	**<0.001**
Blunt trauma presence	0.24	0.17-0.34	**<0.001**
Fall from ground level	1.17	0.90-1.52	0.216
Location of injury, home	2.38	1.84-3.08	**<0.001**
Location of injury, street	2.35	1.73-3.18	**<0.001**
Upper limb injury	1.57	1.21-2.03	**0.001**
Lower limb injury	1.01	0.74-1.36	0.940
Fracture presence	0.84	0.63-1.12	0.248
Disposition, discharge	1.05	0.69-1.61	0.788
ED LOS	0.997	0.996-0.998	**<0.001**

CI: Confidence interval, MTS: Manchester Triage Scale, ED LOS: Emergency department length of stay, p<0.05 considered significant

ETHICS

Ethics Committee Approval: Approval for this study was obtained from the Bakirkoy Dr. Sadi Konuk Training and Research Hospital Institutional Review Board (decision no: 2020-24-06, date: 07.12.2020).

Informed Consent: The informed consent could not be obtained because of the retrospective design.

Authorship Contributions

Surgical and Medical Practices: B.İ., G.B.B., H.D., Concept: B.İ., G.B.B., H.D., Design: B.İ., G.B.B., H.D., Data Collection or Processing: B.İ., G.B.B., H.D., Analysis or Interpretation: B.İ., G.B.B., H.D., Literature Search: B.İ., G.B.B., H.D., Writing: B.İ., G.B.B., H.D.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Research

Does Application of Genicular Nerve Block in Addition to Intra-articular Steroid Injection Increase Efficacy in Patients with Knee Osteoarthritis?

Diz Osteoartritli Hastalarda Eklem İçi Steroid Enjeksiyonuna Ek Olarak Genikuler Sinir Bloğu Uygulanması Etkinliği Artırır mı?

Halil Çetingök

Istanbul University, Istanbul Faculty of Medicine, Department of Anesthesiology and Reanimation, Division of Pain Medicine, Istanbul, Turkey

ABSTRACT

Objective: Knee osteoarthritis is a disease which is characterized by severe pain and joint stiffness. Intra-articular steroid injections improve pain relief and knee mobility and widely used routinely especially if the inflammation and effusion are present in the joint. Genicular nerve block has been reported to be a new successful method in the management of chronic knee pain related to gonarthrosis. The current study assesss whether genicular nerve block application in addition to intra-articular steroid injection provides a more successful result.

Methods: Study was designed retrospectively and was conducted in the pain clinic of a tertiary care hospital. One hundred ten patients admitted to the outpatient clinic with the diagnosis of chronic knee pain between January 2016 and June 2018, were treated with genicular block with intra-articular steroid injection (group 1) and only intra-articular steroid injection (group 2). The patients were asked to rate pain [visual analog scale (VAS)] before the intervention and at the 1st and 6th months after the intervention.

Results: VAS scores (Mean ± standard deviation) before the intervention group 1 was 7.20±0.99 and group 2 was 7.10±1.00; 1st month after the intervention group 1 was 4.30±2.24 and group 2 was 4.39±2.55; and 6th month after the intervention group 1 was 5.72±1.96, in group 2 was 5.20±2.36. No statistically significant difference was found between the groups in pain scores in all three time periods.

Conclusion: In patients suffering from knee pain due to osteoarthritis, genicular nerve block applied in addition to intra-articular steroid injection does not provide additional benefit in pain scores.

Keywords: Knee osteoarthritis, genicular nerve block, intra-articular steroid injection

ÖZ

Amaç: Diz osteoartriti şiddetli ağrı ve eklem sertliği ile karakterize bir hastalıktır. Eklem içi steroid enjeksiyonlarının ağrıyı azalttığı ve diz hareketlerini iyileştirdiği gösterilmiş olup özellikle eklemde iltihaplanma ve efüzyon varsa rutinde yaygın olarak kullanılmaktadır. Geniküler sinir bloğunun gonartroza bağlı kronik diz ağrısı tedavisinde başarılı yeni bir yöntem olduğu bildirilmiştir. Bu çalışma, eklem içi steroid enjeksiyonuna ek olarak geniküler sinir bloğu uygulamasının daha başarılı bir sonuç sağlayıp sağlamadığını değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Çalışma geriye dönük olarak tasarlandı ve üçüncü basamak bir hastanenin ağrı kliniğinde yapıldı. Ocak 2016-Haziran 2018 tarihleri arasında kronik diz ağrısı tanısı ile polikliniğe başvuran 110 hastaya eklem içi steroid enjeksiyonu ve ek olarak geniküler sinir bloğu (grup 1) veya sadece eklem içi steroid enjeksiyonu (grup 2) uygulandı. Hastalara girişim öncesi ve girişim sonrası 1. ve 6. aylarda ağrı skorları [vizuel analog skala (VAS)] soruldu.

Bulgular: Girişim öncesi VAS skorları (Ortalama ± standart sapma) grup 1 7,20±0,99 ve grup 2 7,10±1,00; girişim sonrası 1. ayda grup 1 4,30±2,24 ve grup 2 4,39±2,55; girişim sonrası 6. ayda grup 1 5,72±1,96, grup 2 5,20±2,36 idi. Her üç zaman periyodunda da ağrı skorlarında gruplar arasında istatistiksel olarak anlamlı bir fark bulunmadı.

Sonuç: Osteoartrite bağlı diz ağrısı olan hastalarda eklem içi steroid enjeksiyonuna ek olarak uygulanan geniküler sinir bloğu ağrı skorları açısından ek fayda sağlamamaktadır.

Anahtar Kelimeler: Diz osteoartriti, geniküler sinir bloğu, eklem içi steroid enjeksiyonu

Address for Correspondence: Halil Çetingök, Istanbul University, Istanbul Faculty of Medicine, Department of Anesthesiology and Reanimation, Division of Pain Medicine, Istanbul, Turkey
Phone: +90 530 500 40 58 E-mail: halilcetingok@yahoo.com ORCID ID: orcid.org/0000-0002-6746-9079

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INTRODUCTION

Chronic knee osteoarthritis (OA) is a condition that is more common in elderly and is characterized by severe pain, joint stiffness and disability (1). The aim of treatment in patients with OA is to reduce symptoms, minimize functional disability and prevent the progression of structural changes in the affected joints (1). Intra-articular (IA) corticosteroid therapy is widely used for treating the knee OA. IA steroid injections improve acute pain relief and knee mobility, especially during exacerbation of OA associated with joint inflammation and effusion (2).

The knee joint is innervated by the articular sensory branches of various nerves, including femoral, obturator, saphenous, common peroneal and tibial nerves (3). These nerve branches around the knee joint are known as genicular nerves. Under fluoroscopic or ultrasound guidance, several genicular nerves -superior medial, superior lateral and inferior medial genicular nerves- can be easily percutaneously blocked. Genicular nerve radiofrequency (RF) neurotomy has been reported to be a reliable method in the management of chronic knee pain related to OA (4).

This retrospective study aims to investigating whether genicular nerve blocks (GNB) in addition to IA steroid injection is superior on solely IA steroid injections, in terms of postoperative visual analog scale (VAS) scores for the treatment in patients with chronic pain in knee OA.

METHODS

Study was designed retrospectively and was conducted in the pain clinic of a tertiary care hospital. After the Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethics Committee approval (decision no: 1346, date: 21.11.2019); the patients with stage 3-4 knee OA-related radiological changes based on the Kellgren-Lawrence rating scale who treated with GNB with IA steroid injections or solely IA steroid injections were included to the study as inclusion criteria. Exclusion criteria were determined that acute knee pain, severe neurological or psychiatric disorders, knee IA steroid or hyaluronic acid (HA) injection during the previous 6 months, previous knee surgery, having other pathologies in the same extremity that may cause pain, fibromiyalgia.

The patients were divided into 2 groups retrospectively: Patients who received GNB with IA steroid injection were classified as group 1 and patients who received solely IA steroid injection were classified as group 2. In our clinic, both injections are administered to all patients with routine drugs and doses. Triamcinolone acetonide 40 mg was used for IA steroid injection in the both group and 2 mL 1% lidocaine solution for each nerve was used for GNB and blocked superior medial, superior lateral and inferior medial genicular nerves. All procedures were performed under ultrasound guidance.

The patients were asked to rate pain (VAS) before the intervention and at the 1st and 6th months after the intervention during outpatient control visit.

Statistical Analysis

The data analysis was performed using SPSS Version 20.0. The normal distribution of the variables was assessed using the Kolmogorov-Smirnov test. Wilcoxon test was used to compare preoperative and postoperative VAS scores. The Mann-Whitney U test was used to compare the two groups in terms of nonparametric data. Categorical variables were determined by chi-square test. Tests considered statistically significant if $p<0.05$.

RESULTS

During the retrospective evaluation period, 122 patients were included in accordance with the inclusion and exclusion criteria. However, as 12 patients could not be reached, sufficient data could not be obtained, and as a result, 110 patients were included in the study. Sixty nine patients in group 1 and 41 patients in group 2 were included (Table 1, 2).

Mean ± standard deviation VAS scores in the preoperative period in group 1 was 7.20±0.99 in group 2 7.10±1.00, in the postoperative period during first visit in group 1 was 4.30±2.24, in group 2 was 4.39±2.55 and postoperative period at 6th month in group 1 was 5.72±1.96, in group 2 was 5.20±2.36. Between group 1 and group 2 before the intervention VAS scores there were statistically no significant difference ($p>0.05$). Between group 1 and group 2 one month after the intervention VAS scores there were statistically no significant difference ($p>0.05$). Between group 1 and group 2 six months after the intervention VAS scores there were statistically no significant difference ($p>0.05$) (Table 3).

When evaluated within both groups, Preoperative and postoperative first visit and 6th month VAS scores were compared and statistical significance was found ($p<0.05$) (Figure 1).

DISCUSSION

In our clinic, some patients with chronic knee pain due to OA are given only IA steroid injection, while geniculate nerve block is applied to some of them in addition to IA steroid injection. In this study aim was to compare long term efficacy of these two interventional treatment modalities.

Table 1. Age profile of patients

	Group 1					Group 2				
	n	Mean	SD	Maximum	Minimum	n	Mean	SD	Maximum	Minimum
Age	69	63.07	9.60	79	40	41	61.71	9.47	76	45

Group 1 (GNB + IA steroid inj.), group 2 (IA steroid inj.), p>0.05, SD: Standard deviation, IA: Intra-articular, GNB: Genicular nerve blocks

IA steroid injections are used to provide decrease in pain and increase function of the knee joint. Pain decreases dramatically within the first 24 h and this effect persists for 4-8 weeks (5). Responses to IA steroid injections vary in clinical experience, however some randomized controlled trials (6) has shown short-term benefits in the management of chronic pain with knee OA. Although it has been stated that the injection of IA steroids and derivatives have negative effects on the joint cartilage but it has been reported in various publications in the literature that IA steroid injections are effective in relieving symptoms for chronic knee pain and are safe in the long-term period (7,8).

In their study, Raynauld et al. (8) used 40 mg triamcinolone and reported that there was benefit on night knee pain and joint stiffness during 24 months. They also found there was no loss of joint space in repeated corticosteroid injections. In a prospective, randomized, controlled trial comparing the effect of methylprednisolone, betamethasone, and triamcinolone, the positive effect of all three injections lasted for 12 weeks (9). High doses of corticosteroids ≥40 mg triamcinolone (50 mg equivalent of prednisone) are known in the literature to be more effective than low doses over a long time, such as 16 and more weeks (5). In current study was used 40 mg triamcinolone in both group and we think that's why long term benefit was significant.

In patients with knee OA, GNB is mostly used as a diagnostic procedure before RF ablation of the same nerves. However, following the benefit of the diagnostic block of genicular nerves, RF neurotomy of these nerves appears to be an important treatment alternative in patients suffering from chronic pain that does not heal with conventional treatments or is thought to be inoperable due to their comorbidities (10). However, studies have shown that GNB applied with a mixture of local anesthetic and steroid has similar efficacy with the genicular nerve RF thermocoagulation procedure (11).

Most of the studies in the literature are in the form of comparison of RF neurotomy to the genicular nerves with other interventional procedures. For example Sari et al. (10) compared genicular nerve RF neurotomy to IA injections and reported that in 1st and 3rd months there was significant

Table 2. Gender profile of patients

	Group 1		Group 2
	n		n
Gender	Male	16	3
	Female	53	38

Group 1 (GNB + IA steroid inj.), group 2 (IA steroid inj.), p>0.05, IA: Intra-articular, GNB: Genicular nerve blocks

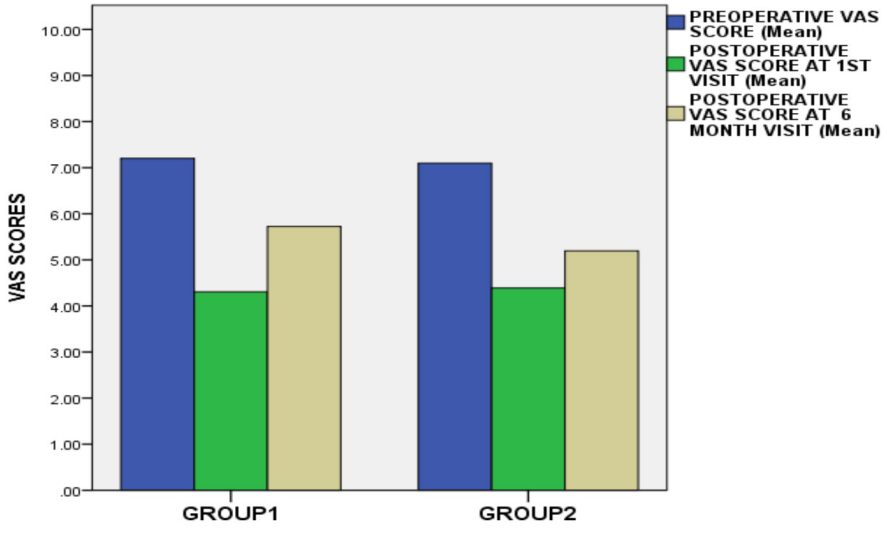

Figure 1. VAS scores of groups
VAS: Visual analog scale

Table 3. VAS score comparison of both groups

		Group 1	Group 2	p-value
VAS score (Mean ± SD)	Before the intervention	7.20±0.99	7.10±1.00	p>0.05
	1st month after the intervention	4.30±2.24	4.39±2.55	p>0.05
	6th month after the intervention	5.72±1.96	5.20±2.36	p>0.05

Group 1 (GNB + IA steroid inj.), group 2 (IA steroid inj.), SD: Standard deviation, IA: Intra-articular, GNB: Genicular nerve blocks, VAS: Visual analog scale

pain reduction in the RF neurotomy-performed group. Choi et al. (4) compared genicular nerves RF neurotomy to the control group in chronic pain with knee patients with OA. They reported that the RF neurotomy group showed superior improvement compared with the control group at both 4 and 12 weeks. Another study showed that genicular nerve RF neurotomy resulted on average in a 60% decrease in baseline chronic knee pain in at least during 6 months (12). In our study RF neurotomy following successful blocks weren't performed. But based on the studies that reminded above, we think that GNB may be effective in the short term, but for long term benefit genicular nerve RF neurotomy should be performed.

GNB has also been compared with non-invasive treatments in patients with chronic knee OA. For example, in the study by Güler et al. (13) two groups were formed to ultrasound guided GNB group and physical therapy group. A comparison was made in terms of both pain and functional parameters. As a result compared to physical therapy, ultrasound-guided GNB helps reduce pain and increasing the functional and physical capacity, with greater retention of effects on the physical capacity seen at 12 weeks (13).

In our study before and after the intervention VAS scores were compared in both groups and the results were found to be significant. However, when the postoperative VAS scores of group 1 and group 2 were compared, our results were not significant and these results indicated that in the management of chronic knee pain IA steroid injection was effective but genicular blocks did not provide additional benefit. In a prospective structured study, contrary to our results, when GNB was added to IA steroid injection, a better analgesic effect and better functional result were obtained (14).

Minimally invasive treatment options for knee patients with OA with chronic pain also include different modalities as IA autologous platelet rich plasma (PRP) and HA injections. HA is a glycosaminoglycan and is a component of the synovial fluid and cartilage matrix (15). Vaishya et al. (16) reported that intraarticular injection of corticosteroid and HA in knee patients with OA with chronic pain relieve the pain temporarily. IA steroids provide relief for approximately 12 weeks, and HA provides relief for up to 6 months.

PRP is prepared from autologous blood by centrifugation to obtain a high-concentration platelet sample (17). In the second edition of the treatment guideline for patients with knee OA published in 2013 by the American Academy of Orthopedic Surgeons study group did not conclusively interpret the evidence for the benefit of IA PRP injection and could not recommend for or against use of IA PRP injection (18).

The current study has several limitations. The study conducted retrospectively. Details of analgesic consumption for 6 months could not be carefully monitored. Questioning functional parameters and patient satisfaction other than pain would have enabled us to reach a clearer result.

Conclusion

This study showed that corticosteroid injection is effective therapeutic modality for chronic pain in knee OA in long-term period. Adding genicular block to IA steroid injection does not show significant benefit. IA steroid injection may be recommended as a long-term useful treatment option for patients with comorbidities who cannot be operated or who do not respond to conservative treatment. Prospective randomized, controlled trials must evaluate the short and long-term effects of genicular block in chronic pain with knee OA as a one of treatment modalities.

ETHICS

Ethics Committee Approval: The study was approved by the Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethics Committee (decision no: 1346, date: 21.11.2019).

Informed Consent: Retrospective study.

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Research

Effects of Dienogest Only Treatment on Lipid Profile

Dienogest Tedavisinin Lipid Profili Üzerindeki Etkileri

Aysun Fendal Tunca[1], Derya Ece Ilıman[1], Sema Karakaş[1], İsmail Alay[2], Ecem Eren[1], Şükrü Yıldız[1], Cihan Kaya[3]

[1]University of Health Sciences Turkey, Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Clinic of Obstetrics and Gynecology, Istanbul, Turkey
[2]Medicana Bahcelievler Hospital, Clinic of Obstetrics and Gynecology, Istanbul, Turkey
[4]Acibadem Bakirkoy Hospital, Clinic of Obstetrics and Gynecology, Istanbul, Turkey

ABSTRACT

Objective: Metabolic effects of dienogest (DNG) may lead to unintended lipid levels, which may predispose to cardiovascular diseases. The main objective of this study was to reveal effects of DNG only treatment on lipid profile.

Methods: Thirty three otherwise healthy women with diagnosed endometriosis were started on 2 mg dienogest/day oral treatment. Blood samples were taken before and after 6 months of therapy to measure triglycerides (TG) low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and total cholesterol levels. Exclusion criteria were withdrawal from DNG treatment, pregnancy, women with incomplete medical records or who were lost to follow-up, allergies for DNG, need for laparoscopy during the 6-month of medical treatment, having familial lipid disorders, and body mass index (BMI) >30 kg/m^2.

Results: There was no significant difference regarding total cholesterol, HDL, and LDL levels between the blood samples taken before and after DNG treatment. However, TG levels were significantly higher at 6th-month blood samples than the pre-DNG blood samples (94 vs. 75, p=0.03). The mean age was 31.4±4.8 years, gravidity was 1.8±1.3, parity was 1.6±1.1, and BMI was 24.6±1.8 (kg/m^2).

Conclusion: Our results suggest that DNG treatment increases TG levels. The metabolic effects of DNG should be clarified as being widely used among women as a progestin-only regimen. Alterations in lipid metabolism may affect the use of this drug in patients with metabolic syndrome or hyperlipidemia.

Keywords: Dienogest, hyperlipidemias, progesterone, endometriosis

ÖZ

Amaç: Dienogest (DNG) kullanımı kan lipid seviyelerinde istenmeyen değişikliklere sebep olarak kardiyovasküler hastalık riskini artırabilir. Bu çalışmanın amacı tek başına DNG kullanımının lipid profiline olan etkisini araştırmaktır.

Gereç ve Yöntem: Endomoetriosis tanısı almış ve ek hastalığı bulunmayan 33 hastaya 2 mg/gün dozunda DNG tedavisi başlanmıştır. Tedavi başlangıcından önce ve tedavinin 6. ayında venöz kanda trigliserid (TG), düşük yoğunluklu lipoprotein (LDL) kolesterol, yüksek yoğunluklu lipoprotein (HDL) kolesterol ve total kolesterol seviyeleri ölçülmüştür. Dışlanma kriterleri ise şunlardır: Tedaviyi bırakmak, gebelik, eksik tıbbi kayıtlar, DNG alerjisi, medikal tedavi sırasında operasyon geçirmek, ailevi lipid hastalığı bulunması ile vücut kitle indeksi (VKİ) > 30 kg/m^2.

Bulgular: Total kolesterol, HDL kolesterol ve LDL kolesterol seviyelerinde tedavi öncesi ve sonrası arasında anlamlı fark gözlenmemiştir. TG seviyelerinde ise DNG tedavisi öncesi ve 6. ay arasında anlamlı fark mevcuttur (94 vs. 75, p=0,03). Ortalama yaş 31,4±4,8, gravide 1,8±1,3, parite 1,6±1,1, ve VKİ 24,6±1,8'dir (kg/m^2).

Sonuç: Çalışmamızın sonuçları DNG tedavisinin TG seviyelerini yükselttiğini göstermektedir. DNG, yalnızca progesteron içeriği ile yaygın bir şekilde kullanılmaktadır ve metabolik etkileri hakkında daha net bilgilere ihtiyaç duyulmaktadır. Bu molekülün kullanımında lipid profilinde görülen değişimler, metabolik sendrom veya ailesel hiperlipidemi gibi ek hastalıkları olan kadınların ilacı kullanması hakkındaki durumu da değiştirebilir.

Anahtar Kelimeler: Dienogest, lipid profili, progesteron, endometriozis

Address for Correspondence: Derya Ece Ilıman, University of Health Sciences Turkey, Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Clinic of Obstetrics and Gynecology, Istanbul, Turkey
Phone: +90 506 669 88 15 E-mail: deryaeceiliman@gmail.com ORCID ID: orcid.org/0000-0002-0409-4089

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INTRODUCTION

Endometriosis is a chronic disease affecting approximately 10% of reproductive-age women (1). It can cause various problems, such as chronic pelvic pain, infertility, dyspareunia, and dysmenorrhea (1). To manage this common complex disorder, medical and surgical treatments are could be used. Although surgery seems to be a quick treatment option, the current data are contrary since the recurrence rates could be as much as 40-50% and may also diminish ovarian reserve (2). Medical treatment is commonly referred to as the first-line option, especially in adolescents, with a previous history of endometriosis surgery and low ovarian reserve to achieve pain control.

Dienogest (DNG) is an Food and Drug Administration-approved gestagen that could be used to treat endometriosis-related pain with its anti-androgenic effects. It is wieldy used for endometriosis treatment, and its progestin component could be found in combined oral contraceptive (COC's) formulations. DNG could be recommended as the initial treatment to reduce chronic pelvic pain and dysmenorrhea in suspicion of endometriosis (3).

DNG has known side effects such as menstrual irregularities, weight gain, and decreased bone mineral density (4). Regarding the effects of progestins on lipid levels change through different generations of gestagens. The first and second-generation progestins could lower high-density lipoprotein (HDL) levels but increase low-density lipoprotein (LDL)-cholesterol and triglyceride (TG) levels (5). However, new generation progestins such as desogestrel have opposite effects on HDL and LDL levels than older generations (6). The fourth-generation progestin, DNG, has a moderate antigonadotrophic activity and does not bind to cortisol-binding- globulin or sex-hormone-binding-globulin (7). A study, evaluating the pharmacological prospects of the DNG concluded that the molecule does not alter lipid levels significantly (7). Although current literature has some evidence regarding the metabolic effects of DNG containing OC's, there is still a lack of evidence considering the effects of DNG on lipid profile.

Therefore, this study evaluated the effect of DNG on lipid profiles in patients with endometriosis.

METHODS

This prospective observational study consisted of 33 otherwise healthy women diagnosed with endometriosis-revised American Society of Reproductive Medicine classification I-IV with either laparoscopically or sonographically in an endometriosis clinic of a tertiary hospital between January 2018 and June 2018. After obtaining Bakirkoy Dr. Sadi Konuk Training and Research Ethics Committee approval of where the study occurred (decision no: 2018-01-21, date: 08.01.2018), the study was conducted, and the guidelines of the Helsinki Declaration on human experimentation were followed. Written consent was obtained from all participants.

Inclusion criteria were as follows: 18-45 years old, prescribed a minimum of 6 months of DNG treatment and agreeing to participate in this study. Exclusion criteria were withdrawal from DNG treatment, pregnancy, women with incomplete medical records or who were lost to follow-up, allergies for DNG, need for laparoscopy during the 6-month of medical treatment, having familial lipid disorders, and body mass index (BMI) >30 kg/m^2.

The patients were assessed with a complete medical history and ultrasound examination. The age, parity, BMI, and main presenting symptoms of the patients and laboratory results were noted. The fasting blood samples were taken from the antecubital vein to measure total cholesterol (TC), TG, HDL cholesterol, and LDL cholesterol levels before starting DNG treatment. All women had a 2 mg/day oral DNG treatment for the next 6 months. After completing the medical therapy, all patients were scheduled for a control blood test to evaluate serum lipids.

Statistical Analysis

The analysis was performed using SPSS (version 20.0; SPSS Inc., Chicago, IL, USA) software. Kolmogorov-Smirnov test was used to analyze the normality of continuous variables. The homogenous data were presented as mean ± standard deviation, and non-homogenous continuous values were presented as median-interquartile range. The Wilcoxon test was used to compare the paired groups. A $p<0.05$ value was considered statistically significant.

RESULTS

The study comprised thirty-three women who received DNG treatment for 6 months. The mean age was 31.4±4.8 years, gravidity was 1.8±1.3, parity was 1.6±1.1, and BMI was 24.6±1.8 (kg/m^2). The main presenting symptoms were dysmenorrhea in 19 (57.6%) women, dyspareunia in 10 (30.3%) women, and dyschezia in 4 (12.1%) women (Table 1). There was no significant difference regarding TC, HDL, and LDL levels between the blood samples taken before and after DNG treatment. However, TG levels were significantly higher at 6th-month blood samples than the pre-DNG blood samples (94 vs. 75, p=0.03) (Table 2).

Table 1. Demographic data of patients

n=33		Mean ± SD
Age		31.4±4.8
G		1.8±1.3
P		1.6±1.1
BMI		24.6±1.8
Main presenting symptom	Dysmenorrhea	19 (57.6%)
	Dyspareunia	10 (30.3%)
	Dyschesia	4 (12.1%)

SD: Standard deviation, BMI: Body mass index

Table 2. Median and interquartile range of both groups. Significant p-values are in bold letters

	Pre dienohest (median-IQR)	6th month control (median-IQR)	p-value
Total cholesterol	178 (31)	169 (33)	0.88
Triglyceride	75 (52)	94 (51)	**0.03**
HDL	46 (13)	47 (11)	0.77
LDL	107 (38.5)	112 (28)	0.35

IQR: Interquartile range, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

DISCUSSION

Our study revealed that DNG treatment might only increase TG levels. However, no significant difference was observed regarding TC, HDL, and LDL levels in pre-and-post DNG treatment.

The current medical treatment options for managing endometriosis have various limitations due to their likely side effects. Considering the metabolic side effects of the medications used for treating endometriosis, earlier generation progestins and danazol, which have androgenic effects, reported to have negative effects on serum lipid profiles (8). The medroxyprogesterone acetate, one of the commonly used progestins recommended in the treatment of endometriosis, could increase free and TC levels while substantially decreasing HDL cholesterol (8). Another agent with androgenic effects, danazol, also decreases HDL cholesterol and increases LDL cholesterol and TG levels (9). These unintended effects on serum cholesterol levels could further lead to an increased cardiovascular disease risk (9).

DNG, is a four-generation progestin containing non-ethylestrone, has anti-androgenic effects (10). The efficacy of DNG in endometriosis-related pelvic pain was demonstrated by multiple randomized placebo-controlled studies and recommended worldwide as the first-line treatment (3,4). Strowitzki et al. (3) conducted a placebo-controlled study in patients with endometriosis-associated pelvic pain. They evaluated the effect of 2 mg DNG on TG, TC, HDL, and LDL levels in both DNG and control groups. They reported a slight increase toward upper limits of TG levels in the DNG group than in the placebo group. TG baseline levels were 0.96 and increased to 1.11 in the DNG group, whereas baseline TG levels of the placebo group were 0.99 and increased to 1.08. However, they concluded that all lipid levels did not differ significantly and remained within normal limits pre- and post-treatment in both study groups. Schindler et al. (5) conducted a study with high dose DNG (20 mg) and found no effect on LDL, TG, and TC levels, yet HDL levels were slightly increased. Our results may differ from the abovementioned studies that higher TG levels were observed after DNG treatment in our study. We may speculate that lower DNG levels could lead to higher TG levels due to its lower anti-androgenic effects compared to higher doses of DNG.

To date, there is only one study conducted in 1989 by Köhler et al. (11) compared blood lipid levels in patients who received DNG treatment due to endometriosis. They evaluated 84 endometriosis patients who received DNG 2 mg/day treatment. The blood samples were taken before, 1, 3, and 6 months of DNG treatment. They concluded that no statistically significant difference in lipid samples taken in different time periods. However, they suggest a tendency toward lower levels of HDL and TG; higher levels of LDL.

Wiegratz et al. (12) found a significant increase in TG levels in women receiving DNG containing COC's. They conducted a randomized controlled trial and four groups were randomly assigned differently expressed COC's. These tablets were monophasic combinations of 30 mg ethynyl estradiol (EE)+2 mg DNG, 20 mg EE+2 mg DNG, 10 mg EE+2 mg estradiol valerate (EV)+2 mg DNG, 20 mg EE+100 mg levonorgestrel (LNG). Three of these drugs contained DNG as the progestin component, and one included LNG. They reported a 40-60% rise in TG levels in DNG containing groups that were more pronounced in 20 EE/DNG and 30 EE/DNG than with 20 EE/EV/DNG, whereas only a 20% non-significant increase was observed in LNG-containing ones. Wiegratz et al. (12) also suggested that the difference between HDL levels in women on LNG or DNG containing pills arises from the HDL-reducing effect of LNG-containing pills. Although it was not a significant increase, there was a slight increase in HDL levels, which is also compatible with our study. It is known that EE reduces the catabolism of HDL2 by decreasing plasma hepatic lipase activity. subgroup. This effect of EE is counteracted

by androgenic progestines. However, the lack of increase in HDL2 suggests that, DNG might have a slight inhibitory function on the abovementioned EE effect despite its anti-androgenic nature. Considering this, it could be postulated that the effects of any progestin on metabolic activity should be considered individually.

Regarding the limitations of our study, the small number of patients can reduce the reliability of our results. Although our data are consistent with the previous reports, some discrepancy exists in the current data on this subject. Therefore, prospective studies on large populations are needed.

CONCLUSION

Our results suggest that DNG treatment increases TG levels. The metabolic effects of DNG should be clarified as being widely used among women as a progestin-only regimen. Alterations in lipid metabolism may affect the use of this drug in patients with metabolic syndrome or hyperlipidemia. As a COC component, the effect of DNG may be masked by the estrogen component, and alterations caused by DNG may be speculated to be estrogen.

ETHICS

Ethics Committee Approval: After obtaining Bakirkoy Dr. Sadi Konuk Training and Research Ethics Committee approval of where the study occurred (decision no: 2018-01-21, date: 08.01.2018), the study was conducted, and the guidelines of the Helsinki Declaration on human experimentation were followed.

Informed Consent: Written consent was obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: S.K., İ.A., C.K., Concept: A.F.T., S.K., İ.A., Ş.Y., C.K., Design: A.F.T., D.E.I., İ.A., E.E., Ş.Y., C.K., Data Collection or Processing: A.F.T., S.K., E.E., Ş.Y., C.K., Analysis or Interpretation: D.E.I., E.E., Ş.Y., C.K., Literature Search: A.F.T., D.E.I., İ.A., Writing: D.E.I., E.E.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Research

The Contribution of Point Shearwave Elastography to Diagnosis in Liver Steatosis, Is There a Threshold Value?

Hepatik Steatozda Point Shearwave Sonoelastografinin Tanıya Katkısının Değerlendirilmesi, Bir Eşik Değer Var mı?

Sevim Özdemir, Tuba Selçuk Can, Behice Kaniye Yılmaz, Rüştü Türkay

University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Radiology, Istanbul, Turkey

ABSTRACT

Objective: The reversible metabolic disorder called fatty liver is an acquired metabolic disorder that results in the collection of triglycerides in hepatocytes. When it turns into chronic, lobular inflammation occurs and the disease can derive to steatohepatitis, fibrosis, cirrhosis, portal hypertension, liver failure, and hepatocellular carcinoma. Chronic diseases of the liver is one of the important health problems today. This prospective study evaluates the contribution of point shearwave elastography (pSWE) to the diagnosis of hepatic steatosis, to determine the threshold value according to steatosis degrees.

Methods: A total of 140 patients who were referred to the radiology department for abdominal ultrasonography (USG) from the internal medicine outpatient clinic due to reasons such as cholesterol-triglyceride elevation, liver enzyme elevation, right upper quadrant pain, fatigue, weakness, hepatomegaly, between January-2019 and April-2020 were included in the study. US elastography was examined. Ten consecutive measurements were carried out, and the resulting median values in kPa were recorded. The interquartile range/median values below 30% were considered in the confidence interval.

Results: The ages of patients were between 32 and 79 (mean age: 55.2±9.2). Of the patients, 54 were male (38%) and 86 were female (62%). The cut-off pSWE values according to the degree of steatosis were (researcher 1/researcher 2) <101.05/<89, <18.2/<22.2 and <5.85/<6.55 respectively for grade 1,2 and 3 steatosis.

Conclusion: This prospective study determines the threshold values for pSWE method considering the steatosis grades in the liver steatosis using the Esaote MyLab9 ultrasound machine and pSWE technique. Our study showed that the pSWE is a reproducible, noninvasive, and easily accessible method for evaluating fatty liver disease. But, more studies are needed, including histopathological verifications.

Keywords: Nonalcoholic fatty liver disease, point shearwave elastography, steatosis

ÖZ

Amaç: Yağlı karaciğer adı verilen geri dönüşümlü bir metabolik hastalık, hepatositlerde trigliseridlerin birikmesiyle sonuçlanan edinilmiş bir metabolik bozukluktur. Kronik hale geldiğinde lobüler enflamasyon gelişir ve steatohepatit, fibrozis, siroz, portal hipertansiyon, karaciğer yetmezliği ve hepatosellüler karsinoma da dönüşebilir. Kronik karaciğer hastalığının nedenleri farklı olsa da prognoz benzerdir. Bu prospektif çalışma, kronikleştiğinde fibrozise dönüşebilen yağlı karaciğeri olan hastalarda yağlanma şiddetine göre karaciğerin point shearwave elastografi (pSWE) ile değerlendirilmesi ve cut-off değer belirlemeyi amaçlamaktadır.

Gereç ve Yöntem: Ocak 2019 ile Nisan 2020 tarihleri arasında, kolesterol-trigliserid yüksekliği, karaciğer enzim yüksekliği, sağ üst kadran ağrısı, yorgunluk, halsizlik, hepatomegali gibi nedenlerle dahiliye polikliniğinden batın ultrasonografisi (USG) için radyoloji bölümüne yönlendirilen 140 hasta çalışmaya dahil edildi. Dört saat açlık sonrasında, sol lateral dekübit pozisyonda karaciğer USG ve pSWE incelemeleri yapıldı. Her hastadan on pSWE ölçümü yapıldı. Çeyrekler açıklığı/medyan değerler %30'un altında olan değerler kabul edildi. Her hasta aynı gün içinde, ardışık olarak iki uzman doktor tarafından değerlendirildi.

Bulgular: Çalışmaya dahil 140 hastanın 54'ü (%38) erkek, 86'sı (%62) kadın olup yaşları 32-79 (55,2±9,2) arasında değişmekte idi. USG'de 32 hastada yağlanma saptanmadı, 38 hastada grade 1, 54 hastada grade 2 ve 16 hastada grade 3 yağlanma kaydedildi. Karaciğerdeki yağlanmanın derecesine göre her iki araştırmacının (araştırmacı 1/ araştırmacı 2) elde ettiği eşik pSWE değerleri evre 1,2 ve 3 steatoz için sırasıyla <101,05/<89, <18,2/<22,2 ve <5,85/6,55 idi.

Address for Correspondence: Sevim Özdemir, University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Radiology, Istanbul, Turkey
Phone: +90 212 414 20 01 E-mail: sevimozdemir76@yahoo.com ORCID ID: orcid.org/0000-0003-4270-6370

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Sonuç: Literatürde nonalkolik yağlı karaciğer hastalığında önemli bir prognostik faktör olan fibrozisin derecelendirmesine yönelik çok sayıda elastografi çalışması olmasına rağmen, karaciğer steatoz derecelerine göre pSWE değerleri gösteren çalışma bulunmamaktadır. Bu prospektif çalışma, Esaote MyLab9 US cihazı ve pSWE tekniği kullanılarak karaciğer steatozunda steatoz derecelerine göre eşik pSWE değerleri belirlemektedir. Çalışmamız pSWE'nin yağlı karaciğer hastalığının değerlendirilmesi için tekrarlanabilir, noninvaziv ve kolay erişilebilir bir yöntem olduğunu göstermiştir. Ancak histopatolojik doğrulamanın dahil edildiği daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Nonalkolik yağlı karaciğer hastalığı, point shearwave elastografi, steatozis

INTRODUCTION

The reversible metabolic disorder called fatty liver is an acquired metabolic disorder that results in the collection of triglycerides in hepatocytes. When it turns into chronic, lobular inflammation occurs and the disease can derive to steatohepatitis, fibrosis, cirrhosis, portal hypertension, liver failure, and hepatocellular carcinoma (1,2). It's essential to diagnosis the steatosis of liver in early stage as these patients are much better used from treatment. In line with the growing obesity epidemic and increasing prevalence of type 2 diabetes mellitus, nonalcoholic fatty liver disease (NAFLD) appear as a leading public health problem in Turkey due to its higher obesity rates compared to the world in general (3). Chronic diseases of the liver is one of the important health problems today. Even though the causes of chronic diseases may be different, the prognosis is similar, thus, for a successful clinical management of chronic liver diseases accurate diagnosis and staging of liver fibrosis is a crucial step (4). Noninvasive, reproducible staging methods are particularly important for monitoring the disease and therapeutic response (5-8). Measures to prevent the formation of steatosis and steatohepatitis that are the first stages of the chronic liver disease, are important tasks.

NAFLD is the most probable cause of liver dysfunction in industrial countries because it's linked with obesity, insülin resistance and dyslipidemia and due to this fact it's recognized as hepatic manifestation of metabolic syndrome (9). Laboratory tests, imaging methods and biopsy are the diagnostic and monitoring possibilities for fatty liver disease and hepatic fibrosis. Ultrasound (US) is an effective method among imaging methods for diagnosis and follow-up (9).

However, liver biopsy is considered the gold standard for chronic liver disease diagnosis it's still an invasivechoise, which can lead to some complications. For this reason non-invasive methods are demanding to diagnose fibrosis (10). US used in conjunction with elastography has recently had a great benefit in the follow-up of such patients. Elastography is a method that quantifies liver fibrosis by measuring the propagation velocity of the US waves passing through the liver; as fibrosis progresses, the liver tissue get-stiffness and the waves propagate faster. It is possible to determine the wave propagation velocity and degree of stiffness, thus the stage of liver fibrosis (1). There are several types of US elastography, the major ones used for liver stiffness assessment are transient elastography, two-dimensional shearwave elastography (2D-SWE), and point shearwave elastography (pSWE) (1). Technical developments and availability of US elastography is still rising. Comparability and standardization of US elastography instruments manufactured by different companies are the most necessary and investigated areas in the evaluation of the follow-up and determination of the response to therapy in liver diseases. For this reason, it is obvious that standard threshold value determination in certain disease groups with SWE technology is a subject of interest.

This prospective study is conducted to evaluate the pSWE values of patients with hepatic steatosis. The primary outcome is to evaluate the contribution of pSWE to the diagnosis of hepatic steatosis, to determine the threshold value according to steatosis degrees. The secondary outcome is the evaluation the reproducibility of the examination.

METHODS

Patients who were referred to the Radiology department for abdominal ultrasonography (USG) from the internal medicine outpatient clinic due to reasons such as cholesterol-triglyceride elevation, liver enzyme elevation, right upper quadrant pain, fatigue, weakness, hepatomegaly, between January-2019 and April-2020 were included in the study. Patients with a known history of chronic liver disease, viral hepatitis, portal hypertension, malignancy, and chemoteraphy were excluded from the study.

Real-time QElaXto-pSWE was examined with 1-8 MHz multifrequency convex probe using the Esaote Mylab9 Digital USG (Italy, Esaote) device with QElaXto Pack software in the Radiology department.

The were examined by two expert radiologists with more than 10 years of USG and 2 years of elastography experience. After for hour fasting, liver US and elastography were examined by two researchers consecutively on the same day for each patient.

The grading of liver steatosis is done using some US findings such as liver brightness, contrast between the liver

and the kidney, US vision of the intrahepatic vessels, liver parenchyma and diaphragm (11). Steatosis was graded as follows: absent (grade 0) when the echotexture of the liver is normal; mild (grade 1), when the liver had higher echogenicity than the right renal cortex, with normal visualization of the diaphragm and of the portal vein wall; moderate (grade 2), a moderate increase in liver echogenicity with slightly impaired appearance of the portal vein wall and the diaphragm; severe (grade 3), marked increase in liver echogenicity with poor or no visualization of portal vein wall, diaphragm, and posterior part of the right liver lobe (11,12).

US elastography was examined by placing the probe in the intercostal space in the slight left lateral decubitis position and telling the patient to hold breath and remain still. The sampling box for pSWE was placed approximately 2 cm from the liver capsule, in the area away from vascular structures and ten consecutive measurements were carried out, and the resulting median values in kPa were recorded (Figure 1). The interquartile range/median values below 30% were considered in the confidence interval. These findings were evaluated to investigate the interobserver compliance.

This prospective study was conducted in accordance with the ethical standards of the local ethics committee on human experimentation and with the Helsinki Declaration of 1075, as revised in 2000 after getting approval from the University of Health Sciences Turkey, Haseki Training and Research Ethics Committee (decision no: 2019-54, date: 26.02.2020). Informed written consent was obtained from all volunteers.

Statistical Analysis

Power analysis was carried out by using the mean and standard deviation values obtained from the study by Suh et al. (13). The sample size for 90% power is calculated as 138 persons.

SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics of evaluation results were given as numbers and percentage for categorical variables, and as mean and standard deviation, minimum and maximum for numerical variables. Comparison of numerical variables between two independent groups were carried out by using Mann-Whitney U test when normally distributed, analyzes of more than two independent groups were performed using the Kruskal-Wallis test when the parametric test conditions could not be fulfilled. Relationships between numerical variables were made using Spearman correlation analysis when parametric test conditions were not met. The statistical significance level of alpha was set as $p<0.05$. Receiver operating characteristic (ROC) curve analysis was used to calculate the cut-off value in the diagnosis and grading of liver steatosis.

RESULTS

The ages of 140 patients included in the study ranged from 32 to 79, the mean age was 55.2±9.2. Of the patients, 54 were male (38%) and 86 were female (62%). Sonografically, steatosis was not detected in 32 patients, mild steatosis was noted in 38 patients, moderate in 54 patients and severe steatosis in 16 patients.

Liver elasticity according to gender determined by both researchers are shown in Table 1. Liver elasticity according to body mass index (BMI) determined by both researchers are shown in Table 2.

The ROC curve of the shear modulus of the determining of the grade 1 liver steatosis is shown in Figure 2.

The ROC curve of the shear modulus of the determining of the grade 2 liver steatosis is shown in Figure 3.

The ROC curve of the shear modulus of the determining of the grade 3 liver steatosis is shown in Figure 4.

Liver mean p-SWE values in steatosis degrees of both researchers are shown in Table 3 and Intraclass Correlation Coefficient (ICC) values are shown in Table 4.

The cut-off pSWE values of grade 1-2 and 3 liver steatosis of both researchers are shown in Table 5.

DISCUSSION

NAFLD is the most common hepatic disease with an estimated one billion patients worldwide (14). NAFLD represents liver steatosis which means intracellular collection of lipids and may get worse and cause nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (15). NAFLD is thought to be the hepatic manifestation of the metabolic syndrome, which comprises central obesity, hyperlipidemia, hyperglycemia, hypertension and insulin resistance that plays a key role (16). NASH can lead to progressive fibrosis, cirrhosis, and end-stage liver disease. NASH is becoming the most common indication for liver transplantation in Western Countries (17). Also, the degree of liver steatosis is linked to increased cardiovascular risk (18).

One of the biggest developments in the field of US recently is the widespread use of US elastography technology. It has started to take its place among the standard practices in many countries as a non-invasive preference in the evaluation and grading of fibrosis, which has great clinical importance,

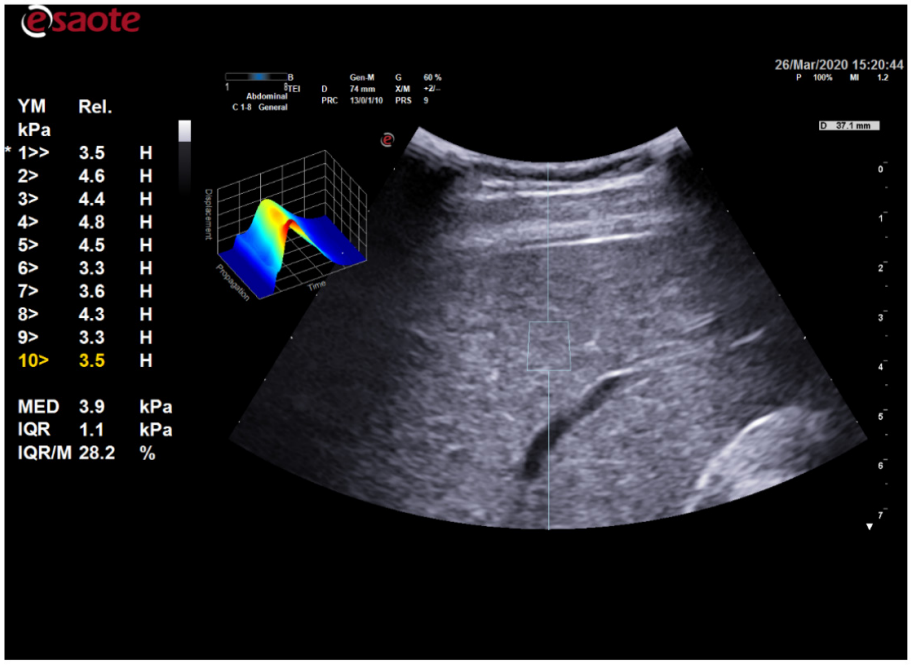

Figure 1. It was shown that the sample box was placed approximately 2 cm distal to the liver capsul, in the area away from vascular structures and ten consecutive measurements were carried out,and the resulting median values in kPa were recorded

especially in chronic parenchymal liver diseases. Currently, the method is being developed, practiced and popularized. In particular, the ability to standardize the versions of the technology offered by different imaging companies in a way that is comparable to each other is one of the most needed and areas being studied at the moment. If this is achieved, the US elastography method seems to be a candidate to become an indispensable component of relevant clinical practice applications. Conventional US is the most commonly employed diagnostic imaging method for the liver steatosis because it is easily accessible, well established, well tolerated, and cheap (19). In practice although US being the most widely used method to evaluate liver steatosis, on follow-up the severity of small alterations in steatosis this method has some difficulties. Thus, after therapeutic interventions of NAFLD patients US is not evaluated as the adequate method. To overpower the limitations of the US, computer-assisted quantitative US techniques are advanced for the follow-up assessment of liver steatosis (20). Other imaging techniques such as computerized tomography (CT), magnetic resonance imaging, magnetic resonance spectroscopy, have similar operating characteristics, but are more expensive, and CT involves radiation, therefore, their widespread use is limited (21). Due to such reasons and limitations, studies on US elastography are getting more popular. Most of the studies on liver elasticity in NAFLD in the literature were graded

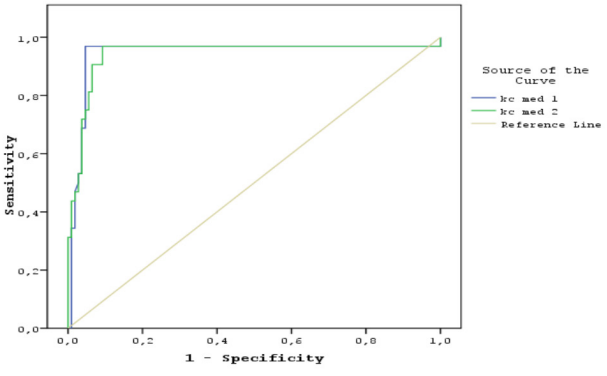

Figure 2. ROC curve of the shear modulus of the determining of the grade 1 liver steatosis
ROC: Receiver operating characteristic

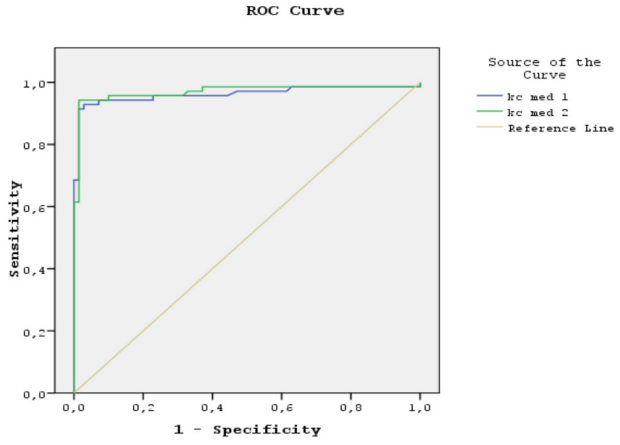

Figure 3. ROC curve of the shear modulus of the determining of the liver steatosis grade 2
ROC: Receiver operating characteristic

of liver fibrosis, which is important as a prognostic factor (22-24).

In the study by Özkan et al. (22), patients with NAFLD were evaluated with the pSWE and the median shearwave speed (SWS) value was reported to be approximately 1.56 m/s for the patients in the study. It has been reported that this SWS value is close to the low-grade histopathologic value and that patients with early stage NAFLD are likely to have histopathologic changes that do not cause significant tissue distortion, but this information should be evaluated by biopsy (22). In the Harris et al. (23) study, in the presence of steatosis, the Acoustic Radiation Force Impulse (ARFI) is very sensitive and accurate in detecting the higher stages of fibrosis, regardless of the severity of the steatosis. It tends to overestimate the fibrosis category in lower stages of fibrosis. This study it's reported that the presence of steatosis or its severity independently alters ARFI measurements are not shown. In our study, the cut-off pSWE values were determined according to the degree of steatosis in the liver and as the degree of liver steatosis increased the stiffness is decreased. Steatosis was evaluated only according to US findings and the histopathological evaluation was not performed. Therefore, it is inadequate to evaluate whether there are conditions that progress to steatohepatitis or fibrosis and its effect on the cut-off pSWE values we determined. A limitation of our study is that histopathological processes such as steatohepatitis or fibrosis were not excluded by biopsy after detecting steatosis with the US method.

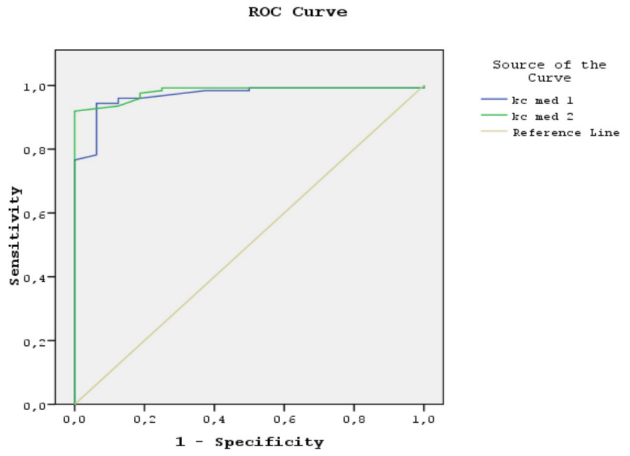

Figure 4. ROC characteristic curve of the shear modulus of the determining of the liver steatosis grade 3
ROC: Receiver operating characteristic

Also, according to the Ultrasound Liver Elastography Consensus Statement of the Society of Radiologists; it has been reported that depending on some published studies characterizing the Baveno VI consensus conference, the consensus panel proposes a vendor-neutral "rule of four" (5, 9, 13, 17 kPa) for the ARFI techniques for viral etiologies and NAFLD: Liver stiffness of 5 kPa (1.3 m/sec) or less has high probability of being normal; liver stiffness less than 9

Table 1. Liver elasticity according to gender determined by both researchers

	Gender				
	Male		Female		
	Mean ± SD	min-max (median)	Mean ± SD	min-max (median)	p
Researcher 1	46.9±51.3	4.4-137.6 (13.2)	55.4±52.8	0-144.5 (33)	0.879
Researcher 2	46.9±49.3	3.4-144.4 (12.8)	52.9±48.3	0-142.7 (35.85)	0.991

SD: Standard deviation, min: Minimum, max: Maximum

Table 2. Liver elasticity according to BMI determined by both researchers

		Researcher 1		Researcher 2	
		Mean ± SD	min-max (median)	Mean ± SD	min-max (median)
BMI	18.5-24.9	63.7±58.9	5.1-134.1 (47.45)	59.9±50.7	6.2-126.2 (67.2)
	25-29.9	39.7±47.5	3.1-142.3 (10.5)	40.0±46.0	3.4-142 (10.7)
	30-34.9	59.5±56.4	3.1-144.5 (33.9)	56.9±52.2	4.1-142.7 (35.15)
	35-39.9	70.1±42.9	0-131.7 (78.75)	67.1±41.2	0-144.4 (75.8)
	≥40:	43.8±46.4	4.6-129.5 (13.5)	42.8±43.7	5.3-116.9 (12.4)
	p	0.118		0.267	

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

Table 3. pSWE values according to liver steatosis grades determined by first and second researcher

		Researcher 1		Researcher 2	
	Grade	Mean ± SD	min-max (median)	Mean ± SD	min-max (median)
Liver steatosis	0	123.7±25.2	0-142.3 (131.75)	114.5±27.2	0-144.4 (113.35)
	1	71.4±34.9	6.2-144.5 (73.15)	72.6±29.1	8.5-131.4 (75.5)
	2	10.1±9.7	5.1-75.5 (7.7)	10.8±10.5	5.5-82.6 (8.4)
	3	4.8±1.2	3.1-7.5 (5.05)	5.1±0.9	3.4-6.4 (5.2)
	p	<0.001		<0.001	

SD: Standard deviation, min: Minimum, max: Maximum, pSWE: Point shearwave elastography

kPa (1.7 m/sec), in the absence of other known clinical signs, rules out compensated advanced chronic liver disease (cACLD); values between 9 kPa (1.7 m/sec) and 13 kPa (2.1 m/sec) are suggestive of cACLD but may need further test for confirmation; and values greater than 13 kPa (2.1 m/sec) are highly suggestive of cACLD (24). In this consensus, it has been shown that liver stiffness increases in case of cACLD development in NAFLD. In our study, liver stiffness in patients with normal liver was found to be quite high compared to values reported in the consensus. As the degree of steatosis increased, the stiffness decreased significantly. However, considering the chronicity of steatosis and the development of fibrosis in NAFLD, it does not mention a value related to liver stiffness in patients who are not chronic or have no clinical findings for cACLD, that is, only in the presence of steatosis. Whereas, in our study, we determined liver stiffness according to the degrees of fatty liver in the NAFLD without clinical findings suggestive of chronic liver disease.

In a study Sharma et al. (25), normal liver stiffness was measured in healthy people. In this study, elastography was performed on Philips iU22 and Affiniti70 US machines (Philips Healthcare, Best, The Netherlands), equipped with ElastPQ feature both using C5-1 probe, and reported as 4.48±0.78 kPa. In this study, it has been reported that, males have significantly higher liver elasticity compared to females, also, age, liver steatosis and BMI have no significant effect on liver elasticity. In the Huang et al. (26) study, they evaluated liver stiffness in 502 healthy subjects. SWE was performed using the Supersonic Imagine Aixplorer US system (Aix-en-Provence, France) that was equipped with an SC6-1 convex array probe with a frequency of 1-6 MHz. In this study, it was reported that the mean value of the SWE measurements in 502 individuals was 5.10±1.02 kPa. It was also reported that BMI had no effect on the results, and gender were also important factor affecting SWE (26). However, in our study, although liver elasticity was higher in males than in females, this difference was not statistically significant (p=0.879-0.991). Additionally, there was no statistically significant difference between the liver elasticity values of BMI (p=0.118-0.267).

In a large study by Fang et al. (27) comparing the interobserver reproducibility of four operators the ICC was found to be 0.88-0.93 for two series of measurements, in which 880 2D-SWE and pSWE velocities were recorded, respectively. Hudson et al. (28) determined that the intra-observer reliability was better for same-day evaluations (ICC=0.91) than the inter-observer reliability (ICC=0.78), they also determined that intra-observer agreement decreased when scans were repeated on a different day. Our pSWE results for two observers are correlated with conventional US grading. High ICC values were found for patients without steatosis and patients with mild steatosis

Table 4. ICC values according to liver steatosis grades

	Researcher 1 vs. researcher 2	
Liver steatosis	P (r)#	ICC (95% CI)*
Grade 0	<0.001 (0.733)	0.853 (0.500-0.944)
Grade 1	<0.001 (0.914)	0.917 (0.847-0.956)
Grade 2	<0.001 (0.847)	0.976 (0.958-0.986)
Grade 3	<0.001 (0.370)	0.518 (0.057-0.799)

#Spearman correlation analysis, *Two-way random-absolute agreement, CI: Confidence interval, ICC: Intraclass Correlation Coefficient

Table 5. The cut-off pSWE values of grade 1-2 and 3 liver steatosis of both researchers

Grade	Researcher	Threshold	Sensitivity	Specificity
1	1	<101.05	0.969	0.954
	2	<89	0.969	0.907
2	1	<18.2	0.929	0.971
	2	<22.2	0.943	0.986
3	1	<5.85	0.944	0.938
	2	<6.55	0.919	1.000

pSWE: Point shearwave elastography

and moderate steatosis. Medium ICC values were found for patients with severe steatosis. Medium ICC values in severe steatosis, may be due to the two investigators' placement of the sample box at different locations due to increased echogenicity of the liver parenchyma or the variability of the pressure applied to the probe to clearly assess the parenchyma. In relation to that the other limitation of our study was that the investigators' intraobserver agreement was not evaluated.

CONCLUSION

Although there are many elastography studies in the literature for grading fibrosis, which is an important prognostic factor in NAFLD however there is no study published investigating pSWE values in liver steatosis grading. This prospective study determines the threshold values for pSWE method considering the steatosis grades and non-steatosis in the liver steatosis using the Esaote MyLab9 US machine and pSWE technique. Our study showed that the pSWE is a reproducible, noninvasive, and easily accessible method for evaluating fatty liver disease. But, more studies are needed, including histopathological verifications.

ETHICS

Ethics Committee Approval: This prospective study was conducted in accordance with the ethical standards of the local ethics committee on human experimentation and with the Helsinki Declaration of 1075, as revised in 2000 after getting approval from the University of Health Sciences Turkey, Haseki Training and Research Ethics Committee (decision no: 2019-54, date: 26.02.2020).

Informed Consent: Informed written consent was obtained from all volunteers.

Authorship Contributions

Surgical and Medical Practices: S.Ö., T.S.C., B.K.Y., R.T., Concept: S.Ö., Design: S.Ö., B.K.Y., Data Collection or Processing: S.Ö., T.S.C., B.K.Y., Analysis or Interpretation: S.Ö., R.T., Literature Search: S.Ö., B.K.Y., R.T., Writing: S.Ö., R.T.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Research

Outcomes of Pediatric Liver Transplantation in Inherited Metabolic Diseases: A Single-center's Experience

Kalıtsal Metabolik Hastalıklarda Pediatrik Karaciğer Nakli Sonuçları: Tek Merkez Deneyimi

Melike Ersoy[1], Vildan Ertekin[2], Güntülü Şık[3], Agop Çıtak[3], Selim Keçeoğlu[4], Remzi Emiroğlu[4]

[1]University of Health Sciences Turkey, Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Metabolism, Istanbul, Turkey
[2]Acibadem Atakent Hospital, Clinic of Pediatrics, Division of Pediatric Gastroenterology Hepatology and Nutrition, Istanbul, Turkey
[3]Acibadem Atakent Hospital, Clinic of Pediatrics, Division of Pediatric Intensive Care, Istanbul, Turkey
[4]Acibadem Atakent Hospital, Organ Transplantation Center, Istanbul, Turkey

ABSTRACT

Objective: To expand on the hitherto limited knowledge of the indications and outcomes of pediatric liver transplantation (LT) for inherited metabolic diseases (IMDs).

Methods: Demographic data, pretransplant clinical and laboratory profiles, post-transplant outcomes and survival rates of twelve patients under 18 years who underwent LT for IMDs between January 2015 and June 2021 were analyzed.

Results: Twelve (6 female) of 104 (11.5%) patients had a diagnosis of IMD. Four of the patients were diagnosed with primary hyperoxaluria type 1; two had Crigler-Najjar syndrome; and there was one patient each having maple syrup urine disease, propionic acidemia, tyrosinemia type 1, glycogen storage disease type 1a, Wilson's disease, and homozygous familial hypercholesterolemia, respectively. The mean current ages and ages at transplantation of the patients were 8.7 (1-14.2) and 6.5 (0.3-12.8) years, respectively. Their mean follow-up time was 2.7 (0.5-6.1) years. The distribution of LT indications was poor metabolic control (42%), the need for frequent hospitalization due to an acute life-threatening attack (17%), progressive neuromotor retardation (8%), and target organ failure (33%) respectively. The mean time between diagnosis and LT was 2.7 (0.5-6.1) years. No neurological, hematological, or metabolic complications were observed after LT. The biliary stricture developed in two (16.7%) patients, separation of arterial anastomosis in one (8.3%) and ascites infection in one (8.3%) patient. One-year patient and graft survival rates were both 100%. A significant difference was observed between the patients' pre-operative and current height and weight standard deviation scores, respectively (p=0.001 and p=0.006).

Conclusion: LT is a good therapeutic option for improving the metabolic control and quality of life of patients with IMDs. Survival rates are excellent compared with other LT indications when appropriate timing and indication is adhered to.

Keywords: Intensive care, metabolic diseases, pediatric surgery

ÖZ

Amaç: Kalıtsal metabolik hastalıklar (KMH) için pediatrik karaciğer nakil (KN) endikasyonları ve sonuçları hakkında şimdiye kadar sınırlı olan bilgileri genişletmektir.

Gereç ve Yöntem: Ocak 2015 ile Haziran 2021 arasında KMH nedeniyle karaciğer nakli yapılan 18 yaş altı on iki hastanın demografik verileri, nakil öncesi klinik ve laboratuvar profilleri, nakil sonrası sonuçları ve sağkalım oranları analiz edildi.

Bulgular: One hundred four (%11,5) hastanın 12'si (6 kız) KMH tanısı aldı. Hastaların dördü primer hiperoksalüri tip 1 tanısı aldı. İkisinde Crigler-Najjar sendromu, sırasıyla akçaağaç şurubu idrar hastalığı, propiyonik asidemi, tirozinemi tip 1, glikojen depo hastalığı tip 1a, Wilson hastalığı ve homozigot ailesel hiperkolesterolemi tanılı birer hasta vardı. Hastaların ortalama güncel yaşları ve nakil sırasındaki yaşları sırasıyla 8,7 (1-14,2) ve 6,5 (0,3-12,8) yıl idi. Ortalama takip süreleri 2,7 (0,5-6,1) yıldı. KN endikasyonlarının dağılımı kötü metabolik kontrol (%42), akut yaşamı tehdit eden atak nedeniyle sık hastaneye yatış ihtiyacı (%17), ilerleyici nöromotor gerilik (%8) ve hedef organ yetmezliği (%33) idi. Tanı ile KN arasındaki

Address for Correspondence: Melike Ersoy, University of Health Sciences Turkey, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Metabolism, Istanbul, Turkey
Phone: +90 533 420 50 59 E-mail: zeynepcey@hotmail.com ORCID ID: orcid.org/0000-0002-2316-0790

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ortalama süre 2,7 (0,5-6,1) yıldı. KN sonrası nörolojik, hematolojik veya metabolik komplikasyon gözlenmedi. İki hastada (%16,7) biliyer darlık, bir hastada (%8,3) arteriyel anastomoz ayrılması ve bir hastada (%8,3) asit enfeksiyonu gelişti. Bir yıllık hasta ve greft sağkalım oranları %100 idi. Hastaların ameliyat öncesi ve mevcut boy ve kilo standart sapma skorları arasında sırasıyla anlamlı fark gözlendi (p=0,001 ve p=0,006).

Sonuç: KN, KMH olan hastalarda metabolik kontrolü ve yaşam kalitesini iyileştirmek için iyi bir tedavi seçeneğidir. Sağkalım oranları, uygun zamanlama ve endikasyonda diğer nakil endikasyonlarına kıyasla daha yüz güldürücüdür.

Anahtar Kelimeler: Yoğun bakım, kalıtsal metabolik hastalıklar, pediatrik cerrahi

INTRODUCTION

Since the first pediatric liver transplantation (LT) was performed in the USA in 1967 and subsequently in Europe in 1968, survival rates have increased with further development of surgical techniques, use of effective new immunosuppressants, and improved postoperative care (1).

Moreover, indications for LT have expanded over time, and inherited metabolic diseases (IMDs) have become one of the leading indications. IMDs are a group of diseases that impair the function of metabolic pathways that result in severe multi-system dysfunction or death. Although rare as individual entities, collectively these diseases occur with considerable frequency, represent the second most common indication for LT after biliary atresia (2). Today, IMDs constitute approximately 20% of pediatric LT indications (3,4). Nowadays, increasing use of next generation sequencing diagnostic methods has already made it possible to identify the fact that IMDs underlie some of the cryptogenic causes (5). LT in IMDs was first performed successfully in a case of tyrosinemia type 1 (TT1) in 1978, and then in a case of ornithine transcarbamylase deficiency in 1989, and, with an increasing number of examples and new indications, it has become an important treatment modality looking toward the future (6).

LT in IMD is mainly performed for two reasons: primary liver diseases (acute liver failure, cirrhosis, malignancy, cholestasis, steatosis) caused by IMDs, which directly affect the liver parenchyma, and secondly due to cases where permanent enzyme replacement therapy is provided in IMDs due to deficiency of enzymes synthesized by liver cells (7) (Table 1).

Despite disease-based indications having been determined, patient-based criteria should also be evaluated in IMDs: 1) failure to respond to medical treatment; 2) need for frequent hospitalization due to an acute life-threatening attack; 3) poor quality of life; 4) progressive neuromotor retardation due to poor metabolic control; 5) growth retardation; 6) laboratory tests that do not improve (ammonia, lactate, cholesterol, etc.); 7) presence or risk of malignancy; and 8) acute liver failure. Before making the LT decision, patients should be evaluated in terms of all these risks and evaluated on an individual-patient basis.

In some cases, LT alone is not enough to replace the missing enzyme. Dual transplantation is needed to prevent insufficiency in the other target organs. Liver-kidney transplantation is the most common combination practice in IMDs. Indications for combined liver-kidney transplantation were primary hyperoxaluria type 1 (PH1), methylmalonic aciduria, glycogen storage disease type 1, and those presenting with or at risk of end-stage renal disease.

We reported our center's experience of pediatric liver and liver-kidney transplantation for IMDs.

METHODS

Patients diagnosed with IMD, <18 years of age, who received a liver-only, or combined liver-kidney transplant participated in the study after providing their consent. Patient and donor demographics, patients' preoperative and postoperative clinical and laboratory data, and post-transplant outcomes were recorded from medical records, and the laboratory results were retrieved electronically from the hospital database. Patient survival and graft survival rates, immunosuppression and concomitant medications were specified. Additionally, preoperative and postoperative growth and neurological status of the patients was compared.

Ethical Statement

This study was prepared in accordance with the ethical principles of the World Medical Association Declaration of Helsinki (2000). Furthermore, it was approved by the Acibadem University Ethics Committee (decision no: 2021-24/01, date: 17.12.2021).

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0. Categorical variables were defined as frequency and percentage rate, and numerical variables were determined as mean ± standard deviation (SD). Student's t-test was performed for normally-distributed numerical variables. Statistically-significant results were defined as those with a p-value of <0.05.

Table 1. Indications for liver transplantation in inherited metabolic diseases

IMDs of primary hepatic origin without parenchymal liver damage	IMDs of primary hepatic origin with parenchymal liver damage
Urea cycle disorders (excluding ASL)	Genetic cholestasis syndromes (PFIC, Alagille syndromes)
Organic acidemias (propionic acidemia, methylmalonic acidemia)	Wilson's disease
Crigler-Najjar syndrome	Hereditary hemochromatosis
Atypical hemolytic uremic syndrome (cobalamin metabolism disorders)	Tyrosinemia type 1
Primary hyperoxaluria type 1	α-1-antitrypsin deficiency
Maple syrup urine disease	Argininosuccinic aciduria
Acute intermittent porphyria	GSD type 1 (adenoma/hepatocellular carcinoma)
Glycogen storage disease type 1a	Lysosomal acid lipase deficiency
Homozygous familial hypercholesterolemia	Mitochondrial depletion syndromes

ASL: Argininosuccinate lyase, PFIC: Progressive familial intrahepatic cholestasis, IMD: Inherited metabolic disease, GSD: Glycogen storage disease

RESULTS

A total of 104 patients underwent liver-only and combined liver-kidney transplantation in our center between November 2015 and January 2021. Twelve of the total (11.5%) had underlying causes of IMDs. Four of the patients were diagnosed with PH1, two with Crigler-Najjar syndrome, and one patient each respectively with maple syrup urine disease (MSUD), propionic acidemia, TT1, glycogen storage disease (GSD) type 1, Wilson's disease, and homozygous familial hypercholesterolemia (HFH) (Figure 1).

All patients had living-donor LT. All donors were first-degree relatives of the patients. Combined liver-kidney transplantation was performed in four patients with PH1. The demographics of the patients and donors are summarized in Table 2.

The distribution of LT indications was determined as poor metabolic control (n=5, 42%), the need for frequent hospitalization due to an acute life-threatening attack (n=2, 17%), progressive neuromotor retardation (n=1, 8%) and target organ failure (n=4, 33%) respectively (Figure 2). The preoperative clinical and laboratory data of the patients have been summarized in Table 3.

The mean length of stay in the pediatric intensive care unit and the total duration of hospital stay post-LT were six days (range: 3-15) and 27.7 days (range: 9 to 71) respectively. Tacrolimus was used as the first-choice drug; only one patient was switched to cyclosporine due to tacrolimus's side effect of renal toxicity. IMD-specific treatment was given for an average of four days post-operatively (range: 2-8). Branched-chain amino acids (leucine, valine, isoleucine) in MSUD and tyrosine levels in TT1 returned to the normal range on the eighth postoperative day. In propionic acidemia, urinary metabolites returned to the normal ranges within an average of 14 days (±3.45 SD) (Figure 3a-3b). On the 3rd and 7th postoperative days, toxic amino acid levels in aminoacidopathies; blood ammonia and glutamine levels in organic acidemia were evaluated. According to these

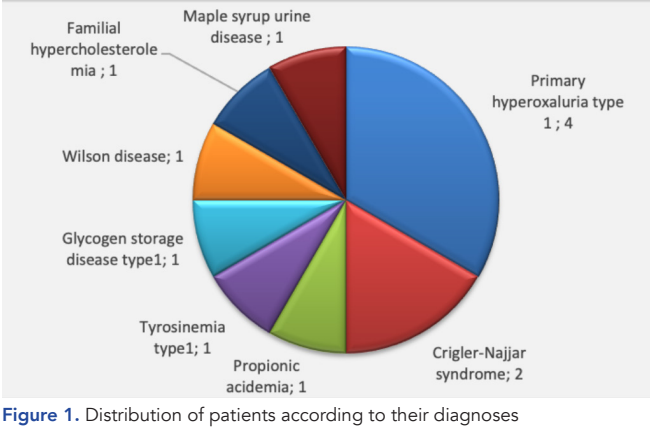

Figure 1. Distribution of patients according to their diagnoses

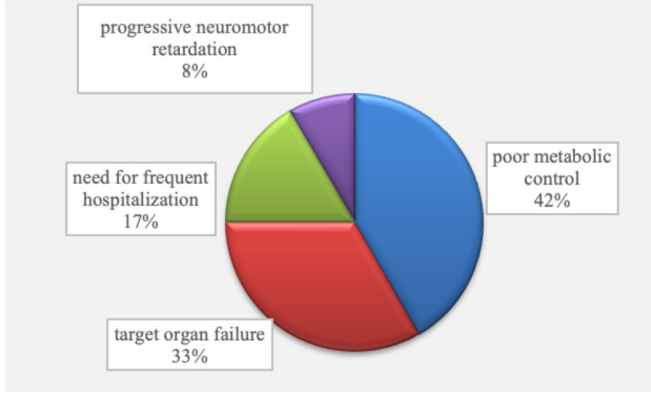

Figure 2. The distribution of patient-based LT indications of the patients
LT: Liver transplantation

levels, protein restriction diet of the patients was reduced and than stopped. None of the patients continued on a protein-restricted diet. Anti-oxidant treatment (coenzyme Q-10, B complex, L-carnitine) of the patient diagnosed with propionic acidemia was continued for one year; and the patient with a diagnosis of TT1 continued to use nitisinone at a low, renal-protective dose.

No neurological, hematological, renal, or metabolic complications were observed in the short-term (≤1 month) postoperative follow-up of any patient, but ascites infection developed in one (8.3%) patient. With respect to long-term surgical complications (>1 month), partial obstruction of the biliary stricture was observed in two (16.7%) cases, and the artery anastomosis separation was seen in one patient (8.3%). Total short-term and long-term complication rates were 8.3% and 25%, respectively. All were reversible and no permanent complications occurred.

The median follow-up period of the patients was 2.5 years (0.5-6.1) and their 1-year patient and graft survival rates were both 100%. (It is impossible to give a 5-year survival rate yet, since the average follow-up period is <5 years.). For the same period, the overall survival rate of all pediatric LT in our center was 94.6%.

A significant difference was observed between pre-operative and current height and weight SDs of the patients (p=0.001 and p=0.006). The MSUD patient with moderate mental retardation remained stable, and the patients with mild mental retardation suffering from propionic acidemia and GSD type 1 showed neurocognitive improvement. All patients were completely cured of metabolic disease.

DISCUSSION

The data of twelve pediatric patients who underwent LT for IMDs, which comprised 11.5% of all LTs, from November 2015 to January 2021 were reported.

Since most enzymes in metabolic pathways are synthesized within the liver, LT is a life-saving procedure and improves

Table 2. Demographics of the patients and the donors

Mean current age (yrs) (min-max)	8.7 (1-14.2)
Mean age at transplantation (yrs) (min-max)	6.5 (0.3-12.8)
Gender (F/M)	6/6
Consanguinity n (%)	9 (81)
Mean time between diagnosis and Tx (yrs) (min-max)	4.2 (0.8-11)
Mean follow-up time (yrs) (min-max)	2.7 (0.5-6.1)
Mean age of donors at transplantation (min-max)	34.2 (21-50)
Gender of donors (F/M)	8/4

F: Female, M: Male, Tx: Transplantation, yrs: Years, min: Minimum, max: Maximum

Table 3. Clinical and laboratory data of patients before transplantation

PELD score	15.1 (5-28)
Elective/Emergency ratio	10/1
Height (SDS)	-0.05 (-2.3- 1.2)
Weight (SDS)	-0.12 (-2.6- 0.9)
Neurological involvement, n (%)	2 (18)
Renal involvement, n (%)	5 (45)
Cardiac pathology, n (%)	1 (8)
Metabolic decompensation	0 (0)
Preop CRRT	3 (27)
INR	1.26 (0.9-2.3)
Albumin (g/dL)	3.14 (2.3-4.6)
Total bilirubin (mg/dL)	7.23 (0.23-28.24)

CRRT: Continuous renal replacement therapy, INR: International normalized ratio, PELD: Pediatric end-stage liver disease, SDS: Standard deviation score

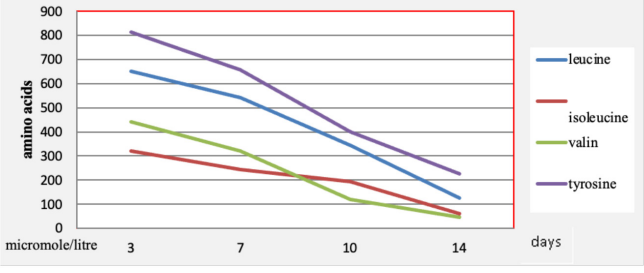

Figure 3a. Postoperative plasma amino acid levels of MSUD and TT1 patients

MSUD: Maple syrup urine disease
TT1: Tyrosinemia type 1

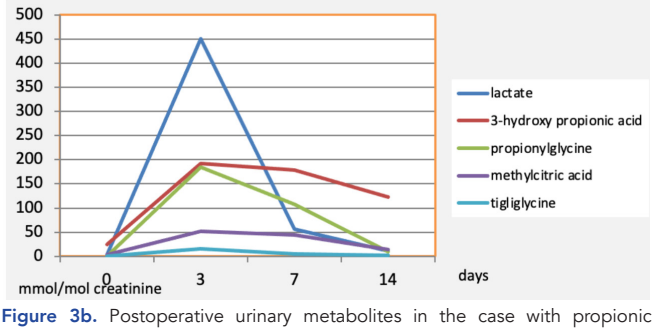

Figure 3b. Postoperative urinary metabolites in the case with propionic acidemia

quality of life in IMDs. As well as preventing liver damage caused by IMDs, it is considered a type of gene transfer which is based on the idea of transferring a genetically-normal liver to correct metabolic imbalances. In this context, poor metabolic control and the need for frequent hospitalizations, which constituted 69% of the total indications, were the leading indications in our study. Target organ failure ranks second among the causes, accounting for 33% of total indications.

We can divide IMDs into two groups according to their post-transplant status: patients who are completely cured and do not need additional metabolic therapy and follow-up; and patients whose metabolic follow-up is continued due to failure to correct enzyme deficiencies in other tissues (8). Our study group consisted of patients who were completely cured.

Overall, the reported patient survival and graft survival at 1 year were 97.3% and 96.6% respectively; 5-year patient survival varied from 88.9-92%, and in terms of graft survival this figure was 83.8% for cases of pediatric LT due to all IMDs (3,9). These rates are higher than those for other indications of LT. In our IMD case series, 1-year survival rates were found to be similar, and as high as has been reported in the literature. This situation is associated with normal liver parenchyma and liver function of LTs performed due to IMDs.

The most common post-LT complications are re-operation (31.7%), hepatic artery thrombosis (6.3%), and portal vein thrombosis (3.2%) over the short-term; and biliary tract complications (13.6%) over the long-term, which were reported by the society of pediatric LT (3). Biliary complications were seen at a similar rate (16.7%), but vascular complications (8.3%) were less common in this study group.

MSUD is caused by decreased activity of the branched-chain alpha-ketoacid dehydrogenase complex, the second enzymatic step in the degradative pathway of the branched-chain amino acids (BCAAs-leucine, isoleucine, and valine). LT is a curative treatment method option for MSUD, which is characterized by high mortality and morbidity due to attacks with a rapid increase in BCAAs (10). A leucine-restricted diet forms the basis of medical therapy. Poor metabolic control and frequent attacks are the most common causes for requiring LT. Our patient was transplanted on the basis of these indications and, post-LT leucine and other BCAAs rapidly decreased to normal levels. The neuromotor development of the patient, without a new metabolic attack, improved. Patients suffering from MSUD, which is one of the IMDs that cause serious mortality and morbidity due to severe metabolic attacks at all ages, should be recommended for LT at the earliest appropriate time.

TT1 is caused by a deficiency of fumarylacetoacetase, the final enzyme of the tyrosine degradation pathway. It is characterized by progressive liver disease and secondary renal tubular dysfunction leading to hypophosphataemic rickets. Medical treatment is following a combination of a tyrosine-restricted diet and nitisinone, a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase to prevent the formation of the toxic substances maleylacetoacetate and fumarylacetoacetate, and their saturated derivatives. LT in TT1 provides a curative treatment with excellent results in experienced centers (11). The indications are (1) failure to respond to primary medical treatment, including diet and nitisinone; (2) acute hepatic failure unresponsive to medical treatment; (3) malignancy: a) hepatocellular carcinoma (HCC), b) liver with nodular cirrhosis (very high risk of developing HCC), c) rising or abnormal alpha-fetoprotein (AFP); and (4) chronic liver/kidney failure, respectively. LT was performed in our patient due to a progressive increase in AFP levels, but no macroscopic HCC was detected. Although we stopped a tyrosine-phenylalanine-restricted diet in this patient, we continued low-dose nitisinone treatment to prevent renal involvement. It seems that close monitoring of AFP level and renal function should be ensured in TT1, and transplantation should be prioritized in cases with persistent AFP elevations.

GSD1a is caused by glucose-6-phosphatase deficiency, characterized by severe hypoglycemia during the first year of life and hepatomegaly caused by accumulating glycogen. Uncooked corn-starch alternating with frequent meals high in complex carbohydrates in daytimes and continuous nocturnal infusion form the basis of medical therapy. Despite good medical treatment, patients may develop liver and kidney failure and severely stunted growth (12). Hepatic adenomas with potential for malignant transformation represent a further indication for LT. According to the metabolic status of the patient, the indication for a liver-only or a combined liver-kidney transplantation is determined. Single organ transplants are preferred because the risk of complications increases in combined transplants. However, liver-only transplant patients should have their kidney function closely monitored (13).

Propionic acidemia is an organic acidemia caused by a deficiency of mitochondrial propionyl CoA carboxylase, resulting in the accumulation of propionic acid metabolites, and dysfunction in both the electron transport chain and urea cycle pathways. It can cause liver, kidney and heart

failure, and severe neuromotor retardation due to the effects of other pathways. Therefore, the risk of developing post-LT complications and mortality is higher compared to other IMDs (14). The overall mortality rate post-LT in PA has been reported at around 30%, which is signficantly higher than for other indications (10-20%) (15,16). The biliary stricture developed in our patient, who recovered following PTC. Post-LT diet and medical treatments were continued for an average of one week. Additionally, anti-oxidant therapy was given for one year for neurocognitive support. In this way, our patient progressed through his developmental stages, and he started walking without support.

PH1 is an inherited metabolic disorder characterized by a deficiency of the liver-specific alanine-glyoxylate aminotransferase, resulting in the overproduction of oxalate and end-stage renal disease: combined liver-kidney transplantation is the best treatment for patients with PH1 with end-stage renal disease (17). Most our IMD patients were PH1 patients who underwent combined kidney-liver transplant. Although there is an increased risk compared with LT-alone, experienced, and multi-disciplinary approaches, and good postoperative care led to excellent results in all patients (18). The renal function of the patients was also stable at their most recent evaluation. Patient survival in PH1 at 2, 5, 10, and 15 years was 87.5%, 87.5%, 78%, and 78% respectively (19). Although it is a small series, the one-year survival for our patients is 100%.

Wilson disease is a multi-systemic IMD causing acute and chronic liver failure. Medical treatments can effectively remedy and protect liver and non-hepatic tissues. LT is offered when the Dhawan score is ≥11 (as this predicts a mortality of greater than 97%) or where there is no response to medical therapies (20,21). Post-LT survival for Wilson disease is excellent with a 5-year survival of up to 90% (22).

HFH is an autosomal dominant disorder that has mortal cardiovascular effects even in pediatric age groups. Medical and dietary therapies have limited effects on patients undergoing lipid apheresis to decrease low-density lipoprotein cholesterol (LDL-C). Since LDL receptors are mainly located in the liver, LT is considered as the only way to correct hepatic cholesterol metabolism (23). After LT, LDL-C rapidly falls below 180 mg/dL. Cardiovascular disease risk is significantly reduced and post-transplant survival rates are also promising in transplanted HFH patients.

Crigler-Najjar syndrome is an autosomal recessive IMD, caused by UDP-glucuronosyltransferase and characterized by high levels of unconjugated hyperbilirubinemia leading to brain damage and even death (24,25). Although it is classified under the group of IMDs of primary hepatic origin without parenchymal liver damage, detection of fibrosis in liver tissue in recent publications is an interesting development, representing new information (26). The cause of the fibrosis and tissue damage is unknown. Phototherapy (12 hours/day), despite being highly effective in the first few years after birth, is socially inconvenient and becomes less effective in older age groups. LT is the only the curative treatment (25). In some study groups, while the outcome was excellent with a patient survival rate of 100%, the graft survival rate was not good (61.5%) (26). Re-transplantation in Crigler-Najjar syndrome is relatively more common compared to other indications for LT. The reason for this situation has not been fully elucidated. Our two patients showed normal neuromotor development without impairment of their activities of daily living or education.

In our study, it was shown that LT performed timely and for the correct indication not only prevented organ damage in IMDs, but also safeguarded the physical and neurological development of patients. Rapid rectification of surgical and medical complications has increased the preference for LT as a treatment due to increased patient survival.

Study Limitations

Although IMDs are in the rare disease group, the small sample size is the limitation of the study.

CONCLUSION

LT is a good therapeutic option for improving the metabolic control and quality of life in cases of IMD. While the risk of complications is less in IMD-induced LTs, their survival rate is better than in other indications.

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ETHICS

Ethics Committee Approval: This study was approved by the Acibadem University Ethics Committee (decision no: 2021-24/01, date: 17.12.2021).

Informed Consent: Written consent was obtained from the participants.

Authorship Contributions

Surgical and Medical Practices: M.E., V.E., G.Ş., A.Ç., S.K., R.E., Concept: M.E., V.E., Design: M.E., V.E., Data Collection or Processing: M.E., V.E., Analysis or Interpretation: M.E., V.E., Writing: M.E, V.E., S.K., R.E.

Conflicts of interest: The authors declare that they have no conflict of interest.

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Research

Severe Scorpion Envenomations in Pediatric Intensive Care Unit

Çocuk Yoğun Bakım Ünitesinde Akrep Sokması Olguları

Hasan Serdar Kıhtır[1], Gökmen Özdemir[2], Abdullah Kocabaş[2], Yasin Bayram[3], Ebru Atike Ongun[1]

[1]University of Health Sciences Turkey, Antalya Training and Research Hospital, Department of Pediatric Critical Care, Antalya, Turkey
[2]University of Health Sciences Turkey, Antalya Training and Research Hospital, Department of Pediatric Cardiology, Antalya, Turkey
[3]University of Health Sciences Turkey, Antalya Training and Research Hospital, Department of Pediatrics, Antalya, Turkey

ABSTRACT

Objective: This study aimed to determine the general characteristics and warning signs for the more severe (grade 3) clinical course in severe scorpion envenomations in the pediatric intensive care unit (PICU).

Methods: This retrospective, cross-sectional study was conducted in 12 beds tertiary care PICU in Antalya Training and Research Hospital. Patients admitted to the PICU between 2017-2021 due to severe scorpion envenomation were admitted to the study.

Results: It was found that there were 2,208 admissions to the intensive care unit during the study period (4 years), and 73 (3.3%) of these cases (35 female and 38 male) were followed up for severe scorpion envenomation. The median age was 52 (26-89) months. Yellow scorpions were described by parents or eyewitnesses in 65 patients (89%) and black scorpions in 8 (11%). Peripheral sympathetic activity (cold extremities, diaphoresis) signs (n=55, 75.3%), hypertension (n=35, 47.9%), and tachycardia (n=21, 28%) were the most common findings. The most common echocardiographic findings were mild-to-moderate mitral regurgitation and systolic dysfunction in 31 (42.5%) and 19 (25.9%) cases, respectively. Sixty-two (89%) patients had grade 2 envenomations findings and 12 (11%) had grade 3. High pro-BNP, hyperglycemia, and hyperamylasemia were observed more frequently in grade 3 than in grade 2 patients on admission. All patients received anti-venom therapy and 7 (9.5%) of them required a second dose of anti-venom therapy due to the unregressed clinical course. Twenty-seven patients (37%) required inotropics, s and the most commonly used inotropics were milrinone in 17 (23.3%) patients and dobutamine in 12 (16.4%) patients. The median PICU length of stay was 4 (3-5) days and the median hospital stay was 5 (4-6) days. All patients survived to discharge.

Conclusion: Hyperamilasemia, hyperglycemia, and elevated pro-BNP levels on admission may be warning signs of more severe (grade 3) patients. Mild-to-moderate mitral regurgitation may be more commonly observed echocardiography findings than systolic dysfunction in severe cases (grade 2 and 3).

Keywords: Scorpion stings, intensive care units, pediatric, hyperamylasemia

ÖZ

Amaç: Bu çalışmanın amacı çocuk yoğun bakım ünitesinde (ÇYBÜ) takip edilen ağır akrep ısırığı olgularının genel özelliklerini ve daha ağır (grade 3) seyirli olgular açısından uyarıcı bulguları ortaya koyabilmektir.

Gereç ve Yöntem: Bu retrospektif, kesitsel çalışma Antalya Eğitim ve Araştırma Hastanesi'nde 12 yataklı üçüncü basamak ÇYBÜ'de yürütülmüştür. ÇYBÜ'ye 2017-2021 yılları arasında ağır akrep sokması nedeniyle yatırılan olgular çalışmaya dahil edildi.

Bulgular: Çalışma periyodunda (4 yıl) çocuk yoğun bakım ünitesine 2.208 olgunun yatırıldığı ve bu olguların 73 (%3,3) tanesinin (35 kız ve 38 erkek) akrep sokması olguları olduğu tespit edildi. Ortanca yaş 52 (26-89) aydı. Ebeveynler tarafından yapılan tanımlamaya göre 65 (%89) olguda sarı akreplerin, 8 (%11) olguda ise siyah akreplerin sorumlu olduğu görüldü. Periferik sempatik aktivite bulguları (soğuk ekstremiteler ve terleme) 55 (%75,3) olguda, hipertansiyon 35 (%47,9) olguda ve taşikardi 21 (%28) olguda mevcuttu. En sık gözlenen ekokardiyografi bulguları 31 olguda (%42,5) hafif-orta mitral kapak regürjitasyonu ve 19 (%25,9) olguda görülen sistolik disfonksiyondu. Altmış beş (%89) olguda grade 2 akrep sokması bulguları varken 12 olguda (%11) grade 3 bulgular mevcuttu. Başvuru sırasında pro-BNP yüksekliği, hiperamilasemi ve hiperglisemi grade 3 olgularda grade 2 olgulara göre daha sık gözlendi. Tüm olgular anti-venom tedavisi alırken 7 (%9,5) olguda klinik gidişin gerilememesi

Address for Correspondence: Hasan Serdar Kıhtır, University of Health Sciences Turkey, Antalya Training and Research Hospital, Clinic of Pediatric Critical Care, Antalya, Turkey
Phone: +90 506 771 88 37 E-mail: serdar.kihtir@gmail.com ORCID ID: orcid.org/0000-0003-0120-8711

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nedeniyle ikinci doz tedavi gerekli oldu. Yirmi yedi (%37) olguda inotrop gereksinimi olurken bu olguların 17'sinde (%23,3) milrinon, 12'sinde (%16,4) ise dobutamin kullanıldı. Ortanca çocuk yoğun bakım süresi 4 (3-5) gün, ortanca hastane yatış süresi ise 5 (4-6) gün olarak tespit edildi. Olgular arasında mortalite gözlenmedi.

Sonuç: Başvuru sırasında gözlenen hiperamilazemi, hiperglisemi ve yüksek pro-BNP düzeyleri daha ağır (grade 3) seyirli olabilecek hastalar açısından uyarıcı bulgular olabilir. Hafif-orta düzeydeki mitral regürjitasyonun ağır olgularda (grade 2 ve 3) sistolik disfonksiyona göre daha sık gözlenebilen bir ekokardiyografi bulgusu olduğu görülmektedir.

Anahtar Kelimeler: Akrep sokmaları, yoğun bakım ünitesi, pediatrik, hiperamilazemi

INTRODUCTION

Scorpions, the oldest arthropod species living on Earth, have been a major problem throughout human history. Nearly 3,000 species of scorpions have been described worldwide, and they live everywhere in the world except Antarctica. In Turkey, 27 species of scorpion have been described in four families (Buthidae, Iuridae, Scorpionidae and Euscorpiidae) (1). The most medically important scorpion species in Turkey are Androctonus, Leiurus and Mesobuthus species from the family Buthidae (2). Although the most cases of scorpion envenomation in Turkey occur below the 39th parallel (central and southern Aegean region, the Mediterranean region, and central, west, and southwestern region of Anatolia), the risk of scorpion envenomation exists in all regions of Turkey (3). The main causes of death in scorpion envenomation are hemodynamic disturbances and pulmonary edema. This study reveals the general characteristics of scorpion envenomation in children and determination of variables that may lead to early recognition of the most severe (grade 3) patients.

METHODS

This retrospective cross-sectional study was conducted in a 12-bed tertiary care pediatric intensive care unit (PICU) of Antalya Training and research Hospital that admits approximately 500 medical and surgical patients annually and is located on the southwestern coast of Turkey. The severity of the patients was determined according to the staging system used by Khattabi et al. (4). Only local manifestations are grade 1, non-life-threatening systemic manifestations (hypertension, nausea, convulsions, lethargy, tachycardia, etc.) are grade 2 (severe), and life-threatening systemic manifestations (hypotension, ventricular arrhythmia, bradycardia, collapse, respiratory failure, neurological failure) are defined as grade 3 (more severe). According to our scorpion stings protocol, only patients with systemic symptoms (grade 2 and 3) were admitted to the PICU.

Equine antivenom (Androctonus crassicauda) was used for anti-venom therapy. Before the anti-venom infusion, a skin test was performed routinely. Five milliliters (one ampoule) of anti-venom was diluted with 50 milliliters of normal saline and infused over 30 min in all patients.

Patient records (between 2017 and 2021) were retrospectively reviewed after University of Health Sciences Turkey, Antalya Training and Research Hospital Ethics Committee approval was obtained (decision no: 1/28, date: 04.03.2021). Patient demographics, signs and symptoms on admission, echocardiography findings, laboratory results, specific treatments (anti-venom, doxazosin), intensive care treatments (inotropic and vasoactive medications, sedatives, respiratory support), intensive care, and length of hospital stay were recorded. Patients, whom scorpion could not be observed and were treated with suspicion based on clinical findings were excluded from the study.

Systolic dysfunction was defined by an ejection fraction of less than 55% (40-55% mild, 30-40% moderate, and <30% severe). Hyperglycemia was defined as blood glucose level >140 mg/dL (5), elevated creatine kinase (CK) defined as CK level >200 U/L (laboratory upper limit), elevated troponin T defined as troponin level >14 ng/L (6), elevated myoglobin level defined as myoglobin level >72 ng/mL (laboratory upper limit), elevated pro-BNP defined as pro-BNP level >300 ng/L (7), hyperamylasemia defined as amylase level >110 U/L (8), hyperlipasemia defined as lipase level >160 U/L (9), and leukocytes (white blood cells) >10x10^3/mm^3 (laboratory upper limit) was defined as leukocytosis.

Statistical Analysis

Categorical variables were expressed as n (%) and continuous variables were expressed as median (interquartile range: 25p-75p). The chi-square test or Fisher's Exact test was used to compare categorical variables between the two groups. Mann-Whitney U test was used for the comparison of continuous variables between the two groups. Statistical calculations were performed with the Statistical Package for Social Sciences (SPSS) for Windows version 23 and MedCalc for Windows version 14.8.1.

RESULTS

It was found that there were 2,208 admissions to the PICU during the study period (4 years), and 73 (3.3%) of these cases (35 female and 38 male) were followed up due to severe scorpion envenomation. Fifty-one (69.8%) of the patients were admitted to the PICU between June and

September. Yellow scorpions were described by parents or eyewitnesses in 65 patients (89%) and black scorpions in 8 (11%). The demographic features of the patients are presented in Table 1.

Peripheral sympathetic activity signs (cold extremities, diaphoresis) were the most common findings on admission (n=55, 75.3%). Other common findings were shortness of breath in 22 (30.1%) patients, hypertension in 35 (47.9%) patients, nausea in 27 (37%) patients, bradycardia in 2 (2.7%) patients, tachycardia in 21 (2.8%) patients, hypotension in 7 (9.6%) patients, priapism in 3 (4.1%) patients, and pulmonary edema in 5 (6.8%) patients.

Abnormal laboratory findings in the patients were as follows. Hyperglycemia in 19 (26.8%), leukocytosis in 47 (66.2%) patients, hyperamylasemia in 25 (42.4%) patients, elevated troponin T in 41 (59.4%) patients, elevated myoglobin in 31 (68.9%) patients, elevated pro-BNP in 17 (23.3%) patients, and elevated CK was detected in 49 (71%) patients (Table 2). Lipase elevation was not observed in the patient.

The median ejection fraction of the patients on echocardiography was 63% (52-66). The most common abnormal echocardiographic finding was mild-to-moderate mitral regurgitation, which was noted in 31 (42.5%) patients. Other abnormal echocardiographic findings were mild systolic dysfunction in 17 (23.2%), moderate systolic dysfunction in 2 (2.7%) patients, and mild tricuspid regurgitation in 13 (17.8%) patients.

All patients received anti-venom therapy and 7 (9.5%) of them required a second dose of anti-venom because of the unregressed clinical course. The most commonly used treatment agent was doxazosin in 49 (67.1%) patients. Furosemide was used in 23 (31.5%) patients. Twenty-seven (37%) patients required inotropic and/or vasoactive support. The following inotropic and vasoactive agents were used in the patients: milrinone in 17 (23.3%) patients, dobutamine in 12 (16.4%) patients, epinephrine in 9 (12.3%) patients, dopamine in 4 (5.5%) patients, and norepinephrine in 5 (6.8%) patients. Dexmetatomidine was used in 21 (28.8%) patients for its sedative, analgesic, and sympatholytic properties. Seventeen patients (22.2%) required invasive positive pressure ventilation and five patients (5.6%) required invasive mechanical ventilation.

Cardiac arrest and cardiopulmonary resuscitation were required in two (2.7%) patients. The median PICU length of stay was 4 (3-5) days and the median hospital stay was 5 (4-6) days. All patients were discharged without morbidity or mortality, except for one patient who developed neuromotor disability because of cardiac arrest.

DISCUSSION

Scorpion envenomation is an important health problem in children, especially those under 5 years of age. This is because most of the reported deaths occur under the age of 5 years (10). It is recommended that patients with scorpion envenomation who present with systemic symptoms should be followed up in the PICU (11). In this study, we show the general characteristics and frequency of children with severe scorpion envenomations in our PICU. The main findings of this study are relevant to laboratory and echocardiographic results. Hyperglycemia, hyperamylasemia, and elevated pro-BNP occur more frequently in grade 3 cases than grade 2 cases. Echocardiographic findings show that mild-to-moderate mitral regurgitation is more common than systolic dysfunction. Although there was no death in our cases, pulmonary edema, which led to cardiac arrest in one case, was seen as the potentially most fatal complication.

It has been reported that the pancreas is frequently but transiently affected in systemic scorpion envenomations (12). Animal studies show that scorpion venom increases biliary and duodenal motility, causing increased pancreatic amylase production (13,14). Although there were no

Table 1. Demographic features of patients (n=73)

Age (months)		52 (26-89)
Age groups	0-24 months	15 (20.5%)
	24-84 months	39 (53.4%)
	84-144 months	11 (15.1%)
	>144 months	8 (11%)
Gender	Female	35 (47.9%)
	Male	38 (52.1%)
Sting site	Head and neck	1 (1.4%)
	Trunk	4 (5.5%)
	Upper extremity	32 (43.8)
	Lower extremity	36 (49.3%)
Stings count	1	63 (86.3%)
	2	10 (13.7%)
Time between sting and PICU admission (hours)		4 (3-6)
Severity	Grade 2	62 (84.9%)
	Grade 3	11 (15.1%)
PRISM score		5 (4-8)
Length of PICU stay (days)		4 (3-5)
Length of hospital stay (days)		5 (4-6)

PICU: Pediatric intensive care unit, PRISM: Pediatric risk of mortality
Severity of scorpion sting was defined by Khattabi et al. (4)

Table 2. Differences between grade 2 and grade 3 scorpion envenomation patients

		Grade 2 (n=62)	Grade 3 (n=11)	p-value
Age (months) median (25-75p)		52 (26-91)	46 (22-57)	0.23
Gender (female/male)		30/32	5/6	0.8
Scorpion	Yellow n (%)	54 (87.1%)	11 (100%)	0.2
	Black n (%)	8 (12.9%)	0	
Admission after sting (hours) median (25-75p)		4 (3-6)	5 (3-12)	0.25
PRISM* score Median (25-75p)		5 (4-7)	12 (8-12)	**<0.001**
Perpiheral sympathetic activity signs n (%)		46 (74.2)	9 (81.8%)	0.58
Hypertension n (%)		28 (45.2%)	7 (63.6%)	0.33
Hypotension n (%)		0 (0%)	7 (63.6%)	**<0.001**
Nause n (%)		18 (29%)	9 (81.8%)	**0.001**
Bradycardia n (%)		0 (0%)	2 (18.2%)	**0.02**
Tachycardia n (%)		16 (25.8%)	5 (45.5%)	0.18
Ejection fraction (%) median (25-75p)		65 (60-69)	48 (40-52)	**<0.001**
Systolic dysfunction n (%)		8 (12.9%)	11 (100%)	**<0.001**
Mitral insufficiency n (%)		20 (32.3%)	11 (100%)	**<0.001**
Tricuspid valve regurgitation n(%)		4 (6.5%)	9 (81.8%)	**<0.001**
pro-BNP (ng/L) median (25-75p)		85 (63-205)	1153 (965-16120)	**<0.001**
Elevated pro-BNP		8 (12.9%)	9 (81.8%)	**<0.001**
Troponin T (ng/L) median (25-75p)		15 (3-177)	515 (512-607)	**<0.001**
Elevated troponin T		30 (51.7%)	11(100%)	**0.002**
Myoglobine (ng/mL) median (25-75p)		87 (30-191)	454 (171-463)	**0.001**
Elevated myoglobine		22 (61.1%)	11 (100%)	**0.04**
Creatinin kinase (U/L) median (25-75p)		248 (163-412)	264 (208-356)	0.78
Elevated creatinin kinase		38 (65.5%)	11 (100%)	**0.02**
Blood glucose (mg/dL) median (25-75p)		116 (102-132)	207 (144-230)	**<0.001**
Hyperglycemia		10 (16.7%)	9 (81.8%)	**<0.001**
White blood cells ($10^3/mm^3$) median (25-75p)		11.3 (7.6-14.4)	20.9 (17.7-26.9)	**<0.001**
Leucocytosis		36 (60%)	11 (100%)	**0.01**
Amilase (U/L) median (25-75p)		77 (59-148)	153 (113-179)	0.09
Hyperamilasemia		16 (33.3%)	9 (81.8%)	**0.003**
Lactate (mmol/L) median (25-75p)		2.2 (1.2-3.1)	4.4 (4.3-4.6)	**<0.001**
Lipase (U/L) median (25-75p)		14 (10-27)	20 (8-23)	0.6
Inotropic support n (%)		16 (25.8%)	11 (100%)	**<0.001**
Non-invasive respiratory support n (%)		6 (9.7%)	11 (100%)	**<0.001**
Invasive mechanical ventilation n (%)		0 (0%)	5 (45.5%)	**<0.001**
Length of Intensive care stay (days) median (25-75p)		4 (3-5)	5 (4-38)	**0.03**
Length of hospital stay (days) median (25-75p)		5 (4-6)	7 (4-38)	**0.03**
Morbidity n (%)		0 (0%)	1 (9%)	0.15

PRISM: Pediatric risk of mortality

statistically significant differences between grade 2 and grade 3 patients in terms of amylase blood levels, there were significant differences in the frequency of hyperamylasemia between the groups. It seems that hyperamylasemia is more common in patients with grade 3 than in patients with grade 2. Although hyperamylasemia is a common manifestation of scorpion sting, we think that pancreatitis is rare because there was no lipase elevation in our patients.

Hyperglycemia is a well-known phenomenon in patients with scorpion envenomation. It is caused by increased catecholamine secretion and other hormonal mechanisms during scorpion envenomation. It has been reported that hyperglycemia during scorpion envenomation is an indicator of disease severity (15). In our study, hyperglycemia was observed in 26.8% of all cases. However, it was observed with a frequency of 81.9% in grade 3 patients and was significantly different from grade 2.

Myocardial injury during scorpion envenomation is a known entity and it is thought that the underlying mechanism may be direct or indirect (severe hypertension) myocardial damage associated with elevated catecholamines or direct myocardial toxicity of scorpion toxins (16,17). Cardiac troponins are the most sensitive biomarkers of myocardial damage. In the early phase (first six hours) of myocardial injury, the most sensitive biomarker is myoglobin (18). However, myoglobin is found not only in the heart but also in greater amounts in striated muscle. In cases such as scorpion bites, where striated muscle may be affected, elevated myoglobin levels may be observed independently of cardiac injury. In a study conducted in southeastern Turkey, it has been reported that severe cases of scorpion envenomation had higher CK levels than mild and moderate cases (11). In our study, grade 3 patients had higher myoglobin, troponin, lactate, and pro-BNP levels than grade 2 patients.

Echocardiographic examination of scorpion bites can determine the degree of heart failure and other dysfunctions (19). In a prospective echocardiographic study conducted in India, it has been reported that heart failure associated with scorpion envenomation can be diagnosed with a frequency of approximately 70% (20). In another study conducted in Israel, the incidence of heart failure was reported to be about 10%. In a study conducted in the Egean region in Turkey (Mesobuthus gibbosus), heart failure and associated pulmonary edema occurred with a frequency of 8.7% (21). In our study, echocardiographic heart failure (low ejection fraction) was found with a frequency of 26%. However, the patients included in our study were those with systemic symptoms, so they do not represent all emergency admissions. Although systolic dysfunction is frequently mentioned in the echocardiographic findings in all studies, our study shows that mitral valve dysfunction (mild to moderate regurgitation) may be seen more frequently.

Antitoxin infusions, inotropic and vasodilator treatments are the main methods of treatment in children with severe scorpion envenomation. In severe cases, the administration of scorpion antitoxin as early as possible increases efficacy (22,23) Bawaskar and Bawaskar (24,25) reported that prazosin is a promising agent to reduce mortality in children with severe scorpion envenomation. The mortality-reducing effect of prazosin was clarified by controlled studies (historical controls) in the following years (26). Doxazosin is an alpha-adrenoreceptor blocker like prazosin but has a longer elimination half-life than prazosin (22 versus 3 h). It has been reported that doxazosin may have the same success rate as prazosin when prazosin is unavailable (27). We used doxazosin instead of prazosin because prazosin was not available at our hospital.

Milrinone is a medicine that has inotropic, lusitropic, and vasodilatory effects. It has the advantage over dobutamine that it does not show tolerance or attenuation of its effects and has a better systemic vasodilatory effect (28). These effects make milrinone a promising agent for treating scorpion envenomation (29). There is no comparative randomized controlled trial of milrinone and dobutamine in scorpion envenomation.

Pulmonary edema is the most dangerous manifestation of scorpion envenomations. There are two different mechanisms responsible for developing pulmonary edema after scorpion envenomation. One of them is the increased permeability of the alveolocapillary membrane due to the direct damage caused by the scorpion venom (30). The other type of pulmonary edema is the cardiogenic type, which is associated with biventricular failure because of venom toxicity (31). In this study, pulmonary edema occurred in only five patients and one of them suffered cardiac arrest due to acute severe hypoxemia.

Single-center data and a retrospective study design are the main limitations of this study. The causative scorpion species could not be clearly defined because the parents' descriptions did not provide sufficient data to clearly identify the scorpion species. Only patients with severe scorpion envenomation were included in this study, so the results cannot be generalized to all cases of scorpion bites.

CONCLUSION

Scorpion envenomation is an important public health issue. Hyperamilasemia, hyperglycemia, and elevated pro-BNP

levels on admission may be warning signs of more severe patients. Mild-to-moderate mitral regurgitation may be more common than systolic dysfunction in severe cases.

ETHICS

Ethics Committee Approval: This study was reviewed and approved by University of Health Sciences Turkey, Antalya Training and Research Hospital Ethics Committee (decision no: 1/28, date: 04.03.2021).

Informed Consent: Informed consent could not be obtained because of the retrospective study design.

Authorship Contributions

Surgical and Medical Practices: H.S.K., G.Ö., A.K., Y.B., E.A.O., Concept: H.S.K., E.A.O., Design: H.S.K., G.Ö., A.K., Y.B., E.A.O., Data Collection or Processing: H.S.K., Analysis or Interpretation: H.S.K., G.Ö., A.K., Y.B., E.A.O., Literature Search: H.S.K., Writing: H.S.K.

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Research

Ex Vivo Ureteroscopy of Living Donor Kidneys: A Single Center Experience

Canlı Donör Böbreklerinde *Ex Vivo* Üreteroskopi: Tek Merkez Deneyimleri

Serdar Karadağ, Ubeyd Sungur

University of Health Sciences Turkey, Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Clinic of Urology, Istanbul, Turkey

ABSTRACT

Objective: In this study, by reviewing the cases who underwent *ex vivo* ureterorenoscopy (exURS) and laser lithotripsy as a bench procedure after nephrectomy of living donors with kidney stones at our clinic, the results were presented.

Methods: The data of 13 donors who had exURS between 2015 and 2021 were analyzed retrospectively. The demographic characteristics of the donors who underwent exURS laser lithotripsy, stone properties, postoperative stone-free rate, recurrence, graft functions and surgical technique were examined.

Results: The mean age was 34.7±5.4 years and the male-to-female ratio was 8:5. The mean stone size was 5.7±1.2 mm. Based on stone locations the number of donors was 1 (7.7%), 4 (30.8%) and 8 (61.5%) in the upper, middle and lower calyces, respectively. Surgical procedures were carried out successfully for all donors and the mean operative time was recorded as 9.4±1.3 min. No postoperative complications occurred in cases. The mean creatinine value of the recipients at postoperative month 1 was 1.1±0.6 mg/dL. No recurrence was observed during an average follow-up period of 26 months (range, 7 to 58 months).

Conclusion: Our experiences demonstrate that exURS is a simple and safe practical operative procedure enabling stone-free status without any effect on allograft function. Studies with large numbers of participants and long follow-up periods would be useful in contributing to the literature.

Keywords: *Ex vivo* surgery, renal transplantation, ureteroscopy, urolithiasis

ÖZ

Amaç: Bu çalışmada kliniğimizde böbrek taşına sahip canlı donörlerde donör nefrektomiden sonra bench masasında *ex vivo* üreterorenoskopi (exURS) ve lazer litotripsi uygulanan vakalar incelenerek olguların sonuçları paylaşıldı.

Gereç ve Yöntem: 2015-2021 arasında exURS yapılan 13 hastanın verileri retrospektif olarak incelendi. exURS lazer litotripsi uygulanan donörlerin demografik bilgileri, taş özellikleri, postoperatif dönemde taşsızlık oranı, rekürens, greft fonksiyonları ve cerrahi teknik incelenerek analiz edildi.

Bulgular: Ortalama yaş 34,7±5,4 ve erkek-kadın oranı 8:5 idi. Ortalama taş boyutu 5,7±1,2 mm idi. Taş lokalizasyonuna göre incelendiğinde böbrek üst, orta ve alt polde olmak üzere sırasıyla 1 (%7,7), 4 (%30,8) ve 8 (%61,5) donör mevcuttu. Tüm hastalara başarılı bir şekilde cerrahi prosedür uygulandı ve ortalama operasyon süresi 9,4±1,3 dakika saptandı. Hiçbir hastada postoperatif komplikasyon gelişmedi. Alıcıların 1. ayda ortalama kreatinin değeri 1,1±0,6 idi. Ortalama 26 aylık (7-58 ay) takip süresinde rekürrens görülmedi.

Sonuç: Deneyimlerimiz *ex vivo* URS'nin allograft fonksiyonunu etkilemeden, taşsızlığın sağlandığı, kolay ve güvenli olarak uygulanabilir bir yöntem olduğunu ortaya koydu. Geniş hasta sayılı ve uzun takip süreli çalışmalar literatüre katkı sağlayacaktır.

Anahtar Kelimeler: *Ex vivo* cerrahi, renal transplantasyon, üreterorenoskopi, ürolitiazis

Address for Correspondence: Ubeyd Sungur, University of Health Sciences Turkey, Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Clinic of Urology, Istanbul, Turkey
Phone: +90 553 495 7980 E-mail: ubeydsungur@gmail.com ORCID ID: orcid.org/0000-0002-8910-9859

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INTRODUCTION

Renal transplantation is the treatment method regarded as the gold standard in patients with end-stage renal disease (ESRD) (1). It is also known that life expectancy after transplant is higher compared to patients receiving hemodialysis and the quality of life has increased significantly (2).

Whilst the number of patients with ESRD on the kidney transplant waiting list continues to rise, no adequate increase has been observed with respect to the number of donors (3). This has ensured that people with a history of hypertension, diabetes, or nephrolithiasis may be considered as "marginal donors" following risk calculations. The donor evaluation criteria of the Amsterdam forum state that the presence of a single calculus below 1.5 cm without nephrocalcinosis on computed tomography (CT) examinations may be accepted as a donor in the absence of any metabolic abnormality or urinary infection (4). Upon recognition of the individuals with a history of urolithiasis as donors, a 5% increase in the number of kidney transplants has been reported (5). Hence, stone surgery in donor kidneys or renal transplantation (RT) is expected to be performed for many cases over the coming years.

As the presence of calculi in the transplanted kidney may lead to outcomes such as obstruction, sepsis and graft loss, its treatment is important. Management of stones less than 4 mm may be by monitoring. Extracorporeal shock wave lithotripsy (ESWL) or retrograde intrarenal surgery (RIRS) is an alternative before transplantation in treating calculi between 4 and 15 mm. Recently, some authors have stated that *ex vivo* stone surgery on the side bench is an option after donor nephrectomy (6-8).

In this study, we published the data and follow-up results of donors who underwent *ex vivo* bench surgery using semirigid ureterorenoscopy (URS) and laser lithotripsy after donor nephrectomy at our center.

METHODS

Following the receival of Ethics Committee approval numbered 2021/527 from Bakirkoy Dr. Sadi Konuk Training and Research Hospital (decision no: 2021-22-21, date: 15.11.2021), a review was conducted retrospectively on patients who had living donor kidney transplantation between the dates of January 2015 and October 2021. During RT operation, individuals who underwent stone surgery performed as *ex vivo* bench procedure via laser lithotripsy using semirigid URS were identified (n=13). General donor assessment was applied to the kidney donors. By screening all donors with urolithiasis for metabolic risk factors in accordance with the European Urology Association guideline recommendations, it was determined that there was no hypocitraturia, hypercalciuria, hyperoxaluria and hyperuricosuria (9). Informed consent was obtained from all donors and renal recipients by providing information related to the risk of calculus recurrence in their kidneys after transplantation and the potential adverse events.

Ex vivo ureterorenoscopy (exURS) was not performed for asymptomatic calculi below 4 mm, instead an *in vivo* double J (DJ) stent was routinely placed into the kidney after transplantation. Therefore, donors with single calculus ranging between 4 and 15 mm identified on CT angiography examinations and who underwent URS with laser lithotripsy as an *ex vivo* bench procedure were included in the study (Figure 1). Along with demographic characteristics of the donors such as age and gender, stone size, stone location, stone fragmentation time, operation time, and postoperative stone-free rate were recorded and monitoring the recipients for stone recurrence and renal allograft functions.

Statistical analysis was not performed in our study.

Ex Vivo Bench URS

Immediately following donor nephrectomy, the kidney was stored in ice on the side bench, and retrograde URS was carried out under low pressure (by placing the irrigation bag at a maximum of 50 cm above kidney level) and manual irrigation with normal saline not using a guidewire. Firstly, the ureter was straightened by spatulation and the distal part was stabilized with permanent sutures. The ureteroscope was then advanced from the ureter into the renal pelvis. The device used was a 7.5 semi rigid ureteroscope (Karl Storz, Germany). While examining the pelvicalyceal system, the kidney was manipulated with the free hand for better

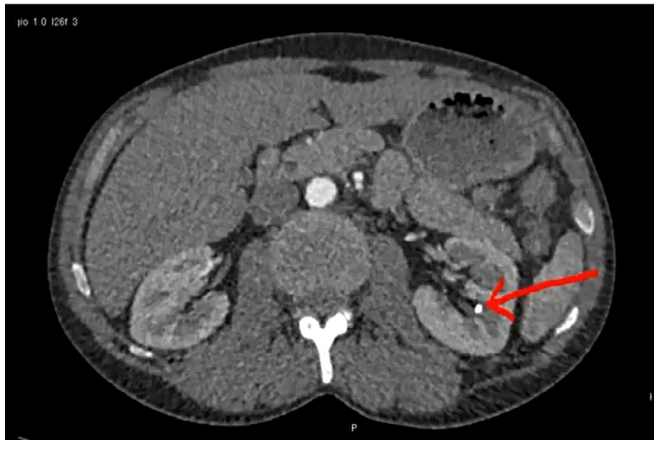

Figure 1. Computed tomography image of 6 mm calculus in the middle pole of left donor kidney as pointed by arrow

visualization of the calculus. In response to the possibility of being unable to reach the pelvis with the semirigid ureteroscope, a 7.5 Fr flexible ureteroscope (F-URS) (UF30 Zhuhai Vision Medical Technology Co., Ltd., China) was set ready for use yet F-URS was not needed. The detected stones were fragmented using 500 mm fiber holmium: yttrium aluminum garnet (Ho:YAG) laser lithotripsy and extracted with endoscopic stone removal forceps.

RESULTS

A total of 13 donors were included in the study following the application of inclusion and exclusion criteria. The female to male-donor ratio was 5:8. The mean stone size was 5.7±1.2 mm. Laser lithotripsy with 7.5 Fr semirigid URS was carried out by a single surgeon (S.K.) for all patients. The average operation time was calculated as 9.4±1.3 min. No complications were observed during or after the surgery. Following transplantation, DJ catheter was removed from the recipients 1 month post procedure and the mean serum creatinine was measured as 1.1±0.6 mg/dL at postoperative month 1. The average long-term follow-up period was 26 months (7-58 months). During follow-up, no recurrence or ureteral stenosis was identified in any patient (Table 1).

DISCUSSION

The selection of suitable donor-recipient pairs is a critical step for a successful kidney transplantation (10). With the spread of minimally invasive kidney surgery over the years, the enlargement of the donor pool has allowed individuals with small renal masses or kidney stones to be living kidney donor candidates as "marginal donors" (11,12). Extensive use of CT angiography in diagnostic studies of living kidney donors has led to greater detection of small asymptomatic kidney stones (13).

In previous studies, nephrolithiasis was a relative contraindication for kidney transplantation (in case of both deceased and living donors) due to the risk of stone formation, which may result in recurrent infections, urinary obstruction and graft loss (14).

During the Amsterdam Forum on the care of the live kidney donor in 2004, it was established that asymptomatic potential donors with a history of single renal calculus could be candidates if they met the following criteria; (a) absence of hypercalciuria, hyperuricemia, metabolic acidosis; (b) absence of cystinuria and hyperoxaluria; (c) the size of existing stone <15 mm and assessed as potentially removable during extraction (4).

As calculi less than 4 mm in size can be followed up due to high spontaneous passage rate, bench URS arises as a recommended treatment option with respect to 4-15 mm stones (15). Thus, the question of when stone-oriented treatment should be applied in transplants carried out from donors with a history of urolithiasis has emerged. Whilst ESWL or RIRS is an option before transplant, performing RT along with successful stone fragmentation using 6.9 Fr semi-rigid URS as a bench procedure right after kidney removal in a single session has been firstly mentioned in a case study of 10 patients conducted by Rashid et al. (8) in 2004. Pushkar et al. (16) reported that the extraction of the stone was done by pyelotomy after reaching the calculus via exURS and manipulating the renal pelvis with a basket. Ganpule et al. (7) used a 6 Fr pediatric cystoscope for exURS and obtained successful results. Olsburgh et al. (5) performed exURS using a laser and a basket with 7.5 Fr F-URS.

Numerous different surgical methods are described because of the variety in devices and techniques used, and it is evident that favorable outcomes have been achieved. Stone-free rate is reported to be between 89.5% and 100% in the literature (17). There are several views on the choice of technique and device to be used. Olsburgh et al. (5) have stated that the best option with respect to the operative management of potential living kidney donors with a history of stones is exURS using F-URS. However, it

Table 1. Demographic characteristics, stone characteristics and outcomes of *ex vivo* ureteroscopy

Parameters (mean ± SD)	Total (n=13)
Age (years)	34.7±5.4
Gender (n; %)	
Male	8 (61.5)
Female	5 (38.5)
Laterality (n; %)	
Left	11 (84.6)
Right	2 (15.4)
Stone size (milimeter)	5.7±1.2
Stone location (n; %)	
Upper calyx	1 (7.7)
Middle calyx	4 (30.8)
Lower calyx	8 (61.5)
Operation time (minutes)	9.4±1.3
Serum creatinine at postop month 1	1.1±0.6
Follow-up time (months)⁺	26 (7-58)

⁺Presented as median (interquartile range), SD: Standart deviation

has been expressed by Pushkar et al. (16) that the use of semi-rigid URS is easier compared to F-URS. The ease of renal manipulation by hand along with the ureteral mobility simplifies the use of semi-rigid URS. In the study by Sarier et al. (17), it has been noted that successful results are obtained with the pediatric cystoscope as it enables better stability and maneuver capability due to shorter shaft length.

We believe that semi-rigid URS should be preferred first because of easier use and short operative time, yet F-URS may be used in cases of acute angulation or difficulty accessing the stone. It has been demonstrated that use of laser in lithotripsy is safer than pneumatic due to the risk of mucosal injury (16).

Operative time is an important issue that needs to be addressed in kidney transplantation. A cold ischemia period of more than 8 h has the potential to cause harm to post-transplant renal function and increase acute rejection rates and affect long-term graft survival (16). However, upon reviewing exURS times, it was observed that the time interval spent for stone surgery was quite short and usual does not not exceed 30 min. In our study, the mean operation time was calculated as 9.4±1.3 min.

Whilst exURS includes potential risks such as hematuria, graft dysfunction, urinary leakage and ureteral trauma, morbidity and complication rates are not revealed to be high on the examination of the literature (15). Mosimann et al. (18) reported a case of graft loss following exURS due to acute ischemia caused by a major intimal flap at the hilum. It was thought that this complication occurred because of URS manipulations within the renal pelvis, leading to an injury of the adjacent artery. Therefore, they recommended considering pyelolithotomy as an alternative to exURS, depending on the clinical circumstances (18).

On a systematic review published by Longo et al. (15) recently, it has been shown that the incidence of short-term complications for exURS is low. It stated that two (22%) of 9 early postoperative complications were due to URS. One of them was noted to be urinary leakage repaired by a primary suture after pyelolithotomy and the other one was complete occlusion of the ureteroneocystostomy treated with revision of the ureteroneocystostomy (15).

During *ex vivo* endourological procedures, manual manipulation of the ureter at minimal level may be applied to avoid ureteral injury and the lowest irrigation fluid flow as well as the use of a DJ ureteral stent might be considered to prevent pyelovenous and pyelolymphatic reflux (7). In our study, no complications were identified in any patient during the early postoperative period and long-term follow-up.

In a previously published series, it was revealed that none of the patients had stone recurrence during follow-up. The role of metabolic factors in stone formation and the importance of metabolic assessment with regard to donor selection should not be overlooked. Also in our study, no recurrence was observed in any patient during the average follow-up period of 2 years. As the number of exURS procedures increases, long-term data along with long follow-up periods will be available. The limitations of our study include its retrospective nature, being performed by one surgeon in a single center, and the small number of cases.

CONCLUSION

We obtained results supporting that ex vivo semi rigid URS may be carried out easily and safely during RT in eligible living kidney donors who have kidney stones, without any impact on allograft function. Easier manipulation of semi rigid URS on the side bench and manual handling of the kidney enable lithotripsy to be performed successfully, not affecting cold ischemia times. In the future, studies with many patients and long follow-up periods would contribute to the literature.

ETHICS

Ethics Committee Approval: This study was approved by the Institutional Ethics Committee of Bakırkoy Dr. Sadi Konuk Training and Research Hospital (decision no: 2021-22-21, date: 15.11.2021).

Informed Consent: Informed consent was obtained from all donors and renal recipients by providing information related to the risk of calculus recurrence in their kidneys after transplantation and the potential adverse events.

Authorship Contributions

Surgical and Medical Practices: S.K., Concept: S.K., U.S., Design: S.K., Data Collection or Processing: U.S., Analysis or Interpretation: S.K., U.S., Literature Search: S.K., U.S., Writing: U.S.

Conflict of Interest: The authors declare that they have no conflict of interest.

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