Journal of Contemporary Medicine

YEAR:2023 VOLUME:13 ISSUE:5

JOURNAL OF CONTEMPORARY MEDICINE

e-ISSN 2667-7180

Formerly Çağdaş Tıp Dergisi

YEAR 2023 VOLUME 13 ISSUE 5

The Owner and Publishing Manager on behalf of the Journal of Contemporary Medicine

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Book

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Journal article on the Internet

Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. Am J Nurs [serial on the Internet] 2002 [cited 12 Aug 2002]; 102. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

Website

Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 Jul 2002]. Available from: www.cancer-pain.org

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Acknowledgements

The source of financial grants and the contribution of colleagues or institutions should be acknowledged.

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Abbreviations that are used should be defined in parenthesis where the full word is first mentioned. Some common abbreviations can be used, such as iv, im, po, and sc.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1316829
J Contemp Med 2023;13(5):724-728

Original Article / Orijinal Araştırma

Frequency of Rotavirus and Adenovirus in Children with Diarrhea

İshal Şikayeti ile Hastaneye Başvuran Çocuklarda Rotavirus ve Adenovirus Sıklığı

Hülya Duran, Fadime Yılmaz Yücel

Tekirdag Dr.I.Fehmi Cumalıoglu City Hospital, Medical Microbiology Laboratory, Tekirdag, Turkey

Abstract

Aim: The aim of this study is retrospective evaluation of the frequency of rotavirus and adenovirus in stool, and their distribution according to gender, age and seasons in children with diarrhea admitted at outpatients or hospitalized in our hospital.

Material and Method: Stool samples of patients aged between 0-18 years received at the Medical Microbiology Laboratory between2021–2022 were evaluated for rotavirus–adenovirus. Rotavirus and adenovirus antigens were determined qualitatively by immunochromatographic cassette test method. Chi-square test was used in the statistical analysis.

Results: A total of 1148 stool samples of pediatric patients were received by our laboratory during these two years for rotavirus and adenovirus antigen test. Of 1148 patients, 8.6% were positive for rotavirus, 5.1% for adenovirus, and 0.6% for both rotavirus and adenovirus antigens. Rotavirus and adenovirus was positive in 7.2% and 5.6% of males, respectively, and 10.6% and 4.5% of females, and there were no statistically significant differences. Rotavirus was most frequently found in the age group 3-5 years (11.6%) and adenovirus was most frequently found in the age group 6-9 years (8.4%), with no significant difference. Rotavirus was most frequently detected in spring (12.9%) while adenovirus was found most frequently in winter (8.1%), without significant differences. Antigen positivity was 4.1% and 4.9% in outpatients for rotavirus and adenovirus, respectively, and 15.1% and 5.5% in hospitalized patients. Rotavirus positivity was significantly higher in hospitalized patients than outpatients, and adenovirus positivity did not show a significant difference.

Conclusion: We found that rotavirus and adenovirus were significant agents causing diarrhea in children, especially those younger than 5 years old, and that its frequency increased in winter and spring, and as rotavirus is a cause of hospitalization, implementation of rotavirus vaccine into routine vaccination programs seem to be beneficial for patients.

Keywords: Rotavirus, adenovirus, diarrhea, children

Öz

Amaç: Bu çalışmada, hastanemize ishal şikayetiyle ayaktan başvuran ya da yatış yapılan çocuk hastalarda rotavirus ve adenovirus sıklığının belirlenmesi, cinsiyet, yaş ve mevsimlere göre dağılımının retrospektif olarak irdelenmesi amaçlanmıştır.

Gereç ve Yöntem: Tıbbi Mikrobiyoloji Laboratuvarına, 2021-2022 tarihleri arasında gelen, 0-18 yaş aralığındaki hastalara ait gaita örnekleri rotavirus-adenovirus açısından değerlendirildi. Rotavirus ve adenovirus antijenleri immünokromatografik kaset test yöntemi ile kalitatif olarak saptanmıştır. İstatistiksel analizde Ki-Kare testi kullanıldı.

Bulgular: İki yıllık sürede rotavirus ve adenovirus antijen testi birlikte istenen toplam 1148 çocuk hastaya ait gaita numunesi laboratuvarımıza ulaşmıştır. 1148 hastanın %8,6'sında rotavirus, %5.1'inde adenovirus, %0,6'sında hem rotavirus hem de adenovirus antijeni pozitif saptanmıştır. Rotavirus ve adenovirus pozitifliği erkeklerde %7.2 ve %5.6, kızlarda %10,6 ve %4,5 oranında saptanmış, istatistiksel olarak anlamlı fark bulunmamıştır. Rotavirus en sık 3-5 yaş (%11,6), adenovirus ise 6-9 yaş (%8,4) grubunda tespit edilmiş, istatistiksel olarak anlamlı fark saptanmamıştır. Rotavirus en sık ilkbaharda (%12,9) saptanırken adenovirus kış (%8,1) aylarında tespit edilmiş, istatistiksel olarak anlamlı fark bulunmamıştır. Antijen pozitiflik oranı rotavirus ve adenovirus için sırasıyla ayaktan hastalarda %4,1 ve %4,9, yatan hastalarda %15,1 ve %5,5 olarak tespit edilmiştir. Rotavirus pozitiflik oranı yatan hastalarda ayaktan hastalara göre istatistiksel olarak anlamlı yüksek bulunmuş, adenovirus için iki grup arasında istatistiksel olarak anlamlı fark saptanmamıştır.

Sonuç: Çalışmamızda çocuklarda, özellikle beş yaşın altında, rotavirus ve adenovirusun önemli birer ishal etkeni olduğu, kış ve ilkbahar aylarında sıklıklarının arttığı, rotavirusun hastaneye yatışlara neden olduğu için aşısının rutin aşılama programına dahil edilmesinin hasta yararına olacağı tespit edilmiştir.

Anahtar Kelimeler: Rotavirus, adenovirus, ishal, çocuklar

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Received *(Geliş Tarihi)*: 20.06.2023 **Accepted *(Kabul Tarihi)*:** 01.08.2023

INTRODUCTION

Inflammation of the stomach and intestines due to various causes is termed acute gastroenteritis. Most frequent symptoms of acute gastroenteritis include diarrhea, nausea, vomiting, fever and abdominal pain. Diarrhea is the second most frequent cause of death globally among children younger than 5 years of age. While a considerable number of deaths occur especially in developing countries, diarrhea is still an important cause of death and public health problem in developed countries. Acute diarrhea is caused by viral, bacterial, parasitic or fungal agents. Most important agents causing serious gastroenteritis in especially in children are viruses (75-90%). Determination of the frequency of viral etiology is important both for avoiding unnecessary use of antibiotics and also for implementation of preventive measures.[1-7]

Rotavirus is the most frequent agent causing diarrhea especially among children younger than 5 years of age globally. Rotavirus infections are seen more frequently during winter in milder climates. Rotavirus infects especially children, while causing a mild illness in adults. The cause of less frequent rotavirus gastroenteritis in adults may be antibodies developed against rotavirus in 95% of children during rotavirus infections in the first 5 years of life. Implementation of necessary hygienic conditions in the hospitals and childcare facilities is especially important for avoidance of infection transmission. Orally administered vaccines against rotavirus infections are very important in fighting gastroenteritis. Considerable decreases were obtained in hospitalizations due to rotaviral diarrhea with the use of these vaccines. While many countries have included rotavirus vaccination in their national vaccination programs, this is not yet present in our routine vaccination program of our country.[2,4,6,8,9]

Adenovirus is the second most frequent cause of diarrhea in children after rotavirus, and unlike rotavirus, it may cause diarrhea in children during the whole year. Infections are most commonly seen in children younger than 2 years old. Symptoms are milder than those seen in rotavirus infections, but the duration of infection is longer.[10]

Fast and accurate detection of diarrhea causes is important for the clinical course and effective treatment. Determination of antigen in stool samples with immunochromatographic method is frequently used in routine diagnosis in gastroenteritis due to rotavirus and adenovirus. A quick result obtained in a short time such as 5-10 minutes, ease of use in the laboratory and low cost are among factors for preferring this test.[11,12]

Our aim in this study was to determine retrospectively the frequency of rotavirus and adenovirus in outpatients or patients, aged between 0-18, hospitalized at our hospital with a complaint of diarrhea, and investigate the distribution of pathogens according to gender, age and seasons.

MATERIAL AND METHOD

The study was carried out with the permission of Tekirdag Dr. I. Fehmi Cumalıoglu City Hospital Clinical Investigations Ethics Committee (Date:14.04.2023, Decision No: 35). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Stool samples of patients aged between 0-18 years received between January 2021 – December 2022 at the Medical Microbiology Laboratory were evaluated in terms of rotavirus–adenovirus. When more than one sample was received from the same patient, only the first sample was included. Samples evaluated for both adenovirus and rotavirus were included, and those that were only evaluated for one agent was excluded.

Rotavirus and adenovirus antigens were determined qualitatively by immunochromatographic cassette test in which specific antibodies were used. Rotavirus–Adenovirus Combo Rapid Cassette Test (CITEST DIAGNOSTICS INC, CANADA) kit was used according to the manufacturer's instructions. This is a rapid test where a colored line occurs at the test site in 10 minutes as a result of the reaction of antigen-antibody complex. Presence of these colored lines at the test line means positive result, while absence of them means a negative one. A colored line is seen, showing that an appropriate amount of sample is put on the control line region, and membrane wicking is done. The manufacturer have reported that sensitivity and specifity of the test is 97.3% and 97.1% for rotavirus, and 95.2% and >97.7% for adenovirus.

Demographic data on patients age, gender and seasonal distribution was obtained from the hospital's automation system, and evaluated retrospectively.

Statistical Analysis

Statistical analysis of the data obtained was evaluated by SPSS 22.0 (SPSS Inc, Chicago, IL, USA). Categorical data was presented as percent. Chi-square test was used in the comparison of independent groups with categorical variables. P values below 0.05 were considered as a statistically significant.

RESULTS

A total of 1148 stool samples of pediatric patients were received by our laboratory during these two years for rotavirus and adenovirus antigen test. Demographic data of these patients included 657 males (57.2%) and 491 females (42.8%), with a mean age ± standard deviation of 3.41 ± 4.04 years. There was no significant differences between the patients in terms of gender ($p>0.05$).

Rotavirus antigen was positive in 99 of 1148 patients (8.6%), and adenovirus was positive in 59 (5.1%). Both rotavirus and adenovirus antigens were positive in 7 patients (0.6%). Rotavirus and adenovirus was positive in 7.2% and 5.6% in males, 10.6% and 4.5% of females, and there were no

statistically significant differences (p=0.323 for rotavirus and p=0.756 for adenovirus). Rotavirus was most frequently found in the age group 3-5 years (11.6%), which was followed by 1-2 years (11.2%), and adenovirus was most frequently found in the age group 6-9 years (8.4%) and 1-2 years (6.3%). There was no significant difference between the age groups for both agents in terms of frequency of presence (p=0.219 for rotavirus and p=0.209 for adenovirus) (**Table 1**).

Table 1. Distribution of rotavirus and adenovirus antigen positivity according to age groups

Age	Patients	Rotavirus positive		p value	Adenovirus positive		p value
	n	n	%		n	%	
0 year	331	16	4.8	0.219	13	3.9	0.209
1-2 years	304	34	11.2		19	6.3	
3-5 years	251	29	11.6		13	5.2	
6-9 years	154	15	9.7		13	8.4	
10-17 years	108	5	4.6		1	0.9	
Total	1148	99	8.6		59	5.1	

In the evaluation of distribution of antigen positivity according to seasons, rotavirus was most frequently detected in spring (12.9%) and winter (12.2%) while adenovirus was found most frequently in winter (8.1%) and autumn (5.4%) (**Figure 1**). There were no significant differences in terms of antigen positivity and season relationship (p=0.086 for rotavirus, and p=0.400 for adenovirus) (**Table 2**).

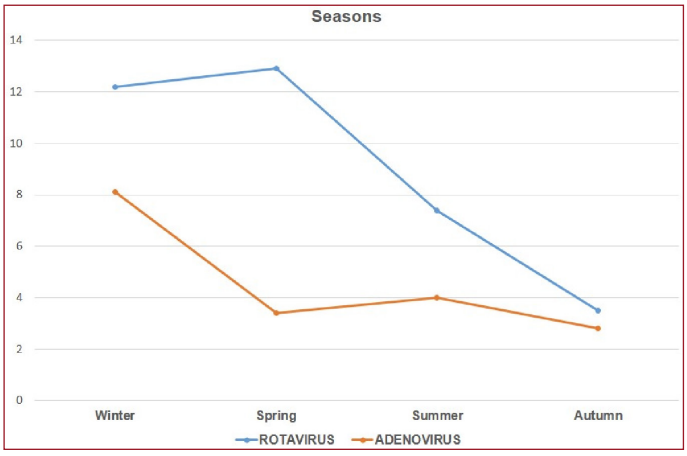

Figure 1. Distribution of rotavirus and adenovirus antigen positivity according to seasons

Table 2. Distribution of rotavirus and adenovirus antigen positivity according to seasons (n/%)

Season	Patients	Rotavirus positive		p value	Adenovirus positive		p value
	n	n	%		n	%	
Winter	246	30	12.2	0.086	20	8.1	0.400
Spring	263	34	12.9		9	3.4	
Summer	324	24	7.4		13	4.0	
Autumn	315	11	3.5		17	5.4	
TOTAL	1148	99	8.6		59	5.1	

When the 1148 patients were grouped according to outpatients and hospitalized patients, 677 (59.0%) were outpatients and 471 (41.0%) were hospitalized ones (clinics / intensive care unit). Antigen positivity was 4.1% and 4.9% in outpatients for rotavirus and adenovirus, respectively, and 15.1% and 5.5% in hospitalized patients. Rotavirus positivity was significantly higher in hospitalized patients than outpatients, and adenovirus positivity did not show a significant difference (p=0.008 for rotavirus, and p=0.756 for adenovirus) (**Table 3**).

Table 3. Distribution of rotavirus and adenovirus antigen positivity according to clinics (n/%)

Clinic	Patients	Rotavirus positive		p value	Adenovirus positive		p value
	n	n	%		n	%	
Outpatients	677	28	4.1	0.008	33	4.9	0.756
Hospitalized patients	471	71	15.1		26	5.5	
TOTAL	1148	99	8.6		59	5.1	

DISCUSSION

Rotavirus and adenovirus are important acute gastroenteritis agents among children younger than 5 years old worldwide.[13,14] While the frequency of these two agents differ between countries and cities, rotavirus is most frequently found as viral gastroenteritis causes, with adenovirus in the second place.[15,16] There are many studies on the frequency of rotavirus and adenovirus presence in stool from Turkey and other countries worldwide. In studies of foreign countries, rotavirus frequency is reported as 11-71% and adenovirus frequency as 2-22.2% while in studies from Turkey showed a frequency of rotavirus infections as 8.1-39.8%, and adenovirus infections as 1.8-15%.[17-19] We evaluated children aged between 0-18 years, and found the frequency of rotavirus presence as 8.6%, frequency of adenovirus as 5.1%, with a higher frequency of rotavirus in comparison with adenovirus, similar to other studies in the literature.

Tokak et al.[20] have found rotavirus frequency as 10.7%, adenovirus frequency as 3.3% in patients with a working diagnosis of acute gastroenteritis, with a significant difference in rotavirus frequency (9.8% in males, 11.7% in female patients), but not in adenovirus frequency. Rotavirus was more frequently found in female patients, and adenovirus was more frequent in males in our study, but there was no significant differences in terms of genders.

In a study evaluating 517 stool samples in Senegal, rotavirus positivity was 6.9%, adenovirus positivity was 3.1%, and co-infection rate was reported as 1.9%. Prevalences of rotavirus and adenovirus were found to be 12.2% and 4.8%, respectively, in children aged between 0-12 months. In an evaluation of seasonal distribution, rotavirus was more frequently detected during September (12.3%) and February (14.9%), while adenovirus was more frequently detected between June-December.[6]

In a study from Poland, where stool samples of 1411 patients aged between 1 month–5 years hospitalized at the Pediatric Gastroenterology Section due to acute gastroenteritis, rotavirus infections were found to be significantly more frequent during winter and spring months, while adenovirus infections were not found to show a significant relationship with seasons.[9]

In a study from the eastern part of Turkey (Siirt), stool samples of 16689 patients were evaluated, in whom rotavirus was positive in 13.6%, adenovirus was positive in 4.9%, and 0.5% was positive for both rotavirus and adenovirus. Rotavirus was most frequently detected in autumn, adenovirus was most frequently detected in summer, and the difference was found to be significant. In the evaluation of positivity rate of viral antigen according to age groups, rotavirus positivity rate was the highest one in 13-24 months age group with 19.6%, and adenovirus positivity rate was the highest one in 3-5 years age group with 5.5%. Also, 89.7% of patients positive for rotavirus and 83.8% of patients positive for adenovirus were found to be younger than 5 years.[10]

In two separate studies from Inner Anatolia Region, Bayrak et al.[1] have found rotavirus positive in stool samples in 25.8% of pediatric patients, and these patients were most frequently (28.6%) at breastfeeding age, and during spring months (34.9%). Sert et al.[21] have found rotavirus positive in 4.7%, and adenovirus positive in 9.1% of stool samples of 1960 patients with a diagnosis of acute gastroenteritis in Konya city, both rotavirus and adenovirus were most frequently found in the age group 1 month–2 years, rotavirus was most frequently detected in winter months, and adenovirus is detected in spring months.

Gür Vural et al.[22] have rotavirus positivity in 8.9% and adenovirus positivity in 4.4% in 5294 stool samples sent to the Microbiology Laboratory with a diagnosis of acute gastroenteritis in Black Sea Region (Samsun). Rotavirus positivity was most frequent between 13-24 months and 2-5 years, in spring and winter months; and adenovirus positivity was most frequent in 2-5 years and over 18 years, in winter and summer months.

Aydın et al.[7] have detected the most frequent rotavirus positivity in 2-3 years and 4-5 years age groups, and the most frequent adenovirus positivity in 12-18 years age group and those younger than 1 year in their study from Aegean Region (Kutahya). In the evaluation of patient distribution according to seasons, adenovirus was most frequently detected in fall, and rotavirus was most frequently detected in winter, spring and summer.

When we evaluated age and antigen positivity in our study, rotavirus was detected most frequently in 3-5 years age group (11.6%), which was followed by 1-2 years (11.2%), and that 79 of 99 patients found to be positive was in the 0-5 years age group. Adenovirus was most frequently detected in 6-9 years (8.4%) and 1-2 years (6.3%), and 45 of 59 positive patients were in 0-5 years age group. Although there were no significant differences between the age groups for these two agents in terms of presence frequency, a great majority of positive patients are under 5 years of age, similar to other studies.

We evaluated the distribution of antigen positivity according to seasons, and found that rotavirus was most frequently detected in spring and winter months, showing a decrease in frequency in summer and autumn. This change was not found to be statistically significant, but p value is near 0.05. As may be seen from other studies mentioned above, rotavirus is not seen frequently only in winter, but also in spring. We are inclined to think that the change in seasons and spring being colder like winter may have caused this. Adenovirus positivity is slightly more frequent in winter, is seen in similar rates, in accordance with other studies.

Use of orally administered vaccines against rotavirus infection have resulted in considerable decreases in hospitalizations due to rotavirus diarrhea.[23] Rotavirus positivity is 4.1% in outpatients and 15.1% in hospitalized patients in the present study, which is an important finding showing a clinical picture requiring hospitalization. Many countries have implemented rotavirus vaccinations into their national vaccination programs, while it is still not part of the national vaccination program in our country.[24] The data of our study supports the belief that inclusion of rotavirus vaccination into the national vaccination program may be beneficial for patients.

Determination of the prevalence of viral agents causing diarrhea is important for avoiding unnecessary use of antibiotics.[25] Many studies were conducted in Turkey in many regions on the frequency of rotavirus and adenovirus frequency. The present study is the first one aiming to determine the frequency of adenovirus and rotavirus in patients younger than 18 years old admitted with a complaint of diarrhea in Thrace Region. Therefore, it is valuable in terms of contributing to the literature. In addition, the retrospective design of our study is a limitation.

CONCLUSION

We have found that rotavirus and adenovirus are important agent causing diarrhea in pediatric patients, especially those younger than 5 years of age, that their frequency increases in winter and spring, and that as rotavirus causes hospitalizations, implementation of rotavirus vaccine into the national vaccination program will be beneficial for patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Tekirdag Dr. I. Fehmi Cumalıoglu City Hospital Clinical Investigations Ethics Committee (Date:14.04.2023, Decision No: 35)

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1330250
J Contemp Med 2023;13(5):729-734

Original Article / Orijinal Araştırma

The Evaluation of Testes by Shear Wave Elastography in Patients with Isolated Hypogonadotropic Hypogonadism

İzole Hipogonadotropik Hipogonadizmli Hastalarda Testislerin Shear Wave Elastografi ile Değerlendirilmesi

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Abstract

Aim: The aim of this study was to evaluate testicular stiffness by shear wave elastography (SWE) in patients with isolated hypogonadotropic hypogonadism (IHH) and to compare it with healthy controls.

Material and Method: In this prospective study, 35 patients with IHH (group 1) and 40 healthy controls (group 2) were evaluated. These two groups were compared in terms of age, testicular volume, and SWE values. In a subsequent analysis, IHH patients were divided into 3 groups: those who were newly diagnosed and did not receive any treatment (group A), those who received testosterone replacement (group B), and those who received human chorionic gonadotrophin alpha (hCG) (group C). Testicular volumes and SWE values were also compared between these subgroups.

Results: Testicular volumes were significantly lower in group 1 than in group 2 (p<.001). Group 1 had significantly higher testicular SWE values than group 2 (p<.001). There was also a negative correlation between the mean value of testicular stiffness and testicular volume in group 1 (r=-0.555, p=.001 for right testes, r=-0.403, p=.016 for left testes). Results of subsequent analysis by treatment status showed that patients in group C had significantly increased testicular volumes. In addition, they tended to have lower SWE values, when compared to groups A and B.

Conclusion: SWE values were significantly higher in IHH patients compared to healthy controls. We found significant improvements in SWE values even in patients receiving short-term hCG replacement. Further research is needed on whether basal SWE values of IHH patients can predict fertility in patients with IHH.

Keywords: Isolated hypogonadotropic hypogonadism, elastography, testicular stiffness, male infertility

Öz

Amaç: Bu çalışmanın amacı, izole hipogonadotropik hipogonadizm (IHH) hastalarında testis sertliğini shear wave elastografi (SWE) ile değerlendirmek ve sağlıklı kontrollerle karşılaştırmaktı.

Gereç ve Yöntem: Bu prospektif çalışmada IHH'lı 35 hasta (grup 1) ve 40 sağlıklı kontrol (grup 2) değerlendirildi. Bu iki grup yaş, testis hacmi ve SWE değerleri açısından karşılaştırıldı. Daha sonra yapılan bir analizde IHH hastaları, yeni teşhis konulan ve herhangi bir tedavi almayanlar (A grubu), testosteron replasmanı uygulananlar (B grubu) ve human koryonik gonadotropin alfa (hCG) alanlar (C grubu) şeklinde üç gruba ayrıldı. Testis hacimleri ve SWE değerleri de bu alt gruplar arasında karşılaştırıldı.

Bulgular: Testis hacimleri grup 1'de grup 2'ye göre anlamlı derecede düşüktü (p<.001). Grup 1'deki olguların testiküler SWE değerleri grup 2'ye göre anlamlı olarak yüksekti (p<.001). Grup 1'deki olgularda testis sertliği ortalama değeri ile testis hacmi arasında da negatif korelasyon vardı (sağ testis için r=-0.555, p=.001, sol testis için r=-0.403, p=.016). Tedavi durumuna göre elde edilen analiz sonuçları, C grubundaki hastaların testis hacimlerinde önemli ölçüde artış olduğunu gösterdi. Ayrıca C grubundaki olgular, A ve B gruplarına göre daha düşük SWE değerlerine sahip olma eğilimindeydiler.

Sonuç: SWE değerleri IHH hastalarında sağlıklı kontrollere göre anlamlı olarak yüksekti. Kısa süreli hCG replasmanı alan hastalarda bile SWE değerlerinde önemli düzelmeler bulduk. IHH hastalarının bazal SWE değerlerinin IHH'li hastalarda fertiliteyi öngörüp göremeyeceği konusunda daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: İzole hipogonadotropik hipogonadizm, elastografi, testiküler sertlik, erkek infertilitesi

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Received *(Geliş Tarihi)*: 20.07.2023 **Accepted *(Kabul Tarihi)*:** 04.09.2023

INTRODUCTION

The onset of puberty and achieving fertility depend on the pulsatile release of hypothalamic gonadotropin-releasing hormone (GnRH), which stimulates luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary.[1] A disruption of this axis in the hypothalamic and/or pituitary region results in hypogonadotropic hypogonadism (HH). In general, there are two types of HH, congenital and acquired. The term isolated/idiopathic HH (IHH) refers to HH without anatomical or functional abnormalities in the hypothalamus or pituitary glands.[2] The prevalence of IHH in men is approximately 1:8,000 and is characterized by lack of sexual development and infertility.[3] The first clinically observable sign of puberty in boys is testicular enlargement, but patients with IHH tend to have low testicular volume. Treatment to induce puberty at the right time is critical for sexual, bone, and metabolic health, as well as for psychosocial effects.[4] The treatment regimen for IHH is principally determined by whether the goal is to promote secondary sexual characteristics or to induce fertility.[5] Testicular volume before treatment is thought to be one of the main indicators of spermatogenesis response in patients with IHH who want to have kids.[6,7]

Ultrasonography (US) is a non-invasive, repeatable and inexpensive imaging method commonly used to examine testes. Elastography is a US-based imaging method used to evaluate the stiffness of the tissues.[8] Strain elastography and shear wave elastography are the two types of elastography that are now obtainable.[9] Strain elastography (SE) measures tissue stiffness by applying a compression force to the lesion's surface. The extent of tissue deformation that occurs is related to the stiffness of the lesion. SE is regarded as operator-dependent due to the elastogram's quality depends significantly on the user's examine and application. Shear wave elastography (SWE) generates shear waves in the underlying tissue with varying velocities dependent on the stiffness of the tissue using acoustic radiation force impulses (ARFI). Shear wave velocity readings can be collected as a single value in a fixed region of interest (ROI) or as multiple values for each point in a field of view (FOV). The latter is often referred to as two-dimensional shear wave elastography (2D-SWE).[10] There have been several studies on the use of SWE in normal testis and these studies have provided an adequate basis for more systematic investigations.[11-13]

The aim of this study was to evaluate the testicular stiffness of IHH patients with SWE and to compare the results with the normal healthy control group.

MATERIAL AND METHOD

This was a single-center prospective case-control study conducted between December 2021 and July 2022. The local ethical committee approved the study protocol according to the Helsinki Declaration (29.11.2021-HRU/21.21.05). All participants provided written consent prior to data collection.

Study Participants

Female patients with IHH were not included in the study. A total of 35 male patients with IHH (Group 1) and 40 healthy control males (Group 2) were included in this study. The results of the physical examination, laboratory tests, and radiological imaging were used to diagnose IHH. The following diagnostic criteria were used: a lack of spontaneous puberty before the age of 18, a decrease in testosterone concentration below the normal range for adults, a low or inappropriately normal level of FSH and LH, and a normal result of hypothalamo-pituitary magnetic resonance imaging. None of the patients had hyposmia, anosmia, or a family history of IHH. Patients with IHH who registered to the endocrine outpatient clinic underwent to ultrasound and elastography exams based on these diagnostic criteria. During the ultrasound and elastography examination, the radiologist was unaware of the patients' clinical information. Following an ultrasound and elastography examination the patients were then divided into three groups based on their treatment status. The first group (Group A) consisted of newly diagnosed patients who did not receive any treatment; the second group (Group B) consisted of patients who received parenterally administered testosterone; and the third group (Grup C) consisted of patients who received human chorionic gonadotrophin alpha (hCG). The control group was composed of healthy male employees at our hospital.

Ultrasound and SWE examination

Ultrasonography and shear-wave elastography examinations of testes was performed by a single radiologist who had 14 years of ultrasonography and 4 years of elastography experience. The examinations were performed by using the Siemens ACUSON S2000 US system (Siemens Medical Solution, MountainView, CA, USA) with a 9L4 probe. The 2D-SWE method utilized in this study was the most recent SWE approach that used acoustic radiation force. While the patient or volunteer were in the supine position, the gray scale US examination of both testes was performed first. Patients with testicular lesions, hydrocele, or varicocele were excluded from the study at this point. All testes were measured in the largest three dimensions (length (L) × width (W) × height (H)), and the testicular volume was then automatically calculated by US device. In order to prevent additional compression and stabilize the elastography images, the linear array transducer was applied very gently to the skin. The sampling box was adjusted to the testis, and a SW quality map was first acquired. Green on the map denotes good SW quality, yellow for marginal SW quality, and red for poor SW quality. After that, SW velocity mode was initialized, and a 2D color map of shear wave velocity (SWV) distribution within the testes was obtained. The color of the map represents the SWV from high (red or orange), intermediate (yellow or green), to low (dark or light blue). A high quality SWE image was selected and the SWV was then measured by a fixed ROI (2×2 mm) in the shear wave velocity map. SWE values were measured in the longest longitudinal plane. SWE values were obtained in both speed mode (m/s) and elasticity mode (kPa). Nine ROI were placed in each testis. Three ROI placed on the

upper pole, three on the middle region, and three on the lower pole of the testis (**Figure 1**). Based on the mean value of nine SWE measurements, a statistical analysis was conducted.

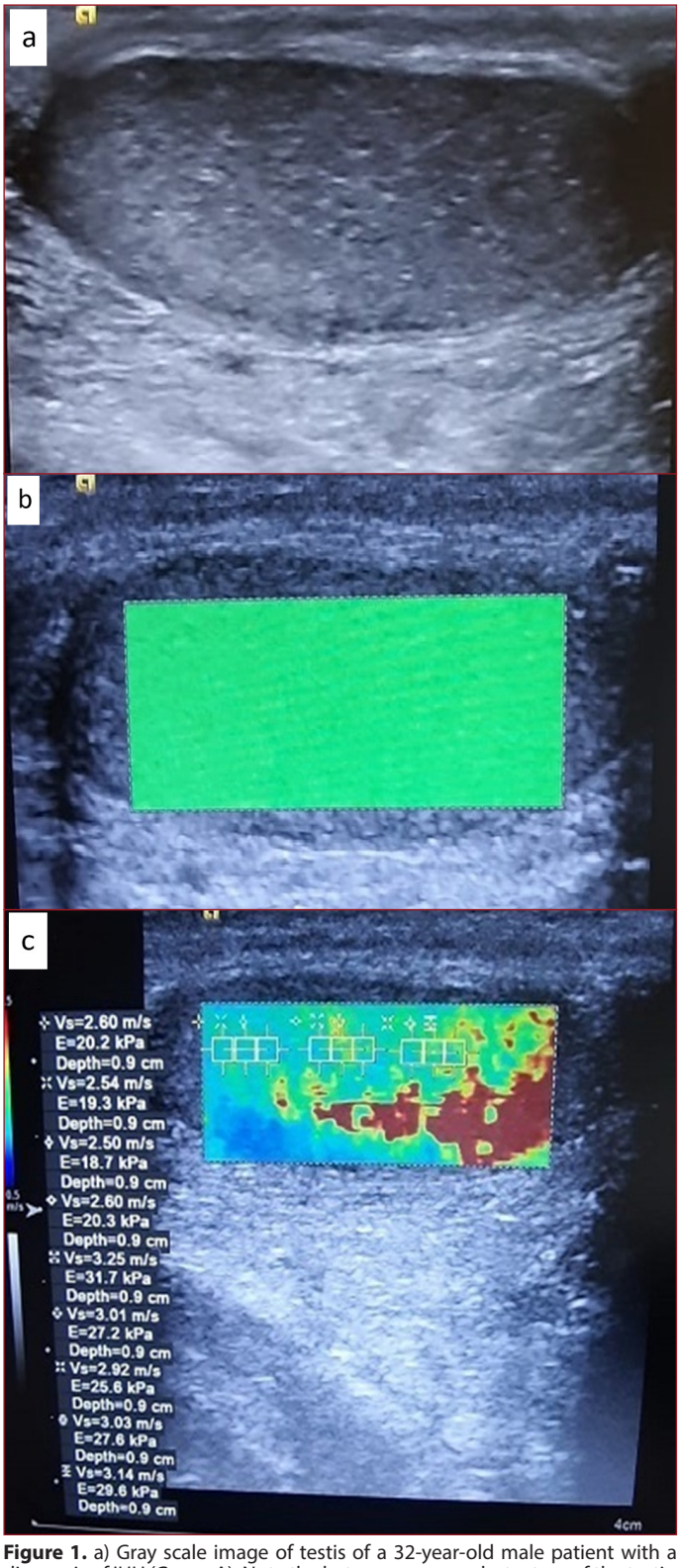

Figure 1. a) Gray scale image of testis of a 32-year-old male patient with a diagnosis of IHH (Group A). Note the heterogeneous echotexture of the testis. b) The quality map of same patient. c) Three measurements were obtained from each part of testis in the longest longitudinal plane. SWE images were displayed in speed mode (m/s) and elasticity mode (kPa).

Statistical Analysis

The Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago IL, USA) was used for the statistical analysis. The Kolmogorov-Smirnov test was used to verify the normality of the data. According to the distribution of the data, the mean±standard deviation or median and interquartile range were calculated. The continuous variables were analyzed using independent samples t-tests or Mann-Whitney U tests, based on their distribution. We compared categorical variables with the Chi-square test. Homogeneity of variances was evaluated with Levene's test. If the data were normally distributed, one-way analysis of variance (ANOVA) was used to compare three or more groups. In post-hoc analyses, Tukey's test was used if homogeneity of variance was assumed. Whenever normality tests failed, the Kruskal-Wallis test was used to compare three or more groups and pairwise comparisons were conducted for subgroup analysis.

RESULTS

In this study, 75 participants were included, 35 patients with IHH in group 1 and 40 healthy controls in group 2. Group 2 had a higher mean age, but this difference was not statistically significant(group1: 25.97±6.06, group 2: 29.02±7.29, p=.054). In the group 1 patients, the right testicular volume (RTV) was 4.45±2.83 ml and the left testicular volume (LTV) was 4.22±2.58 ml, which was significantly lower than the testicular volumes in group 2 (RTV: 13.74±2.46ml, LTV: 13.50±2.38ml (p<.001 for both). On the basis of elasticity and velocity parameters, IHH patients had mean SWE values of 14.88±4.01 kPa and 2.20±0.29 m/s for right testes, and median 14.6 (11.52-16.42) kPa and 2.20 (1.95-2.33) m/s for left testes. In the control group, the mean SWE values were 5.17±1.22 kPa and 1.29±0.15 m/s for right testes, and median 4.28 (3.77-5.79) kPa and 1.24 (1.18-1.43) m/s for left testes. Patients in group 1 had significantly higher stiffness values in both testicles than those in group 2 (p<.001) (**Table 1**).

Table 1. Group-wise baseline characteristics of subjects

Parameters	Healthy control	IHH	P-value
Age (years)	29.02±7.29	25.97±6.06	.054[a]
RT Volume (ml)	13.74±2.46	4.45±2.83	<.001[a]
LT Volume (ml)	13.50±2.38	4.22±2.58	<.001[a]
RT-SWVV (m/s)	1.29±0.15	2.20±0.29	<.001[a]
LT-SWVV (m/s)	1.24 (1.18-1.43)	2.20(1.95-2.33)	<.001[b]
RT-EM (kPa)	5.17±1.22	14.88±4.01	<.001[a]
LT-EM (kPa)	4.28 (3.77-5.79)	14.6 (11.52-16.42)	<.001[b]

Abbreviations: IHH; Isolated hypogonadotropic Hypogonadism, SWVV; Shear Wave Velocity Values, EM; Elastic Modulus RT; Right Testis, LT; Left Testis. Data areexpressed as the mean and Standard deviation or median (first and third quartile) values. p value< 0.05 was considered significant. Significant p values are highlighted in bold .a: Independent samples t-test. b: Mann-Whitney U test

Correlation analysis showed that the volume of the testicles increased with increasing age in patients with IHH (r=0.423, p=.011 for right testes, r=0.460, p=.005 for left testes). There was also a negative correlation between the mean value of testicular stiffness and testicular volume (r=-0.555, p=.001 for right testes, r=-0.403, p=.016 for left testes) (**Table 2**).

Table 2. A correlation analysis of group 1 patients regardless of their treatment status

		RT Volume (ml)	LT volume (ml)	RT-SWV (m/s)	LT-SWV (m/S)
Age (years)	r value	.423*	.460**	-.142	.052
	p value	.011	.005	.415	.793
RT Volume (ml)	r value		.944***	-.555**	-.392*
	p value		<.001	.001	.020
LT Volume (ml)	r value			-.531**	-.403*
	p value			.001	.016
RT-SWVV (m/s)	r value				.761***
	p value				<.001

Abbreviations: RT; Right Testis, LT; Left Testis, r: Pearson's correlation, p value< 0.05 was considered significant. Significant p values are highlighted in bold

In the final analyses, patients were divided into three groups according to their treatment status (Group A, B, and C) (**Table 3**). The mean age of patients in group A was significantly lower than those in group B and C (p=.001). There was a significant increase in mean testicular volume in group C patients when compared with both group A and B (p<.001). The values of testicular stiffness in group C patients were significantly lower than those in group A. However, there was no significant difference between group A and group B in terms of testicular stiffness.

Table 3. The comparison of IHH patients based on their treatment status

	Group A (n:11) (Treatment-naive)	Group B (n:10) (IM testosterone)	Group C (n:14) (hCG alpha)	p value
Age (years)	20.90±3.93^{a**b**}	29.20±3.64	27.64±6.49	.001
RT Volume (ml)	2.21±1.35^{b***c*}	3.98±2.59	6.26±2.04	<.001
LT Volume (ml)	2.20±1.07^{b***c*}	3.68±2.64	6.19±1.97	<.001
RT-SWVV (m/s)	2.36±0.28^{b*}	2.20±0.28	2.06±0.24	.032
LT-SWVV (m/s)	2.21±0.24	2.24±0.26	2.05±0.29	.200
RT-EM (kpa)	17.18±4.18^{b*}	14.95±3.97	13.04±3.10	.033
LT-EM (kpa)	14.89±3.36	15.50±3.77	12.96±3.80	.215

Abbreviations: HCG; Human chorionic gonadotrophin, IM; Intramuscular, SWVV; Shear Wave Velocity Value, EM; Elastic Modulus, RT; Right Testis, LT; Left Testis
Data are expressed as the mean and standard deviation. p value<.05 was considered significant. Significant p values are highlighted in bold
The definition of post hoc analysis: a: between group A and B, b: between group A and C, c: between group B and C, *: p value between .05-.01, **: p value between .01-.001, ***: p value<.001

DISCUSSION

The most important distinguishing feature of this study is that SWE was used for the first time to determine testicular stiffness in patients with IHH. It was already expected that testicular volumes would be lower in patients with IHH than in healthy controls. These patients also displayed a significant increase in testicular stiffness in comparison to healthy controls. One of the most interesting aspects of our study is the observation that the degree of stiffness in the testicles may vary according to the treatment regimen used. Despite a relatively limited number of patients and a relatively short treatment period, we found significant differences in testicular volume increase and reduced testicular stiffness in patients receiving human chorionic gonadotropin alpha versus other groups. This could indicate that optimal hormone replacement therapy (LH and FSH) is associated with improved testicular parenchyma in patients with IHH. There is already evidence to suggest that testosterone replacement alone is not sufficient to stimulate testicular growth or spermatogenesis in patients with IHH.[6]

The effectiveness of SWE in assessing the stiffness of tissues or lesions has been demonstrated in a variety of organs, including the thyroid, breast, and liver.[14-16] In recent years, SWE has become one of the more common methods for evaluating testicles. A significant increase in testicular stiffness was observed with the SWE method in patients with testicular tumors, varicocele and torsion.[17-21] Based on a meta-analysis of studies that used the SWE to distinguish between malignant and benign testicular lesions, the researchers found that the pooled sensitivity was 87% and the pooled specificity was 81%. As a general rule, malignant lesions are considered to be harder than benign lesions.[22] It should be noted, however, that stiffness measurements of some benign lesions with calcification may be higher and, stiffness measurements of some malignant lesions with necrosis and liquefaction may be lower.[17] In varicoceles, stiffer testicles are thought to be associated with germ cell atrophy, thickened tubular basement membranes, and increased interstitial fibrosis.[18] In both animal and human studies, testicular torsion has been associated with increased testicular stiffness. Increased stiffness is believed to be associated with increased intratesticular pressure due to venous obstruction, tissue edema, bleeding and necrosis.[20,21]

A number of studies have demonstrated that infertile males have increased testicular stiffness.[23-26] Urologists use tissue palpation to assess scrotal stiffness, but it is a subjective tool that requires experience. An abnormal spermiogram may indicate parenchymal damage. Due to the invasive nature of testicular biopsy, it is no longer routinely recommended for assessing histological features of parenchymal damage.[27] According to an experimental study on white rabbits, increased testicular stiffness after testicular torsion was positively correlated with impaired spermatogenesis.[23] In a study involving 1,116 men undergoing in vitro fertilization treatment, increased testicular stiffness was found to be inversely related to total sperm count. This condition has been linked to fibrotic thickening of the walls of seminiferous tubules in the testicles.[24] It was also observed in another study by Erdogan et al. that infertile men exhibited significantly higher testicular SWE values than healthy controls. They also stated that testicular stiffness increased with decreasing testicular volumes. The increased testicular stiffness values have been attributed to parenchymal damage that impairs spermatogenesis.[25] In the study conducted by Illiano et al. similar findings were reported as well.[26] In testicular biopsy

samples taken from azoospermic males, Li et al. observed an increase in the thickness of lamina propria and a decrease in the diameter of seminiferous tubules and spermatogenetic epithelium height.[28]

In our patient group, in addition to increased testicular stiffness, we also found a decrease in testicular echo and heterogeneity on gray scale imaging. According to histopathological findings in patients with IHH, the seminiferous tubules are separated by an interstitial space that consists of blood vessels, connective tissue cells, and collagen fibers. However, typical adult Leydig cells were not detected. Moreover, only immature sertoli cells and early type A spermatogonia were found in the cords.[29] This findings suggests that increased testicular stiffness in IHH patients may be related to increased connective tissue.

The Study's Strengths and Limitations

Our study had some limitations. Firstly, the study included a relatively small number of patients. Secondly, all SWE measurements were performed by a single radiologist, and only one measurement was taken. However, we believe that taking nine separate measurements from each part of the testis would result in a higher level of accuracy. A third limitation involves the lack of analysis of sperm parameters and the inability to compare histopathological findings among patients. One of the strengths of our study is that testicular stiffness in IHH patients was evaluated with SWE for the first time in the literature. A further noteworthy finding was the significant reduction in testicular stiffness observed in patients receiving hCG alpha in comparison to those receiving testosterone replacement therapy.

CONCLUSION

Testicular stiffness was significantly higher in IHH patients than in healthy controls. A significant improvement in testicular stiffness was observed in patients treated with hCG alfa compared with those treated with testosterone. In patients with IHH, detection and monitoring of testicular stiffness using the SWE may be useful in demonstrating the effectiveness of treatment. Future prospective studies with a larger sample size are needed to confirm this study's findings..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Harran University Non-interventional Clinical Researches Ethics Committee (Date: 29.11.2021, Decision No: HRU/21.21.05).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1328246
J Contemp Med 2023;13(5):735-740

Original Article / Orijinal Araştırma

Assessment of the Attitudes and Changes in Attitudes of Individuals Aged 65 and Over Toward the Vaccine after Being Informed about COVID-19 Vaccines

COVID-19 Aşıları Konusunda Bilgilendirme Yapılan 65 Yaş ve Üzeri Bireylerin Aşı Tutumları ve Aşı Tutumlarındaki Değişimin Değerlendirilmesi

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Abstract

Aim: Study aimed to assess the states of getting the vaccine and attitudes of the population at the age of 65 and above who was at the risk group in terms of mortality caused by COVID-19 after being informed about the COVID-19 vaccines.

Material and Method: Data, retrospectively scanned. Study population consisted of individuals aged 65 and above who were authorized to get the vaccine in the city center of Kayseri and who had not gotten the COVID-19 vaccine yet by the 1st of June 2021.

Results: According to the decisions of getting the vaccine after phone calls, 45% of the participants decided to get the vaccine while 42.9% stated that they would not get the vaccine. mRNA vaccine was the most preferred vaccine (35.4%) after the phone calls.

Conclusion: Results of study reveal that the attitude toward COVID-19 vaccine can be affected by many personal and non-personal factors.

Keywords: COVID-19 vaccines, information, 65 years and above, vaccine attitude

Öz

Amaç: Çalışma, COVID-19 aşıları hakkında bilgilendirildikten sonra, COVID-19'un neden olduğu ölümler açısından risk grubunda olan 65 yaş ve üzeri nüfusun aşı yaptırma durumlarını ve tutumlarını değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: Veriler, retrospektif olarak taranmıştır. Çalışma evreni, 1 Haziran 2021 tarihine kadar Kayseri il merkezinde aşı yaptırma izni olan ve henüz COVID-19 aşısı yaptırmamış 65 yaş ve üzeri bireylerden oluşmaktadır.

Bulgular: Telefon görüşmeleri sonrasında aşı yaptırma kararlarına göre katılımcıların %45'i aşı yaptırmaya karar verirken, %42,9'u aşı yaptırmayacağını belirtmiştir. mRNA aşısı telefon görüşmeleri sonrasında en çok tercih edilen aşı olmuştur (%35,4).

Sonuç: Çalışmanın sonuçları, COVID-19 aşısına yönelik tutumun kişisel ve kişisel olmayan birçok faktörden etkilenebileceğini ortaya koymaktadır.

Anahtar Kelimeler: COVID-19 aşıları, bilgi, 65 yaş ve üstü, aşı tutumu

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Received *(Geliş Tarihi)*: 16.07.2023 **Accepted *(Kabul Tarihi)*:** 01.09.2023

INTRODUCTION

COVID-19, caused by SARS-CoV-2, is a major health problem of the 21st century.[1] Given its high infectivity, negative impact on the economy and healthcare systems, and lack of effective treatment, it's crucial to develop a safe and effective vaccine. Vaccines are successful and cost-effective in preventing infectious diseases, and are important in controlling COVID-19.[2,3]

COVID-19 vaccine research and development has improved greatly, but vaccination efforts face significant challenges. One major obstacle is uncertainty around vaccine acceptance, which is linked to public perception of disease risk, attitudes towards vaccines, and overall demand. High vaccination rates are crucial to effectively combat infectious diseases, particularly novel ones, and ensure successful immunization programs.[4–6] Studies show that vaccine acceptance for pandemics depends on several factors, such as perception of risk, attitude towards vaccination, ease of getting vaccinated, vaccine effectiveness and reliability, vaccination history, price, physician recommendations, and sociodemographic characteristics.[4,6–10]

The infectious agents are the primary cause of death in one third of the individuals aged 65 and above.[11] Old age is one of the most important factors affecting mortality and COVID-19 anxiety in COVID-19.[12,13] According to the Chinese Center of Disease Control and Prevention, while the rate of mortality caused by COVID-19 is 2.3% in general population this rate is 8% in the ages between 70 and 79 and 15% above the age of 80.[14]

mRNA and inactive COVID-19 vaccines in phase 3 which are supplied with the agreements made by the Republic of Türkiye Ministry of Health have been approved for urgent use in our country. On 19th of December 2020, the health personnel and individuals aged above 65 started to get vaccinated in Israel.[15] COVID-19 vaccination also started in Türkiye beginning with the specific groups (healthcare workers, adults aged above 65, etc.).

This study aimed to assess the states of getting the vaccine and attitudes of the population at the age of 65 and above who was at the risk group in terms of mortality caused by COVID-19 and gradually increasing in number in our country after being informed about the COVID-19 vaccines.

MATERIAL AND METHOD

The study was carried out with the permission of Karabük University Non-interventional Clinical Researches Ethics Committee (Date: 06/08/2021, Decision No: 2021/607), and necessary permissions from Kayseri Provincial Health Directorate were obtained for the study. The ethical rules and the principles of the Declaration of Helsinki performed out all procedures.

The data obtained from the practice of COVID-19 vaccine information designed as a public health intervention were retrospectively scanned. The study population consisted of 6494 individuals aged 65 years and over who had permission to be vaccinated in the vaccination program that started on February 12, 2021 within the scope of the COVID-19 Vaccine-National Vaccination Strategy of the Ministry of Health of the Republic of Turkey within the scope of the COVID-19 Vaccine-National Vaccination Strategy in Kayseri city center and who had not yet received COVID-19 vaccine until June 1, 2021. The minimum sample size was calculated as 328, assuming a prevalence of vaccine refusal-ambivalence of 34%, alpha error level (a): 0.05, test power (1- ß): 0.80 and deviation level (d): 0.05.[16] The individuals aged 65 and above were called by the central operation team of Kayseri Provincial Health Directorate to give information about COVID-19 vaccines in accordance with the instructions of the Republic of Türkiye Ministry of Health between the 2nd of June 2021 and 11th of June 2021. On the phone calls, the individuals who were accessed were informed about the issues such as the vaccine types, effectiveness of the vaccines, undesired effects after the vaccines, and the importance of getting the vaccine in the groups at risk based on the documents prepared by the Republic of Türkiye Ministry of Health about COVID-19 vaccines and then questioned about their decisions on getting the vaccine. In addition, the questions asked by the individuals were answered and the answers were recorded on electronic media. The recorded data were retrospectively scanned and a total of 700 individuals were included in the study after those with missing and incorrect records were excluded.

Statistical Analysis

The study analyzed participants' demographics, vaccine status, and COVID-19 history using Jamovi 1.8.1. Frequency tables and statistical tests were used to assess distribution of numerical data. Parametric tests were used for normally distributed groups and non-parametric tests for groups that did not meet parametric assumptions. Statistically significant values were determined as $P<0.05$.

RESULTS

The study included 700 participants aged 65 and above, with 60.6% in the age range of 65-75 and 39.4% aged 75 and above. Male participants accounted for 39.1% and 71.3% of participants resided in urban areas. The mean age was 73.9 (±7.74) for the entire group, 73.2 (±7.85) for males, and 74.3 (±7.64) for females. (**Table 1**)

Table 1: Sociodemographic Characteristics of the Participants

Characteristics		n	%
Age group	Between 65-75	424	60.6
	75 and above	276	39.4
Gender	Male	274	39.1
	Female	426	60.9
Place of residence	Urban	499	71.3
	Rural	201	28.7

The most common reasons for not getting the vaccine were having diseases (31.1%) and not being able to get an appointment (20.9%). Hesitancy (5%) and a request for a domestic vaccine (3.7%) were the least common reasons. After phone calls, 45% of participants decided to get the vaccine while 42.9% stated they would not. The mRNA vaccine was the most preferred (35.4%) after the calls. (**Table 2**)

Table 2: Participants' Reasons for not getting the Vaccine, Decisions on the Vaccine after Phone calls and Vaccine Preferences

Features		n	%
Reasons for not getting the vaccine	Having a disease	218	31.1
	Unable to get an appointment	146	20.9
	COVID-19 (+) within the last 6 months	104	14.9
	Thought that the vaccine is unnecessary	75	10.7
	Unable to contact a health institution	50	7.1
	Fear of vaccine/injection	46	6.6
	Hesitant	35	5.0
	Request for getting the domestic vaccine	26	3.7
Total		700	100.0
Decision on getting the vaccine after phone calls	Will get the vaccine	315	45.0
	Hesitant	85	12.1
	Will not get the vaccine	300	42.9
Total		700	100.0
Vaccine preference if s/he will get the vaccine	Pfizer/Biontech (mRNA)	112	35.4
	Sinovac (Inactive)	35	11.1
	Any of them	79	25.2
	Does not know	89	28.3
Total		315	100.0

After phone calls, over half of the participants with medical conditions, almost 90% who thought the vaccine was unnecessary, about 72% who feared vaccines, and 77% who requested the domestic vaccine said they would not get vaccinated. (**Table 3**)

Table 3: Attitudes of the Participants after Phone Calls

Reason for not getting the vaccine	Will get the vaccine	Hesitant n (%)	Will not get the vaccine n (%)	Total* n (%)
Diseases	63 (28.9)	33 (15.1)	122 (56.0)	218 (100.0)
Unable to get a vaccine	129 (88.4)	11 (7.5)	6 (4.1)	146 (100.0)
COVID-19 (+) within the last 6 months	65 (62.5)	13 (12.5)	26 (25.0)	104 (100.0)
Thought that the vaccine is unnecessary	4 (5.3)	4 (5.3)	67 (89.3)	75 (100.0)
Unable to contact a health institution	29 (58.0)	3 (6.0)	18 (36.0)	50 (100.0)
Fear of vaccine	8 (17.4)	5 (10.9)	33 (71.7)	46 (100.0)
Hesitancy	13 (37.1)	14 (40.0)	8 (22.9)	35 (100.0)
Request for domestic vaccine	4 (15.4)	2 (7.7)	20 (76.9)	26 (100.0)
Total	315 (45.0)	85 (12.1)	300 (42.9)	700 (100.0)

*: Line totals of numbers and percentiles were given.

After phone calls, 61.7% of male participants were hesitant or unwilling to get the vaccine (p<0.005). Age and place of residence did not affect attitudes (p>0.005). The highest rate of vaccine uptake was seen in participants who previously hesitated or had diseases (p<0.001). Fear of vaccine/injection, domestic vaccine preference, and belief in vaccine necessity did not affect vaccine uptake after phone calls (p>0.005). (**Table 4**)

Table 4: Relationship of the participants' sociodemographic characteristics and reasons for not getting the vaccine with their attitudes after phone calls

Variables	Will get vaccine n (%)*	Hesitant-will not get the vaccine n (%)*	Total n	X2	p
Gender					
Male	105 (38.3)	169 (61.7)	274	8.110	0.004
Female	210 (49.3)	216 (50.7)	426		
Age Group					
65-75 years	201 (47.4)	223 (52.6)	424	2.510	0.113
75 years and above	114 (41.3)	162 (58.7)	276		
Place of residence					
Urban	220 (44.1)	279 (55.9)	499	0.584	0.445
Rural	95 (47.3)	106 (52.7)	201		
Reasons for not getting the vaccine**					
Vaccine hesitancy	13 (37.1)[a]	22 (62.9)[a]	35	23.100	<0.001
Diseases	63 (28.9)[b]	155 (71.1)[b]	218		
Fear of vaccine/ injection	8 (17.4)[c]	38 (82.6)[c]	46		
Request for domestic vaccine	4 (15.4)[c]	22 (84.6)[c]	26		
Thought that vaccine is unnecessary	4 (5.3)[c]	71 (94.7)[c]	75		

*: Line totals of numbers and percentiles were given. **: Difference between the groups shown with the same exponential letter is not significant.

Vaccine preferences were statistically similar according to male and female genders, age groups and participants' places of residence (p=0.850, p=0.562 and p=0.087 respectively). (**Table 5**)

Table 5: Relationship between the participants' sociodemographic characteristics and vaccine preferences

Variables	Btc (mRNA) n (%)*	Snv (Inactive) n (%)*	Total n	X2	p
Gender					
Male	40 (76.9)	12 (23.1)	52	0.037	0.850
Female	71 (75.5)	23 (24.5)	94		
Age group					
65-75	68 (73.9)	24 (26.1)	92	0.337	0.562
75 and over	43 (79.6)	11 (20.4)	54		
Place of residence					
Urban	73 (71.6)	29 (28.4)	102	2.920	0.087
Rural	38 (86.4)	6 (13.6)	44		

DISCUSSION

Morbidity and mortality caused by COVID-19 increases by age.[12] Therefore, this study including a population aged 65 and above who was admitted as the group at risk aimed to provide anticipation about the elderly and vaccination during COVID-19 pandemic.

Although the COVID-19 vaccine attracts intense attention some of the elderly are hesitant to get the vaccine.[16,17] There are a limited number of studies on vaccine hesitancy of the elderly in the society. In the study assessing the vaccination frequency and awareness of 303 individuals aged 65 and above in Istanbul, mean age of the participants was 71.3 and 56.4% were female.[18] In the study assessing the COVID-19 vaccine hesitancy in old individuals, 45% of the participants were between the ages of 65 and 74 and 55% were above the age of 75. Mean age of the participants in our study was 73.9. The age range in our study was similar to those in literature. Of the participants in our study, 60.9% were female, which is different from and higher than the rates in similar studies in literature. This may be because 28.7% of our participants lived in rural areas and the gender may be effective in access to the vaccine.

Attitudes and behaviors toward the COVID-19 vaccine can vary according to the age groups.[16] In another study in which the participants who refused or were hesitant to get the vaccine in Istanbul were asked about their reasons for not getting the vaccine, 75.9% were afraid of the vaccine side effects as it was a new vaccine, 34.4% did not trust the companies producing the vaccine, 20.9% thought that the vaccine would not prevent COVID-19 (thought that the vaccine was unnecessary), 15.6% did not think himself or herself in the risky group, 12.7% did not need the vaccine as they took their own measures, and 3.4% were generally anti-vax.[19] The reasons for not getting the vaccine among the participants in our study were having a disease for 31.1%, being unable to get an appointment for 20.9%, being COVID-19 (+) within the last 6 months for 14.6%, thought that the vaccine was unnecessary for 10.7%, being unable to contact with the health institution for 7.1%, fear of vaccine/injection for 6.6%, hesitancy about getting the vaccine for 5%, and desire to get the domestic vaccine for 3.7%. The characteristics of the participants such as the place of residence, education levels or local and cultural factors may have caused variable and different orders of the rates and frequencies in the reasons for not getting the vaccine in the studies. Moreover, the first reason for not getting the vaccine was "not having knowledge of the necessity of getting the vaccine" in the study by Mutlu, which suggests that the other adult vaccines are known less compared with the COVID-19 vaccines. On the other hand, the first reason for not getting the vaccine was "being afraid of side effects as it is a new vaccine" in the study by Mert, which reveals that the awareness on COVID-19 vaccines is higher.

As a result of the study performed online on 1293 individuals by Mert, while 41.2% of the participants had positive attitude toward getting the COVID-19 vaccine 37.9% were hesitant.[19] According to the studies, the rate of giving positive answer to getting the vaccine was 91.3% in China, between 88% (China) and 54% (Russia) in the study performed jointly in 19 countries, and 83% in the UK and 66% in Türkiye in the study performed jointly in the UK and Türkiye.[20–22] After 700 individuals aged 65 and above were called by the central operation team of Kayseri Provincial Health Directorate to give information about COVID-19 vaccines 45% of the participants stated that they would get the vaccine, 42.9% stated that they would not get the vaccine and 12.1% were hesitant to get the vaccine. Although the individuals were informed by phone calls the result obtained from our study reveals that the acceptance level of COVID-19 vaccine in Türkiye is low, which is consistent with some studies in Türkiye, compared with the other countries despite the ongoing COVID-19 pandemic.

The participants who would get the vaccine were assessed in terms of their vaccine preferences and according to the results, 35.4% preferred Comirnaty (BNT162b2, Pfizer/Biontech), the mRNA vaccine, 11.1% preferred Coronavac, the inactive SARS-CoV-2 vaccine, 28.3% did not know which one to prefer, and 25.2% could prefer both of the vaccines. In a study in Istanbul, 51.3% of the participants preferred Comirnaty (BNT162b2, Pfizer/Biontech), the COVID-19 vaccine of German origin, and 18.5% preferred Coronavac, the inactive SARS-CoV-2 vaccine of Chinese origin.[19] Comirnaty, the mRNA vaccine, was preferred more in the two studies in Türkiye, which may be because of the positive information transfer about mRNA vaccines in the country and the attitude of the public toward the vaccines as well as mRNA-inactive vaccine types.

In a study in which 82 individuals refusing to get their children vaccinated were called to give information and in which the effect of COVID-19 on the decision of vaccination was investigated, none of the participants changed their minds on getting their children vaccinated after phone calls and 64.3% did not change their minds on getting themselves vaccinated.[23] According to the attitudes of the participants who did not get the vaccine, 89.3% of those who thought the vaccine was unnecessary, 76.9% of those who wanted to get the domestic vaccine, 71.7% of those who were afraid of vaccines, and 56% of those who could not get the vaccine due to diseases did not change their minds after the informative phone calls. High rates of participants who did not change their minds after the informative phone calls in the studies may be due to including individuals who support vaccine refusal in the study populations, personal characteristics that cannot be changed in a short time such as diseases and fear of vaccine and non-personal characteristics such as the desire of domestic vaccine. The statistical significance in the relationship between the participants' reasons for not getting the vaccine and their attitudes after the phone calls makes the proportional changes between the reasons for not getting the vaccine more important ($p<0.001$) and this is supported by the result of our study that 88.4% of those who did not get the vaccine as they could not get an appointment and 58% of those who could not access a health institution changed their minds to get the vaccine after the phone calls.

According to the relationship between the sociodemographic characteristics of the participants in our study and their attitudes after the phone calls, the rate of female gender who changed their mind to get the vaccine was higher compared

with the male gender, which was statistically significant (p:0.004). This result is not consistent with some studies revealing that male individuals have more positive attitude toward getting the vaccine in literature.[19,20,23–25] However, there is also a study revealing that women have more positive attitude toward the vaccine like in our study.[22] Women in reproductive age group can be more hesitant to get the vaccine due to the instinct to protect their reproductive health, fetus or babies they breastfeed; however, higher number of women in our study changed their minds in a positive way as they were old individuals whose reproductive age ended. Moreover, women are generally more interested in medical issues including the vaccines and more sensitive to information about the vaccines compared with the men, which may have caused this result.[26]

There was no statistical significance in the relationship of the participants' sociodemographic characteristics with their vaccine preferences. As there are studies in which no significance has been found in the relationship of sociodemographic characteristics with vaccine preferences there are also studies in which significance has been found.[20,24,25,27] The reason why no significant relationship was found between the sociodemographic characteristics such as gender, age group and place of residence and vaccine preferences in our study may be the equality of the use of similar informative ways by all classes of the society and our informative phone calls as well as the participants' inadequate level of knowledge of the vaccines.

CONCLUSION

Our study found that the attitudes of people aged 65 and older towards COVID-19 vaccines are influenced by personal and non-personal factors. With high mortality and morbidity rates in this age group, it's important to increase vaccination rates. To achieve this, we suggest raising awareness, providing reliable information through media, and improving health literacy. While our study sheds light on vaccine hesitancy in this population, further research is needed due to the limited number of studies conducted in Türkiye.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karabük University Non-interventional Clinical Researches Ethics Committee (Date: 06/08/2021, Decision No: 2021/607).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1324094
J Contemp Med 2023;13(5):741-745

Original Article / Orijinal Araştırma

A Comparison of Curettage Only and Curettage with Electrocautery after Partial Matrixectomy for Ingrowing Toenail

Tırnak Batması Cerrahisinde Parsiyel Matrisektomi Sonrası Sadece Küretaj Yöntemi ile Küretaj ve Elektrokoterin Birlikte Kullanıldığı Yöntemin Karşılaştırılması

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Abstract

Aim: Ingrowing toenail is a very common disease which causes workforce losses. Although different techniques have been described in surgical treatment, one of the most frequently preferred methods is partial matrixectomy. The aim of this study was to compare the two techniques of curettage only and curettage together with electrocautery(C&E) used in addition to partial matrixectomy in ingrowing toenail surgery.

Material and Method: Patients who were operated for ingrown nails between 2018 and 2022 were evaluated retrospectively. Two groups were formed of 43 patients applied with curettage only and 35 patients applied with C&E. The groups were compared in respect of operating time, postoperative complications and clinical results.

Results: No significant difference was determined between the groups in respect of age, gender, affected side, classification, follow-up time, surgical duration and recovery time. Recurrence rate was higher in the curettage group (p=0.020) It occurred in 9 (20.9%) cases in the curettage group, while it occurred in 1 (2.9%) case in the C&E group. In the curettage group, the duration of erythema was observed to be significantly longer (p<0.001) and there was a need for more dressings (p<0.001). In the C&E group, serous exudate was seen for a longer period (p=0,007).

Conclusion: The disadvantages of curettage applied in addition to partial matrixectomy in ingrown toenail surgery are, a higher rate of recurrence, longer duration of erythema, need for more dressings while the disadvantage of C&E is the longer duration of serous exudate. In respect of infection rates and time to recovery, no difference was determined between the two techniques.

Keywords: ingrown nail, matrixectomy, currettage, electrocautery

Öz

Amaç: Tırnak batması iş gücü kayıplarına neden olan çok yaygın bir hastalıktır. Cerrahi tedavide farklı teknikler tanımlanmış olsa da en sık tercih edilen yöntemlerden biri parsiyel matriksektomidir. Bu çalışmanın amacı; tırnak batması cerrahisinde parsiyel matriksektomiye ek olarak kullanılan sadece küretaj tekniği ile küretaj ve elektrokoterin (C&E) birlikte kullanıldığı tekniği karşılaştırmaktır.

Gereç ve Yöntem: Bu retrospektif çalışmada 2018-2022 yılları arasında tırnak batması nedeniyle ameliyat edilen olgular değerlendirildi. Sadece küretaj uygulanan 43 olgu ve C&E uygulanan 35 olgu çalışmaya dahil edilerek iki grup oluşturuldu. Gruplar; operasyon süresi, operasyon sonrası komplikasyonlar ve klinik sonuçlar açısından karşılaştırıldı.

Bulgular: Gruplar arasında yaş, cinsiyet, etkilenen taraf, batık ayak tırnağı sınıflandırması, takip süresi, ameliyat süresi ve iyileşme süresi açısından fark saptanmadı.. Küretaj grubunda nüks oranı daha yüksekti. (p=0,020) Küretaj grubunda 9 (%20,9), C&E grubunda 1 (%2,9) olguda nüks görüldü. Küretaj grubunda eritem süresinin daha uzun olduğu (p<0.001) ve daha fazla pansuman ihtiyacı olduğu görüldü (p<0.001). C&E grubunda daha uzun süre seröz eksüda görüldü (p=0,007). Takip süresince hiçbir olguda enfeksiyon saptanmadı.

Sonuç: Bu çalışmaya göre; tırnak batması cerrahisinde parsiyel matriksektomiye ek olarak uygulanan küretajın dezavantajları daha yüksek nüks oranı, daha uzun eritem süresi ve daha fazla pansuman ihtiyacı olması iken C&E'nin dezavantajı daha uzun süre seröz eksüda görülmesidir. Enfeksiyon oranları ve iyileşme süresi açısından iki teknik arasında fark yoktur.

Anahtar Kelimeler: Tırnak batması, matrisektomi, küretaj, elektrokoter

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Received *(Geliş Tarihi)*: 07.07.2023 **Accepted *(Kabul Tarihi)*:** 13.08.2023

INTRODUCTION

Ingrowing toenail is one of the most frequently seen foot problems.[1] As a result of the nail plate growing towards the periungual skin, it is a disease in which problems such as pain, inflammation, and infection develop.[2] Treatment is generally planned according to the stage of the disease.[3] Techniques have been described such as the application of chemical substances to the nail bed,[4] partial excision of the nail bed,[5] and matrixectomy with carbon dioxide laser application.[6] One of the most widely used methods in current surgery is partial matrixectomy.[7] The main aim of this method is the removal of the germinal matrix. Various additional methods have been described for the removal of matrix remnants after matrixectomy, of which two often used methods are curettage and electrocautery.[8,9] Few publications have compared these two techniques.[10] No study could be found in literature that has compared the curettage only method with the method of curettage together with electrocautery (C&E). The aim of this study was to compare the results of the application of the curettage only technique and C&E after partial matrixectomy.

MATERIAL AND METHOD

Patient Selection

The study was carried out with the permission of Adnan Menderes University Non-interventional Clinical Researches Ethics Committee (Date: 02.08.2022, Decision No: E.210031). Informed consent was obtained from all patients. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A retrospective examination was made of 116 cases who underwent surgery for ingrowing toenail between 2018-2020. The grading of the ingrowing toenails was made as described by Heifetz et al.[11] The cases included in the study were those who underwent partial matrixectomy because of ingrowing nail in the thumb. Those who were operated on due to ingrown nails other than the thumb (n=4), those who could not be followed (n=5), those who were operated on both the medial and lateral sides of the same nail (n=7), those who had their nail totally removed (n=11), those who were operated for recurrence (n=8) and those with diabetes (n=3) were excluded from the study.

Surgical Technique

Ingrowing toenail operations are applied in our clinic with the partial matrixectomy technique. Surgical treatment was applied to Stage 2 and Stage 3 ingrowing toenails. The two different techniques of curettage only or curettage together with electrocautery were used according to the preference of the surgeon. All the cases were operated on by the same surgeon.

Antibiotics of the amoxicillin-clavulonic acid group were administered for one week preoperatively at a dose appropriate to the age of the patient. The operation was performed on completion of the antibiotherapy. Surgery was applied to all the cases under digital block, for which 2% lidocaine was used. Following block anaesthesia and sterile draping, an elastic band tourniquet was applied to the toe.

After the routine preparation, a no. 15 scalpel was used to make a 5-8 milimeter vertical cut to the eponychium to be at the border of the nail resection. With the sharp side of the scalpel uppermost, the cut was made from the distal nail as far as the proximal germinal matrix border. Using a Freer elevator, the nail plate was dissected with blunt dissection to include the periostium. Sharp dissection was continued with a scalpel between the medial skin layers and the ingrowing toenail. The visalisation of fatty tissue was accepted as a sufficient margin. By raising in a wedge-shaped pattern from the distal, the germinal matrix was dissected as far as the proximal and removed. The remaining matrix tissues were excised with curettage to include the periostium. In patients to be applied with electrocautery, preparation was made in 35W coagulation mode, and the germinal matrix and nail bed were destroyed for 5-9 seconds, as described by Zuber et al.[12] Cautery was not applied to the medial flap and other regions. (**Figure 1**) After both methods, the wound was closed with nylon suture material. A 3/0 polypropylene suture was applied to the eponychium and the medial flap side. Postoperatively, amoxicillin-clavulonic acid group antibiotics were prescribed at a dose appropriate to the age and body weight of the patient and it was recommended to use it for one week.

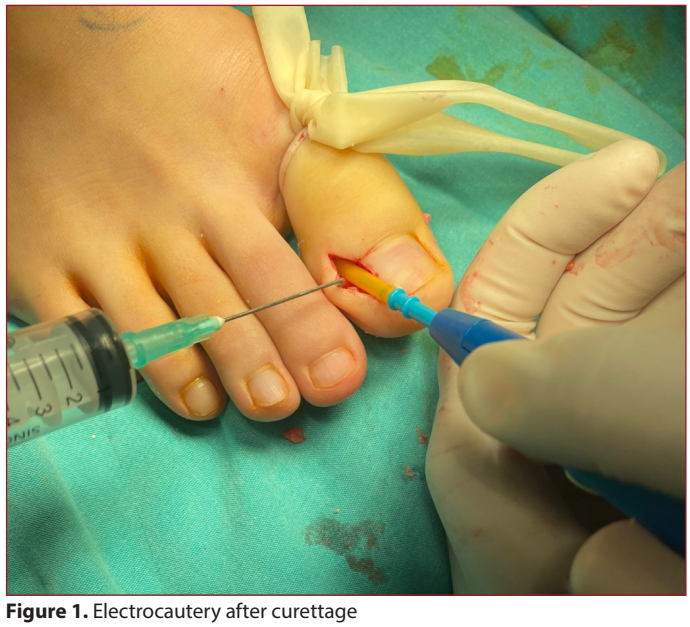

Figure 1. Electrocautery after curettage

Postoperative Evaluation

Two groups were formed for this study as the curettage only group and the C&E group. The same clinical protocol was applied to all the patients in the postoperative follow-up period. In cases with no wound site problems, the sutures were removed on the 15th day. The patients were called for follow-up examination every day for the first 7 days, then every other day. They were advised to return to the

hospital immediately if the dressing was contaminated. After complete wound healing, follow-up examinations were made at 2, 6, and 12 months. After the first year, annual control was done. The healing criteria were defined as being able to wear shoes without pain and being able to perform daily living and work activities without experiencing pain. During the follow-up period, inward growth of the nail edge or the formation of spicula was evaluated as recurrence.

The two groups were compared in respect of operating times, and clinically, whether or not there was erythema around the wound when changing the dressings in the first 7 days, and if so, for how many days it lasted postoperatively. The presence of serous exudate was checked on the daily dressings in the first 7 days. After that time, evaluation was made according to patient presentation because of soiling of the dressing and it was noted for how many days it lasted after the operation. Comparisons were also made of how many dressing changes were required postoperatively, the time to healing, and recurrence rates at 6 and 12 months.

Statistical Analysis

Conformity of numerical variables to normal distribution was assessed with the Kolmogorov-Smirnov test. Independent groups were compared with the Mann Whitney U-test. Relationships between qualitative variables were examined with Chi-square analysis. Numerical variables were stated as median (25^{th}-75^{th} percentile) and categorical variables as number (n) and percentage (%). A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The curettage group included 43 patients with a mean age of 22.06±8.82 years and the C&E group included 35 patients with a mean age of 21.22±8.03 years. No significant difference was determined between the groups in respect of age, gender, affected side, classification and follow-up time (0.932, p=1.000, p=0.911, p=1.000, p=0.394) (**Table 1**).

Table 1. Comparison of baseline parameters between groups.

	Group		p
	Curettage (n=43)	C&E (n=35)	
Age	22.06±8.82	21.22±8.03	0.932
Gender			
Male	18 (41.9)	14 (40)	1.000
Female	25 (58.1)	21 (60)	
Side			
Lateral	25 (58.1)	19 (54.3)	0.911
Medial	18 (41.9)	16 (45.7)	
Stage			
Stage 2	24 (55.8)	20 (57.1)	1.000
Stage 3	19 (44.2)	15 (42.9)	
Follow-up time (month)	27.23±8.07	25.57±9.02	0.394

Abbreviations: C&E, curettage together with electrocautery

The duration of surgery was determined to be mean 17.23±1.29 minutes in the curettage group and 17.35±1.48 minutes in the C&E group (p=0.800). Postoperatively, erythema was observed for mean 3.84±0.93 days in the curettage group and for mean 2.31±0.99 days in the C&E group (p<0.001). While serous exudate was observed for a mean of 3.81±1.42 days in the Curretage group, a mean of 4.40±1.12 days postoperatively in the C&E group (p=0,007). Dressings were required for mean 5.20±0.86 days in the curettage group and for mean 3.40±0.55 days in the C&E group (p<0.001). Recovery time was similar between groups (p=0.258). The mean recovery time was 15.39±2.70 days in the curettage group, while it was 15.18±2.84 days in the C&E group. Infection was not observed in any case during the follow-up period (**Table 2**).

Table 2. Comparison of clinical results between groups.

	Group		p
	Curettage (n=43)	C&E (n=35)	
Surgical duration (minute)	17.23±1.29	17.35±1.48	0.800
Erythema (day)	3.84±0.93	2.31±0.99	<0.001
Serous exudates (day)	3.81±1.42	4.40±1.12	0.007
Number of dressings	5.20±0.86	3.40±0.55	<0.001
Recovery time (day)	15.39±2.70	15.18±2.84	0.258
Recurrences			
Yes	9 (20.9)	1 (2.9)	0.020
No	34 (79.1)	34 (97.1)	

Abbreviations: C&E, curettage together with electrocautery

Recurrence was determined in 9 (20.9%) of the curettage group and in 1 (2.9%) of the C&E group (p=0. 0,020) (**Table 2**). The recurrence was determined at the 12-month postoperative follow-up examination. All the cases with recurrence were operated on with the protocol applied in the initial treatment. No chemical methods were used in addition to partial matrixectomy in any of the cases with recurrence.

DISCUSSION

There is no consensus in literature on the selection of treatment for ingrowing toenails. Partial or full nail avulsion is a widely used traditional treatment method.[14] However, as these procedures cannot completely eliminate the germinal matrix, they result in high recurrence rates.[15] Therefore, different techniques have been described in the surgical treatment of ingrowing toenails, which aim for a rapid recovery without damaging the soft tissue or increasing infection rates and that try to reduce recurrence rates by eliminating matrix remnants.[4,6,10,13,16-19] However, superiority of any one of these methods over another has not been clearly shown.

In this study, the results were compared of cases applied with curettage only in addition to partial matrixectomy and cases applied with curettage together with electrocautery after partial matrixectomy. We did not find any studies reporting the results of combining these two techniques. In literature there are few studies that have compared the applications of curettage only and electrocautery only after partial matrixectomy.[10,20] One of those studies by Ozan et al.[10] reported that no recurrence was seen in the electrocautery group, and in 2 cases in the group applied with curettage after

partial matrixectomy . Kim et al.[20] determined recurrence in 2 of 32 patients applied with curettage only after partial matrixectomy, and in 4 of 29 patients in the electrocautery group. Although recurrence was seen in both groups, it could not be shown which of the two methods was more advantageous for sole use. It was stated that curettage is an easy-to apply method which only requires simple equipment, but it may not be sufficient to completely remove the matrix.[20] In our study, we found that the recurrence rates were significantly reduced by comparing these two techniques.

It is known that recurrence rates increase when adequate matrix resection is not achieved with partial matrixectomy.[21,22] It can be thought that combining these two methods will reduce the probability of the matrix remaining. It is clear that the results of this study strengthen this view. It showed that recurrence was seen only in 9 cases in the curettage group and in 1 case in the C&E group. In other words, by combining the two techniques, more matrix destruction can be achieved and recurrence rates can be reduced. In addition, as seen in this study, there was no increase in the operation time with the combination of the two methods.

Successful results have been reported following chemical matrixectomy, which is another frequently used method in the treatment of ingrowing toenails.[13] There are also studies stating that phenolisation following partial matrixectomy is a safe method with low recurrence rates.[18] Misiac et al.[23] compared the application of phenol and cauterisation after partial matrixectomy and determined recurrence at the rate of 16% in the phenol group and 26% in the cauterisation group. Despite the antiseptic and anaesthetic effects of chemicals such as phenol, it is known that as in other agents used in chemical matrixectomy, they can lead to various complications such as tissue damage, delayed wound healing, pain and allergic reactions.[24] Despite the excellent hemostasis of electrocautery used in the combined method of the current study, there is known to be thermal damage to tissues.[25]

It has been reported that necrotic areas emerging with the use of electrocautery can create wound problems and may be a cause of infection.[12] In the current study cases operated on with the method that combined curettage and electrocautery, serous exudate was seen for a longer period postoperatively. However, as no infection was seen in any case of either group, it can be said that the serous exudate spontaneously recovered without any adverse clinical effect.

In another method, Turan et al.[26] could not obtain a response to treatment in approximately 20% of patients treated with cryotherapy, and recurrence was determined at a high rate after 6 months of follow up. Although the sole use of cryotherapy is effective symptomatically, high recurrence rates have been seen when it is used alone. In a study aiming to destroy the matrix by Yilmaz et al.[19] cryotherapy was applied after partial matrixectomy and recurrence was determined at the rate of 2.6%. In that study, intense serous accumulation was observed in the cryotherapy region. However, the serous fluid regressed during follow up without the development of infection, as in the current study, and it was emphasized that cryotherapy was a method that can be used to eliminate matrix remnants after partial matrixectomy. In this study, in which the combination of the two methods was evaluated for the first time after partial matrixectomy, recurrence developed in 2.9% of the cases with the combined use of curettage and electrocautery. This rate was considerably lower than the group in which curettage was added as the only method.

This study had some limitations, primarily its retrospective design and the low number of patients included in the groups. In addition, comparisons were made with the curretage method, which is one of the two most commonly used methods. It would be more beneficial to make a triple comparison by forming a separate group from patients who were operated on only with electrocautery.

CONCLUSION

This study compared cases with curettage applied in addition to partial matrixectomy with cases applied with C&E in addition to partial matrixectomy in the surgical treatment of ingrowing toenails. The disadvantages seen in the curettage group were the longer duration of erythema, the need for more dressings, and a higher rate of recurrence, while the disadvantage of C&E was the longer duration of postoperative serous exudate.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Adnan Menderes University Non-interventional Clinical Researches Ethics Committee (Date: 02.08.2022, Decision No: E.210031).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1321009
J Contemp Med 2023;13(5):746-751

Original Article / Orijinal Araştırma

Evaluation of Restless Legs Syndrome in Children with Allergic Rhinitis

Alerjik Rinit Tanılı Çocuklarda Huzursuz Bacak Sendromunun Değerlendirilmesi

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Abstract

Aim: It was aimed to evaluate the frequency of restless legs syndrome (RLS) in children with a diagnosis of allergic rhinitis (AR).

Material and Method: The study is case-control type. Age, gender, height, weight, Body Mass Index (BMI), allergic rhinitis symptom score, allergic rhinitis severity, allergy tests, total IgE, eosinophil values of the case group were examined. Gender, age, height, weight and BMI were also calculated in the control group. Patients in both groups were questioned using the International Restless Legs Syndrome Study Group's (IRLSSG) questionnaire containing the latest diagnostic criteria and severity scoring revised for the pediatric age group. Neurological examination, questionnaire and RLS severity scoring results of the patients were performed by a pediatric neurologist.

Results: In the study, the data of a total of 230 children, 115 AR cases and 115 control groups, were evaluated. The frequency of restless legs syndrome in children with allergic rhinitis was significantly higher than in the control group (15.7% and 5.2%, respectively; p=0.010). The clinical severity of RLS patients was mostly moderate in both the case and control groups [44.4% (n=8) and 50% (n=3), respectively].

Conclusion: According to the results of our study; restless legs syndrome was observed more frequently in patients with allergic rhinitis compared to the control group.

Keywords: Allergic rhinitis, allergy, restless legs, children

Öz

Amaç: Alerjik rinit (AR) tanılı çocuklarda huzursuz bacak sendromu (HBS) sıklığının değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çalışma vaka kontrol tipindedir. Olgu grubunun yaş, cinsiyet, boy, kilo, Vücut Kitle İndeksi (VKİ), alerjik rinit semptom skoru, alerjik rinit şiddeti, alerji testleri, total IgE, eozinofil değerleri incelendi. Kontrol grubunda da cinsiyet, yaş, boy, kilo ve VKİ incelendi. Her iki gruptaki hastalar, pediatrik yaş grubu için revize edilmiş en son tanı kriterlerini ve şiddet puanlamasını içeren Uluslararası Huzursuz Bacak Sendromu Çalışma Grubu anketi kullanılarak sorgulandı. Hastaların nörolojik muayeneleri, anket uygulanması ve huzursuz bacak sendromu şiddet skorlaması çocuk nöroloğu tarafından gerçekleştirildi.

Bulgular: Çalışmada 115 AR olgusu ve 115 kontrol grubu olmak üzere toplam 230 çocuğun verileri değerlendirildi. Alerjik rinitli çocuklarda huzursuz bacak sendromu sıklığı kontrol grubuna göre anlamlı olarak yüksekti (sırasıyla %15,7 ve %5,2; p=0,010). HBS hastalarının klinik şiddeti hem vaka hem de kontrol gruplarında çoğunlukla orta düzeydeydi [sırasıyla %44,4 (n=8) ve %50 (n=3).

Sonuç: Çalışmamızın sonuçlarına göre, alerjik rinitli hastalarda kontrol grubuna göre huzursuz bacak sendromu daha sık gözlendi.

Anahtar Kelimeler: Alerjik rinit, alerji, huzursuz bacak, çocuklar

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Received *(Geliş Tarihi)*: 01.07.2023 **Accepted *(Kabul Tarihi)*:** 13.08.2023

INTRODUCTION

The prevalence of allergic diseases is increasing, especially in middle- and low-income countries.[1] Allergic rhinitis (AR) and asthma are among the most common allergic diseases.[2] AR disease occurs as a result of the immunoglobulin E-mediated inflammatory response of the nasal mucosa against allergens.[3,4] Common clinical findings of AR include some nasal symptoms like sneezing, itching and runny nose, nasal congestion. Besides the nasal symptoms, redness and tearing in the eyes can occur in patients with allergic rhinits.[5]

Clinical findings related to the disease can negatively affect the quality of life in children.[6] There are also studies showing that school performance and sleep are adversely affected in children with allergic rhinitis.[7-9] It has been shown that nasal congestion caused by AR contributes to sleep-disordered breathing.[6,10] According to a study in the literature; in children with moderate and severe allergic rhinitis, the frequency of sleep disorders was reported to be higher than the control group, even when they continued the treatment regularly. Nighttime breathing disorders, sleepiness during the day, parasomnias are the sleep disorders that have been reported.[11] Various studies have also shown that allergic rhinitis is associated with shorter sleep times, bruxism, night sweats, and nocturnal enuresis.[12-15]

Restless legs syndrome (RLS) is a sleep-related periodic sensorimotor disorder. In RLS, people experience a feeling of discomfort, which creates the need to move their legs, especially at rest and/or before falling asleep.[16] RLS is seen in approximately 2-4% of children and is not a rare disease for childhood.[17,18] Symptoms related to RLS may negatively affect children's daily living activities, cognitive and behavioral characteristics by impairing their sleep quality.[17] Studies have shown that RLS is associated with other sleep disorders, and people with RLS generally experience a delay in falling asleep, difficulty in maintainance of the sleep, and a reduction in total sleep time.[19,20] Although the etiopathogenesis is not clearly known, iron depletion and dopaminergic dysfunction are thought to play a role in the central nervous system.[21] Recent studies show that immune dysregulation and inflammation may also play a role in the pathogenesis of RLS.[22,23] It has been shown that RLS is associated with many chronic diseases such as chronic respiratory diseases, diabetes, Parkinson's, cancer, osteoarthritis, anemia, and multiple sclerosis. Iron deficiency is the most common condition in the etiology.[24-27]

In a study conducted among children aged 8-18 years, the incidence of restless legs syndrome in the patient group diagnosed with allergic rhinitis was found to be more than twice the frequency in the control group.[28] Although there is no statistical significance, the frequency of restless legs syndrome in the patient group diagnosed with allergic rhinitis is higher than the control group, suggesting that these two diseases may be related to each other. In the same study, the severity of restless legs syndrome in children found to be significantly higher in children with allergic rhinitis than in the control group. The fact that the frequency and severity of the diagnosis of restless legs syndrome is higher in children with a diagnosis of allergic rhinitis suggests that the relationship between these two diseases should be evaluated.

In this study, we aimed to evaluate the frequency of restless legs syndrome in children diagnosed with allergic rhinitis. We also aimed to evaluate the frequency of restless legs syndrome in the healthy control group in order to compare the frequency of co-occurrence of restless legs syndrome in patients with allergic rhinitis compared to the general pediatric group.

MATERIAL AND METHOD

The study was carried out with the permission of Health Sciences University Ümraniye Training and Research Hospital Ethics Committee (Date: 29/09/2022, Decision No: 315). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent was obtained from the participants.

Study Type and Sampling

The study is case-control type. The population of the study consists of children aged 10-18 years with a diagnosis of AR who applied to the pediatric allergy and immunology clinic for the case group. The population of the control group, on the other hand, consisted of children aged 10-18 years, who had no AR and any other chronic disease, applied to the pediatrics outpatients clinic of our hospital. In the sample size calculation, the incidence of restless legs syndrome in AR patients was accepted as 9.1%, the margin of error was 5%, and the confidence level was 95%, and it was calculated as 128. For the control group, the incidence of restless legs syndrome was accepted as 4.2%, the margin of error was 5%, and the confidence level was 95%, and it was calculated as 62.[28] The study was conducted with children aged 10-18 years. Children younger than ten years of age were not included in the study. Since most of the children who applied to our clinic with the diagnosis of AR are over the age of 10 years, the study was planned to be conducted with children in this age group. Except this, patients with anemia, active cancer, peripheral vascular disease, polyneuropathy/myelopathy, and patients using neuroleptic/antiepileptic drugs were also excluded from the study.

Evaluations

In the study; age, gender, weight, height, Body Mass Index (BMI) z scores, allergic rhinitis symptom score and allergic rhinitis severity of the case group were evaluated. In addition, as laboratory data; specific IgE, total IgE and eosinophil values were evaluated. Gender, age, weight, height, BMI z-score values were also examined in the control group. Ferritin, vitamin B12, folic acid, thyroid stimulating

hormone (TSH), free T4 and vitamin D values of patients diagnosed with RLS in the case and control groups were also examined within the scope of the study. The diagnosis of restless legs syndrome for both groups was established by using the International Restless Legs Syndrome Study Group (IRLSSG) questionnaire containing the latest diagnostic criteria and severity scoring revised for the pediatric age group.[29] Evaluation of the questionnaire and neurological examination were performed by a pediatric neurologist.

Rhino Conjunctivits Scoring System (RCSS) was used for the investigation of the severity of AR symptoms. RCSS questions 6 symptoms including nasal itching, nasal congestion, rhinorrhea, sneezing, redness of the eye and watery eyes. Each symptom is scored by patients as 0 (none), 1 (mild), 2 (moderate), 3 (severe). The total RCSS is calculated by dividing the sum of the scores for each 6 symptoms into 6.

Patients with AR symptoms of less than 4 days in a week or less than 4 weeks are classified as intermittent AR; those with symptoms lasting more than 4 days per week and longer than 4 weeks were classified as persistent AR. AR patients presenting with at least one of the symptoms of sleep disturbance, impairment in daily activities, recreational and/or sports activities, deterioration in school or work performance, and disturbing symptoms were classified as moderate-severe AR. Mild AR patients are those in whom none of these findings are observed.[30]

Statistics

SPSS (Statistical Package for Social Sciences) for Windows 25.0 program was used for the analysis of the data. Median, minimum, maximum values, numbers (n) and percentages (%) were used for the descriptive data. Conformity of continuous variables to normal distribution was evaluated with visual (histogram and probability charts) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Mann Whitney U test was used for the non-normally distributed variables. Chi-square test was used for the categorical data. Logistic regression test was used as a multivariate analysis for the investigation of the factors associated with the presence of RLS in AR patients. $p < 0.05$ was accepted as the statistical significance level.

RESULTS

Within the study, 115 children with allergic rhinitis were analyzed as the case group, and 115 children without allergic rhinitis or any other chronic disease were analyzed in the control group. Case and control groups were similar in terms of age and gender. While the percentage of girls in the control group was 51.3%, this rate was 42.6% in the case group. The median age was 13.0 years (10.0-18.0) in the case group, while it was 12.0 years (10.0-17.0) in the control group. Case and control groups were also statistically similar in terms of weight, height and BMI z-scores (**Table 1**).

Table 1. Gender, age and anthropometric measurements of the case and control groups

		Case (n=115)	Control (n=115)	P value
Gender, n (%)	Female	49 (42.6)	59 (51.3)	0.186
	Male	66 (57.4)	56 (48.7)	
Age (years), median (min-max)		13.0 (10.0-18.0)	12.0 (10.0-17.0)	0.422
Weight z scores, median (min-max)		0.66 (-2.27-3.00)	0.56 (-2.71-2.93)	0.871
Height z scores, median (min-max)		0.12 (-2.56-4.48)	0.26 (-3.05-3.08)	0.531
BMI* z scores, median (min-max)		0.67 (-2.53-2.51)	0.47 (-2.36-2.65)	0.773

*BMI:Body Mass Index

When the laboratory and clinical features of allergic rhinitis patients are evaluated; absolute eosinophil, eosinophil (%), and total IgE median values were 260.0 103/uL (31.0-2930.0), 3.4% (0.17-24.1), 178.0 IU/mL (3.0-2472.0), respectively. The median RCSS-Nose and RCSS-Eye scores were 2.0 (0-3.0) and 1.0 (0-3.0), respectively. 67.0% (n=77) of the patients had positive blood specific IgE levels, and 40.3% (n=31) of them had specific IgE levels positive for more than one allergen. 67% (n=77) of the patients had persistent AR (**Table 2**).

Table 2. Laboratory and clinical features of the patients with allergic rhinitis

Laboratory parameters	Median (min-max)
Eosinophil (absolute)(103/uL)	260.0 (31.0-2930.0)
Eosinophil (%)	3.4 (0.17-24.1)
Total IgE (IU/mL)	178.0 (3.0-2472.0)
RCSS scores	Median (min-max)
RCSS-Nose	2.0 (0-3.0)
RCSS-Eye	1.0 (0-3.0)
Specific IgE Positivity	n (%)
No	38 (33.0)
Yes	77 (67.0)
Specific IgE* Positivity for house dust mite	76 (66.1)
Specific IgE Positivity for cat	26 (22.6)
Specific IgE Positivity for pollen	16 (13.9)
Specific IgE Positivity for peanut	3 (2.6)
Specific IgE Positivity for more than one allergen	n (%)
Positivity for one allergen	46 (59.7)
Positivity for more than one allergen	31 (40.3)
Clinical severity of AR*	n (%)
Intermittent	38 (33.0)
Mild	29 (25.2)
Moderate-Severe	9 (7.8)
Persistent	77 (67.0)
Mild	33 (28.7)
Moderate-Severe	44 (38.3)

IgE: Immunoglobulin E, AR:Allergic rhinitis

When the RLS frequency of the case and control group was compared; RLS was seen in 15.7% (n=18) of the case group and 5.2% (n=6) of the control group. The frequency of RLS in AR patients was significantly higher than the control group ($p<0.05$). The clinical severity of RLS patients was mostly moderate in both the case and control groups (44.4% [n=8] and 50% [n=3], respectively). RLS patients in the case and control groups were statistically similar in terms of clinical severity (p=1.000) (**Table 3**).

Table 3. Frequency of restless legs syndrome in case and control groups

Restless legs syndrome	Participants		P value
	Case group	Control group	
Yes	18 (15.7)	6 (5.2)	0.010
No	97 (84.3)	109 (94.8)	
Severity of RLS*			
Mild	6 (33.3)	2 (33.3)	1.000
Moderate	8 (44.4)	3 (50.0)	
Severe	4 (22.2)	1 (16.7)	
Very severe	0 (0)	0 (0)	

*RLS:Restless legs sydrome

When the presence of RLS was evaluated according to the clinical and demographic characteristics of AR patients; the presence of RLS was found to be higher in patients with persistent AR than in patients with intermittent AR (19.5% and 7.9%, respectively). But statistical significance was not observed (p=0.108). There was no statistical significance between gender, age, multiple allergen sensitivity, weight, height and BMI z scores and the presence of RLS (**Table 4**).

Table 4. Frequency of restless legs syndrome according to the clinical and demographic features of patients with allergic rhinitis

	Restless legs syndrome		P value
	No	Yes	
Gender, n (%)			
Female	41 (83.7)	8 (16.3)	0.864
Male	56 (84.8)	10 (15.2)	
Clinical presentation of AR*, n (%)			
Intermittant	35 (92.1)	3 (7.9)	0.108
Persistent	62 (80.5)	15 (19.5)	
Sensivity to multiple allergens, n (%)			
No	33 (86.8)	5 (13.2)	0.605
Yes	64 (83.1)	13 (16.9)	
Age, median (min.-max)	13.0 (10.0-18.0)	12.0 (10.0-17.0)	0.795
Weight z scores, median (min-max)	0.67 (-2.35-2.93)	0.04 (-2.71-3.0)	0.125
Height z scores, median (min-max)	0.20 (-3.05-3.08)	-0.09 (-2.65-4.48)	0.429
BMI* z score, median (min.-max)	0.75 (-2.31-2.51)	0.17 (-2.53-2.10)	0.108

*AR:Allergic rhinitis, BMI: Body Mass Index

The median values of ferritin, vitamin B12, folic acid, thyroid stimulating hormone (TSH), free T4 and vitamin D measurements of patients diagnosed with RLS in the case and control groups were compared. There was no significant difference between the laboratory parameters of RLS patients in both groups, except for folic acid (**Table 5**).

Table 5. Laboratory parameters of the patients diagnosed with RLS

	RLS* Patients		
	In AR Group	In Control Group	P value
	Median (min-max)	Median (min-max)	
Ferritin (ng/mL)	42.0 (6.0-80.0)	10.0 (9.0-36.0)	0.189
Vitamin B12 (ng/L)	342.0 (111.0-879.0)	233.0 (220.0-264.0)	0.180
Folic acid (µg/L)	6.8 (4.2-13.7)	3.7 (3.1-4.1)	0.009
TSH (mIU/L)	2.5 (0.8-5.2)	2.3 (1.5-4.7)	1.000
Free T4 (mg/dL)	1.2 (1.0-1.5)	1.1 (1.1-1.2)	0.233
25-OH vitamin D 7(ng/mL)	13.0 (4.7-32.0)	8.6 (7.8-14.0)	0.517

*RLS:Restless legs symdrome, TSH: Thyroid stimulating hormone

Variables that may be associated with RLS syndrome in AR patients were evaluated with logistic regression analysis. In the regression model, the presence of RLS was accepted as the dependent variable, while age, gender, BMI z score, persistent AR, and multiple allergen sensitivity were considered the independent variables. According to the logistic regression model, there was no statistical significance between the presence of RLS in AR patients and the variables of gender, age, BMI z score, persistent AR, multiple allergen sensitivity (**Table 6**).

Table 6. Logistic regression analysis for the restless legs syndrome diagnosis in AR patients

	P value	OR†	95% C.I. OR †	
			Lower	Upper
Gender*	0.787	1.178	0.360	3.848
Age	0.486	0.918	0.721	1.168
BMI z score	0.058	0.627	0.387	1.016
Persistant AR†	0.085	4.049	0.826	19.852
Sensivity to multiple allergens	0.575	1.410	0.424	4.688

*Female was the reference value for the gender, †AR:Allergic rhinitis, OR:Odds ratio, C.I.:Confidence Interval

DISCUSSION

Allergic rhinitis is a disease that is common in childhood and can negatively affect quality of life and sleep quality. Since chronic diseases may occur with similar pathophysiological mechanisms, some diseases can be seen together in childhood. In this context, we aimed to evaluate the frequency of restless legs syndrome in patients diagnosed with allergic rhinitis and to examine whether there was an increase in the frequency compared to the control group.

In a case-control type study conducted in children aged 8-18 years in our country, the frequency of restless legs syndrome in children with AR and in the control group was examined. While the frequency of RLS in children with AR was reported as 9.1%; the frequency of RLS in the control group was reported as 4.2%.[28] Similarly, in our study, the presence of RLS in AR patients was higher than in the control group (15.7% vs 5.2%). According to the results of our study and the study in the literature; it can be thought that AR and RLS diseases can have co-existence. However, since the number of studies in this area is very limited, further studies are needed to explain the underlying pathophysiological mechanisms in the interrelated relationship between the two diseases.

In our study, factors related to the presence of RLS in AR patients were evaluated; the presence of RLS was found to be higher in patients with persistent AR than in patients with intermittent AR (19.5% and 7.9%, respectively). In the study in the literature, the frequency of RLS in patients with persistent AR is approximately 2 times that of patients with intermittent AR.[28] Although there was no statistical significance in the study in the literature and in ours, the higher frequency of RLS in persistent AR suggests that the disease clinic and RLS may be associated. In addition, while 16.9% of AR patients with multiple allergen sensitivity were diagnosed with RLS in our study; 13.2% of those without multiple allergen sensitivities have RLS. In a study in the literature, the frequency of RLS was also found to be higher in patients with AR who had a higher number of allergens to which they were sensitive.[28] This suggests that allergic mechanisms may play a role in the underlying pathophysiology of RLS. In a study in the literature; a relationship between mast cell activation syndrome, which is an allergic and inflammatory disorder, and RLS has been found.[31] In another study, a higher rate of RLS was observed in patients with atopic dermatitis, which is one of the allergic diseases, compared to the control group. In addition, the rate of RLS was found to be higher in patients with active atopic dermatitis in the same study.[32] According to the results of a different study in our country, the diagnosis of RLS is more common in people with asthma than in healthy individuals, and the frequency of RLS increases as asthma control decreases.[33] In the literature, there is also a study showing that the frequency of RLS is higher in urticaria patients than in the control group.[34] Since studies evaluating the relationship between allergic diseases and RLS are mostly conducted in adult patients, further studies are needed to evaluate the relationship between different allergic diseases and RLS, especially in the pediatric patient group.

In studies, an increased risk for the development of restless legs syndrome has been reported in many inflammatory diseases. However, the role of inflammatory factors in the pathogenesis of RLS is not fully understood, since there are very few studies evaluating serum/plasma levels of inflammatory factors.[35] According to the results of a meta-analysis in the literature, serum/plasma C reactive protein (CRP) and NLR were reported to be higher in patients with RLS than in the control group.[35] In a study conducted in pediatric allergic rhinitis patients, the NLR value of patients with a diagnosis of allergic rhinitis was found to be significantly higher than the control group.[36] The fact that NLR, which is an important measure for systemic inflammation, was increased in both diseases suggests that there may be common inflammatory mechanisms in the development of the two diseases. Further studies are needed to explain the mechanism of the relationship between RLS and allergic rhinitis.

Strengths and Limitations

While investigating the frequency of RLS in allergic rhinitis patients in our study, the evaluation of the effects of disease severity and laboratory parameters on the frequency of RLS contributed to the literature in this area from a broad perspective. This is the strength of our study. As we know, there is only one study in the literature investigating the frequency of restless legs syndrome in children with allergic rhinitis, and this study was also conducted in our country. The limited number of studies in this area makes the results of the studies carried out on the subject valuable. This is another strength of our work. Besides the strengths of our study, there are also some limitations. The fact that our study was conducted in a clinic of a single hospital creates a limitation in terms of the generalizability of the research results. In our study, an increase in the frequency of restless legs syndrome was observed in children with a diagnosis of allergic rhinitis. Since the study was not conducted prospectively, the co-existence of two diseases in a single time frame was evaluated. For this reason, it is difficult to interpret the temporal relationship between the two diseases in the study. This is another limitation of the study. Further prospective studies can be planned for a better understanding of the subject.

CONCLUSIONS

According to the results of our study, restless legs syndrome was observed more frequently in patients with allergic rhinitis compared to the control group. Both diseases can be seen frequently in childhood and negatively affect quality of life and sleep. For this reason, the coexistence of some chronic diseases in childhood will increase the burden of disease in children. Thus, holistic approaches should be adopted in the diagnosis, treatment and management of childhood diseases. Additional diseases that may be associated with the child should be investigated with detailed system inquiries. As the results of our study emphasize that patients diagnosed with allergic rhinitis should also be evaluated in terms of restless legs syndrome when necessary. Further studies are needed to explain the underlying pathophysiological mechanisms between the two diseases.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Ümraniye Training and Research Hospital Ethics Committee (Date: 29/09/2022, Decision No: 315).

Informed Consent: Informed consent was obtained for the study.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1341018
J Contemp Med 2023;13(5):752-757

Original Article / Orijinal Araştırma

Kidney Health of Refugee Children: An Ongoing Challenge

Mülteci Çocukların Renal Sağlığı: Süregelen bir Zorluk

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Abstract

Aim: Its geographical proximity to Syria makes Turkey an important destination and transit country for refugees from various countries. The aim of this study is to determine the kidney and urological disease profile and to reveal the ongoing problems of refugee children who applied to a single center in Adana, home to a dense refugee population. To the best of our knowledge, this study is the largest single center experience with the refugee pediatric patient population in this field.

Material and Method: Medical records of 614 refugee children who were admitted to the pediatric nephrology and urology clinics between February 2020 and May 2022 were evaluated retrospectively. A total of 530 patients were included in the study.

Results: Median age of the 530 patients (301 male/229 female) was 72 months. The median follow-up time was 7 months (IQR 14 months). Congenital anomalies of the kidney and urinary tract with 181 patients (34.2%) is the most common diagnosis. The frequency of chronic kidney disease (CKD) of the patients was determined as 25% with 132 patients. 64 (12%) of the patients required surgical intervention. It was observed that 322 (61%) of the patients did not come to their regular follow-ups and delayed their follow-up.

Conclusion: Irregular follow-up and the delay of the treatment can lead to vitally severe consequences in patients with CKD in the long term. We believe that regular patient follow-ups will have a positive impact on the long-term follow-up results of the patients and the health costs of the country hosting the refugee patient profile.

Keywords: Refugee, children, acute kidney disease, chronic kidney disease

Öz

Amaç: Suriye'ye olan coğrafi yakınlığı, Türkiye'yi çeşitli ülkelerden gelen mülteciler için önemli bir varış noktası ve geçiş ülkesi yapmaktadır. Bu çalışmanın amacı, yoğun bir mülteci nüfusuna ev sahipliği yapan Adana'da tek merkeze başvuran mülteci çocukların böbrek ve ürolojik hastalık profilini belirlemek ve devam eden sorunlarını ortaya koymaktır. Bildiğimiz kadarıyla bu çalışma, bu alanda mülteci pediatrik hasta popülasyonu ile ilgili en büyük tek merkezli deneyimdir.

Gereç ve Yöntem: Şubat 2020 ve Mayıs 2022 tarihleri arasında pediatrik nefroloji ve üroloji bölümlerine başvuran 614 mülteci çocuğun tıbbi kayıtları retrospektif olarak değerlendirildi. Çalışmaya toplam 530 hasta dahil edildi.

Bulgular: Beş yüz otuz hastanın (301 erkek/229 kız) ortanca yaşı 72 ay idi. Ortalama takip süresi 7 ay idi (IQR 14 ay). En sık görülen tanı yüz seksen bir hasta (%34,2) ile böbrek ve idrar yollarının konjenital anomalileri idi. Kronik böbrek hastalığı (KBH) sıklığı 132 hasta ile %25 olarak belirlendi. Hastaların 64'üne (%12) cerrahi girişim gerekti. Hastaların 322'sinin (%61) düzenli kontrollerine gelmediği ve takiplerini ertelediği görüldü.

Sonuç: Düzensiz takip ve tedavinin geciktirilmesi uzun vadede KBH hastalarında üzücü sonuçlara yol açabilmektedir. Düzenli hasta takibinin, hastaların uzun dönem takip sonuçlarına ve mülteci hasta profilini barındıran ülkenin sağlık maliyetlerine olumlu etki edeceğine inanıyoruz.

Anahtar Kelimeler: Mülteci, çocuklar, akut böbrek hastalığı, kronik böbrek hastalığı

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Received *(Geliş Tarihi)*: 10.08.2023 **Accepted *(Kabul Tarihi)*:** 11.09.2023

INTRODUCTION

Turkey is a principal destination and transit country for refugees from diverse countries.[1] Because of the geographical proximity to Syria Turkey currently hosts more than 60% of the Syrian refugee population and provides free access to shelter, education, and health care since the Syrian civil war (2011).[2,3] By January 2019, Istanbul, Sanliurfa, Hatay, Gaziantep and Adana were the five provinces with the highest Syrian populations among the 81 provinces of Turkey. Over half of the refugees are under the age of 18.[4] In terms of health and wellbeing, several health risks and other vulnerabilities have been observed to affect Syrian refugee children in the Turkish context since 2011.[1,2] Since 2011, healthcare professionals in Turkey have faced a pediatric population with kidney disease with no previous medical records. The hospital where this study was conducted is the largest tertiary hospital in the region where refugee patient referrals are made. Unfortunately, limited data from Syria regarding kidney disease profile of the children makes management of this population challenging. The aim of this study is to determine the kidney and urological disease profile and reveal the ongoing problems in the refugee children who applied to a single center in Adana.

To the best of our knowledge, this study is the largest single center experience with a refugee pediatric patient population in this field.

MATERIAL AND METHOD

The study was carried out with the permission of Adana City Training and Research Hospital Ethics Committee (Date: 21/04/2022, Decision No: 1911). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

The study was carried out in the Pediatric Nephrology and Urology Departments of City Training and Research Hospital, a tertiary medical center bearing the health burden of the vast majority of Syrian refugee patients. Electronic medical records of Syrian refugee children (aged 0-18) were retrospectively analyzed. 614 refugee children were admitted to the pediatric nephrology and urology departments from February 2020 to May 2022. Eighty-four patients with missing medical records were excluded from the study. A total of 530 patients were included in the study.

Data Collection

The demographic data, clinical and laboratory findings, diagnosis, surgery, hospitalization, intensive care needs, and outcomes of the patients were evaluated retrospectively. Diagnosis and follow-up of glomerular diseases were made in accordance with the KDIGO Glomerulonephritis guideline.[5] Chronic kidney disease was defined as the 'The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines.[6]

Analyses

This study was performed in retrospective cohort design with Syrian refugee children. Statistical analyses were performed with SPSS version 21 software package. Continuous data were defined by means of mean±SD under parametric conditions and median (interquartile range-IQR) under nonparametric conditions. Normal distribution of numeric variables was tested with Kolmogorov-Smirnov test. Categorical variables were defined by number and percentage. Chi square analysis was used for categorical variables. P values less than 0.05 were considered to be statistically significant.

RESULTS

Of the 530 patients included in the study, 301 (57%) were male and 229 (43%) were female. Median age of the patients was 72 months (IQR 17-125 months). 445 of the patients were admitted to the pediatric nephrology department, and 85 to the pediatric urology department. The median follow-up time was 7 months (IQR 14 months). Eight of the patients (2%) were diagnosed in their home country, while 522 (98%) diagnosed in Turkey. The median number of applications to nephrology or urology departments was 2 times (IQR 3 times). It was observed that 322 (61%) of the patients did not come to their regular follow-ups and delayed their follow-ups. The frequency of CKD of the patients was determined as 25% with 132 patients. Sixty-four (12%) of the patients required surgical intervention.

Congenital anomalies of the kidney and urinary tract (CAKUT) with 181 patients (34.2%) are the most common diagnoses. It was followed by incontinence/enuresis with 76 patients (14.3%), and nonspecific hydronephrosis in 62 patients (11.7%), respectively. The diagnosis of the Syrian refugee children was shown in **Table 1**. The most common diagnosis in the etiology of CAKUT was vesicoureteral reflux (VUR) with 50 patients (27.6%), followed by neurogenic bladder (NB) in 43 patients (23.8%) and ureteropelvic junction obstruction (UPJO) in 25 patients (13.8%). The etiological classification of the patients with CAKUT is shown in **Table 2**.

Table 1: The diagnosis of the 530 Syrian refugee children admitted to Pediatric Nephrology and Urology Departments

Diagnosis	Number of the patients, n (%)
CAKUT	181 (34.2)
Daytime incontinence/ Nocturnal enuresis	76 (14.3)
Nonspecific hydronephrosis	62 (11.7)
Urinary system stone disease	61 (11.5)
Urinary tract infection	46 (8.7)
Glomerular disorders	34 (6.4)
Hematuria/ Proteinuria	23 (4.3)
Hypertension	12 (2.3)
Acute kidney injury	12 (2.3)
Tubular disorders	12 (2.3)
Cystic kidney diseases	7 (1.3)
Others (tumor/nutcracker)	4 (0.8)

CAKUT: Congenital anomalies of the kidney and urinary tract

Table 2: The etiological classification of the 181 patients with Congenital Anomalies of the Kidney and Urinary Tract

CAKUT	Number of the patients, n (%)
Vesicoureteral reflux	50 (27.6)
Neurogenic bladder	43 (23.8)
Ureteropelvic junction obstruction	25 (13.8)
Hypodysplasia/ atrophy	13 (7.2)
Agenesis	12 (6.6)
Ectopic kidney	10 (5.5)
Multicystic dysplastic kidney	8 (4.4)
Posterior Urethral Valve	6 (3.3)
Ureterovesical junction obstruction	5 (2.8)
Others	9 (5.0)
- Duplex collecting system	3 (1.7)
- Ureterocele	2 (1.1)
- Megaureter	2 (1.1)
- Bladder diverticulum	1 (0.6)
- Horseshoe kidney	1 (0.6)

CAKUT: Congenital Anomalies of the Kidney and Urinary Tract

The most common cause in patients, followed up with a diagnosis of glomerular diseases, was nephrotic syndrome (NS) in 28 (82.4%) of the 34 patients. Other causes of glomerular disease were Henoch Schoenlein nephritis with three patients, post streptococcal glomerulonephritis with one patient, hemolytic uremic syndrome with one patient, and Wegener's granulomatosis with one patient, respectively. One of the patients with NS was diagnosed with congenital nephrotic syndrome in his country and was given intermittent albumin infusions. This patient applied only once and did not show up to their follow up. One of the patients was started on prednisolone treatment with a preliminary diagnosis of idiopathic NS. However, the patient did not come to the 1st month follow-up to evaluate the steroid response. Of the 26 patients diagnosed with NS with regular clinical follow-up, 35.7% (10 patients) had steroid-sensitive NS, 35.7% (10 patients) had steroid-resistant NS, 17.9% (5 patients) had steroid-dependent NS, and 3.9% (1 patient) was evaluated as frequent relapse NS. Pathological diagnosis of 9 of 10 patients with steroid-resistant NS who underwent kidney biopsy was reported as focal segmental glomerulosclerosis (FSGS), and 1 as membranoproliferative glomerulonephritis (MPGN).

Two (16.7%) of 12 patients diagnosed with acute kidney injury (AKI) had prerenal acute kidney injury. One of these patients developed AKI secondary to dehydration, while the other developed hepatorenal syndrome secondary to neonatal cholestasis. Of the nine (75%) patients with renal AKI, 6 had tubulointerstitial nephritis (TIN) and 3 had acute tubular necrosis (ATN). One of the patients with TIN, had Tubulointerstitial nephritis and uveitis syndrome (TINU). In one (8.3%) patient, post-renal AKI developed secondary to abdominal mass compression. In two of the AKI cases, one with hepatorenal syndrome and the other with cerebral palsy with severe malnutrition diagnosed with ATN, chronic kidney disease was developed.

The frequency of CKD of the 530 patients was determined as 25.6% with 136 patients. The majority of CKD patients were stage 1 patients with a frequency of 61.8%. The distribution of CKD stages of the refugee patients was shown in **Figure 1**. The leading cause of CKD was CAKUT (73.5%), followed by glomerular diseases (11.8%), tubular diseases (6.6%), urinary system stone disease (3.7%), AKI (1.5%), cystic kidney diseases (1.5%), proteinuria secondary to glycogen storage disease (1.5%) and bilateral Wilms tumor (1.5%). Detailed information of patients with CKD stage 3-5 is shown in **Table 3**.

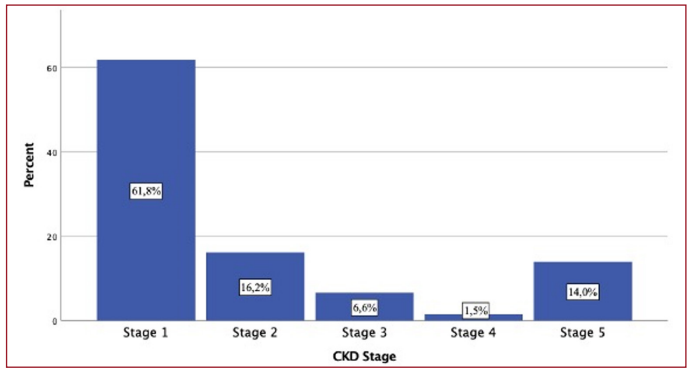

Figure 1: Distribution of chronic kidney disease stages of the refugee patients

Table 3: Detailed information of patients with Chronic Kidney Disease Stage 3-5

	Sex	Age (month)	CKD Stage	RRT	Etiology	Follow-up	Survival
1	F	88	Stage 5	HD	Urinary system stone disease	No	Alive
2	F	187	Stage 5	HD	NB	No	Alive
3	M	184	Stage 5	-	SB+ NB	Yes	Alive
4	F	186	Stage 5	HD	Anorectal malformation+ NB	No	Alive
5	F	211	Stage 5	HD	Wolfram syndrome+ NB	Yes	Alive
6	M	95	Stage 5	HD	PUV+NB	No	Dead
7	M	195	Stage 5	HD	SB+ NB	Yes	Alive
8	M	175	Stage 5	HD	VUR	No	Alive
9	M	32	Stage 5	HD	VUR	Yes	Alive
10	M	56	Stage 5	HD	PUV	Yes	Alive
11	M	125	Stage 5	HD	PUV	No	Alive
12	F	124	Stage 5	HD	Hypodysplasia/ atrophy	Yes	Alive
13	F	62	Stage 5	PD	NS	Yes	Alive
14	M	27	Stage 5	HD	HD	No	Alive
15	M	192	Stage 5	HD	HSP Nephritis	Yes	Alive
16	F	159	Stage 5	HD	Prolonged ATN sequelae	No	Alive
17	F	108	Stage 5	HD	Primary hyperoxaluria	No	Dead
18	F	72	Stage 5	HD	Cystinosis	No	Dead
19	F	9	Stage 5	PD	Polycystic kidney disease	Yes	Alive
20	F	200	Stage 4	-	Hypodysplasia/ atrophy	Yes	Alive
21	F	49	Stage 4	-	NS	Yes	Alive
22	F	5	Stage 3	-	HRS sequelae	Yes	Dead
23	F	38	Stage 3	-	VUR	Yes	Alive
24	M	3	Stage 3	-	VUR	Yes	Alive
25	M	31	Stage 3	-	VUR	Yes	Alive
26	M	6	Stage 3	-	VUR	Yes	Alive
27	M	18	Stage 3	-	PUV	No	Alive
28	M	3	Stage 3	-	Hypodysplasia/ atrophy	Yes	Alive
29	F	95	Stage 3	-	UVJO	Yes	Alive
30	F	99	Stage 3	-	Bilateral Wilms	No	Alive

F: Female, M: Male, CKD: Chronic Kidney Disease, RRT: Renal replacement therapy, HD: Hemodialysis, PD: Peritoneal dialysis, NB: Neurogenic bladder, SB: Spina bifida, PUV: Posterior urethral valve, VUR: Vesicoureteral reflux, NS: Nephrotic syndrome, HSP: Henoch Schoenlein Purpura, HRS: Hepatorenal Syndrome, UVJO: Ureterovesical junction obstruction

Hospitalization to the inpatient service was required in 18.3% (97 patients) of the 530 refugee children. Of these patients, 16.4% (16 patients) needed follow-up in the pediatric intensive care unit (PICU). Surgical reasons such as urogenital surgery or catheter placement were the most common reason for hospitalization with 93 (47.4%) of 196 hospitalizations. CKD complications such as hypervolemia, hypertensive encephalopathy, acidosis/electrolyte imbalances, and hypertensive cardiomyopathy were the most common causes of PICU hospitalization with a frequency of 66.7%.

CKD was present in 13 (81.3%) of the 16 patients admitted to the PICU. Ten (76.9%) of these patients had stage 5 CKD. In the presence of CKD, hospital and PICU hospitalization rates were 49.3% and 9.6%, those without CKD, these rates were determined as 7.1% and 0.8%, respectively. This difference was found to be statistically significant ($p<0.001$).

Five patients (0.94 %) died during the follow-up period. Demographic data, primary diagnosis and causes of mortality of these patients are shown in **Table 4**.

Table 4: Demographic data, primary diagnosis and causes of mortality of the deceased patients.

	Sex	Age (months)	Diagnosis	CKD	Cause of mortality
1	M	95	PUV+ NB	Stage 5	pulmonary edema
2	F	108	Primary hyperoxaluria	Stage 5	Sepsis
3	F	72	Cystinosis	Stage 5	Sepsis
4	F	4	Bartter Syndrome	Stage 1	Sepsis
5	F	6	Spina bifida+ NB	-	VP shunt dysfunction

M: Male, F: Female, PUV: Posterior urethral valve, NB: Neurogenic bladder, VP shunt: ventriculoperitoneal shunt

DISCUSSION

In presented study, CKD frequency among refugee children population detected to be 25.6%. Spectrum of kidney problems in the lifetime of the refugee population can vary and may remain permanent in case of inappropriate management. There are few studies evaluating specific diseases in refugee population in Turkey.[5-8] Considering that the refugee issue has become a reality not only for cities neighboring Syria, but also for the whole country determining the profile of kidney diseases in the aforementioned population will also make positive contributions to their management.

Kara et al. reported CAKUT to be the most frequent diagnosis among refugee children with a percent of 26.2% in their study conducted in Gaziantep. Neurogenic bladder and VUR were reported to be the most common cause of CAKUT.[7] Multicenter retrospective study from Gaziantep reported the frequency of CAKUT in Syrian children to be 31% with non-obstructive hydronephrosis being the main reason.[8] As in the literature, in our study, CAKUT with 34.2% was the most common diagnosis among the refugee children, and the most frequent etiology of CAKUT was detected to be VUR. We think that percentages obtained from studies conducted from border cities are not sufficient for detection of the real incidence of CAKUT because the data in the current studies have been obtained from refugee children population born in Turkey who can access health services. It is a big challenge to determine the real incidence of any disease in this kind of populations, considering that the populations are unable to access healthcare services, give birth at home, prefer to receive health care services from illegal refugee health workers, or refuse to receive any healthcare because of religious/social/trust issues. For instance, in presented study, of 614 patients admitted to Pediatric Nephrology and Urology departments 84 excluded because of the irregular follow-up.

Balat et al.[8] reported glomerular diseases as the second most common cause in the refugee population with a frequency of 19.9%, and NS was stated as the most common cause of glomerular diseases. Al Saegh et al.[9] published their single center experiences in Iran. In their study, it was reported that NS was the most common clinical presentation and FSGS was the most common glomerulonephritis with a frequency of 30% in 58 kidney biopsies. In our study, the incidence of glomerular disease was 6.4%, and nephrotic syndrome was the most common pathology among glomerular diseases with a percent of 82.4%. FSGS is the leading pathological diagnosis of a small number of biopsies performed. We think that the low rate of glomerular disease, compared to the literature, may be related to the presence of a University Hospital in the city, providing healthcare to the refugee population.

Various etiologies may take role in the development of AKI in children. There is an increased risk of CKD even after several years in patients experienced AKI. Direct or indirect renal injury during armed conflicts in healthy children may cause AKI and , with the most frequent cause reported to be being crush syndrome. Inappropriate management of AKI may increase risk of CKD.[6] There were 12 cases diagnosed with AKI. Two of the AKI cases developed CKD in our study. There was only one patient with postrenal AKI who applied with huge intraabdominal mass compression. Common feature of three overmentioned cases with catastrophic results is late admission. Besides proper management of AKI, basic information about basic care, well-being, and access to free health care, defined as a fundamental right for the refugee patient population, can prevent catastrophic consequences.

North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) reported that CAKUT, with 48%, is the leading underlying etiology of CKD.[10] This distribution has been reported with similar frequencies in European countries (47-62% in Turkey and other countries in the Middle East).[11] One study of 55 pediatric CKD patients from Syria reported NB to be the most frequent reason.[12] Multicenter study including data of 633 pediatric refugee children from pediatric nephrology centers in Turkey reported CKD incidence to be 14.8% and CAKUT to be more frequent.[8] Celakıl et al.[13] evaluated 79 refugee pediatric patients with end stage renal disease (ESRD) and diagnosis of various stages of CKD and the

most common cause was reported to be CAKUT (37.9%). In our presented study the frequency of CKD was determined slightly higher (25.6%), with the leading cause being CAKUT (73.5%). There is limited data about exact frequency of CKD or urinary tract anomalies in refugee children population. Due to the prevalence of consanguineous marriages, the frequency of CKD caused by CAKUT may also be expected to be more frequent in this geographical region.

A study from Turkey reported acute community-acquired infections to be the major cause of hospitalization, while the rate of chronic diseases was approximately 16.3%.[14] Studies from other countries were also revealed the cause of hospital admission infectious diseases.[15,16] Yucel et al.[17] presented the largest number of hospitalized pediatric refugee patients' data. Frequency of PICU admission of reported to be 21.9% which was significantly higher than the non-refugee patient population. Gungor et al.[18] reported PICU hospitalizations frequency in their study conducted of 623 refugee inpatients, to be 6.7%. In our study, 81% of the patients admitted to the PICU had CKD, and the most common reason for PICU hospitalization was CKD complications. In those without CKD, hospital and PICU admission rates were determined as 7.1% and 0.8%, respectively. These results confront us with the fact that CKD increases the risk of hospitalization and PICU admission, and that the management of complications is more difficult in this patient population.

Sekkarie et al.[19] in their study evaluated cultural challenges and tried to suggest approaches to remedy these challenges of ESRD patients. It has been detected that language challenges leading to medical errors, cultural and religious challenges that hinder certain medical practices, trust challenges, dietary and medication challenges, and perception challenges affect the treatment of ESRD patients. A survey conducted by Lemke et al.[20] in 2018 showed that the group of refugee children arriving to Germany between 2015–2017 accounts for approximately 20% of the total pediatric dialysis population in Germany. As a conclusion they argue that provision of medical care for these children and their families is often hampered by psychosocial problems, cultural differences, language barriers, and administrative issues. Despite regular financial and logistic resources of the 530 patients 322 (61%) did not come to their regular follow-ups or delayed their follow-up. Etiological causes of mortality in our study were: PUV, NB , Bartter syndrome, cystinosis and primary hyperoxaluria, respectively. Unfortunately, common feature of these patients was incompliance to treatments and follow-ups.

CONCLUSION

Children with acute/chronic kidney disease are most vulnerable and most likely to be affected during armed conflict, migration or disaster. Beside experienced specialists well-equipped infrastructure is required for the management of such patient population. Caregivers or families of ESRD and CKD should be informed in detail about what they should do and where they should apply in overmentioned situations. Considering the socio-economic status of the population, it should be explained that kidney diseases are treatable and preventable, and if the treatment is delayed, it can lead to sad consequences in the long term. We believe that this approach beside prevention from catastrophic health problems will have a positive impact on the health costs of the country that hosts refugee patient profile.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Adana City Training and Research Hospital Ethics Committee (Date: 21/04/2022, Decision No: 1911).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1283820
J Contemp Med 2023;13(5):758-762

Original Article / Orijinal Araştırma

Analysis of Chest Disease Consultations Requested by an Emergency Unit in Summer and Winter Months

Yaz ve Kış Aylarında Acil Birimi Tarafından Talep Edilen Göğüs Hastalığı Konsültasyonlarının Analizi

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Abstract

Aim: This study aims to show seasonal differences by analysing the chest disease consultations requested by an emergency unit in summer (June, July, and August) and winter (December, January, and February) months.

Material and Method: Patients over the age of 18 years who were directed by an emergency unit to the Department of Chest Diseases between 1 December 2021 and 31 August 2022 and whose thoracic computerized tomography results were available were included in the study. Variables such as the patients' demographic characteristics, complaints, resultsof the examinations done in the emergency unit, hospitalization rates, place of hospitalization (clinical service or intensive care), and pre-diagnosis before hospitalization were evaluated. The statistical significance level was accepted as $p<0.05$ in all calculations and statistical analysis of the data was conducted using IBM SPSS Statistics 26 (IBM Corp., Armonk, NY, USA).

Results: For the 409 patients included in thisstudy,more consultations were requested in the winter months (n=239, 58.4%). We identified significant differencesbetween the seasonal groups in terms of the complaints and the additional radiological imaging findings of patients consulted in summer and winter months ($p<0.05$). The most common complaint in both seasons was shortness of breath. Pleural effusion was less common among the additional radiological findings of both seasons.

Conclusion: This study has revealed significant differencesbetween seasonal groups in terms of complaints and additional radiological imaging findings of patients with consultationsin summer and winter months. However, there were no significant differencesbetween the seasonal groups in terms of age, sex, pre-diagnosis, place of hospitalization, or main radiological findings.

Keywords: Chest diseases, emergency unit, consultation

Öz

Amaç: Bu çalışma, yaz (Haziran, Temmuz ve Ağustos) ve kış (Aralık, Ocak ve Şubat) aylarında acil servis tarafından talep edilen göğüs hastalıkları konsültasyonlarını inceleyerek mevsimsel farklılıkları göstermeyi amaçlamaktadır.

Gereç ve Yöntem: 1 Aralık 2021-31 Ağustos 2022 tarihleri arasında acil servis tarafından Göğüs Hastalıkları Kliniğine yönlendirilen ve toraks bilgisayarlı tomografi sonuçları mevcut olan 18 yaş üstü hastalar çalışmaya alındı. Hastaların demografik özellikleri, şikayetleri, acil serviste yapılan tetkik sonuçları, yatış oranları, yatış yeri (hastane servisi veya yoğun bakım), yatış öncesi ön tanıları gibi değişkenler değerlendirildi. Tüm hesaplamalarda istatistiksel anlamlılık düzeyi $p < 0,05$ olarak kabul edildi ve verilerin istatistiksel analizi IBM SPSS Statistics 26 (IBM Corp., Armonk, NY, ABD) kullanılarak yapıldı.

Bulgular: Bu çalışmaya dahil edilen 409 hasta için kış aylarında daha fazla konsültasyon istendi (n = 239, %58,4). Yaz ve kış aylarında başvuran hastaların şikayetleri ve ek radyolojik görüntüleme bulguları açısından mevsimsel gruplar arasında anlamlı fark saptadık ($p < 0.05$). Her iki mevsimde de en sık görülen yakınma nefes darlığıydı. Her iki mevsimin ek radyolojik bulguları arasında plevral efüzyon daha az görüldü.

Sonuç: Bu çalışma yaz ve kış aylarında konsülte edilen hastaların şikayetleri ve ek radyolojik görüntüleme bulguları açısından mevsimsel gruplar arasında anlamlı farklılıklar ortaya koydu. Ancak yaş, cinsiyet, ön tanı, yatış yeri veya ana radyolojik bulgular açısından mevsimsel gruplar arasında anlamlı fark yoktu.

Anahtar Kelimeler: Göğüs hastalıkları, acil ünite, konsültasyon

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Received *(Geliş Tarihi)*: 15.04.2023 **Accepted *(Kabul Tarihi)*:** 25.07.2023

INTRODUCTION

Emergency departments are healthcare units that provide uninterrupted service 7 days a week and 24 hours a day. Accordingly, they are the departments where both emergency patients and other patients receive healthcare services outside of the main working hours. Emergency unitsare the hospital units with the highest numbers of patients and patient diversity. Because of the large variations among cases, emergency physicians might have some cases for which they should consult with doctors of internal medicine or surgical branches. Chest diseases are of particularly great significance among the internal medicine branches, and in some studies, it was found that 0.5-1% of patients presenting to an emergency unit had consultations with the Department of Chest Diseases.[1] In another previous study, among all internal medicine consultations requested by an emergency service, the Department of Chest Diseases ranked second, after the Department of Cardiology.[2] The most common complaint of patients presenting to emergency services and consulting with the Department of Chest Diseases is shortness of breath andthe most common imaging technique used for these patients in the emergency unit is chest radiography. In cases where chest radiography is not sufficient, thoracic computerized tomography is used. The pre-diagnosis of a major portion of patients hospitalized after emergency consultation is requested from the Department of Chest Diseases is pneumonia, asthma attack, or chronic obstructive pulmonary disease (COPD) exacerbation.[3,4]

Especially after the COVID-19 epidemic, although it is essentially a systemic infection, the fact that it causes pneumonia has caused chest diseases to spend more time with these patients than almost the infection department. Therefore, there has been an increase in the workload, especially in recent years. Chest diseases departments also have to spare a significant amount of time for patients who are relatively chronic, recurrent and therefore require a significant workforce. With this workload, we conducted this study in order to determine how and in what way we should allocate time to the emergency departments, and thinking that its contribution to the literature would be meaningful.

As a primary aim we tried to identify any seasonal differences by analysing the chest disease consultation requests made by the emergency unit in summer (June, July, and August) and winter (December, January, and February) months. As the secondary aim, possible differences between summer and winter in terms of demographic data, diagnoses and hospitalization were investigated.

MATERIAL AND METHOD

The study was carried out with the permission of Adıyaman University Ethics Committee (Date: 13.12.2022, Decision No: 2022/9-14). Informed consent was waived from the patients because of the study which was designed as a retrospective study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection

In this study, we included patients treated in the emergency unit of Adıyaman Training and Research Hospital who had consultations with the Department of Chest Diseases between December 2021 and August 2022 based on hospital information management system and patient files. All patients were over the age of 18 years and their thoracic computerized tomography results were available. Together with the demographic data of the patients, such as age and sex, data including the findings of thoracic computerized tomography, pre-diagnosis before hospitalization, and place of hospitalization (hospital ward or intensive care unit) were also analysed. Patients with missing data were excluded from the study.

Statistical Analysis

Descriptive statistics for the categorical variables (demographic characteristics) of the study were evaluatedas frequencies and percentages. The compliance of numerical variables with normal distribution was checked using the Shapiro-Wilk test. Descriptive statistics for numerical variables were given as mean ± standard deviation (x±SD) for normally distributed data and median (min-max) for non-normally distributed data. The Mann-WhitneyU test was used in the comparison of variables without normal distribution between summer and winter months.Then, the relationships between age, gender, pre-diagnosis, and radiological findings were evaluated as categorical variablesPearson chi-square test was determined as statistical test.The statistical significance level was considered as $p<0.05$ in all calculations and statistical analysis of the data was conducted using IBM SPSS Statistics 26 (IBM Corp., Armonk, NY, USA).

RESULTS

The data obtained from 409 patients presenting to the emergency unit were used in this study. The mean age of patients with summer consultations was 75(70.650±17.691) (21-106) years and the mean age of patients with winter consultations was 74 (71.350±15.880) (20-104) years (p= 0.830).While 170 of those emergency patients consulted with the Department of Chest Diseases in summer, 239 of them consulted in winter. In the summer months, 100 (58.8%) of these patients were male and 70 were female; in winter, 135 were male and 104 were female (p= 0.637)(**Table 1**) (**Table 2**).

Table 1.Comparison of demographic information of patients according to the season in which they presented

Variable	Summer		Winter		Chi-square	p
	n	%	n	%		
Sex						
Male	100	58.82	135	56.49	0.222	0.637p
Female	70	41.18	104	43.51		
Complaint						
Fever	16	9.41	31	12.97		
Haemoptysis	10	5.88	11	4.60		
Shortness of breath	69	40.59	125	52.30	12.260	0.016p
Coughing	18	10.59	26	10.88		
Non-respiratory	57	33.53	46	19.25		
Hospitalization						
Yes	106	62.35	144	60.25	0.185	0.667p
No	64	37.65	95	39.75		
Pre-diagnosis						
Asthma	12	11.32	23	15.86		
Bronchiectasis	4	3.77	7	4.83		
COPD	33	31.13	54	37.24	2.194	0.139p
Pneumonia	47	44.34	47	32.41		
Pulmonary thromboembolism	10	9.43	14	9.66		
Place of hospitalization						
Clinical Service	70	66.04	110	75.9	2.914	0.088p
ICU	36	33.96	35	24.1		
Radiological findings-1						
Emphysema	17	10.00	31	12.97		
non-emergency, nonspecific	95	55.88	147	61.51	3.941	0.268p
Embolism	8	4.71	10	4.18		
Consolidation	50	29.41	51	21.34		
Radiological findings-2						
None	146	85.88	226	94.56	9.093	0.003p
Pleural effusion	24	14.12	13	5.44		

P: Pearson chi-square test, COPD: chronic obstructive pulmonary disease, ICU: intensive care unit

Table 2.Comparison of patients' ages according to the season in which they presented

Variable	Summer		Winter		U	p
	Median	Min-Max	Median	Min-Max		
Age	75	21-106	74	20-104	20062.5	0.830

U: Mann-Whitney U test

The most common complaint of the patients consulted in both seasons was shortness of breath at rates of40.6% and 52.3% in summer and winter, respectively, andthe second most common was non-respiratory causes at rates of 33.5% and 19.2%. Patients were mostly hospitalized in the winter months due to a pre-diagnosis of COPD exacerbations (37.2%) and in summer due to pneumonia (%44.3) . In addition, patients were also hospitalized with pre-diagnoses of asthma attacks, bronchiectasis, and pulmonary thromboembolism at varying rates. In the radiological imaging of the patients who consulted in summer and winter, the most common radiological finding was "other"or "non-emergency"at rates of55.8% and 61.5%, respectively. Emphysema, consolidation and pulmonary thromboembolism were seen as radiological findings in summer 10%, 29.4% and 4.7%, respectively. Emphysema, consolidation and pulmonary thromboembolism were seen as radiological findings in winter12.9%, 21.3% and 4.1%, respectively. As an additional imaging finding, pleural effusion was observed in the radiological imaging results of 24 patients who consulted insummer and 13 patients who consulted in winter (p= 0.268) (**Table 1**).

Significant differences were identified between the groups in terms of the complaints and additional radiological imaging findings of patients who consulted in summer and winter ($p<0.05$). The most common complaint was shortness of breath in both seasons, while pleural effusion was observed as an additional radiological finding in 14.1% in summer and 5.4% in winter.(**Table 1**).

Of the 170 patients who consulted in summer, 106 (62.3%) were hospitalized, with 36 of them in the intensive care unit and 70 in clinical service. Of the 239 patients who consulted in winter, 145 (60.2%) were hospitalized, with 35 of them in the intensive care unit and 110 of them in clinical service. Despite the higher mean age of the patients who consulted in summer, no significant difference was observed between the seasons. Proportionately, patients were mostly hospitalized due to pneumonia in summer and due to COPD exacerbations in winter. However, no significant difference was found between the seasons in terms of pre-diagnosis before hospitalization. The highest numbers of consulted patients were hospitalized in clinical service both seasons andno significant difference was found between the seasons. Additionally, there were no significant differences between the seasons in terms of main radiological findings($p>0.05$) (**Tables 1** and **2**).

DISCUSSION

This study was undertaken with the aim of identifying seasonal differences in the chest disease consultations requested by an emergency unit. One of the first notable findings obtained was the higher number of consultation requests in winter months compared to summer months. The unique parameters we evaluated in our study provide important information about the variables between summer and winter periods about the chest diseases consultations requested from the emergency department. We have revealed that there is a significant difference between the complaints of patients who applied to the emergency department in the summer and winter periods and were consulted. We showed that there was no significant difference in parameters of age, gender, hospitalization, pre-diagnosis and radiological findings.

In the study conducted by Dönmez et al.[2] in which the consultation processes in the emergency department were examined, it was determined that male patients were the most frequently consulted in all branches, and the average age of the patients who applied for consultation was 45.[2]Additionally, out

of 147 patients who consulted with the Department of Chest Diseases, 54 (36%) of them were hospitalized.[2] Compared to that study, the present study has some similarities in terms of high numbers of male patients and hospitalization rates. However, the mean age is higher in the present study. The data that we obtained here support the hypothesis that older patients are often treated in the Department of Chest Diseases.

In the study conducted by Begümet al.[1] in which chest diseases consultations requested from the emergency department of a state hospital were examined, it was seen that the average patient age was 72.8, 53.9% of the patients were male, and the most common complaint was shortness of breath.[1] In the same study, it was revealed that 52.7% of the consulted patients were hospitalized, the most common pre-diagnosis was pneumonia, and the most common computerized tomography finding was consolidation.[1] In comparison to that study, the present study has some similarities in terms of age, sex, complaints, and the most frequent pre-diagnosis in summer months. On the other hand, the most important differences between that study and ours are that the most frequent pre-diagnosis in winter was COPD, the most frequent computerized tomography finding was "other"or "non-emergency" findings, and the hospitalization rate was 61.1% in our study.

In a previous study that evaluated the chest disease consultations of hospitalized patients, it was revealed that the mean age of the patients was 62 years, 51.2% of the patients were male, the most frequent complaint was coughing, and the most frequent radiological finding was "other" or "non-emergency". Patients from the emergency unit were not included in thatstudy.[4] In comparison, our patients were similar in terms of sex distribution and radiological findings, but they differed regarding mean age and complaints. We can also conclude that the profile of hospitalized patientstreated by chest disease doctors in the previous study included younger patients who were more stable.

In the study conducted by Emreet al.[5] chest diseases consultations requested from hospitalized patients were evaluated. In this study, the mean age was 64 years, 53.6% of the patients were male, the most common complaint was dyspnea, and the most common radiological imaging finding was "non-emergency nonspecific" and the most common diagnosis was COPD exacerbation.Patients from the emergency unit were not included in thatstudy.[5] In comparison, our study has some similarities in terms of sex distribution, complaints, radiological findings, and winter pre-diagnoses. However, we obtained different results in terms of the mean age of the patients and summer pre-diagnoses.

In the study conducted by Annakkaya et al.[6] in which the chest diseases consultations requested in emergency service and hospitalized patients were evaluated, the mean age was 57, 56.9% of the patients were male, the most common complaint was dyspnea, and the most common radiological imaging finding was "non-urgent, non-specific".[6] Seasonal differences werenot considered in this study.[6] In comparison, our study has some similarities in terms of sex distribution, complaints, and radiological findings. However, the mean age of patients in the previous study was lower compared to ours.

In the study conducted by Balbayet al.[3] when the requested chest diseases consultations in the emergency department and hospitalized patients were evaluated, the mean age of the patients was 62, 65.1% of the patients were male, the most common complaint was dyspnea, and the most common radiological imaging was radiological imaging. appeared to have been done.[3] In comparison, our study has some similarities in terms of sex distribution, complaints, and radiological findings. However, once again, the mean age of patients in our study was higher.

In the study conducted by Arslanet al.[7] in which the consultations requested from the patients hospitalized at the University Hospital were examined, the mean age of the patients was 63 years, 60% of the patients were male, the most common complaint was dyspnea, the most common preliminary diagnosis was COPD, the most common radiological imaging finding was "non-urgent, non-specific". was.[7] Emergency unit patients were not included in that study.[7] In comparison, our study has similarities in terms of sex distribution, complaints, radiological findings, and winter pre-diagnoses. However, the mean age of the mentioned study was lower than ours and we also obtained different results in terms of summer pre-diagnoses.

The present study had several limitations. The retrospective nature of the study and the fact that it was conducted in a single center might have inevitably led to bias in case selection. This resulted in high consultation rates due to co-morbid patients as well as surgical candidates who applied to the emergency department without respiratory complaints. This is an area that requires further evaluation of patients in this group with extensive studies. In addition, studies to be carried out can clearly show how the findings observed in radiological imaging should be evaluated even though they do not cause respiratory complaints. Prospective studies with larger populations are needed. Despite the limitations of this study, it will contribute and guide the studies to be done in the literature in terms of the results of summer and winter periods.

CONCLUSION

In this study, we revealed that there is a significant difference between summer and winter months in terms of complaints and additional radiological imaging findings in the evaluation of consultations requested by the emergency department from the Department of Chest Diseases.At the same time, we found no significant differences between winter and summer in terms of patients' ages, sex distribution, pre-diagnosis before hospitalization, place of hospitalization, and main radiological findings. As far as we know, no other studies have been conducted on this subject to date; therefore, our study will make important contributions to the literature.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Adıyaman University Ethics Committee (Date: 13.12.2022, Decision No: 2022/9-14).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Acknowledgement: We thank the patients and their families for participating in the study.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1317433
J Contemp Med 2023;13(5):763-768

Original Article / Orijinal Araştırma

Unveiling the Prognostic Significance of Immature Granulocytes and Nucleated Red Blood Cells in Geriatric Pneumonia Severity and Mortality Outcomes

Geriatrik Pnömoni Ciddiyeti ve Mortalite Sonuçlarında İmmatür Granülositler ve Çekirdekli Eritrositlerin Prognostik Önemi

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Abstract

Aim: The progression of pneumonia in the senior-age population can be catastrophic. Biomarkers capable of assessing the severity of pneumonia play a pivotal role in prognosis. We conducted an evaluation of the kinetics of immature granulocytes (IG) and nucleated red blood cells (NRBC) as potential indicators of the severity of geriatric pneumonia.

Material and Method: In this retrospective cross-sectional study, patients diagnosed with pneumonia were categorized using two prominent severity scoring systems, CURB-65 (Confusion, Urea, Respiratory rate, Blood pressure, age >65) and PSI (Pneumonia severity index). Additionally, the patients' discharge status and infection process markers were noted.

Results: A total of 80 patients were included in the evaluation, with a mean age of 72.23±7.26. Excluding the mortality rate of 49% when including oncology patients, the overall mortality rate was 26%. The deceased patients had longer hospitalization durations, higher CURB-65 and PSI category classifications, and elevated NRBC results. In CURB-65-based categorization, there was an increase only in NRBC levels associated with disease severity, whereas, in PSI-based categorization, the increase is in both NRBC and IG levels. No statistical difference was observed in NRBC and IG levels when excluding oncology patients from the analysis.

Conclusion: In geriatric pneumonia cases, the dynamics of NRBC appear to be more crucial in indicating disease severity compared to IG. However, this opportunity seems to be missed or compromised in patients with oncological comorbidities.

Keywords: CURB-65, Immature granulocyte, Nucleated red blood cell, Pneumonia severity index.

Öz

Amaç: Yaşlı nüfusta pnömoninin seyri katastrofik olabilir. Pnömoninin ciddiyetini değerlendirebilen biyobelirteçler, prognozda önemli rol oynamaktadırlar. Bu çalışmada, geriatrik pnömoninin ciddiyetinin potansiyel göstergeleri olarak, immatür granülositlerin (İG) ve çekirdekli eritrositlerin (ÇE) kinetikleri değerlendirilmiştir.

Gereç ve Yöntem: Bu retrospektif ve kesitsel çalışmada, pnömoni tanısı konan hastalar, CURB-65 (Konfüzyon, Üre, Solunum sayısı, Kan basıncı, yaş >65) ve PSI (Pnömoni ciddiyet endeksi) olmak üzere iki önde gelen ciddiyet skorlama sistemine göre kategorize edilmiştir. Ayrıca, hastaların taburculuk durumu ve enfeksiyon süreci belirteçleri kaydedilmiştir.

Bulgular: Toplamda 80 hasta değerlendirmeye dahil edilmiştir ve yaş ortalamaları 72.23±7.26'dır. Onkoloji hastaları dahil edildiğinde %49 olan mortalite oranı, hariç tutulduklarında %26 idi. Ölen hastaların hastanede yatış süreleri daha uzundu, CURB-65 ve PSI kategori dereceleri daha yüksek sınıftaydı ve ÇE seviyeleri yükselmişti. CURB-65 tabanlı kategorizasyonda, hastalık şiddeti ile sadece ÇE düzeyinde artış gözlenirken, PSI tabanlı kategorizasyonda hem ÇE hem de İG düzeylerinde artış mevcuttu. Onkoloji hastaları analizden çıkarıldığında ÇE ve İG düzeylerinde istatistiksel fark gözlenmedi.

Sonuç: Geriatrik pnömoni vakalarında, ÇE'nin dinamiklerinin, İG'ye kıyasla hastalık şiddetini belirtmede daha hayati olduğu görünmektedir. Ancak, onkolojik komorbiditesi olan hastalarda bu fırsatın zayıfladığı ya da kaybolduğu görülmektedir.

Anahtar Kelimeler: CURB-65, Çekirdekli eritrosit, İmmatür granülosit, Pnömoni ciddiyet endeksi

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Received *(Geliş Tarihi)*: 20.06.2023 **Accepted *(Kabul Tarihi)*:** 28.09.2023

INTRODUCTION

Pneumonia is widely acknowledged as a profound global health concern, primarily attributed to bacterial, fungal, or viral infections. Its ramifications, particularly in vulnerable populations, including the elderly, immunocompromised individuals, and those afflicted with underlying chronic ailments, render it a pressing matter necessitating intensive care interventions.[1] Prominently in these senior-age groups, the imperative for early diagnosis, judicious administration of antimicrobial agents, and comprehensive adjunctive measures cannot be overstated, as these pivotal interventions constitute the cornerstone in mitigating the incidence of pneumonia-associated complications and mortality rates.[2,3]

The severity of pneumonia is evaluated based on the patient's clinical symptoms, physical examination findings, and radiological outcomes.[4] Several scoring systems are available to assess pneumonia severity. One such system is the Pulmonary Severity Index (PSI), which calculates a score based on several parameters, including the patient's clinical findings, laboratory test results, and demographic factors.[5,6] Another prominent scoring system is the CURB-65 (Confusion, Urea, Respiratory rate, Blood pressure, age 65 and over) score, which predicts the severity of pneumonia by considering the patient's age, level of consciousness, urea level, respiratory rate, and blood pressure.[7,8]

In addition to clinical assessment, laboratory and imaging modalities are utilized minimally to confirm or provide supportive evidence for diagnosing pneumonia in patients. Besides the established markers such as C-reactive protein (CRP) and procalcitonin, novel parameters, including immature granulocytes (IG) and nucleated red blood cells (NRBC), have gained prominence as reliable indicators for predicting the severity of infection in pneumonia cases.[9] These parameters are commonly employed in the evaluation of pneumonia.

In the scientific literature, a wealth of studies elucidating the relationship between pneumonia severity indices and mortality outcomes exists. Within the scope of our investigation, our primary objective was to meticulously assess the dynamic alterations in immature granulocytes (IG) and nucleated red blood cells (NRBC), revered as indicators of heightened infection severity, across two preeminent and disparate severity index stratifications. Subsequently, we intended to discern the profound implications of these hematological changes on mortality rates, thereby contributing to the expanding body of knowledge on geriatric pneumonia management.

MATERIAL AND METHOD

This study, conducted with a retrospective cohort design, obtained the approval of the Ethical Committee of Necmettin Erbakan University Meram Faculty of Medicine on July 10, 2019, (2019/1973), and the study hereby asserts its adherence to the principles outlined in the Helsinki Declaration.

The samples were created by scanning the discharge epicrisis of patients treated for pneumonia in the Internal Medicine clinic in the year 2019, prior to the pandemic. CURB-65 and PSI scores of the patients were calculated from the discharge epicrisis and nurse observation charts. Patients transferred from other services, voluntarily discharged during treatment, <65 years of age, and those with inconsistencies between CURB-65 and PSI scores were excluded from the study. The presence of comorbidities was not used as an exclusion criterion; nevertheless, comorbidities were additionally noted. Routine complete blood counts and primary biochemical test results of the patients at admission were retrospectively obtained from the hospital's digital system. The discharge status of the patients was recorded as death or survival. And concurrent demographic characteristics were noted. The patients categorized based on CURB-65 and PSI scores were compared with their available data.

Statistical analysis: The data in our study were analyzed using GraphPad Prism version 8 and IBM SPSS Statistics version 24. The data distributions were assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests for normality. Accordingly, independent t-tests were employed for non-categorical paired data analysis for non-skewed data, and one-way ANOVA with Bonferroni correction was used for multiple data analysis. In cases where the data did not follow a normal distribution, the Mann-Whitney U test was utilized for paired data evaluation, and the Kruskal-Wallis test was preferred for assessment among multiple groups. Non-parametric tests were chosen for subgroup analysis due to the reduced number of groups. The chi-square test was applied to compare groups, while Fisher's exact test was preferred for small-sample groups. A significance level of 0.05 was considered for rejecting the null hypothesis (H0) in all analyses.

RESULTS

A retrospective evaluation was conducted on a cohort of 107 patient files, from which exclusion criteria were applied, resulting in a final sample of 80 patients for the study. The mean age of the overall population was 72.23±7.26. Of the total, 36 patients were female (45%), and 32 (40%) had a cancer diagnosis.

In the study, which observed 27 patient deaths, the overall mortality rate was determined to be 49%. Notably, when cancer patients were excluded from the analysis, the mortality rate was reevaluated to 26%. The average duration of hospitalization was 11.72±4.01. No statistically significant differences were observed in terms of gender concerning length of hospital stay and age ($p > 0.05$). The demographic and laboratory characteristics of the patients, categorized based on both CURB-65 and PSI, are provided in **Table 1**.

Table 1. Patient characteristics based on pneumonia severity

	CURB-65*				PSI†				
	Low (n=16)	Moderate (n=20)	High (n=44)	p value	Low (n=6)	Moderate (n=5)	High (n=20)	Very High (n=49)	p value
Age, year	67.68±3.19	75.05±8.06	72.61±7.28	0.006*	68.33±3.82	67.4±2.5	71.6±6.62	73.46±7.83	0.116
Gender, F/M, n (%)	7(44)/9(56)	11(55)/9(45)	18(41)/26(59)	0.572	3(50)/3(50)	0(0)/5(100)	13(65)/7(35)	20(41)/29(59)	0.052
Hospitalization day	7.56±1.15	10.95±2.13	13.59±4.09	0.001*	7.73±1.36	8.6±0.54	10.05±2.76	13.26±4.02	0.001*
Cancer, n (%)	3 (19)	7 (35)	22 (50)	0.080	0 (0)	0 (0)	7 (35)	25 (51)	0.018*
Mortality, (%)	0	33	95	0.001*	0	0	25	85	0.017*
CRP‡, mg/L	48 (43-115)	147 (95-253)	122 (90-250)	0.001*	45 (42-51)	52 (44-303)	135 (78-228)	122 (93-240)	0.003*
Procalcitonin, µg/L	1.3 (0.3-4.1)	0.7 (0.4-1.9)	2 (0.7-44.2)	0.039*	1.2 (0.07-1.4)	3.6 (0.5-4)	0.8 (0.6-9.3)	1.9 (0.5-15)	0.392
WBC§, 103/uL	11 (9.4-12.7)	13.7 (8.5-17)	14 (8.9-18.8)	0.398	11.6 (10-12)	18.5 (16.7-21)	10.2 (8.5-15)	13.5 (8.7-17)	0.087
IG¶, 103/uL	0.13(0.04-0.4)	0.2 (0.08-0.3)	0.2 (0.08-0.4)	0.456	0.05 (0.01-0.1)	0.14 (0.13-0.2)	0.33 (0.1-0.4)	0.2 (0.08-0.4)	0.031*
NRBC**, 105/uL	0 (0-0.7)	0.5 (0-4)	1 (0-8)	0.013*	0 (0-0.2)	0 (0-0.5)	1 (10-17)	1 (0-7)	0.046*

The data are expressed in mean and standard deviation or median and percentiles. The p-values were calculated by comparing subgroups based on disease severity. The Fisher's exact test and the Kruskal-Wallis test were utilized for the calculations. *, Confusion-Urea-Respiratory rate-Blood pressure-age 65 and over score; †,Pneumonia severity index; ‡,C-Reactive protein; §, White blood cell; ¶,Immature granulocyte; **,Nucleated red blood cell.

Significant statistical differences were observed between deceased patients and survivors with respect to variables including length of hospital stay (p=0.001, η2=0.174), CURB-65 (p=0.001, η2=0.212) and PSI scores (p=0.001, η2=0.195), and NRBC counts (p=0.001, η2=0.038) (**Figure 1**). Deceased patients exhibited a significantly prolonged duration of hospitalization, elevated CURB-65 and PSI scores, and NRBC counts approximately twofold higher than the survivors.

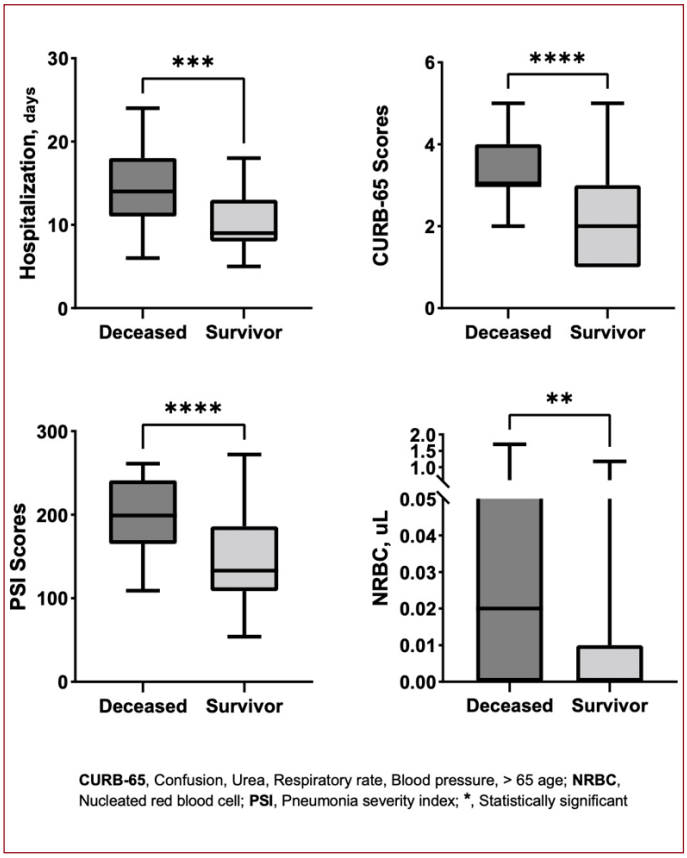

Figure 1. Differential parameters between survivors and non-survivors: a comparative analysis.

Among patients with an increased NRBC count, a statistically significant rise in CURB-65 score was detected (p=0.045). While a similar trend was observed in the PSI index, the difference did not reach the threshold of statistical significance (p=0.056).

When patients were evaluated based on the severity of the disease, comparisons of three subgroups using CURB-65 revealed significant age differences (p=0.006, ε^2=0.148), duration of hospitalization (p=0.001, ε^2=0.310), CRP levels (p=0.001, ε^2=0.179), procalcitonin levels (p=0.039, ε^2=0.057), and NRBC counts (p=0.013, ε^2=0.077) (**Figure 2a**).

Furthermore, when comparing four subgroups based on PSI, statistically significant differences were observed among the groups in terms of hospitalization duration (p=0.001, ε^2=0.207), CRP levels (p=0.003, ε^2=0.111), IG levels (p=0.031, ε^2=0.061), and NRBC counts (p=0.046, ε^2=0.054) (**Figure 2b**).

An additional assessment was carried out, excluding cancer patients and disregarding their prognostic impact. When cancer patients were excluded from the analysis, the statistically significant results for parameters hospitalization time (p=0.005, η2=0.158) and procalcitonin levels (p=0.047, η2=0.083), observed in the previous evaluation between deceased and survivors, continued to demonstrate statistical significance. However, when considering both the CURB-65 and PSI scores, there was no statistically significant correlation observed with either IG or NRBC (p > 0.05).

In the analysis of our patients, investigating the influence of IG and NRBC on pneumonia mortality, we found that NRBC exhibited a more significant effect (**Figure 3a**). However, this effect was not observed in cases of pneumonia among oncology patients (**Figure 3b**).

The following were noteworthy among the multiple correlations identified: NRBC demonstrated a moderate positive correlation with mortality (p=0.008, r=0.376). The duration of hospitalization displayed a significantly positive correlation with CURB-65 (p=0.001, r=0.790) and PSI (p=0.001, r=0.701) scores and a moderate correlation with NRBC (p=0.024, r=0.326) and mortality (p=0.005, r=0.399).

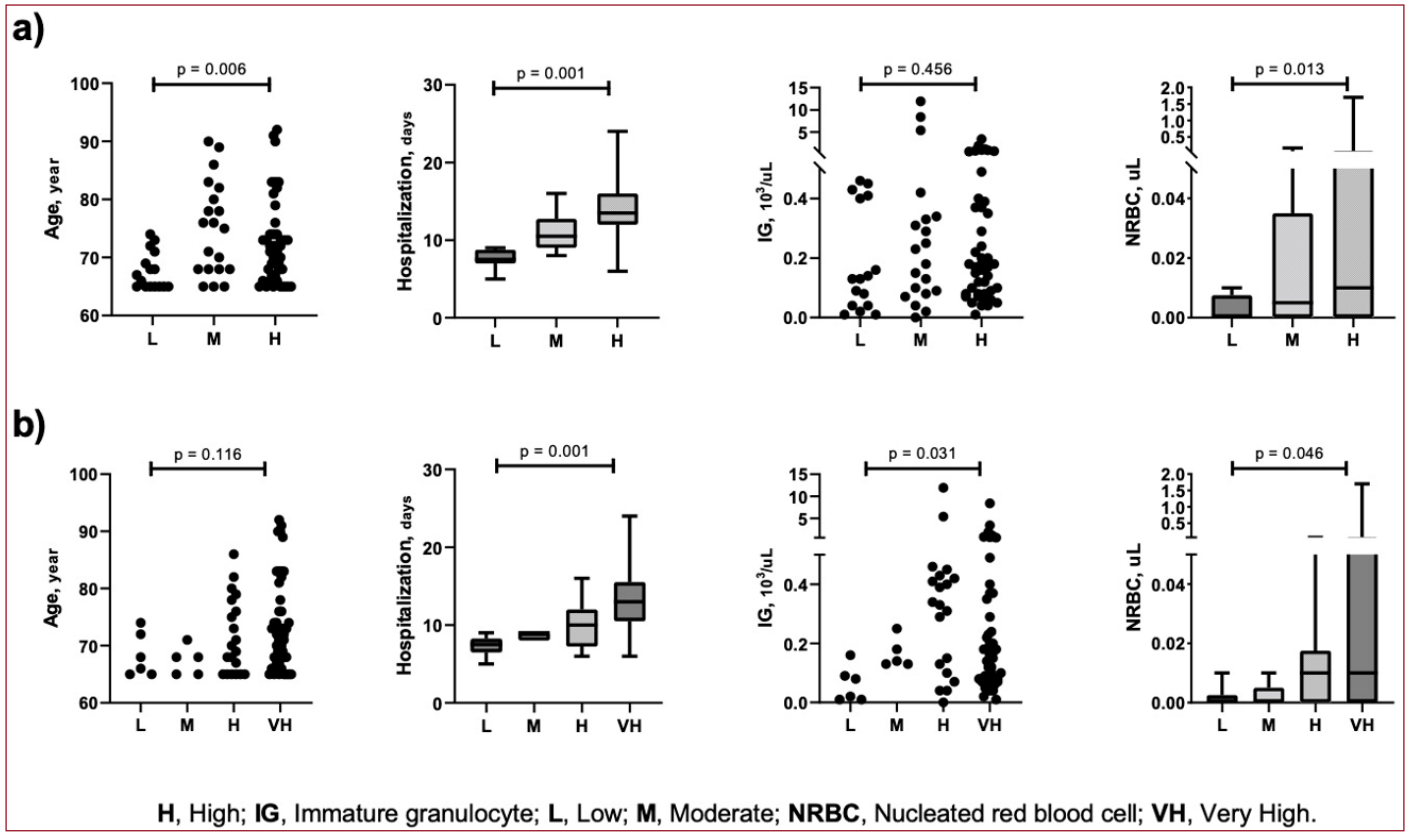

Figure 2. Comparison of Key Parameters Among Different Pneumonia Severity Indices, **a)** CURB-65, **b)** PSI.

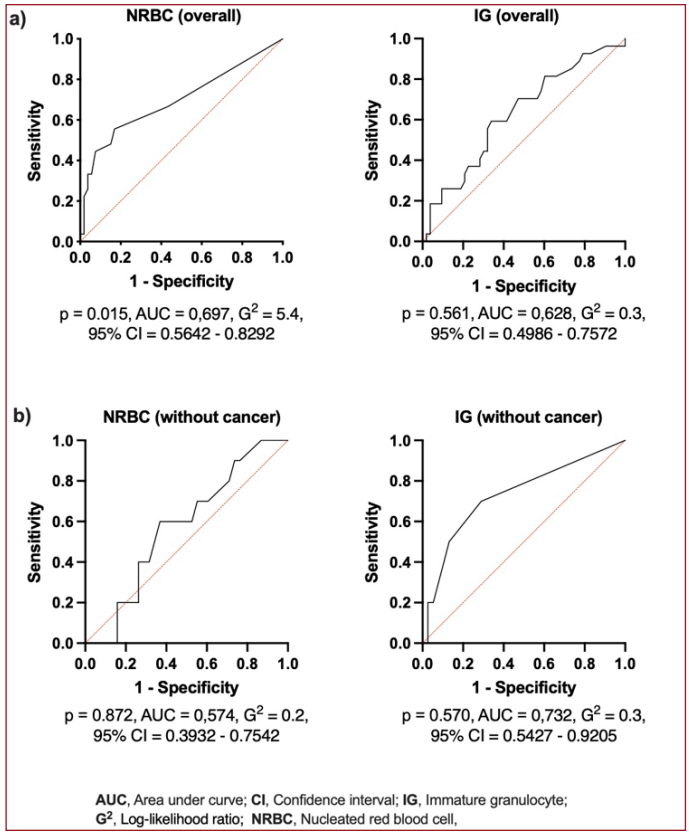

Figure 3. Impact of IG and NRBC results on mortality in a) All patients and b) Excluding oncology patients.

DISCUSSION

Our present study was primarily aimed at assessing the variations of IG and NRBC about disease severity graded according to two different pneumonia scoring indices in geriatric pneumonia. Based on our investigation, which centered on two severity indices showing comparable grading, NRBC variability emerged as a more prominent factor compared to IG, alongside well-established infection markers. This finding persisted in favor of NRBC, even beyond conditions that introduce an unfavorable bias to prognosis, such as cancer. Elevated NRBC values were directly associated with higher mortality rates.

In the realm of infectious diseases, it is well-established that the aging process engenders a propensity for attenuated immune responses.[10] Notably, advanced age manifests as a state wherein the human immune system exhibits compromised efficacy in mounting robust defenses against a diverse array of pathogens.[11] Alongside the currently established biomarkers that forecast the trajectory of infections, the inclusion of nearly validated novel biomarkers will offer valuable support in informing therapeutic adjustments for these types of infections. Within this context, it is crucial to acknowledge the abundance of scientific literature and ongoing research that has extensively explored the relationship between IG and NRBC. Numerous studies have provided substantial support and scientific evidence regarding

the association of IG and NRBC on infectious diseases. Within our investigation, we identified alterations in the context of pneumonia severity that were attributed to IG, albeit to a lesser extent than NRBC. Importantly, these modifications were observed in patients without a cancer diagnosis.

Hereby, in relation to the exclusions made for oncology patients in our study, which are prominently discussed in our manuscript, it is necessary to acknowledge the direct association of the oncological condition or treatment process with immunity, which may lead to an elevated pneumonia severity score.[12-14] Thus, the parameters we selected for evaluation aimed to better represent real-life situations, considering the higher likelihood of detecting oncological comorbidities in our study population within the specified age group.

Studies examining IG have encompassed a wide range of infectious scenarios within the literature. A consistent observation that has emerged is the applicability of IG as an indicator for evaluating the severity of sepsis and infectious diseases.[14-16] In a similar vein, our investigation revealed that IG exhibited an adequate level of effectiveness in reflecting disease severity among our patient cohorts classified according to disease severity determined by the PSI.

Research studies examining the correlation between NRBC and infection/sepsis in the literature seem to exhibit a relatively superficial nature.[17-19] In light of this, our assessments of NRBC have demonstrated sufficient efficacy in reflecting disease severity and even mortality, regardless of factors such as oncological comorbidities that notably compromise immune function or being part of the geriatric population.

The most probable limitation of the study, despite the robustness of both severity indices, was the categorical difference between CURB-65 (3 categories) and PSI (4 categories). This discrepancy had the potential to adversely affect statistical calculations due to the need for group adjustments within the patient cohorts. Nevertheless, as both indices classified patients in the severe category, there was no numerical misrepresentation concerning prognostic estimations.

CONCLUSION

Our study assessed the variations of IG and NRBC in geriatric pneumonia across varying levels of severity. NRBC was deemed more consequential than IG as an indicator of disease severity and mortality. Based on our results, elevated NRBC levels, irrespective of an oncological background, may be considered a risk factor for mortality in seniors with pneumonia.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study, conducted with a retrospective cohort design, obtained the approval of the Ethical Committee of Necmettin Erbakan University Meram Faculty of Medicine on July 10, 2019, (2019/1973)

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

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: This study was supported by Necmettin Erbakan University Research Fund

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

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CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1331649
J Contemp Med 2023;13(5):769-775

Original Article / Orijinal Araştırma

Proverb Comprehension in Primary Progressive Aphasia

Primer Progresif Afazide Atasözlerini Anlama ve Kavrama

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Abstract

Aim: Proverb comprehension was tested in 22 patients with primary progressive aphasia utilizing idiom explanation task. The aim of this study was to determine proverb comprehension in PPA patients using the Proverb Scale.

Material and Method: To assess the participants, Montreal Cognitive Assessment Scale, the Pyramid and Palm Trees test and the Proverb Scale were used.

Results: As a result of statistical analysis, there was a significantly difference between svPPA and lvPPA regarding idiom comprehension scores, the Pyramid and Palm Trees Test Scores and MoCA scores.

Conclusion: It is an important study to understand how the abstraction in PPA works regarding the language. In PPA subtypes, semantic memory, proverb and MoCA scores were significantly different between logopenic and semantic variants. Although MoCA and proverb comprehension were correlated in svPPA, no correlation was found in lvPPA. With similar studies in the field, it would be possible to better explain the effects of PPA, a disorder characterized by language disorders.

Keywords: Proverb, primary progressive aphasia, semantic, logopenic

Öz

Amaç: Atasözü açıklama görevi kullanılarak primer progresif afazili 22 vakada atasözlerini anlama ve kavrama becerileri değerlendirildi. Bu çalışmanın amacı, soyutlama, anlama ve kavrama ile ilgili ölçek ve testler kullanarak PPA hastalarında atasözü anlama düzeylerini belirlemektir.

Gereç ve Yöntem: Katılımcıları değerlendirmek için Montreal Bilişsel Değerlendirme Ölçeği, Piramit ve Palmiye Ağaçları testi ve Atasözü Ölçeği kullanıldı.

Bulgular: İstatistiksel analiz sonucunda atasözü anlama puanları, Piramit ve Palmiye Ağaçları Test Puanları ve MoCA puanları açısından svPPA ve lvPPA arasında anlamlı bir fark bulunmuştur.

Sonuç: PPA'daki soyutlamanın dil açısından nasıl çalıştığını anlamak için önemli bir çalışmadır. PPA alt tiplerinde semantik bellek, atasözlerini anlama ve MoCA skorları anlamlı olarak logopenik ve semantik varyantlar arasında değişiklik göstermektedir. svPPA'da MoCA ve atasözü anlama arasında bir korelasyon olmasına rağmen lvPPA'da herhangi bir korelasyon bulunamamıştır. Bu gibi çalışmalar sayesinde dildeki bozulmalar ile karakterize bir bozukluk olan PPA'nın etkilerini daha iyi açıklamak mümkün olabilecektir.

Anahtar Kelimeler: Atasözü, primer progresif afazi, semantik, logopenik

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Received *(Geliş Tarihi)*: 24.07.2023 **Accepted *(Kabul Tarihi)*:** 20.09.2023

INTRODUCTION

Primary progressive aphasia (PPA) is a clinical syndrome characterized by the gradual decline of language skills.[1,2] Although additional cognitive symptoms and non-linguistic disorders may occur in the advanced stages of the disease, the resulting impairments must be predominately linguistic for at least two years to qualify as PPA. PPA can be classified into 3 subtypes: semantic variant (svPPA), nonfluent variant (nfvPPA) and logopenic variant (lvPPA).[3]

Patients with svPPA exhibit well-structured, well-articulated speech that lacks of all meaning. Common symptoms include a lack of precise expression and an increased difficulty locating words, especially nouns (also known as a "loss of memory for names"). Patients with nfvPPA typically have labored, slow, hesitant, and jumbled speech. Common speech sound problems include'slurring' or mispronouncing words can also occur. In the lvPPA, word-finding difficulties and conversational lapses are present.[4]

The use of figurative expressions, whose meaning differs from the literal meaning of their component terms, is an aspect of linguistic communication; these expressions include proverbs, hyperboles, metaphors, and idioms. Idioms are among the most prevalent figurative language forms. They are typically described as frozen phrases whose meanings are explicitly stipulated in a mental lexicon, and the speaker's meaning cannot be deduced from an examination of the words' typical meanings.[5] These expressions are distinguished by a semantic eccentricity: their meaning is not a direct function of the meanings of their constituent words. For instance, the meaning "die suddenly" is not produced when the meanings of the words "kick," "the," and "bucket" are constructed according to the syntactic relations that exist between them. According to Glucksberg and McGlone, a person must be familiar with the convention in order to appropriately interpret it.[6]

When compared to controls, patients with Alzheimer's disease (AD) were impaired in interpreting abstract meanings: when presented with alternative interpretations of familiar phrases, they chose concrete responses. As for Kempler, Van Lancker, and Read it implies that they were using lexical (single word), referential meaning to interpret the phrases.[7] It has also been shown that interpreting proverbs, which is a method of assessing abstraction skills, is associated with other executive functions such as planning, problem solving, fluency and set changing in patients with frontal lobe dysfunction.[8,9]

Yamaguchi et al. observed that as dementia severity increased in patients, scores for understanding proverbs decreased and confabulation increased.[10] Successful interpretation of proverbs requires both basic language skills, that is, one's ability to understand the meanings of words and express their answers, and the ability to integrate the meanings of words into abstract principles or concepts in a coherent way, that is, high-level executive functions.[11]

Even in the early stages, patients with Alzheimer's disease have impaired executive functions.[12] Given that Alzheimer's disease patients with normal propositional language comprehension have been found to have impaired figurative language comprehension, we decided to investigate idiom comprehension in patients with primary progressive aphasia, which is type of a dementia.[13,14]

As PPA is relatively focal degeneration of the brain systems that govern language, it is important to explore how abstract thinking is affected. Therefore, the main goal of this study was to assess whether the comprehension of idiomatic expressions in PPA is affected. In light of this literature, we seek answers to the following research questions:

1. How are the group scores for the Proverb Scale, PPTT and MoCA?
2. Is there a difference between svPPA and lvPPA groups regarding the Proverb Scale, PPTT and MoCA scores?
3. Is there a correlation among MoCA, the Phrase Comprehension test and PPTT in svPPA?
4. Is there a correlation among MoCA, the Phrase Comprehension test and PPTT in lvPPA?

MATERIAL AND METHOD

Design

This study is a cross-sectional descriptive study to examine the idiom comprehension of patients with PPA. The study was carried out with the permission of Bahçeşehir University Research and Publication Ethics Committee (Date: 27/04/2023, Decision No:E-85646034-604.02.02-59908). Informed consent was obtained from all participants. The time period for the collecting of the data was from May, 2023 through June, 2023. Participants were selected from individuals willing to volunteer to take part in the study.

Participants

The diagnosis of PPA is determined by the criteria recommended by Mesulam.[1,2] Further analysis for subtypes of PPA, Gorno-Tempini et al. criteria was used.[15] As for Gorno-Tempini et al., PPA can be classified into one of three types at three different levels: clinical, imaging-supported, or confirmed pathologic diagnosis. When a case exhibits speech and language characteristics of a certain variation, clinical diagnosis is made. **Table 1**. shows the criteria for PPA by Mesulam.

Table 1. PPA Diagnosis criteria for inclusion and exclusion

Inclusion: criteria 1–3 must be answered positively	Exclusion: criteria 1–4 must be answered negatively for a PPA diagnosis
1. Most prominent clinical feature is difficulty with language	1. Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders
2. These deficits are the principal cause of impaired daily living activities	2. Cognitive disturbance is better accounted for by a psychiatric diagnosis
3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease	3. Prominent initial episodic memory, visual memory, and visuoperceptual impairments
	4. Prominent, initial behavioral disturbance

PPA: Primary Progressive Aphasia

In the study group, ages ranged from 51 to 63 years (for PPA semantic 57.00±3.25; for PPA logopenic 57.27±2.49). Detailed demographic information of the participants were reported in supplement 1. For our study, the inclusion criteria for PPA were as follows: (1) having been diagnosed as PPA by a neurologist; (2) history of no other psychiatric or neurological disease other than PPA; (3) being native speaker of Turkish; (4) not having depression; (5) having adequate sensory acuity to complete the tasks; and (6) giving consent to attend to the study. The exclusion criteria for our study were as follows: (1) having a history of other psychiatric or neurological disase, (2) not having adequate sensory acuity to complete the tasks, (3) not completing all the assessments, (3) having depression.

In order to evaluate the participants' semantic knowledge, cognitive ability, and proverb comprehension, The Pyramids and Palm Trees Test (PPTT), the Montreal Cognitive Assessment Scale (MoCA), and the Proverb Test were utilized respectively. For data collection, two speech and language therapists trained in the assessment tools applied all the tools in the same session, taking a 15-minute break after each task. In the following paragraphs, detailed explanations for each test will be given.

The Pyramids and Palm Trees Test (PPTT): The Pyramids and Palm Trees Test, also known as the PPTT, is a memory test that is frequently utilized for the purpose of evaluating semantic memory.[16] The examination consists of 52 different word or picture combinations. Each group consists of either three words or three illustrations. The subject is shown with three items and asked, "Which one of the lower two items goes with the upper item?" The stimulus, which could be, for example, a pyramid, is placed on top. The participant is responsible for correctly matching it with the target item (for example, the palm tree), while disregarding the distractor item (for example, the pine tree) in accordance with the available semantic knowledge. Normative data for PPTT turkish was collected by Bozdemir and Gurvit.[17]

The Montreal Cognitive Assessment Scale (MoCA): It was developed by Nasreddine et al. in order to make a rapid assessment of cognitive impairment and to distinguish especially healthy individuals from Mild Cognitive Impairment. [18] It is used to evaluate various cognitive functions such as concentration, executive functions, memory, language, visual construction skills, abstract thinking, calculation, and orientation. The lowest score that can be obtained from the scale is 0, and the highest score is 30. Adaptation of MoCA to Turkish was made by Selekler et al.[19]

The Proverb Scale: This scale was developed for Turkish by Aydın et al. and it has 20 items. Items were balanced according to their abstraction and frequency.[20] On the Proverbs Scale, items were given values of 0, 1, and 2 according to their accuracy and relatedness. In the Proverb test, they were asked to give an oral explanation to the proverbs that they are given and they were scored according to their explanations. Answers that were wholly unrelated to the question were awarded a score of 0.

Procedures

All participants were asked to complete MoCA, PPTT, and the Proverb test in the same order. All participants were first answered questions regarding to their demographic information and then continued with the tasks in the same session, which lasted 30 minutes to 2 hours. Before the assessment, participants and their relatives were informed in detail about the tests, scales, and duration of the assessment. Participants were informed that they had the right to terminate the assessment at any time. Data collection was carried out in a clinical environment without external noise or distracting sound or image exposure.

Statistical Analysis

The study's data were analyzed using the SPSS 25 (Statistical Package for the Social Sciences). The results were evaluated using a 95% confidence interval and a significance level of $p < 0.05$. Frequency (n) and percentage (%) are used in descriptive statistics. For normality, a Kolmogorov-Smirnov test indicated that MoCA scores of the participants followed a normal distrubition (p=0.200); however PPTT (p=0.035) and idiom comprehension tasks (p=0.004) did not. Therefore, independent t test was used to compare MoCA scores and Mann Whitney-U test was used to compare PPTT and idiom comprehension. Correlation coefficent was also calculated for svPPA and lvPPA groups.

RESULTS

In the study, we examined the proverb comprehension of a total of 22 individuals including 11 svPPA and 11 lvPPA. It was determined that the mean age of 11 (50%) participants with svPPA was 57.00±3.25 and 11 (50%) participants with lvPPA was 57.27±2.49. While 9.1% (2 participants) of the participants had a middle school education, 45.5% (10 participants) had a high school education and 45.5% (10 participants) had a university education. Detailed information for demographics were shown in the **Supplement 1**.

In **Table 2**, the statistical analyses performed to assess the differences between svPPA and lvPPA groups regarding the Proverb Scale and PPTT scores of are shown. As shown in the **Table 2**, there was a significant difference between svPPA and lvPPA group regarding proverb comprehension and PPTT (p=0.012). When this was analyzed, it was revealed that those with svPPA had lower scores in proverb comprehension and higher scores in PPTT.

Table 2. Mann Whitney-U test results for PPTT and the Proverb Scale

Variables		svPPA (N=11)	lvPPA (N=11)	Z score	P score
PPTT	Mean Rank	14.95	8.05	-2.507	0.012*
	Summary of Ranks	164.50	88.50		
Proverb comprehension	Mean Rank	6.00	17.00	-4.011	0.000*
	Summary of Ranks	17.00	187.00		

*<.05 **<.01 ***<.001 SD: standard deviation, PPTT: The Pyramids and Palm Trees Test, svPPA: Semantic Variant Primary Progressive Aphasia, lvPPA: Logopenic Variant Primary Progressive Aphasia

Supp 1. Detailed information for demographics

ID	Gender	Year of Birth	Educational status	Job	Marital status	Aphasia Type	Damage Area	Diagosis of aphasia	Dominant hand	ADD (Total 292)
L1	W	1970	High School	Officer	Single	Logopenic (PPA)	left posterior perisylvian atrophy	7 months ago	Right	198
L2	M	1967	University	Engineer	Married	Logopenic (PPA)	left posterior perisylvian atrophy	5 months ago	Right	177
L3	W	1966	High School	Housewife	Married	Logopenic (PPA)	left posterior perisylvian atrophy	6 months ago	Right	176
L4	M	1969	University	Banker	Married	Logopenic (PPA)	left posterior perisylvian atrophy	7 months ago	Right	161
L5	M	1971	High School	Textile	Married	Logopenic (PPA)	left parietal atrophy	6 months ago	Right	198
L6	W	1973	Vocational School	Worker	Married	Logopenic (PPA)	left parietal atrophy	6 months ago	Right	200
L7	W	1974	High School	Housewife	Married	Logopenic (PPA)	left posterior perisylvian atrophy	4 months ago	Right	192
L8	M	1966	University	Engineer	Married	Logopenic (PPA)	left posterior perisylvian atrophy	5 months ago	Right	157
L9	W	1966	High School	Housewife	Married	Logopenic (PPA)	left posterior perisylvian atrophy	6 months ago	Right	168
L10	M	1969	University	Banker	Married	Logopenic (PPA)	left posterior perisylvian atrophy	7 months ago	Right	183
L11	M	1971	High School	Textile	Married	Logopenic (PPA)	left parietal atrophy	6 months ago	Right	194
S1	M	1971	High School	Officer	Married	Semantic (PPA)	anterior temporal lobe atrophy	5 months ago	Right	206
S2	M	1968	High School	Officer	Married	Semantic (PPA)	anterior temporal lobe atrophy	7 months ago	Right	204
S3	W	1967	High School	Officer	Married	Semantic (PPA)	anterior temporal lobe atrophy	5 months ago	Right	198
S4	W	1970	University	Academician	Single	Semantic (PPA)	anterior temporal lobe atrophy	6 months ago	Right	179
S5	W	1974	High School	Housewife	Married	Semantic (PPA)	anterior temporal lobe atrophy	4 months ago	Right	150
S6	W	1974	High School	Artisan	Married	Semantic (PPA)	anterior temporal lobe atrophy	3 months ago	Right	175
S7	M	1971	University	Business manager	Married	Semantic (PPA)	anterior temporal lobe atrophy	7 months ago	Right	208
S8	M	1970	High School	Officer	Married	Semantic (PPA)	anterior temporal lobe atrophy	5 months ago	Right	216
S9	M	1968	High School	Teacher	Married	Semantic (PPA)	anterior temporal lobe atrophy	7 months ago	Right	176
S10	W	1966	High School	Organizasyon Şirketi	Married	Semantic (PPA)	anterior temporal lobe atrophy	5 months ago	Right	170
S11	W	1978	University	Banker	Single	Semantic (PPA)	anterior temporal lobe atrophy	6 months ago	Right	164

ID: Identification Document, W: Women, M: Male, PPA: Primary Progressive Aphasia, ADD: Aphasia Language Assessment Test.

In **Table 3**, the statistical analyses performed to assess the differences between svPPA and lvPPA groups regarding MoCA scores are shown. As shown in the **Table 3**, there was a significant difference between svPPA and lvPPA group regarding MoCA scores (p<0.001). When this was analyzed, it was revealed that those with svPPA had higher scores in MoCA.

Table 3. Independent samples t-tests for MoCA

Variables	svPPA (N=11)		lvPPA (N=11)		t	p
	M	SD	M	SD		
MoCA	9.36	2.203	4.45	2.252	5.168	0.00*

*<.05 **<.01 ***<.001, M: Mean, SD: standard deviation, MoCA: The Montreal Cognitive Assessment Scale, svPPA: Semantic Variant Primary Progressive Aphasia, lvPPA: Logopenic Variant Primary Progressive Aphasia

We then performed correlation analysis for each PPA groups regarding MoCA, The Proverb Scale and PPTT. As shown in **Table 4**, there was a high correlation between the Proverb Scale and MoCA scores in svPP (p=0.711). In the other variables, there was no correlation between proverb comprehension and PPTT. We also performed correlation analysis for lvPPA group regarding MoCA, The Proverb Scale and PPTT. **Table 5** shows correlation analysis for lvPPA. As shown in **Table 5**, there was no correlation between idiom comprehension, MoCA and PPTT.

Table 4. Correlation for svPPA

		MoCA	Proverb	PPTT
MoCA	r	1	0.711*	0.427
	p		0.14	0.190
	N	11	11	11
The Proverb Scale	r	0.711*	1	0.282
	p	0.014		0.401
	N	11	11	11
PPTT	r	0.427	0.282	1
	p	0.190	0.401	
	N	11	11	11

*p<.05 significant relationship; ** r= 0-.30 weak, .30-.50 low , .50-.70 medium , .70 and above high correlation (+/-)., MoCA: The Montreal Cognitive Assessment Scale, PPTT: The Pyramids and Palm Trees Test, svPPA: Semantic Variant Primary Progressive Aphasia

Table 5. Correlation analysis for lvPPA

		MoCA	Proverb	PPTT
MoCA	r	1	-0.112	-0.175
	p		,744	0.607
	N	11	11	11
The Proverb Scale	r	-0.112	1	-,062
	p	0.744		,857
	N	11	11	11
PPTT	r	-0.175	-0.062	1
	p	0.607	0.857	
	N	11	11	11

*p<.05 significant relationship; ** r= 0-.30 weak, .30-.50 low , .50-.70 medium , .70 and above high correlation (+/-). MoCA: The Montreal Cognitive Assessment Scale, PPTT: The Pyramids and Palm Trees Test, lvPPA: Logopenic Variant Primary Progressive Aphasia

DISCUSSION

The primary objective of this study was to determine whether the understanding of proverbs in PPA is impaired by comparing semantic and logopenic variants. nodules. It is an important study, as there is no other study of Turkish speaking PPA patients proverb comprehension as for our knowledge. As for the aim of our study, we found out that all participants had low scores in the PPTT task, which is a semantic network assessment task. In this task, the highest score a person can get is 52, in both PPA groups, it was comparatively low. Especially in lvPPA, access to the semantic network is impaired, when compared to svPPA patients. In the literature it was suggested that svPPA is distinguished from logopenic variant primary progressive aphasia (lvPPA) and nonfluent agrammatic variant primary progressive aphasia (nfvPPA) based on performance on semantic memory tasks.[15] One of the interesting findings of our study that lvPPA group had lower score when it was compared to svPPA. As in the literature it was suggested that only svPPA patients had impaired object semantics, however in our study group lvPPA had also lower scores.

Apart from PPTT scores, MoCA scores were found to be significantly different between svPPA and lvPPA. In the previous studies, it was evident that PPA patients can be differentiated by using language and attention subtest of MoCA, when it was compared with AD.[21] It can be explained by the nature of PPA, as it starts with the decline in language abilities and continues to detoriate. Even though it was evident in the cognitive assessment that different PPA subtypes can be significantly different in cognitive abilities, it is still very important to conduct comprehensive and rigorous neuropsychological assessment to clinically diagnosis of dementia phenotypes.

When it comes to the proverb comperehension, patients with svPPA had significantly lower scores than lvPPA. This can be explained Marshall et al., the problem in svPPA is not merely a problem of accessing words in memory, but erosion of vocabulary itself. Therefore, the most significant change is in the ability to retrieve words from storage. It is more accurately described as a lack of comprehension or recognition of words and objects than anomia.[4]

The higher the MoCA score, the higher the proverb comprehension in the participant with svPPA. It is an important finding to show that there is a strong correlation between executive functinos and cognition when it comes to language and comprehension. Idioms are multiword constructs whose metaphorical meanings cannot be computed from the literal meanings of their component words, yet are understood swiftly and easily by unimpaired Individuals diagnosed with lvPPA frequently struggle with comprehension of sentences.[22-25]

Also, we found a high correlation between the MoCA and proverb comprehension in svPPA.

Individuals diagnosed with lvPPA frequently struggle with comprehension of sentences.[15-27] Our results in idiom comprehension were in line with this finding of previous research. The highest score achieved was 23 out of 40, so their explanations for idioms were almost half correct and it shows that they have difficulty in abstraction. It is also quite important to note that familiarity is an indicator for proverb comprehension. The data from these several measures of understanding all demonstrate the fact that familiarity improves proverb comprehension.[27]

Inhibition is also very important in understanding PPA. As the neurodegeneration progress, so does the deterioration in executive functions. Papagno et al. suggested that patients with Alzheimer's disease are aware of the proverb's meaning, but that the literal interpretation, which is also activated, significantly interferes with it; it also indicates that patients do not choose the literal interpretation based on a single word in the idiom.[5] It appears that patients are unable to suppress literal interpretation when it is represented explicitly. It can be the case in the primary progressive aphasia. Therefore, more comprehensive research should be conducted to understand the difference in PPA.

Clinical Implications

Since Primary Progressive Aphasia (PPA) is considered a language-related class of dementia, it is diagnosed by focusing on different cognitive and executive symptoms, and the loss of naming skills and differentiation in speech production may be overlooked. For this reason, in the clinical context, understanding the precursor symptoms at the initial stage will contribute to maintaining the communication and quality of life of the cases as much as possible, even in a neurodegenerative condition. The assessment procedures of comprehension and abstraction skills remain incomplete from the perspective of speech and language therapy due to the need to develop Turkish assessment procedures and the limited availability of language assessment batteries for PPA. For these reasons, studies for the PPA group, which has minimal access, are critical for the processes to be understandable in these case groups. It is essential for the evaluation processes to provide information findings in terms of the abstraction ability of proverbs and to provide inferences about naming performances.

Limitations

One of the limitations of the study is the number of the participants, as PPA is hard to reach population. More comprehensive studies with larger groups including nfvPPA may help understanding PPA more. Also, other means of proverb comprehensin tools can be used in order to explain the findings such as matching pictures etc.

As a case group, access to PPA is very difficult and limited. In this respect, the multidimensional and costly evaluation procedures and the evaluation of PPA as a general dementia group, and the studies carried out on dementia variants are of great importance. Access to case groups and all types remains quite limited, and the study is limited in terms of the number of participants. The fact that the participants' emotional states are negative in terms of decreased attention process and neurodegenerative features causes the test and evaluation tools applied to be limited. In this respect, our study was carried out as a single center with 2 variants and limited evaluation tools.

CONCLUSION

The proverb comprehension task can help shed light on PPA by providing evidence of sound, word, and sentence production. For the further studies, item analysis for literal and non-literal meanings for idioms can be explored. According to our research, one of the primary factors that contributes to impairment in proverb comprehension may be difficulties accessing figurative meanings. In order to understand this phenomenon better, further studies should be conducted.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bahçeşehir University Research and Publication Ethics Committee (Date: 27/04/2023, Decision No:E-85646034-604.02.02-59908)

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1331897
J Contemp Med 2023;13(5):776-781

Original Article / Orijinal Araştırma

Evaluation of Neutrophil-Lymphocyte Ratios According to Gupta Perioperative Myocardial Infarction or Cardiac Arrest (MICA) Risk Index in Elderly Patients Undergoing Hip Surgery

Kalça Operasyonu Yapılan Yaşlı Hastalarda Gupta Perioperatif Miyokard Enfarktüsü veya Kardiyak Arrest (MICA) Risk İndeksine Göre Nötrofil-Lenfosit Oranlarının Değerlendirilmesi

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Abstract

Aim: Perioperative cardiac events are a leading cause of mortality after surgery. Consequently, risk stratification for perioperative myocardial ischemia and cardiac arrest has gained significant importance before surgery. The Gupta perioperative myocardial infarction or cardiac arrest (MICA) risk index provides a risk estimate for perioperative myocardial infarction or cardiac arrest. This study aimed to investigate the relationship between the MICA risk index and neutrophil-lymphocyte ratios (NLR) in elderly patients undergoing hip surgery.

Material and Method: The medical records of patients operated on for hip fracture surgery between 01.10.2021 and 30.04.2022 were retrospectively analyzed. Demographic data, comorbidities, clinical and laboratory characteristics, NLR, and length of hospital stay were evaluated. Subsequently, MICA scores were computed. According to the MICA score, patients were categorized into two groups: a high-risk group (risk greater than 1%) and a low-risk group, and the preoperative NLR of these two groups was compared.

Results: The study included 83 patients aged 65 and older out of a total of 191 patients who underwent hip fracture surgery. The patients were assessed based on their MICA cardiac risk scores, and they were categorized into two groups: those with a MICA score<1 (n=30) and those with a MICA score≥1 (n=53). Gender and body mass index (BMI) showed no significant differences between the groups. However, there were statistically significant variations observed in terms of age (p<0.001), the American Society of Anaesthesiologists (ASA) classification (p<0.001), and comorbidities (p=0.042). Patients with a MICA score≥1 exhibited significant differences when compared to those with a MICA score<1 in terms of postoperative intensive care unit admission (p=0.003), complication rate (p<0.001), mortality (p=0.004), and length of hospital stay (p=0.025). Furthermore, there was a positive correlation between the MICA score and preoperative NLR (p=0.619, r=0.055), although no significant difference was found between the two groups (p=0.486). While the NLR was higher in patients with adverse outcomes (exitus) compared to those without, this difference did not reach statistical significance (p=0.165).

Conclusion: A comprehensive multidisciplinary approach is crucial for assessing preoperative risk factors and devising appropriate treatment strategies in elderly patients undergoing hip surgery. The MICA score can serve as a valuable tool for predicting perioperative risk in this patient population. Our study revealed no significant association between preoperative NLR and the MICA score.

Keywords: MICA score, hip fracture surgery, NLR, perioperative period, elderly patient

Öz

Amaç: Perioperatif kardiyak olaylar, cerrahi sonrası önde gelen ölüm nedenlerindendir. Bu nedenle, perioperatif miyokard iskemisi ve kardiyak arrest için risk sınıflaması, cerrahi öncesi önemli hale gelmiştir. Gupta perioperatif miyokard enfarktüsü veya kardiyak arrest (MICA) risk indeksi, perioperatif miyokard enfarktüsü veya kalp durması için bir risk tahmini sağlar. Bu çalışmanın amacı, kalça operasyonu geçiren yaşlı hastalarda MICA risk indeksi ve nötrofil lenfosit oranları (NLR) arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem: Kalça kırığı nedeniyle 01.10.2021 ve 30.04.2022 tarihleri arasında opere edilen hastaların dosyaları retrospektif olarak tarandı. Hastaların demografik bulguları, komorbiditeleri, klinik ve laboratuvar özellikleri, NLR'i, hastanede kalış süreleri değerlendirildi. MICA skorları hesaplandı. MICA skoruna göre yüksek riskli grup (%1 'in üzeri yüksek risk) ve düşük riskli grup olarak 2 gruba ayrıldı ve bu iki grup hastaların preoperatif NLR'i karşılaştırıldı.

Bulgular: Kalça kırığı nedeniyle opere edilen 191 hastadan 65 yaş ve üzeri 83 hasta çalışmaya dahil edildi. Hastaların MICA skorları hesaplanarak, MICA skoru<1 olanlar (n=30) ve MICA skoru≥1 olanlar (n=53) olarak 2'ye ayrıldı. Gruplar arasında hastaların cinsiyetleri, vücut kitle indeksleri (VKİ) açısından farklılık gözlenmezken, yaşları (p<0.001), Amerikan Anestezistler Derneği (ASA) sınıflamaları (p<0.001) ve ek hastalık açısından anlamlı farklılık mevcuttu (p=0.042). MICA skoru≥1 olan hastaların MICA skoru<1 olan hastalara göre postoperatif yoğun bakıma çıkış (p=0.003), komplikasyon görülme oranı (p<0.001), mortalite (p=0.004)ve hastane kalış süresi (p=0.025) açısından anlamlı farklılık mevcuttu. Hastaların MICA skoru ile preoperatif NLR arasında (p=0.619, r=0.055) pozitif yönlü korelasyon gözlenirken gruplar arasında anlamlı farklılık gözlenmemiştir (p=0.486). Mortalite açısından baktığımızdan exitus olanlarda NLR, olmayanlara göre daha yüksek çıksa da anlamlı farklılık gözlenmemiştir (p=0.165).

Sonuç: Kalça operasyonu olan yaşlı hastalarda preoperatif risk faktörlerinin belirlenmesi ve bu riske yönelik tedavi planlamasında multidisipliner yaklaşım önemlidir. Bu hastalarda perioperatif riski tahmin etmek için MICA skoru kullanılabilir. Çalışmamızda preoperatif NLR'nın MICA skoru ile ilişkili olmadığı sonucunu bulduk.

Anahtar Kelimeler: MICA skoru, kalça kırığı cerrahisi, NLR, perioperatif dönem, yaşlı hasta

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Received *(Geliş Tarihi)*: 24.07.2023 **Accepted *(Kabul Tarihi)*:** 05.09.2023

INTRODUCTION

Due to the potentially severe consequences of hip fractures in elderly populations, such as mortality and inability to perform daily tasks, it becomes crucial to identify high-risk patients preoperatively. Determining preoperative risk can provide valuable insights into the optimal timing of surgery, the requirement for intensive care during treatment, and the overall prognosis for these patients.[1]

The Gupta perioperative myocardial infarction or cardiac arrest (MICA) score derived from the National Surgical Quality Improvement Programme (NSQIP) has become a commonly employed tool for evaluating the risk of experiencing intraoperative or postoperative myocardial infarction and cardiac arrest following non-cardiac surgeries. This score is calculated using parameters including age, preoperative creatinine value (mg/dl), American Society of Anaesthesiologists (ASA) classification, functional status (active mobile-passive mobile-bed-dependent), and surgical site.[2]

The 2014 American College of Cardiology and American Heart Association guidelines on perioperative assessment recommend differentiating low-risk (<1%) and high-risk (≥1%) patients for cardiac complications to guide appropriate preoperative testing. One of the recommended tools for evaluating perioperative risk is the MICA risk calculator. The validity of the MICA score has been established as a predictor for major cardiovascular events, including myocardial infarction and cardiac arrest, occurring within 30 days following orthopedic surgeries.[3]

Neutrophil-to-Lymphocyte Ratio (NLR), a marker of inflammation, is defined as the ratio of neutrophil count to lymphocyte count. It is a low-cost and easily accessible laboratory marker that can be routinely employed in clinical practice. Extensive research has demonstrated that NLR is a valuable tool for predicting the risk of mortality after surgery.[4] In this study, we aimed to investigate whether there is a correlation between MICA score and NLR.

MATERIAL AND METHOD

This study was conducted retrospectively between November 2021 and March 2022. The study was carried out with the permission of Afyonkarahisar Health Sciences University Faculty of Medicine Clinical Researches Ethics Committee (Date: 03.06.2022, Decision No: 2022/7). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study included all patients ≤ 65 years of age who underwent hip operations. However, certain criteria were used to exclude specific patient groups, including those whose medical records could not be accessed from the hospital's medulla system, cancer patients, patients with active infections, patients with severe hepatic and renal failure, those diagnosed with hematological diseases, and patients undergoing immunosuppressive therapy.

In this study, demographic data, comorbidities, clinical and laboratory characteristics, preoperative NLR, postoperative complications and length of hospital stay were evaluated, and MICA scores were computed for each patient. Based on the MICA cardiac risk score, the patients were categorized into two groups: the high-risk group (with a risk greater than 1%) and the low-risk group. Subsequently, a comparison was made between the NLR values of these two groups. Postoperative mortality of the patients was also evaluated.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 20. The data were presented as percentages (%), median, interquartile range (IQR), and mean ± standard deviation. The conformity of the variables to normal distribution was determined by visual (histogram) and analytical methods (Kolmogorov-Smirnov test). Student T or Mann-Whitney U test was used to compare continuous variables, and the Chi-square test was used to compare categorical variables. Correlation coefficients were calculated to assess the relationships between variables where at least one of the variables was either not normally distributed or ordinal, and statistical significance was calculated by the Spearman test. P<0.05 values were considered statistically significant.

RESULTS

The study comprised 83 patients aged 65 and older out of the total 191 patients who were operated on for hip fractures between November 2021 and March 2022. Based on their MICA cardiac risk scoring, patients were categorized into two groups: MICA score<1 (n=30) and MICA score≥1 (n=53) (**Figure 1**). Among the participants, 63.4% were female, and 36.6% were male, with no statistically significant difference observed in terms of gender between the two groups (p=0.991, **Table 1**). The median age of patients with MICA score<1 was 72 years, while the median age of the group with MICA score≥1 was 81 years, indicating a statistically significant difference between both groups in terms of age (p<0.001, **Table 1**).

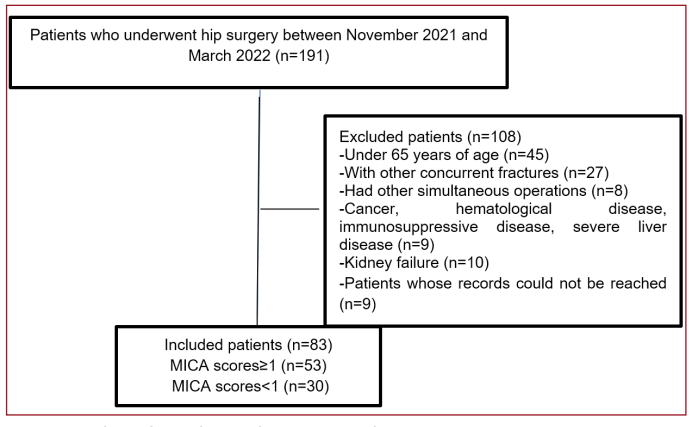

Figure 1. Flow chart shows the patient selection process

The body mass indexes (BMI) of the patients in both groups did not exhibit a statistically significant difference (p=0.183, **Table 1**). However, a significant difference was observed between the ASA distributions of the patients (p<0.001, **Table 1**). Among the patients, 84.1% had comorbidities, while 15.9% did not. Nevertheless, there was no significant difference in the distribution of comorbidities between the two groups (p=0.042). Regarding anesthesia type, 54.9% of the patients underwent surgery under general anesthesia, and 45.1% underwent regional anesthesia (p=0.831, **Table 1**).

The preoperative NLR values were found to be higher in the group with a MICA score≥1; however, this difference was not statistically significant (p=0.486, **Table 2**). In the Spearman correlation analysis, a positive correlation was observed between the calculated MICA score of the patients and the entry NLR (p=0.619, r=0.055) (2). When analyzing the NLR values according to the mortality status of the patients, it was observed that the median NLR values in the patients with exitus (10.95; 8.80) were higher compared to the NLR values in the living patients (7.07; 7.06). However, this difference did not reach statistical significance (p=0.165, **Table 2**).

Postoperatively, 51.8% of the patients were transferred to the ward, while 48.2% were transferred to the intensive care unit. Patients with MICA score≥1 had a significantly higher rate of postoperative intensive care unit visits than patients with MICA score<1(60.4%, 26.7%, p=0.003, **Table 3**, respectively). While the duration of surgery was similar in both groups, the median length of hospital stay was significantly higher in patients with MICA score≥1 (p=0.025, **Table 3**). The 30-day mortality rate was 20.5% in all patients. Mortality was significantly higher in patients with MICA score≥1 than in patients with MICA score<1 (p=0.004, **Table 3**). Postoperative complications were observed in 30.5% of the patients, with pneumonia being the most common complication, occurring at a rate of 24%, and there was a significant difference between the groups in terms of complications (p<0.001, **Table 3**). A positive correlation was observed between the MICA score and preoperative NLR values (p=0.619, r=0.055); however, no significant difference was detected between the groups (p=0.486). Upon analyzing the NLR values in terms of mortality, it was observed that NLR values were higher in patients with exitus compared to those without; however, this difference did not reach statistical significance (p=0.165).

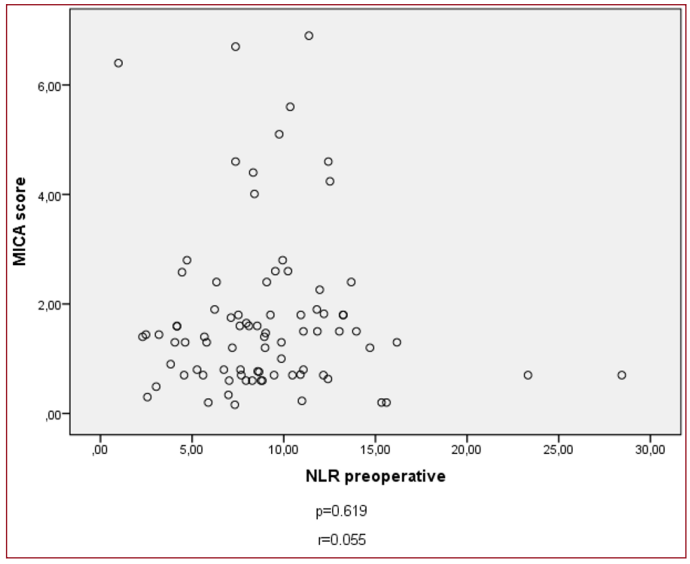

Figure 2. Correlation analysis between MICA score and entry admission NLR

Table 1. Comparison of patients' demographic data and anesthesia methods

	MICA score<1 (n=30)	MICA score≥1 (n= 53)	Total (n=83)	p
Gender, F/M, n (%)	19 (63.3) / 11 (36.7)	33 (63.5)/ 19 (36.5)	52 (63.4)/ 30 (36.6)	0.991*
Age, year Median; IQR	72; 9	81; 12	77; 14	<0.001#
BMI, median; IQR	29.34; 7.58	26.26; 12.38	28,40; 10.38	0.183#
ASA, n (%) II III IV	10 (33.3)/ 20 (66.7)/ 0	2 (3.8)/ 41 (78.8)/ 9 (17.3)	12 (14.6)/ 61 (74.4)/ 9 (11)	<0.001*
Co-morbidity, yes/no, n (%)	22 (73.3)/ 8 (26.7)	47 (90.4)/ 5 (9.6)	69 (84.1)/ 13 (15.9)	0.042*
Co-morbidity type Co-morbidity, n (%) Hypertension COPD More than 1 co-morbidity Heart disease Other	7 (31.8) 0 9 (40.9) 4 (18.2) 2 (9.1)	6 (12.8) 1 (2.1) 26 (55.3) 9 (19.1) 5 (10.6)	13 (18.8) 1 (1.4) 35 (50.7) 13 (13.8) 7 (10.1)	0.160*
Form of anesthesia, general/regional, n (%)	16 (53.3)/ 14 (46.7)	29 (55.8)/ 23 (44.2)	45 (54.9)/ 37 (45.1)	0.831*

*Chi-Square, #Mann Whitney U. Values number, median; It is given as the Interquartile Range (IQR). F/M; Female/Male, BMI; body mass index, ASA: American Society of Anesthesiologists
COPD: chronic obstructive pulmonary disease, Other; dementia, cerebrovascular disease

Table 2. Comparison of NLR values according to patients' MICA scores and mortality status

	MICA score<1 (n=30)	MICA score≥1 (n=53)	Total (n=83)	p#
NLR preoperative	6.70;7.39	8.02;6.73	7.38;7.02	0.486
	Mortality yes (n=17)	Mortality no (n=66)		
NLR preoperative	10.95;8.80	7.07;7.06	7.38;7.02	0.165

#Mann Whitney U. Values are median; It is given as the Interquartile Range (IQR). NLR; Neutrophil Lymphocyte Ratio

Table 3. Comparison of patients' postoperative discharge, length of stay, mortality, and complications

	MICA score<1 (n= 30)	MICA score≥1 (n= 53)	Total (n=83)	p
Postoperative discharge, n (%)				
Service	22 (73.3)/	21 (39.6)/	43 (51.8)/	0.003*
ICU	8 (26.7)	32 (60.4)	40 (48.2)	
Operation time, min, median; IQR	115;64	120;43	120;60	0.868#
Length of hospital stay, days	7;2	8;8	7;6	0.025#
Mortality is 30 days, n (%)				
Yes	1 (3.3)/	16 (30.2)/	17 (20.5)/	0.004*
No	29 (96.7)	37 (69.8)	66 (79.5)	
Complication, n (%)				
Yes	2 (6.7)/	23 (44.2)/	25 (30.5)/	<0.001#
No	28 (93.3)	29 (55.8)	57 (69.5)	
Type of complication, n(%)				
Kidney injury	0	3 (13)	3 (12)	
Pneumonia	0	6 (26.1)	6 (24)	
DVT	1 (50)	0	1 (4)	
MI	0	2 (8.7)	2 (8)	
Embolism	0	4 (17.4)	4 (16)	0.068*
SVO	0	1 (4.3)	1 (4)	
Wound site infection	1(50)	2 (8.7)	3 (12)	
Kidney injury + infection	0	1 (4.3)	1 (4)	
Sepsis, ARDS	0	3 (13)	3 (12)	
Other	0	1 (4.3)	1 (4)	

*Chi-Square, #Mann Whitney U. Values number (%), median; Interquartile Range (IQR). YB; intensive care, MI; myocardial infarction, SVO; cerebrovascular event, Renal failure; kidney failure, DVT; deep vein thrombosis, inf; infection, ARDS; acute respiratory distress syndrome

DISCUSSION

There are many studies on the use of NLR in orthopedic surgery.[8,17,18] While there are studies on the use of the MICA score in perioperative risk prediction in different surgeries.[19-21] We identified a research gap in the literature regarding the use of the MICA score in the context of orthopedic hip fractures. Consequently, our study evaluated the effectiveness of the MICA score in hip surgery and investigated its potential relationship with NLR.

A meta-analysis including 1563 hip fracture patients over 65 years of age found that high pre- and postoperative NLR was associated with long-term (1-year) mortality risk after hip fracture surgery.[14] Another study reported that an NLR value >5 on the fifth postoperative day following hip fracture surgery was associated with a high mortality risk.[8] Again, in a study in which patients over 60 years of age with acute coronary syndrome were followed up, it was concluded that there was a correlation between NLR measured at the time of hospital admission and the length of hospital stay.[15] Fisher et al.[16] found that preoperative high NLR was an important risk factor for postoperative myocardial damage, high inflammatory response, and in-hospital mortality. Our study did not reveal a significant association between preoperative NLR and mortality. However, it is important to consider that different results may emerge when patients are followed up over the long term.

Hip fractures pose significant morbidity and mortality risks, particularly in elderly individuals.[5] In most studies, age is identified as a prominent risk factor for mortality in hip fracture patients.[6] For instance, a study investigating the mortality rates of hip fracture patients reported a 30-day mortality of 19%.[7] Moreover, the 1-year mortality rate among individuals aged 65 years and older who underwent hip fracture surgery varied from 8.4% to 36%, as reported in other studies.[8] In our study, we observed a 30-day mortality rate of 30.2% in the high-risk group with a MICA score≥1, while the low-cardiac-risk group with a MICA score<1 had a significantly lower 30-day mortality rate of 3.3%. The higher mortality rate in the high-risk group may be attributed to the fact that our patients had traumatic fractures, and there might have been concomitant injuries to other organs. The fact that other traumas accompanying hip fractures were not analyzed is one of the limitations of our study.

It is believed that the application of risk models such as the Revised Cardiac Risk Index (RCRI) or NSQIP MICA in the preoperative period may reduce unnecessary cardiac tests and preoperative cardiology referrals in patients.[22]

ASA scoring is widely recognized as the most valid and widely accepted system for assessing the overall health status of surgical patients.[9] Studies have shown a substantial association between ASA scores and mortality rates following hip fractures.[10] In our study, we also

observed that patients in the high-risk group with a MICA score≥1 had higher ASA scores.

BMI>30 kg/m² is associated with prolonged surgical time, cardiac complications, and mortality risk.[11,12] However, our study did not identify a statistically significant difference in BMI among high cardiac-risk patients with a MICA score≥1. This may be due to sarcopenia and weight loss, which are commonly observed in frail elderly individuals

According to the findings of Forget et al.[8] several factors have been identified as significant predictors of mortality, cardiovascular morbidity, and infections in the early and late postoperative period of hip fracture surgery patients. These factors include advanced age, comorbidities, fifth-day (NLR), and male gender. Temiz et al.[23] showed that the NLR value at presentation could be used to determine the mortality risk in elderly patients with hip fracture.

Cardiac and infectious complications are common after hip fracture surgery.[17] Existing studies have established a link between NLR and postoperative complications after hip fracture surgery.[8,16] Our study found no correlation between postoperative complications and preoperative NLR. However, postoperative complications were higher in patients with a MICA score≥1.

A multicentre study investigating the relationship between comorbidity and mortality in hip fracture patients found that diabetes and cognitive impairment were linked to higher early and late mortality rates among geriatric patients who underwent hip fracture surgery. Our study results revealed no significant relationship between comorbidity and mortality. Additionally, no significant difference was observed between the groups with and without high cardiac risk concerning the presence of comorbidities.[13]

The limitations of our study encompass its retrospective nature, the exclusion of NLR measurement in the postoperative period, and the absence of long-term follow-up for the patients. Prospective studies in larger patient groups with long-term follow-up of patients can be planned.

CONCLUSION

Numerous parameters can be utilized to predict the risk in patients during this procedure. One of these parameters is the NLR and the MICA risk score, which is employed to predict cardiac risk and complications in patients. Our study revealed a positive correlation between the MICA score and preoperative NLR values; however, no statistically significant difference was observed between the groups. Nonetheless, we firmly believe that prospective large-scale studies are imperative, encompassing both parameters to predict mortality and assess risk effectively.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Afyonkarahisar Health Sciences University Faculty of Medicine Clinical Researches Ethics Committee (Date: 03.06.2022, Decision No: 2022/7).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1331937
J Contemp Med 2023;13(5):782-785

Original Article / Orijinal Araştırma

Clinical Outcomes of Percutaneous Endoscopic Gastrostomy in the Respiratory Intensive Care Unit

Solunum Yoğun Bakım Ünitesinde Perkütan Endoskopik Gastrostominin Klinik Sonuçları

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Abstract

Aim: Percutaneous endoscopic gastrostomy (PEG) is a feeding method used in patients who are expected to require enteral nutrition for more than 2-3 weeks. We aimed to evaluate PEG indications, complications, and post-procedural patient prognosis in patients followed up in our intensive care unit and fed via PEG.

Material and Method: We retrospectively reviewed 51 patients receiving PEG between January 1, 2017, and December 31, 2022, in the Respiratory Intensive Care Unit.

Results: Among the patients receiving PEG, 30 (58%) were male. The average age was 63.9, ranging from 23 to 90. The mean scores for the Glasgow Coma Scale (GCS), Acute Physiology and Chronic Health Evaluation II (APACHE II), and Sepsis Related Organ Failure Assessment (SOFA) were 8.47, 22, and 7.45, respectively. The mean duration until PEG placement was 24.8 days, and the average intensive care unit (ICU) hospitalization was 48.8 days.PEG was performed in 21 patients (41.2%) due to cerebrovascular disease, in 19 patients (37.3%) due to Alzheimer, dementia, or Parkinson's disease, and 18 patients (35.3%) due to prolonged mechanical ventilation. The complication rate associated with PEG was 13.7%. Among the patients who underwent PEG, 35 (68.6%) were discharged, while 16 (31.4%) died.

Conclusion: Considering its easy use at bedside, low complication, and mortality rates, PEG insertion is appropriate for continuing enteral therapies, especially in intensive care patients with insufficient oral intake.

Keywords: Percutaneous endoscopic gastrostomy, intensive care unit, indications and complications, prognosis, nutrition

Öz

Amaç: Perkütan endoskopik gastrostomi (PEG), 2-3 haftadan daha uzun süreli enteral beslenmeye ihtiyaç duyması beklenen hastalarda kullanılan beslenme yöntemidir. Yoğun bakım ünitemizde takip ettiğimiz ve beslenmelerini PEG açarak sağladığımız hastalarda PEG endikasyonlarını, komplikasyonlarını ve işlem sonrası hasta prognozlarını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Hastanemiz Solunum Yoğun Bakım Ünitesinde 1 Ocak 2017 – 31 Aralık 2022 tarihleri arasında PEG uyguladığımız 51 hastayı retrospektif olarak incelendi.

Bulgular: PEG uygulanan hastaların 30'u (%58) erkekti. Hastaların yaş ortalaması 63,9 (min 23-max 90)du. Hastaların Glasgow koma skalası (GKS) ortalaması 8,47, Akut Fizyoloji ve Kronik Sağlık Değerlendirme II (APACHE II) skoru ortalaması 22, Sepsis İlişkili Organ Yetmezliği Değerlendirmesi (SOFA) skoru ortalaması 7,45, PEG açılma günü ortalaması 24,8, yoğun bakım yatış gün ortalaması 48,8 di. Hastaların 21'ine (%41,2) Serobrovasküler hastalık(SVH), 19'una (%37,3) Alzhemier/ Demans/ Parkinson, 18'ine (35,3) uzamış mekanik ventilasyon nedeniyle PEG açıldı. PEG komplikasyon oranı %13,7 idi. PEG açılan hastaların 35'i (%68,6) taburcu, 16'sı (%31,4) exitus oldu.

Sonuç: Hasta başında kolayca uygulanabilmesi, komplikasyon ve mortalite oranlarının son derece az olması nedeniyle özellikle oral alımı yeterli olmayan yoğun bakım hastalarında enteral tedavilerin sürdürülebilmesi için PEG takılması uygundur.

Anahtar Kelimeler: Perkütan endoskopik gastrostomi, yoğun bakım ünitesi, endikasyon ve komplikasyon, prognoz, nutrisyon

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Received *(Geliş Tarihi)*: 24.07.2023 **Accepted *(Kabul Tarihi)*:** 23.08.2023

INTRODUCTION

Nutrition is a basic need for patients who are followed up and treated in the intensive care unit.[1] In cases where the patient cannot be fed orally, parenteral or enteral nutrition is administered. Enteral nutrition is used for patients with a functioning gastrointestinal system but cannot be fed orally. Enteral nutrition aims to protect the patient's mucosal integrity, mucosal barrier function, intestinal immune response, and normal flora structure.[2] The most appropriate technique for long-term enteral nutrition is gastrostomy or, less frequently, jejunostomy. There are three ways to create a gastrostomy: surgical gastrostomy, radiologic gastrostomy, or percutaneous endoscopic gastrostomy.[3] Percutaneous endoscopic gastrostomy (PEG) is a feeding method used in patients expected to need enteral nutrition for more than 2-3 weeks and was first applied to children by Gauderrer and Ponsky in 1980.[4,5] PEG is preferred in the endoscopy or intensive care unit because it is easy to perform, safe, low-cost, and less invasive.[6] In this study, we aimed to evaluate PEG indications, complications, and post-procedural prognosis of patients who were followed up in our intensive care unit and whose nutrition was provided by PEG.

MATERIAL AND METHOD

The study was carried out with the permission of Health Sciences University Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee (Date: 10.11.2022, Decision No: 2022-293). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We retrospectively analyzed 51 patients who underwent PEG between January 1, 2017, and December 31, 2022, in the Respiratory Intensive Care Unit of our hospital. Routine laboratory tests were requested from all patients with PEG indication before the procedure. Feeding of patients receiving enteral nutrition via the nasogastric route was stopped at least 8 hours before the procedure. Prophylactic antibiotics were not administered because all patients were on antibiotics for their primary diseases. All patients were evaluated for contraindications such as bleeding disorders [international normalized ratio (INR): <1.5, Platelet (Plt): >50.000], a pathology that might interfere with gastroscopy, diffuse abdominal ascites, and gastrointestinal obstruction. Peripheral oxygen saturation, electrocardiography (ECG), and systolic and diastolic blood pressure values were monitored continuously during the procedure. Sedation and analgesia were administered by an intensive care physician. The percutaneous access site was sterilized. Translumination was achieved by gastroscopy, and the puncture site was determined by finger fluctuation. The procedure was performed with the pull technique. In this study, Fujinon® Fujifilm EG-590 WR fiber endoscope was used, and a 20-Fr percutaneous endoscopic gastrostomy set EzFeed (ZKSK®-Germany) was placed in all procedures. After PEG placement, the intragastric part of the tube was determined to be fully inserted into the mucosa with a gastroduedonoscope, and bleeding control was performed. Leakage control was performed with 50 cc water 12 hours after PEG placement. Patients were gradually fed with enteral nutrition solution at a rate of 20 ml/hour 24 hours after PEG application.

The data of the patients were recorded from the patient files and the electronic archive system of the hospital. Age, gender, Charlson comorbidity index (CCI), Glasgow Coma Scale (GCS), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, number of days of hospitalization in the intensive care unit, PEG indication, PEG opening day, PEG complications, and patient prognosis were recorded.

Statistical Analysis

Descriptive statistics were used for demographic and clinical data, Chi-square analysis was used to show the relationship between categorical data, and Student T-test analysis was used for continuous variables. A p-value < 0.05 was considered significant in the study. SPSS program (Version 22, SPSS Inc., Chicago, IL, USA) was used for calculations.

RESULTS

Thirty (58%) of the patients who underwent PEG were male. The mean age of the patients was 63.9 years (min 23-max 90). The mean values of GCS, APACHE II score, SOFA score, mean PEG insertion day, and mean number of intensive care unit hospitalization are presented in **Table 1**.

Table 1: Demographic data of the patients

Mean age (years) mean (min-max)	63.9 (23-90)
Female/Male n (%)	21/30 42/58
GCS mean value	8.47 (6-15)
APACHE II score mean value mean	22.00 (4-33)
The mean value of the SOFA score	7.45 (2-11)
PEG deployment day average	24.80 (4-67)
The average number of days of intensive care hospitalization	48.80 (8-190)

GCS: Glasgow Coma Scale, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, PEG: Percutaneous Endoscopic Gastrostomy, n: Number of patients, %: Percentage, min: Minimum, max: Maximum

PEG was performed in 21 patients (41.2%) for cerebrovascular disease (CVD), 19 patients (37.3%) for Alzheimer's/ Dementia/ Parkinson's disease, and 18 patients (35.3%) for prolonged mechanical ventilation. The indications for PEG opening and PEG complications are given in **Table 2**. All PEG complications were minor, and no mortality was observed during the procedure in any patient. Compression tamponade was applied to one patient with minor bleeding, and the bleeding stopped without additional intervention. In two patients, infectious discharge developed around the PEG, and no additional treatment was performed because they received antibiotics. Enteral feeding was stopped in one patient who developed feeding intolerance, and the PEG cannula was placed in free drainage. Enteral motility was increased by intravenous metoclopramide, and enteral feeding was started. The PEG cannula was opened with pressurized water in a patient with tube obstruction.

Table 2: Patients' PEG deployment indications and complications

PEG deployment indications	n	%
Tracheo-esophageal fistula (TOSF)	1	2,0
Multiple Sclerosis (MS)	1	2,0
Cerebral Palsy (CP)	2	3,9
Inadequate oral intake	5	9,8
Cerebrovascular disease (CVD)	21	41,2
Prolonged ventilation	18	35,3
Alzheimer/Dementia/Parkinson's	19	37,3
PEG Complications	**n**	**%**
Early complication (<30 days)		
Minor bleeding	1	1,9
Leakage/non-infectious	1	1,9
Leaking/infectious	2	3,9
Nutritional intolerance	1	1,9
Late complication (>30 days)		
Obliteration	2	3,9
Total complications	7	13,7

n: Number of patients, %: Percentage

Among the patients who underwent PEG, 35 (68.6%) were discharged, 16 (31.4%) were exited, and the conditions and parameters affecting the prognosis are given in **Table 3**.

Table 3: Parameters affecting the prognosis of the patients

Factors affecting prognosis					
Variables	**Discharged**		**Exitus**		**p value**
	%	**n**	**%**	**n**	
Tracheostomy status					
No	65.7	23	87.5	14	0.176
Yes	34.4	12	12.5	2	
Gender					
Female	40	14	43.8	7	0.801
Male	60	21	56.3	9	
Charlson comorbidity index (CCI)					
0-2	57.1	20	25	4	0.033*
>3	42.9	15	75	12	
Age (Mean±SD)	65.07±21.27		63.49±15.66		0.067
SOFA score (Mean±SD)	6.36±2.24		7.86±1.75		0.001*
APACHE II score (Mean±SD)	19.29±8.40		23.05±6.19		<0.0001*
PEG deployment day (Median)	10		22		0.130
Number of days in the intensive care unit (Median)	24		46		0.183

*: Statistically significant difference, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiology and Chronic Health Evaluation II, PEG: Perkütan Endoskopik Gastrostomy, SD: Standard deviation, n: Number of patients, %: Percentage

DISCUSSION

The enteral route is preferred in patients with inadequate oral intake if gastrointestinal system functions are normal. The most important reasons for this are; low cost, protection of intestinal mucosal barrier function and intestinal immune response, maintenance of normal flora structure, and reduction of bacterial translocation/bacteremia risks.[7,8]

Nasoenteric (gastric, duodenal, or jejunal) catheters can be inserted in the early period to use the enteral route. Long-term use of these methods has complications such as pharyngeal ulceration, esophagitis, esophageal ulceration, and gastric erosion. If the enteral route is used for more than four weeks, gastrostomy is recommended.[9-11]

In the study of Tok et al., PEG deployment was found to be 28.8 days on average. In our patients hospitalized in our respiratory intensive care unit, PEG opening took a mean of 24.8 days, and in some patients, the hesitancy of relatives to give consent prolonged the process, similar to the literature.[12,13]

The Charlson comorbidity index (CCI) consists of 19 disease group variables. It is widely used in studies because of its simple structure and ability to facilitate patient evaluations. In the study conducted by Düzenli et al., their patients' mean CCI value was 4.8.[14] In our study, the mean CCI value was 2.9, and mortality was high in patients with a CCI value of 3 and above (p=0.033).

In our study, the mean APACHE II score was 22, and the mean GCS score was 8.4. In the study by Çelik et al., the mean APACHE II score was 18.5, and the mean GCS score was 8.6. In another study, the mean APACHE II score was 11.4.[12-15] In our study, APACHE II, SOFA, and CCI scores were significantly higher in patients with exitus (p=<0.0001, p=0.001, p=0.033). These values were consistent with the literature.

The neurologic patient group constitutes the majority of patients in whom PEG was placed. In the study by Kartal et al.[16] this rate was CVD at 74.6% and Alzheimer's/Dementia/Parkinson's at 10.8%. In the study by Tokunaga et al.[9] 75% of the patients had CVD. In our study, these rates were CVD at 37.2%, prolonged ventilation at 35.3%, and Alzheimer's/Dementia/Parkinson's at 37.3%. We attributed the higher proportion of patients requiring long-term ventilation compared to the literature to the fact that our intensive care unit is a respiratory intensive care unit.

In our study, two patients with Cerebral Palsy (CP) and one with Multiple Sclerosis (MS) underwent early PEG. Swallowing disorders or dysphagia are common in adults with cerebral palsy. These disorders can occur at various stages of development but are typically caused by damage to the nervous system, head, or neck.[17,18] In our patients diagnosed with CP, PEG was opened on the fourth and fifth days of intensive care unit hospitalization to prevent aspiration pneumonia and to ensure feeding. Since dysphagia may develop in patients with multiple sclerosis, these patients need nutritional support. Most of the time, the oral route for nutrition may be inadequate. PEG insertion is indicated in these patients.[19,20] PEG was laced on the sixth day of intensive care unit hospitalization in our patient diagnosed with MS.

Although PEG is a minimally invasive procedure, different complication rates have been reported.[21,22] Major complications reported with a rate of 0-2% in the literature include bleeding, perforation, gastrocolic fistula, and aspiration pneumonia.[23,24] No major complication was observed in our study. The most common minor complication is wound site infection, which has been reported with a rate of 3-30%.[25] Less common minor complications include leakage

from the tube edge and tube occlusion.[26] In our study, leakage from the tube edge occurred in one patient, and obstruction occurred in two patients. Our minor complication rate was 13.7%.

This study had some limitations. The first and most important limitation was that the study was retrospective, and the number of patients was small. Secondly, the study was single-center, and the data do not reflect the characteristics of the general population because it was a respiratory intensive care unit.

CONCLUSION

Since it can be easily applied at the bedside and the complication and mortality rates are extremely low, PEG insertion is appropriate to maintain enteral nutrition and treatments, especially in intensive care patients with insufficient oral intake..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee (Date: 10.11.2022, Decision No: 2022-293).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Note: *Presented as an oral presentation at National Lung Health Congress with International participation, March 15-18, 2023 at Sueno Deluxe Hotel, Belek Antalya.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1338980
J Contemp Med 2023;13(5):786-790

Original Article / Orijinal Araştırma

The Role of Communication with the Field during the Pandemic Period: A District Intervention Example in Preventive Health Services

Pandemi Döneminde Sahayla İletişimin Rolü: Koruyucu Sağlık Hizmetlerinde Bir İlçe Müdahale Örneği

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Abstract

Aim: The aim of this study was to examine the effect of administrative meetings with family health center staff on cancer and autism screenings in a district of Istanbul.

Material and Method: The study was designed as an intervention research conducted in a district of Istanbul. The population of the study consisted of employees working in family health centers (24 family health centers) in Sultanbeyli district. The meetings were held at the end of February 2022 at the District Health Directorate building. During the meetings, the aspects that need to be improved, especially regarding cancer and autism screenings, were conveyed. Following these meetings for field staff, the changes in preventive health services (number of screenings) at the district level were analyzed. All data were analyzed retrospectively from district health directorate records.

Results: For cervical cancer screening, the total number of screenings in Sultanbeyli district in January-February and March-April were 144 and 235, respectively. For colon cancer, the total number of screenings in January-February and March-April were 54 and 277, respectively. The total number of autism screenings in January-February and March-April were 565 and 1388, respectively. Cervical cancer screenings, colon cancer screenings and autism screenings showed statistically significant increases after the meetings ($p=0.002$, $p<0.001$ and $p<0.001$, respectively).

Conclusion: After the field meetings, there was an increase in cervical cancer, colorectal cancer and autism screenings in the district. Our study results underline the importance of communication with primary care field workers and informative meetings.

Keywords: Family health centers, cancer screening, autism screening

Öz

Amaç: Bu çalışmanın amacı, İstanbul'un bir ilçesinde aile sağlığı merkezi çalışanlarıyla yapılan idari toplantıların kanser ve otizm taramaları üzerindeki etkisini incelemektir.

Gereç ve Yöntem: Çalışma, İstanbul'un bir ilçesinde yürütülen bir müdahale araştırması olarak tasarlandı. Araştırmanın evrenini Sultanbeyli ilçesindeki aile sağlığı merkezlerinde (24 aile sağlığı merkezi) görev yapan çalışanlar oluşturmuştur. Toplantılar 2022 yılı Şubat ayı sonunda İlçe Sağlık Müdürlüğü binasında gerçekleştirildi. Toplantılarda özellikle kanser ve otizm taramaları ile ilgili iyileştirilmesi gereken yönler aktarıldı. Saha personeline yönelik bu toplantıların ardından ilçe düzeyinde koruyucu sağlık hizmetlerindeki (tarama sayıları) değişimler analiz edildi. Tüm veriler ilçe sağlık müdürlüğü kayıtlarından retrospektif olarak analiz edildi.

Bulgular: Serviks kanseri taraması için Sultanbeyli ilçesinde Ocak-Şubat ve Mart-Nisan aylarında yapılan toplam tarama sayısı sırasıyla 144 ve 235'tir. Kolon kanseri için Ocak-Şubat ve Mart-Nisan aylarında yapılan toplam tarama sayısı sırasıyla 54 ve 277'dir. Otizm taramalarının toplam sayısı Ocak-Şubat ve Mart-Nisan aylarında sırasıyla 565 ve 1388'dir. Serviks kanseri taramaları, kolon kanseri taramaları ve otizm taramaları toplantılardan sonra istatistiksel olarak anlamlı artış göstermiştir (sırasıyla $p=0.002$, $p<0.001$ ve $p<0.001$).

Sonuç: Saha toplantılarından sonra ilçede serviks kanseri, kolorektal kanser ve otizm taramalarında artış olmuştur. Çalışma sonuçlarımız, birinci basamak saha çalışanları ile iletişimin ve bilgilendirme toplantılarının önemini vurgulamaktadır.

Anahtar Kelimeler: Aile sağlığı merkezleri, kanser taraması, otizm taraması

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INTRODUCTION

Treatment services and preventive health services are offered together in primary health care institutions.[1] Preventive health services constitute an important part of health services. Because of the complex nature, multiple determinants, and causation of diseases, a broad, comprehensive and sustained effort is required for preventive strategies. Expectations of the benefits of health promotion and disease prevention are of the extremely importance.[2]

Preventive health measures are grouped as primary prevention, secondary prevention and tertiary prevention in order to prevent the related stages of diseases.[3] Primary prevention is expressed as the measures applied to eliminate the causes of the disease before the person becomes ill.[4] Secondary prevention is the early detection of diseases, usually in the form of screening programs. Easier and more effective treatments can be applied to the patient by early detection of diseases with screening programs carried out within the scope of preventive health services.[5] Services offered under tertiary protection are treatments and rehabilitation programs, and services aimed at reducing possible complications of the disease.[6]

Raising awareness in the society about cancer, creating social awareness and cancer screenings are among the most effective methods in the fight against cancer. Early diagnosis of cancer cases can be provided through cancer screenings; thus, early intervention can be possible before the disease progresses and mortality and morbidity can be reduced.[7] In our country, screening is performed in three cancer types recommended by the World Health Organization within the scope of secondary prevention services.[8] The screened cancers are breast cancer, cervical cancer and colon cancer. Within the scope of the breast cancer screening program in women in our country, it is recommended to provide the necessary counseling for women to perform breast self-examination once a month, clinical breast examination once a year and mammography every 2 years for women aged 40-69 years. As part of the cervical cancer screening program, it is recommended that women between the ages of 30 and 65 years undergo a pap smear and HPV-DNA test every 5 years. As part of the colorectal cancer screening program, men and women between the ages of 50 and 70 years are offered a fecal occult blood test every 2 years. In addition, colonoscopy is recommended every 10 years in this age group.[8]

Autism, which is increasing in frequency, is an important public health problem today.[9] Autism is a neurodevelopmental disorder and according to World Health Organization data, one in every 100 children has autism.[10] Since the communication and social skills of individuals with autism can be improved with early diagnosis and interventions, autism screenings conducted in primary care are extremely important.[10] In our country, within the scope of the 'National Autism Action Plan', psychosocial examination of children aged 18-36 months is performed by family physicians and children deemed risky are referred to child and adolescent mental health outpatient clinics.[11]

Studies aiming to protect and improve human and community health fall under the concept of health communication.[12] Health communication is extremely important in preventing diseases and improving health.[13] The success of preventive health services can be increased with accurate health communication. Many studies in the literature have focused on patient-physician communication. However, communication of administrative units with healthcare professionals is also important. The aim of this study was to examine the effect of administrative meetings with family health center staff on cancer and autism screenings in a district of Istanbul.

MATERIAL AND METHOD

The study was carried out with the permission of İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 26/10/2022, Decision No: 898). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was designed as an intervention research conducted in a district of Istanbul. The population of the study consisted of employees working in family health centers (24 family health centers) in Sultanbeyli district, and no sample selection was made. The meetings were held at the end of February 2022 at the District Health Directorate building. A total of 8 meetings were held with family physicians and family health workers separately in 4 groups. Each family health center was invited to one meeting. The meetings were similar in content and duration (approximately 2 hours) to the physicians and family health workers working in the family health center. During the meetings, district health indicators were presented to family physicians and family health workers working in the field. The aspects that need to be improved, especially regarding cancer and autism screenings, were conveyed. The necessity of screenings conducted in family health centers and the importance of early diagnosis in terms of the course of diseases were mentioned. Following these meetings for field staff, the changes in preventive health services (number of screenings) at the district level were analyzed. All data were analyzed retrospectively from district health directorate records. Apart from this, no data were collected from the individuals themselves.

Statistical Analysis

Statistical analysis of the research data was performed with SPSS 24.0 package program. Descriptive data were presented as number and percentage for categorical variables and minimum and maximum values and median values for continuous variables. Chi-square test was used to compare categorical variables. Wilcoxon test was used for statistical comparison of two dependent groups (number of screenings before and after the meetings). Statistical significance was accepted as $p<0.05$.

RESULTS

Within the scope of the study, the staff of 24 family health centers were interviewed. When 99 units affiliated to family health centers were evaluated, the number of units where both the physician and the family health worker attended the meeting was 63 (63.6%), while in 30 (30.3%) units, one of the physician or family health worker attended the meeting. Six (6.1%) units did not attend the meetings.

Of the 71 family physicians who attended the meeting, 27 (38.0%) were female and 44 (62.0%) were male. The median age of family physicians was 43.0 years (26.0-66.0). The median duration of family physicians' employment in family health centers was 6.0 years, with a minimum of 2 months and a maximum of 11 years. All 84 family health workers who attended the meeting were women. The median age of family health workers was 37.5 years (25.0-52.0). The median duration of employment of family health workers in family health centers was 4.5 years, with a minimum of 1 month and a maximum of 11 years (**Table 1**).

Table 1. Sociodemographic characteristics of family physicians and family health workers

	Family physicians (n=71)	Family health workers (n=84)
Gender, n (%) Female Male	 27 (38.0) 44 (62.0)	 91 (100.0) 0 (0)
Age, median (min-max)	43.0 (26.0-66.0)	37.5 (25.0-52.0)
Duration of working in FHC, median (min-max)	6.0 years (2 months-11 years)	4.5 years (1 month -11 years)

FHC:Family health center

Within the scope of the study, the number of cervical and colon cancer screenings and the number of autism screenings performed by family health centers were evaluated in a 4-month period between January and April 2022. For cervical cancer screening, the total number of screenings in Sultanbeyli district in January-February and March-April were 144 and 235, respectively. For colon cancer, the total number of screenings in January-February and March-April were 54 and 277, respectively. The total number of autism screenings in January-February and March-April were 565 and 1388, respectively.

The median values of the number of screenings in all units in the district before (January-February) and after (March-April) the field meetings organized within the scope of the study were compared. Cervical cancer screenings, colon cancer screenings and autism screenings showed statistically significant increases after the meetings (p=0.002, p<0.001 and p<0.001, respectively). The total number of screenings in our district in the months before and after the meetings are shown in **Figure 1**.

Units of family health centers that attended the meetings with both family physicians and family health workers were considered as fully participating units. Units that attended the meeting with only a family physician or only a family health worker and units that did not participate at all were considered as units that did not fully participate in the meeting, and the increase in the number of screenings in the months after the meeting was compared. The rates of increase in all three screenings were higher in units with full participation in the meeting. The rate of increase in the number of cervical cancer screenings was 36.1% (n=13) in units that did not fully participate in the meeting and 46.0% (n=29) in units that fully participated in the meeting (p=0.337). The rate of increase in the number of colon cancer screenings was 41.7% (n=15) in units that did not fully participate in the meeting and 49.2% (n=31) in units that fully participated in the meeting (p=0.469). The median rate of increase in the number of autism screenings in the post-meeting months was 55.6% (n=20) in units that did not fully participate in the meeting and 76.2% (n=48) in units that fully participated in the meeting. This rate of increase in the number of autism screenings in the units that fully participated in the meeting was statistically significant compared to the units that did not fully participate in the meeting (p=0.033) (**Table 2**).

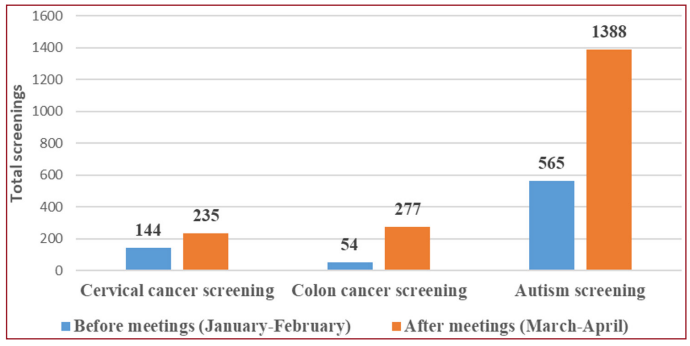

Figure 1. Total number of screenings in the district in the months before and after the meeting

Table 2. Increase in the number of screenings in the months following the meeting with full participation in the meeting

Screenings	Increase in the number of screenings n (%)		P value
	Not fully participating in the meeting (n=36)	Fully participated the meeting (n=63)	
Cervical cancer screening	13 (36.1)	29 (46.0)	0.337
Colon cancer screening	15 (41.7)	31 (49.2)	0.469
Autism screening	20 (55.6)	48 (76.2)	0.033

Factors that may be associated with the increase in the number of screenings were evaluated. No significant correlation was found between the rate of increase in the number of all three screenings and the gender and age of family physicians in the district (p>0.05). Units in family health centers with a population of 3000 or more were considered as high population units and units with a population of less than 3000 were considered as low population units. Units with a low number of population had higher rates of increase in all three screenings, but statistical significance was not observed (p>0.05) (**Table 3**).

Table 3. The relationship between the increase in the number of screenings and the number of family physicians in terms of age, gender and the population of the unit

	Increase in the number of screenings n (%)	Cervical cancer screening	Colon cancer screening	Autism screening
Gender of the physician	Female	18 (47.4)	17 (44.7)	27 (71.1)
	Male	24 (40.7)	28 (47.5)	40 (67.8)
P value		0.516	0.793	0.735
Age of the physician	Above 40	23 (46.9)	25 (51.0)	34 (69.4)
	40 and below	19 (39.6)	20 (41.7)	33 (68.8)
P value		0.465	0.356	0.946
Population of the unit	Low population units (n=12)	2 (16.7)	5 (41.7)	6 (50.0)
	High population units (n=87)	40 (46.0)	41 (47.1)	62 (71.3)
P value		0.054	0.722	0.184

DISCUSSION

Screenings, especially cancer screenings, have an important place in primary health care services. Informative meetings were organized for family health center staff about cervical cancer, colorectal cancer and autism screenings among the screening services offered in family health centers. In this study, we aimed to evaluate the effect of these meetings on the number of screenings and compared the number of screenings before and after the meetings.

In the meetings organized within the scope of our study, 6.1% of the family health center units did not participate. This low rate suggests that family physicians and family health workers have a high interest in the field trainings and meetings to be organized. If trainings are organized to increase the level of knowledge and awareness in other preventive health services provided in primary care, participation may be similarly high. According to the literature, more effective health care is provided with primary health care services provided by well-trained family physicians.[14] For this reason, it is important to maintain communication and interaction with primary healthcare professionals at certain intervals.

In health services, it is necessary to evaluate not only the high level of participation in informative trainings and meetings, but also the extent to which benefits are derived from such participation. In this context, the evaluation of field data before and after the training can give an idea about the efficiency and effectiveness of the meetings organized. In our study, the total number of cervical cancer screenings performed in family health centers in the district in the two-month period before the meetings were 144 and 235. For colon cancer, the number of screenings before and after the meeting were 54 and 277, respectively. For autism screening, the total number of screenings before and after the meeting were 565 and 1388. It is encouraging to see an increase in the total number of screenings for all three screenings we evaluated. In an intervention study in the literature, physicians were provided with reminders such as monthly seminars on cancer screenings and an increase in cancer screening performance was observed after 9 months of intervention.[15] In another intervention study in the literature, electronic reminders about cancer screenings and training of physicians and allied health professionals had a positive effect on colon cancer screening rates.[16] In a study conducted in our country, it was reported that healthcare workers' awareness of the national cancer screening program was not sufficient. In the same study, individual participation rates of healthcare workers in cancer screening were reported to be insufficient.[10] In a different study in our country, similarly, the level of knowledge of primary health care workers about the National Cancer Screening Standards was found to be low. In the same study, the level of knowledge about screening was found to be higher in those who received training.[17] According to the literature and our study results, in order for screening programs to be successful, periodic trainings and meetings should be organized, with emphasis on the areas in which physicians and healthcare professionals working in the field are deficient.

In our study, the rate of increase in all three screenings was higher in units that fully participated in the meetings compared to units that did not fully participate in the meetings. It is likely that this high rate was achieved through participation in the meeting and increased awareness after the meeting. On the other hand, there was an increase in the number of screenings in units that did not fully participate in the meeting, although proportionally lower. This suggests that health workers providing preventive health services are in interaction and information exchange in the field.

When the gender and age of the family physicians who participated in the meeting, which may be related to the increase in the number of screenings, were evaluated, no significant effect of age and gender on the number of screenings was observed. This finding reflects that younger and older physicians and physicians of both genders have similar attitudes towards the provision of screening services.

In the literature, decreases in cancer screening rates have been observed in our country and in different countries with the COVID-19 pandemic.[18-20] The fact that screening rates lag behind other health services may be due to reasons such as closures as a pandemic measure and a decrease in the interest of the society.[19] In one of the studies conducted in our country during the pandemic period, delays in vaccinations offered in primary care were reported.[21] In preventive health services, counseling services and information to be provided to the target group are extremely important. For this, the healthcare professionals who will provide counseling services should also have a high level of knowledge and awareness. We think that our study, which we conducted during the pandemic period, increased awareness about screening. In this way, we anticipate that the possible decrease in the number of screenings with the pandemic will be prevented and screenings will gain importance again in family health centers in the district.

Primary health care providers need sufficient time to carry out screening programs as well as their level of knowledge and awareness in terms of the success of screening services. In primary healthcare services, preventive and curative healthcare services are carried out together.[22] In family health center units with a high number of population, sufficient time may not be allocated for preventive health services. In the literature, lack of time has been reported as one of the main obstacles in the provision of preventive health services in primary care.[23] In our study, no significant correlation was observed between the number of population of the family health center unit and an increase in screening. Qualitative studies examining the barriers encountered by healthcare workers in the delivery of preventive healthcare services are needed.

Limitations and strengths

The fact that the study is based on data from a single district creates a limitation in terms of generalizability of the results. Another limitation is that other factors that may explain the increase in the number of screenings, such as the number of applications to family health centers, were not evaluated within the scope of the study. In addition, since the number of studies similar to our study in the literature is limited, we believe that our study makes an important contribution to the literature.

CONCLUSION

Screenings, which have an important place among health services, should be made widespread and their accessibility should be increased. For this purpose, it is extremely important to increase the level of knowledge and awareness of family health center employees who provide screening services. In the study we conducted in this context, the rate of participation in informative field meetings was high. After the field meetings, there was an increase in cervical cancer, colorectal cancer and autism screenings in the district. This increase was more evident in units that fully participated in the meeting, especially in autism screening. Our study results underline the importance of communication with primary care field workers and informative meetings. Similar interventions can be planned to increase other preventive health services.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 26/10/2022, Decision No: 898).

Informed Consent: Since the study conducted retrospectively, no informed consent was obtained.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1338911
J Contemp Med 2023;13(5):791-795

Original Article / Orijinal Araştırma

Comparison of Abdominal Initial Entry Techniques in Gynecological Laparoscopy

Jinekolojik Laparoskopide Abdominal İlk Giriş Tekniklerinin Karşılaştırılması

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Abstract

Aim: The aim of this study is to assess the safety of laparoscopic entry techniques.

Material and Method: Within the scope of the study, medical records of patients who underwent laparoscopy due to various gynecological indications at our clinic between January 1, 2011, and July 1, 2015, were examined. Evaluation was conducted using our hospital's electronic database.

Results: In the patient cohort, direct trocar placement was preferred in 91.8% (1025 patients), Veress needle placement was used in 7.4% (82 patients), and an open technique was used in 0.8% (9 patients). In terms of entry sites, umbilicus was the most commonly chosen option, being preferred in 97.2% (1085 patients) of cases. In 2.4% of patients (27 patients), the midline abdominal trocar was preferred as the initial trocar insertion site. Among these patients, suprapubic incision was preferred in 62% (17 patients), while Lee-Huang point was chosen as the entry site in 38% (10 patients).Looking at the history of previous surgeries, 18.5% (206 patients) had a history of prior abdominal surgery, and 3.5% (39 patients) had undergone two previous surgical procedures. Only 0.1% (1 patient) had undergone three or more abdominal surgeries.

Conclusion: No clear superiority of one initial entry technique over another has been proven. Despite the extensive literature on laparoscopic entry, debates regarding the most effective method to prevent significant complications continue.

Keywords: Abdominal entry, direct trocar entry, laparoscopy, technique, complication

Öz

Amaç: Bu çalışmanın amacı, laparoskopik giriş tekniklerinin güvenliğini değerlendirmektir.

Gereç ve Yöntem: Çalışma kapsamında, 1 Ocak 2011 ile 1 Temmuz 2015 tarihleri arasında kliniğimizde çeşitli jinekolojik endikasyonlar nedeniyle laparoskopi geçiren hastaların tıbbi kayıtları incelenmiştir. Hastanemizin elektronik veritabanı kullanılarak değerlendirme yapılmıştır.

Bulgular: Hasta kohortu içinde, doğrudan trokar yerleştirilmesi %91.8'lik bir tercih oranıyla (1025 hasta), Veress iğnesi yerleştirilmesi %7.4'lük bir oranla (82 hasta) ve açık bir teknik %0.8'lik bir oranla (9 hasta) kullanılmıştır. Giriş bölgeleri açısından, umblikus vakaların %97.2'sinde (1085 hasta) tercih edilmiştir.Hastaların %2.4'ünde (27 hasta), ilk trokar giriş yeri olarak trokar orta hat abdomen tercih edilmiştir. Bu hastaların %62'sinde (17 hasta) suprapubik insizyonu tercih edilirken, %38'inde (10 hasta) giriş noktası olarak Lee-Huang noktası seçilmiştir. Geçmiş cerrahi öyküsüne bakıldığında, hastaların %18.5'inde (206 hasta) bir önceki karın cerrahisi operasyonu bulunurken, %3.5'inde (39 hasta) iki önceki cerrahi operasyonu bulunmaktadır. Yalnızca %0.1'i (1 hasta), üç veya daha fazla abdominal cerrahi geçirmiştir.

Sonuç: Bir ilk giriş tekniğinin diğerine göre açık bir üstünlüğü kanıtlanmamıştır. Laparoskopik giriş hakkında yaygın literatür olmasına rağmen, önemli komplikasyonları önlemek için en etkili yöntem konusundaki tartışmalar devam etmektedir.

Anahtar Kelimeler: Abdominal giriş, direkt trokar girişi, laparoskopi, teknikler, komplikasyon

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Received *(Geliş Tarihi)*: 11.08.2023 **Accepted *(Kabul Tarihi)*:** 05.09.2023

INTRODUCTION

Laparoscopic surgery has gained significant recognition over the past three decades, emerging as a preferred technique in various procedures like tubal sterilization, salpingectomy, and endometriosis.[1] This approach offers notable advantages, including lower risk of complications, quicker recovery, reduced postoperative discomfort, and improved cosmetic results.

Performing laparoscopic surgery necessitates adapting to a two-dimensional visual field on a screen, utilizing elongated instruments, grasping depth perception, and operating with minimal tactile feedback.[2-4] Proficiency in these skills hinges on proper training, embracing laparoscopic methods, and investing time to master them.[2,3]

The evolution of three-dimensional imaging methods and advancements in laparoscopic equipment have contributed to the expansion and widespread adoption of endoscopic procedures. Enhanced educational initiatives have the potential to establish laparoscopy as the preferred approach, making it more economically accessible and stimulating increased industrial research due to its growing popularity.

Despite the rapid progress in laparoscopic surgery, complications linked to initial trocar insertion remain a major concern, accounting for around 40-50% of the most frequent complications and representing the riskiest phase of the operation. Ensuring safe entry systems in laparoscopy is of utmost importance. A range of laparoscopic entry techniques exists, and multiple strategies, instruments, and approaches have been explored to lower complication rates. This study aims to assess the safety of laparoscopic entry methods through a retrospective analysis of patient records selected for laparoscopy for various gynecological reasons in our clinic.

MATERIAL AND METHOD

The study was carried out with the permission of Bağcılar Training and Research Hospaital Non-interventional Clinical Reesearches Ethics Committee (Date: 07.08.2015, Decision No: 2015-407). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study encompassed all individuals who underwent laparoscopic procedures at a tertiary care hospital's Obstetrics and Gynecology clinic between January 1, 2011, and July 1, 2015. We retrospectively gathered patient information from both medical records and the computerized information system. Our investigation aimed to explore various facets, including the approach utilized for the initial laparoscopic entry, the selected entry point, previous surgical history, the presence of adhesions, and the intended surgical procedure. In total, our study involved 1116 patients. Prior to the operation, all patients were duly informed about potential complications, and their informed consent was duly obtained. Statistical analysis of the data was performed using SPSS (Statistical Package for Social Sciences) software version 15.0.

RESULTS

When we analyzed the data, we found that 91.8% of cases (1025 patients) used direct trocar insertion, 7.4% (82 patients) used the Veress needle technique, and 0.8% (9 patients) underwent an open approach for the initial laparoscopic entry. Among the different entry sites, the most popular choice was the umbilicus, selected by 97.2% of cases (1085 patients). In a subset of patients (2.41%), the first trocar was inserted through the midline abdomen. Among them, the suprapubic region was the preferred entry site for 62% (17 patients), while the Lee-Huang point was chosen by 38% (10 patients). A small proportion of patients (0.35%) used the Palmer point as their entry site.

During the surgery, it was observed that 25.2% (281 patients) had adhesions, while 74.8% (835 patients) did not have adhesions. Among the patients, 77.95% (870 patients) had no history of abdominal surgery. On the other hand, 18.45% (206 patients) had undergone one abdominal surgery, 3.49% (39 patients) had undergone two, and only one patient had experienced three or more abdominal surgical procedures (**Table 1**).

Table 1. Distribution of Patients According to Entry Site, Presence of Adhesions, and History of Previous Surgery

	Number of Patients	Percentage
Entry Site		
Umblicus	1085	%97,2
Midline abdomen	27	%2,41
Palmer's point	4	%0,35
Presence of Adhesions		
Present	281	%25,2
Absent	835	%74,8
History of Previous Surgery		
Absent	870	%77,95
1	206	%18,45
2	39	%3,49
3	1	%0,0008

When evaluating patients with umbilical entry as the initial site for laparoscopy, it was observed that direct entry was applied in 1006 patients. The Veress needle entry technique was used in 75 patients, while the open technique was employed in 4 patients, making a total of 1085 patients with the umbilical region chosen as the first entry site. Among the 27 patients with midline abdominal entry, it was found that 19 chose direct entry, 3 chose the Veress needle technique, and 5 preferred the open technique. Additionally, out of these patients, 5 had undergone 1 previous surgery, 2 had undergone 2 surgeries, and 20 had previous surgical history.

In the case of 4 patients where the Palmer point was selected as the initial entry site, the Veress entry method was also used. Among these patients, 1 had undergone 1 previous abdominal surgery, 1 had undergone 2 surgeries, and 2 had no previous abdominal surgeries.

Among the group of patients without any previous surgeries (870 patients), Veress needle entry was chosen for 64 of them, while 6 opted for the open technique for entry.

Among the patients who preferred the Veress needle entry, 12 had undergone 1 previous surgery, and 2 had undergone 2 surgeries. In the case of a patient who had undergone laparoscopic surgery three times due to infertility, direct entry through the umbilicus was selected as the first entry site, and adhesions were noted.

Furthermore, among patients with previous surgical history, the most common choice for the entry method was direct entry. Among the 1025 patients where the direct entry method was preferred for the initial site for laparoscopy, 796 had no prior abdominal surgeries, while 191 had undergone one, 37 had undergone two, and 1 had undergone three abdominal surgeries. (**Table 2**).

Table 2. Relationship Between Entry Site, Number of Previous Surgeries, and Choice of Entry Technique

	Entry Technique			Total
	Direct	Veress	Open Technique	
Entry Site				
Umblicus	1006	75	4	1085
Midline Abdomen	19	3	5	27
Palmer's Point	0	4	0	4
History of Previous Surgery				
Absent	796	64	6	870
1	191	12	3	206
2	37	2	0	39
3	1	0	0	1

Umbilical entry was chosen in 848 patients who had no prior abdominal surgeries, representing the highest proportion. Among the 246 patients with previous abdominal surgeries, umbilicus was also the most commonly selected entry site in 237 cases. For patients in whom the Palmer point was chosen as the entry site, one had undergone 1 previous abdominal surgery, one had undergone 2 surgeries, and two had no prior abdominal surgeries. Out of the 246 patients with previous abdominal surgeries, the open technique for entry was chosen in only 3 cases during the patients' surgeries.

Out of the 870 patients without prior surgical history, 184 had adhesions, while 686 did not exhibit any. Among the 281 patients with adhesions, 82 had undergone 1 previous surgery, 14 had undergone 2 surgeries, and 1 had undergone 3 surgeries. Notably, out of the 206 patients with one previous abdominal surgery, 124 had adhesions, and among the 39 patients with two previous abdominal surgeries, 25 had adhesions (**Table 3**).

Table 3. Relationship Between Entry Site, Presence of Adhesions, and Number of Previous Surgeries

	History of Previous Surgery			
	Absent	1	2	3
Entry Site				
Umblicus	848	200	36	1
Midline abdomen	20	5	2	0
Palmer's Point	2	1	1	0
Presence of Adhesions				
Absent	184	82	14	1
Present	686	124	25	0

DISCUSSION

Upon analyzing the data from this study, it becomes evident that the preferred method in our clinic, chosen for 1029 out of 1116 patients, is the direct trocar entry technique. Particularly during the initial 8-month period of introducing laparoscopic surgery, the Veress needle technique was employed for entry; however, subsequent phases saw a shift towards the direct entry technique, accounting for 87.5% of cases. In this notable change in laparoscopic entry, the primary distinction lies in the fact that the Veress needle entry involves three blind steps compared to the direct trocar entry. These blind steps encompass two blind insertions and one blind gas insufflation. Furthermore, the decision to opt for direct trocar entry is influenced by the potential for damage related to needle entry being overlooked for an extended duration after removing the Veress needle from the abdomen prior to the primary trocar entry.

In contrast to the Veress needle, direct trocar entry reduces the number of blind steps from three to one. This technique not only offers the advantage of fewer blind insertions but also theoretically mitigates complications linked to blind gas insufflation often encountered in the Veress needle technique. Utilizing direct trocar entry anticipates encountering fewer instances of preperitoneal insufflation, subcutaneous or omental emphysema, needle-associated vascular or visceral injuries, delayed diagnosis of gas embolism, or bowel damage. The increased occurrence of preperitoneal insufflation, subcutaneous and omental emphysema, or gas embolism observed in patients entered using the Veress needle may be attributed to blind gas insufflation.[5] Furthermore, subcutaneous emphysema can extend from the facial planes to the neck, serving as an indicator of mediastinal emphysema development, which could lead to pneumothorax and cardiovascular collapse in severe cases.[6]

The direct trocar entry technique does not require secondary confirmation tests, allowing the surgical focus to remain on anatomical knowledge during laparoscopic entry, and immediate confirmation is achieved through direct observation. Direct trocar entry also reduces the risks of multiple attempts and failed entry. Studies have indicated that preperitoneal insufflation is associated with difficulties in placing the primary trocar, numerous entry attempts, failed entry, and prolonged operation duration.[6] Consistently, compared to direct trocar entry, the Veress needle group has shown a significant increase in the risks of multiple attempts and failed entry; after two entry attempts, the risk of preperitoneal insufflation was found to be 50%. Unfortunately, in our study, data could not be examined from this perspective as we couldn't access the number of initial laparoscopic entry attempts from hospital database and patient records.

Altun et al. conducted a study in 2010 to assess the reliability of the direct trocar entry method in laparoscopy. Their findings suggest that the direct trocar entry method can be

deemed as as rapid and reliable technique.[7] In laparoscopic surgery, the direct trocar entry technique proves advantageous due to its immediate confirmation without the need for secondary tests. This approach allows surgeons to focus on anatomical knowledge during entry. Moreover, it reduces the risks associated with multiple attempts and failed entries. Previous studies have linked preperitoneal insufflation to challenges in placing the primary trocar, numerous entry attempts, failure, and prolonged operation time.[6]

In comparison, the Veress needle technique has been observed to pose a higher risk of multiple attempts and failure. Studies indicate that after two entry attempts with the Veress needle, the risk of preperitoneal insufflation soars to 50%. Unfortunately, our study couldn't assess the exact number of initial laparoscopic entry attempts due to data accessibility constraints from our hospital database and patient records. Despite these concerns, a 2006 research paper by Cakir et al. emphasized the safety profile of the Veress needle. They found that it hasn't been definitively associated with organ damage, highlighting its safety.[8] However, the Veress needle's use in laparoscopic surgery has been tied to several complications in prior studies.[9] A notable finding is the documented incidence of major injuries during Veress needle entry into the peritoneal cavity at 0.9/1000 cases.[10] In response to such concerns, the open laparoscopic entry technique was introduced to reduce the chances of vascular and visceral njuries through direct visualization. This technique is particularly favored in high-risk patient populations with a history of multiple abdominal surgeries, severe endometriosis, or pelvic inflammatory disease. However, compared to other methods, the open technique is relatively less preferred due to its relatively longer duration and greater difficulty in achieving pneumoperitoneum without gas leakage. In 2012, Bozkurt et al. executed a prospective study comparing the outcomes, complications, and postoperative pain associated with the direct trocar entry method versus open entry method. Their conclusion indicated that each technique possesses its own set of advantages and disadvantages.[11]

The modified Hasson technique, a variant of the open entry technique, was introduced at the Labbafinejad Medical Center by Shayani-Nasab and colleagues.[12] However, existing scientific data do not conclusively establish the advantages of this method, particularly in preventing intra-abdominal damage, including bowel injuries.

Upon analyzing our clinic's data, we observed that the open entry technique was utilized in a total of 9 cases. Among these patients, only 3 had undergone a single previous abdominal surgery, suggesting limited preference for the open technique in such scenarios. Surprisingly, Surgeons did not opt for the open technique in patients with a history of 2 or more previous abdominal surgeries. Instead, the direct trocar entry method was preferred by 95% of these patients (38 patients). Notably, the umbilicus was the most commonly selected entry site.

Although previous abdominal surgery could be a confusing variable, studies conducted have not shown a significant difference between the direct trocar and Veress needle entry techniques in patients with a history of previous surgery. While laparoscopic entry complications could be a risk factor in the context of previous abdominal surgery, there is no study that has conducted subgroup analysis on this matter. Therefore, the question of whether direct trocar entry reduces complications in this patient group remains unanswered. In our study as well, no superiority of one technique over another has been determined.

CONCLUSION

Our analysis highlights the significant advantages of the direct trocar entry technique, offering a streamlined, immediate, and anatomically precise approach that effectively reduces the risks associated with multiple attempts and unsuccessful entries. However, while this method holds potential benefits, the question of its superiority over the Veress needle technique in patients with a history of prior abdominal surgery remains a topic worth exploring further.

Despite the merits of laparoscopic techniques, the initial trocar entry remains a point of concern, contributing to 40% of laparoscopic complications and a noticeable number of laparoscopy-related deaths. This concerning statistic has remained consistent over the past 25 years, leading to ongoing research and discussions about the methods and entry locations. The trajectory of future laparoscopic tools aims to enhance precision and minimize trauma during surgical procedures. As technology continues to advance, we can anticipate the emergence of instruments tailored for smaller ports and the development of more compact laparoscopes enriched with advanced digital capabilities. This trajectory envisions a future of laparoscopic surgery characterized by fewer, less invasive, and less painful incisions.

However, conducting meta-analyses capable of providing substantial insights into the safety outcomes of the initial laparoscopic entry technique faces notable challenges. Only a comprehensive study involving multiple centers, randomized control, and encompassing over 10,000 patients in each group, rigorously assessing the direct trocar, Veress needle, and open entry techniques for major complications, could definitively establish conclusive evidence (6). However, the feasibility and cost-effectiveness of such an ambitious study are subject to doubt. Consequently, potential correlations and trends are extrapolated from clinical data and meta-analyses. Research studies that generously share clinical information, similar to the one at hand, become very important resources for this effort.

CONCLUSION

Drawing from our study and the existing body of literature, we maintain the perspective that complication rates are intricately linked to the surgical expertise of the operator. Moreover, such rates are expected to decrease with accumulated experience, solidifying the notion that proficiency in surgical practice holds the key to reducing complications over time.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bağcılar Training and Research Hospaital Non-interventional Clinical Reesearches Ethics Committee (Date: 07.08.2015, Decision No: 2015-407).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1341824
J Contemp Med 2023;13(5):796-801

Original Article / Orijinal Araştırma

Comparison of Analgesic Efficacy of Cooling Spray and Saline Spray in Wrist Trauma; Randomized Controlled Double Blind Study

Bilek Travmasında Serinletici Sprey ve Salin Spreyin Analjezik Etkinliğinin Karşılaştırılması; Randomize Kontrollü Çift Kör Çalışma

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Abstract

Aim: Cooling spray application is commonly used in sports injuries to manage acute pain and reduce tissue edema. However, its effectiveness in treating acute trauma in the emergency department remains understudied. This prospective randomized controlled trial assessed the efficacy of cooling spray for pain management in patients with wrist injuries.

Material and Method: A randomized trial was conducted in a tertiary care hospital's trauma department. Patients with wrist trauma were assigned to cooling spray or placebo (saline spray) groups. The cooling spray was Cryos®Spray (Phyto Performance, Italy), while the placebo was chilled saline in an identical bottle. Pain scores and radiographic images were evaluated.

Results: In 131 patients (mean age: 35.60±19.58 years, 26.7% fractures), cooling spray (n=73) yielded a delta pain score of 1.74±1.88, while saline (n=58) had 0.84±1.54 (p=0.003). Cooling spray's delta score for fracture patients was 2.26±1.88, compared to saline's 0.0±0.96 (<0.001). Non-fracture patients showed similar efficacy between cooling spray (1.55±1.85) and saline (1.16±1.60, p=0.258). Logistic regression indicated that cooling spray reduced pain 1.174 times more effectively than saline.

Conclusions: Cooling sprays demonstrated superior acute pain control, notably in fractures, outperforming the placebo. Similar efficacy was observed in non-fracture cases.

Keywords: Cooling spray, wrist trauma, analgesic

Öz

Amaç: Soğutma spreyi uygulaması akut ağrıyı kontrol etmek ve doku ödemi ile başa çıkmak için genellikle spor yaralanmalarında kullanılır. Ancak, acil serviste akut travmanın tedavisindeki etkinliği yetersiz bir şekilde araştırılmıştır. Bu prospektif randomize kontrollü çalışma, bilek yaralanması olan hastalarda ağrı yönetiminde soğutma spreyinin etkinliğini değerlendirdi.

Gereç ve Yöntem: Bir üçüncü basamak hastanenin travma bölümünde randomize bir deneme yapıldı. Bilek travması olan hastalar soğutma spreyi veya plasebo (salin spreyi) gruplarına ayrıldı. Soğutma spreyi Cryos®Spray (Phyto Performance, İtalya) olarak kullanıldı, plasebo ise aynı görünüme sahip soğutulmuş bir salin şişesiydi. Ağrı skorları ve radyografik görüntüler değerlendirildi.

Bulgular: 131 hastada (ortalama yaş: 35.60±19.58 yıl, %26.7 kırık), soğutma spreyi (n=73) 1.74±1.88 delta ağrı skoru üretirken, salin (n=58) 0.84±1.54 (p=0.003) değerini verdi. Kırık hastalar için soğutma spreyinin delta skoru 2.26±1.88 iken salin grubunda 0.0±0.96 olarak saptandı (<0.001). Kırık olmayan hastalarda soğutma spreyinin (1.55±1.85) ve salinin (1.16±1.60, p=0.258) benzer etkinlik gösterdiği görüldü. Lojistik regresyon, soğutma spreyinin ağrıyı salin grubuna göre 1.174 kat daha etkili bir şekilde azalttığını gösterdi.

Sonuç: Soğutma spreyleri plaseboyu aşan akut ağrı kontrolü sağladı, özellikle kırıklarda daha başarılı oldu. Kırık olmayan vakalarda benzer etkinlik gözlendi.

Anahtar Kelimeler: Soğutma spreyi, el bileği travması, ağrı

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Received *(Geliş Tarihi)*: 12.08.2023 **Accepted *(Kabul Tarihi)*:** 07.09.2023

INTRODUCTION

Musculoskeletal injuries are one of the most common causes of emergency department visits. These injuries occur during daily activities or due to sports accidents and account for 20% of emergency department admissions.[1] One of the problems of musculoskeletal injuries in emergency department management is pain and limitation of movement during examination and imaging procedures. Therefore, saving the patient from uncomfortable pain sensations during diagnostic procedures is realized with successful pain control by emergency physicians.[2]

Cryotherapy is a therapeutic cold application procedure for relieving pain and discomfort caused by injury. Cooling sprays have become the first treatment choice for all musculoskeletal injuries, mainly due to their ease of application, repetitive use, and use on all body surfaces. In addition to reducing pain and edema, cooling sprays provide local anesthesia for up to 30 minutes with their effect on nerve conduction. Therefore, they can relieve spasms caused by trauma.[3] Therefore, cryotherapy is one of the most recommended methods for pain control. The literature has studies on cooling sprays for different body parts.[4-6] However, there are few studies on using cooling spray in the emergency department.

This study aimed to determine the efficacy of cooling spray application for pain control in patients admitted to emergency departments with isolated wrist trauma. Our secondary objective was to compare the efficacy of fractured and nonfractured patients.

MATERIAL AND METHOD

The study was carried out with the permission of Izmir Katip Çelebi University Clinical Research Ethics Committee (Date: 24/02/2022, Decision No: 0063). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Setting

This prospective randomized, controlled, double-blind study was conducted in the trauma area of a university hospital emergency medicine clinic over six months between March and September 2022. Patients were admitted to the study during working hours when the study team was available. This hospital operates as a trauma center accepting referrals from 6 districts in the metropolitan area and serves a population of approximately 1.5 million. The emergency department trauma area has six beds with vital monitoring facilities, four mechanical ventilators, one portable, and two handheld ultrasound devices. All trauma patients brought to the emergency department by ambulance or outpatients are admitted to this area. Signed informed consent was obtained from the relatives of all patients included in the study.

Study Population

All adult patients over 18 years of age who presented to the hospital's trauma department with wrist trauma alone and who agreed to participate were included in the study. Patients with primary acute trauma were included in the study, and patients who presented after 24 hours of trauma, those who did not give voluntary consent, patients under 18 years of age, pregnant women, and patients with trauma elsewhere other than the wrist that may affect pain perception were excluded from the study.

Study protocol

Before the start of the study, a 2-person study team consisting of an emergency department faculty member and a senior resident was formed, and patients were accepted to the study when one of these teams was on duty. Patients were assigned to the SF or Cold spray groups by simple randomization with probability. According to the examination findings, patients with fracture expectations (shape deformity, severe tenderness and edema, and bruising) were sub-randomized and distributed to the study groups.

The cold spray cooling spray (Cryos ®Spray, Phyto Performance, Italy) and +4 C* SF bottles to be applied were set in the same view and numbered 1 and 2. Bottle numbers were changed at random time intervals under the supervision of a non-team faculty member. The physician and the patient were blinded to the content in which number. Randomization and sub-randomization groups were formed according to the numbers on the bottle. The randomization groups were rearranged each time a non-team member changed the number.

After the patient was accepted to the study, Numerical Rating Scale (NRS) (10) pain score was measured and recorded. Then, cold spray or SF was applied according to the randomization order. The application method was the same for both sprays spraying from a distance of 20 cm from the injured area for 5-10 seconds, as recommended by the manufacturer for cooling spray. Patients were directed to the imaging unit for radiographic imaging 10 minutes after spray application. The emergency medicine specialist finalized the radiographs based on the results reported by radiology. After the necessary imaging and interventions were performed, the NRS pain scale was measured 10 minutes later and recorded. Patients were asked if they needed any additional painkillers. Additional pain relief was administered to those who felt the need. Demographic characteristics, vital signs, X-ray results, and the need for additional analgesics were recorded on the data recording form. The images were re-evaluated with the orthopedic specialist in the study from the hospital system to classify the fractures, if any, and the fracture classification was made according to the Arbeitsgemeinschaft für Osteosynthesefragen (AO) (**Figure 1**).

Patients were grouped according to whether there was a fracture, and those with fractures were grouped according to the fracture scale. In this way, pain scores of each group and subgroup were obtained on arrival and after emergency department management. The obtained data were processed daily by the team leader, who had the content information in the bottle numbers. Demographic information, diagnoses, and treatments administered in the emergency department or inpatient hospitalization were recorded after all examinations.

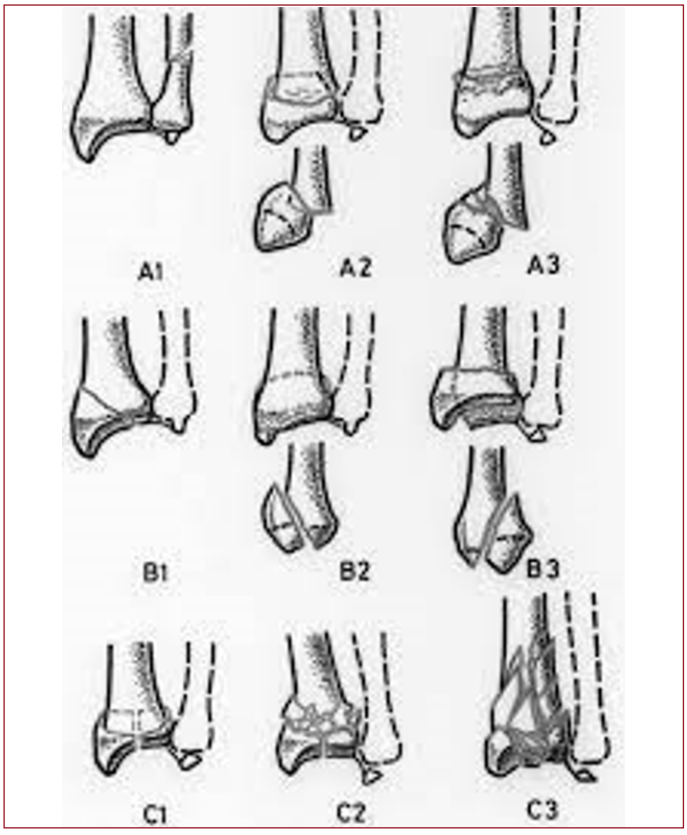

Figure 1. Working Group for Osteosynthesis Issues (AO) sınıflaması

Outcome Measures

The primary outcome measure of this study was the change in patients' pain scores with cold spray and SF administration. For this purpose, the difference between the patient's pain scores on arrival and after examinations/interventions were calculated and analyzed to see if there was a difference between cold spray and placebo. Secondarily, cold spray and placebo were compared between the fracture and non-fracture groups. Thus, whether cold spray made a difference between the fracture and non-fracture groups was calculated.

Statistical Analysis

Descriptive statistics were obtained, including frequency, percentage, mean, standard deviation, median, minimum, and maximum values. Number and percentage were calculated for categorical variables, and mean, standard deviation, minimum and maximum values, and interquartile range (IQR) were calculated for numerical variables. Histogram curves, kurtosis, skewness values, and the Shapiro-Wilks test were used to test whether continuous variables were normally distributed. Student's t-test was used when parametric test prerequisites were met, and Mann Whitney - U test was used when not met. Group regression analysis of the effects of cooling spray and cold saline was performed.

Statistical calculations were performed with SPSS 24.0 software, and all calculations were performed with a 95% confidence interval. $P<0.05$ was considered statistically significant.

RESULTS

789 patients were admitted with wrist trauma during the study period, and 131 patients who met the study criteria were included. The distribution of patients accepted and included in the study was shown in the consort diagram (**Figure 2**).

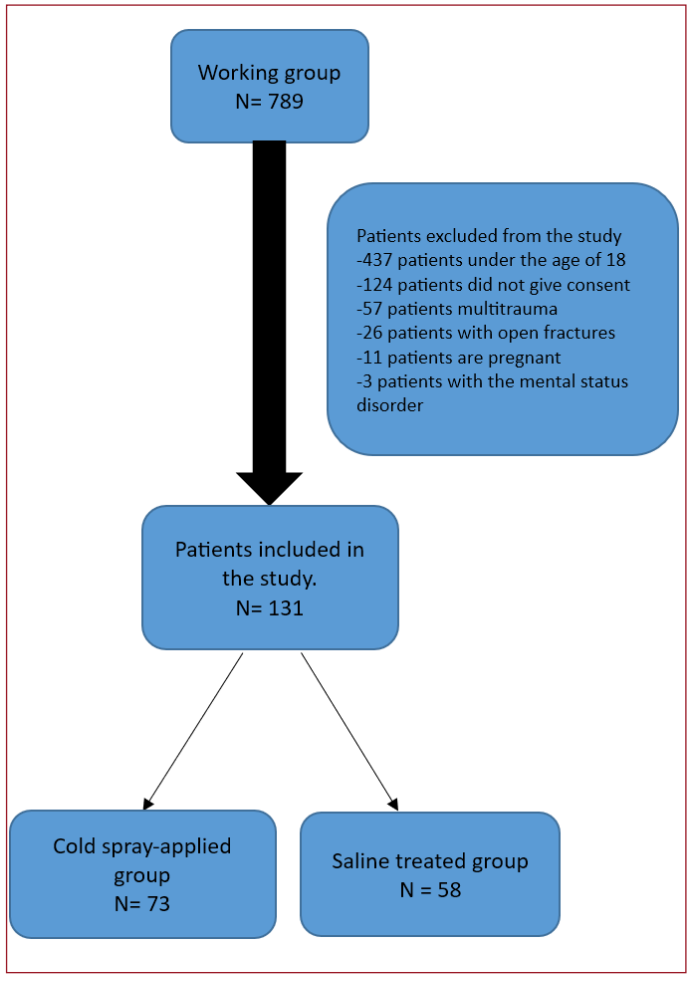

Figure 2. Consort Diagram

Of the patients included in the study, 56 were female, and 75 were male. The mean age was calculated as 35.60±19.58 years. 96 patients (73.3%) had isolated musculoskeletal injuries, and 35 (26.7%) had fractures. Fracture classification was evaluated according to the AO classification, and the most common injury type was A2 type with 15 (42.9%) patients. Regarding the side of injury, left-sided injuries were slightly more common than right-sided injuries, with 67 (51.1%). The radial region was the most common site of tenderness, with 38.9% of the patients.

The sprays' distribution was cold spray in 73 (55.7%) patients and saline in 58 (44.3%) patients. No additional analgesia was administered in 121 (92.4%) patients, while 10 (7.6%) patients received additional analgesia. Descriptive statistics and AO classification distribution of the patients are shown in **Table 1**.

Table 1: Descriptive statistics

Variables	Statistics
Gender, (%)	
Woman	56 (42.7)
Male	75 (57.3)
Age	
x̄± hs	35.60±19.58
M (min-max)	31.5 (9-92)
Spray Applied, (%)	
Cold Spray	73 (55.7)
Serum Physiological	58 (44.3)
Wrist Direction, (%)	
Right	64 (48.9)
Left	67 (51.1)
Sensitivity Zone, (%)	
radial	51 (38.9)
ulnar	40 (30.5)
Radial+Ulnar	30 (22.9)
Phalanx	10 (7.6)
Analgesia in the Emergency Department, (%)	
Not Implemented	121 (92.4)
Done	10 (7.6)
Fracture, (%)	
None	96 (73.3)
Exist	35 (26.7)
Fracture Classification	**N (%)**
A1	2 (5.7)
A2	15 (42.9)
A3	5 (14.3)
B2	3 (8.6)
B3	1 (2.9)
C1	2 (5.7)
C2	3 (8.6)
C3	4 (11.4)

The difference between the pre-treatment pain score, defined as delta pain, and the post-treatment pain score was 1.34±1.78 for the whole group. There was a statistically significant difference in the delta pain score between patients treated with cold spray and patients treated with saline (p=0.003). No statistically significant difference was found in terms of analgesia administration in the emergency department, presence of fracture, and fracture classification (p<0.05) (**Table 2**)

Table 2: Distribution of descriptive data by delta pain

	Delta Agri		Test Statistics	
	x̄± hs	M (min-max)	Test Value	p value
Delta Pain	1.34±1.78	1 ((-2)-6)		
Spray Applied				
Cold Spray	1.74±1.88	1.48 ((-2)-6)	z=2,940	0.003
Serum Physiological	0.84±1.54	0.54 ((-2)-6)		
Analgesia in the emergency department				
Not Implemented	1.34±1.79	0.92 ((-2)-6)	z =0.005	0.996
Done	1.40±1.90	0.80 ((-1)-4)		
Broken				
None	1.39±1.76	0.98 ((-2)-6)	z=0.519	0.604
Exist	1.23±1.90	0.75 ((-2)-6)		
Fracture Classification				
A1	2.0±2.83	2 (0-4)		
A2	0.93±1.75	0.56 ((-2)-5)		
A3	2.20±0.84	2.25 (1-3)		
B2	0.67±1.15	-0.67 ((-2)-0)	H=9,341	0.223
B3	0.0±0.0	0 (0-0)		
C1	3.0±2.83	3 (1-5)		
C2	2.0±3.46	2 (0-6)		
C3	1.0±1.41	0.67 (0-3)		

Logistic regression analysis is shown in **Table 3**. According to this, cold spray application is 1.174 times more likely to reduce pain than saline application.

Table 3: Evaluation of Before-After Pain Scores according to application types

	B	SE	Wald	df	p	OR ¥
Delta Agri	0.161	0.113	7,614	one	0.006	1,174
Constant	-0.311	0.223	0.518	one	0.472	0.733

¥ Logistic Regression

In subgroup analyses, there was no difference between the type of spray applied and the need for analgesia in the emergency department when the variables were compared according to the presence or absence of fracture (p>0.05). When the pre-application pain score and post-application pain score were analyzed, the pain score was calculated as 8.0±2.11 in the group with fracture and 6.88±1.83 in the group without fracture, and the difference was statistically significant (p=0.002). Accordingly, the pain score before and after the application was 6.77±2.34 in the fracture group and 5.54±2.34 in the non-fracture group, and the difference between them was significant (p=0.017). Cryotherapy to be applied after the injury was found to be effective in reducing the pain of the patients (**Table 4**).

Table 4: Comparison of variables according to the presence of fracture

	Broken		Test Statistics	
	None	There is	Test value	p-value
Spray Applied				
Cold spray	54 (74.0)	19 (26.0)	0.040	0.841
Serum physiological	42 (72.4)	16 (27.6)		
Pre-Application Pain Score				
x̄± hs	6.88±1.83	8.0±2.11	3,047	0.002
M (min-max)	7 (2-11)	8 (2-10)		
Post-Application Pain Score				
x̄± hs	5.54±2.34	6.77±2.34	2,394	0.017
M (min-max)	6 (1-10)	7 (2-10)		
Analgesia in the Emergency Department				
Not Implemented	91 (75.2)	30 (24.8)	2,997	0.083
Done	5 (50.0)	5 (50.0)		

In the comparison made according to the type of application, cold spray application was more effective than saline use in patients with fractures, and this effect was statistically significant (**Table 5**).

Table 5: Comparison of fracture cases according to application types

	APPLICATION		Test Statistics	
	Cold Spray	Serum Physiological	z value	p-value
	x̄± hs	x̄± hs		
Broken				
None	1.55±1.85	1.16±1.60	1,131	0.258
Exist	2.26±1.88	0.0±0.96	3,632	<0.001

Retrospective Power Analysis

No previous studies used similar data and our research perspective; therefore, we evaluated our findings to describe the radiographic scoring. If both patient groups included at least 55 patients, the power of the test was estimated at 0.90 and the type 1 error at 0.01.

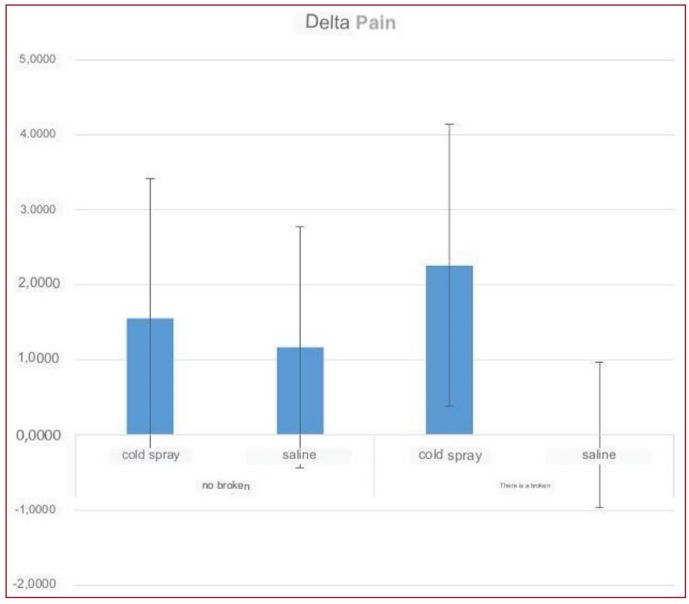

Figure 3: Comparison of fracture phenomenon according to application types

DISCUSSION

Trauma-related injuries are among the most common causes of admission to emergency departments. In the emergency department management of traumatic injuries, it is aimed to facilitate the preferred radiologic interventions, increase patient comfort, and rapidly reduce the intensity of the emergency department. A large proportion of musculoskeletal traumas are superficial mechanism injuries [7] These patients should be evaluated rapidly, and investigations and treatment procedures should be completed. It aims to facilitate the diagnostic procedures and simultaneously start the treatment with the patient's comfort to be obtained by relieving the pain due to the injury. Cryotherapy is one of the most practical and effective options among these methods. Especially compared to standard cryotherapy, cooling sprays are compelling thanks to their ease of application and reproducibility. It increases patient satisfaction by reducing pain, muscle spasms, and edema. It allows the emergency department's planned examination and imaging processes to be completed effectively and quickly. They have few side effects and form part of the treatment.

The use of cooling sprays in injuries caused by daily activities is widespread, and many studies show successful results in sports injuries [3,8] . However, their use in emergency departments has remained limited. Our study was planned based on evaluating the effect of cooling sprays on patient comfort in emergency departments. It was aimed to ensure patient comfort for an easy examination and examination process. Imaging results and patient pain severity were evaluated separately for the study. Since pain is a subjective finding and independent of injury, the Numerical Rating Scale (NRS-10) was used, and the results were analyzed. This study is one of the first studies regarding its design and use in emergency departments.

Cooling sprays are not limited to sports injuries and are becoming increasingly widespread. In a recent study, it has been reported that they can be used effectively in reducing pain and edema after subcutaneous ejections (9). The role of cooling sprays in coastal injuries occurring in geriatric patient groups was studied, and pain control was reported to be highly effective in the acute period [10] It was shown that patients' diagnosis and treatment processes were completed more rapidly by reducing acute pain. In a similar study, Gür et al. reported successful results in reducing pain and providing patient comfort in acute ankle injuries with a cooling spray [11] Park et al. reported that it could be used for pain control in the preoperative period, but its efficacy in controlling long-term pain and reducing edema is limited [3] In parallel with previous studies, this study evaluated that the use of cooling spray in emergency departments was effective in acute pain control in emergency departments.

Our study analyzed patients presenting to emergency departments with wrist injuries. The cooling spray was applied to these patients before the necessary examinations and imaging for diagnosis, and pain scores were analyzed. The results were compared with a placebo. As a result, cooling sprays were effective in controlling acute pain. The effectiveness of these sprays was at least as successful in controlling the pain needed in patients with fractures as in patients without fractures. However, no additional pain control was required in patients without fractures who received cooling sprays in the emergency department. When all these results are evaluated together, using cooling sprays may be beneficial in increasing patient comfort and faster circulation in emergency departments with high workloads.

Limitation

The fact that our study is a single-center study limits generalization due to the limited number of patients included.

CONCLUSION

This study found that acute pain in patients admitted to emergency departments with wrist trauma and fractures could be controlled more successfully with cooling sprays than placebo. Cooling sprays may comfort patients during uncomfortable procedures such as physical examination and radiologic imaging in emergency departments. As a secondary result, cold spray application in the emergency department limits the use of analgesics during pain control. Therefore, cold spray applications should be used as a valuable practice because they form a practical part of the treatment, provide patient comfort, and speed up the operation of the emergency department.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Izmir Katip Çelebi University Clinical Research Ethics Committee (Date: 24/02/2022, Decision No: 0063).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1341545
J Contemp Med 2023;13(5):802-808

Original Article / Orijinal Araştırma

Pseudoangiomatous Stromal Hyperplasia of the Breast: Multimodality Imaging Findings

Memenin Psödoanjiomatöz Hiperplazisi: Görüntüleme Bulguları

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Abstract

Aim: Pseudoangiomatous stromal hyperplasia (PASH) is a rare benign mesenchymal proliferative breast lesion. The literature contains limited information on the radiological results of this uncommon tumor. In this study, we aim to define the radiologic findings of PASH through our institutional experience.

Material and Method: Patients with PASH of the breast reported in the surgical database of our institution from 2020 to 2023 were retrospectively reviewed. PASH was detected in 11 female patients among the patients who underwent a total of 2172 breast tru-cut biopsies. Nine patients whose imaging studies could be recalled from the picture archiving systems (PACS) were included in the study. BI-RADS 5th edition was used to analyze and classify radiologic findings.

Results: The median age of cases was 41 (range 22–53). Our single-center incidence was found to be 0.5%. Considering the sonographic findings, all of the lesions had an oval shape. On mammography, they were defined as focal asymmetry or circumscribed masses. MRI was available in 3 cases. All 3 cases were hypointense on T1-weighted sequences and hyperintense on T2-weighted sequences. They displayed type 1 or type 2 enhancement curves in the dynamic contrast-enhanced images. No diffusion restriction was detected.

Conclusion: In this study, tumor-forming PASH were generally circumscribed, oval hypoechoic solid masses with minimal vascularity and no posterior acoustic features on ultrasound. On mammography calcification, architectural distortion or spiculation were not present in any of the cases. MRI findings were t2 hyperintensity, type 1–2 enhancement kinetics, and no diffusion restriction. In all imaging modalities, the imaging characteristics point to a benign lesion.

Keywords: Breast tumor, pseudoangiomatous stromal hyperplasia, ultrasound, mammography, MRI

Öz

Amaç: Psödoanjiyomatöz stromal hiperplazi (PASH) memenin nadir görülen benign mezenkimal proliferatif lezyonudur. Literatür, bu nadir tümörün radyolojik sonuçları hakkında çok az bilgi içermektedir. Bu çalışmada PASH'ın radyolojik bulgularını kurumsal deneyimlerimizden hareketle tanımlamayı amaçladık.

Gereç ve Yöntem: Kurumumuzun cerrahi veri tabanında 2020-2023 yılları arasında bildirilen meme PASH'li hastalar retrospektif olarak incelendi. Toplam 2172 meme tru-cut biyopsisi yapılan hastalardan 11'inde kadın hastada PASH saptandı. Görüntüleme çalışmaları resim arşivleme sistemlerinden (PACS) geri çağrılabilen dokuz hasta çalışmaya dahil edildi. BI-RADS 5. baskı, radyolojik bulguları analiz etmek ve sınıflandırmak için kullanıldı.

Bulgular: Olguların ortanca yaşı 41'di (22-53 arası). Tek merkezli insidansımız %0,5 olarak bulundu. Sonografik bulgulara bakıldığında lezyonların tamamı oval bir şekle sahipti. Mamografide fokal asimetri veya sınırlı kitleler olarak tanımlandı. 3 olguda MRG mevcuttu. 3 vakanın tümü, T1 ağırlıklı sekanslarda hipointens ve T2 ağırlıklı sekanslarda hiperintens idi. Dinamik kontrastlı görüntülerde tip 1 veya tip 2 geliştirme eğrileri gösterdiler. Difüzyon kısıtlaması saptanmadı.

Sonuç: Bu çalışmada, tümör oluşturan PASH'lar genel olarak sınırlı, minimal vaskülariteye sahip, ultrasonda posterior akustik özelliği olmayan, oval hipoekoik solid kitlelerdi. Mamografide kalsifikasyon, distorsiyon veya spikülasyon olguların hiçbirinde yoktu. MRG bulguları t2 hiperintensite, tip 1-2 kontrastlanma kinetiği ve difüzyon kısıtlaması olmamasıydı. Tüm görüntüleme modalitelerinde, görüntüleme özellikleri iyi huylu bir lezyona işaret etmekteydi.

Anahtar Kelimeler: Meme tümörü, psödoangiomatöz hiperplazi, ultrason, mamografi, MRG

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Received *(Geliş Tarihi)*: 11.08.2023 **Accepted *(Kabul Tarihi)*:** 07.09.2023

INTRODUCTION

Pseudoangiomatous stromal hyperplasia (PASH) of the breast is a benign mesenchymal proliferative disease. Vuitch et al described PASH in 1986.[1] It is hypothesized that hormonal influences contribute to its development.[2] It may present clinically as a mass or incidental microscopical finding. Rarely does PASH cause tumor. However, PASH might be discovered incidentally in up to 23% of breast biopsies.[3] Histologically, it must be distinguished from low-grade angiosarcoma and phyllodes tumors when there is a mass. It is identified by stromal cells with slit-like channels lined by myofibroblasts that resemble vascular channels on pathology specimens. As a result, PASH can be misdiagnosed as a low-grade angiosarcoma histologically. Angiosarcoma can be differentiated based on malignant cytology and positive immunohistochemical staining to endothelial markers. However, no association of PASH with malignancy has been proven.

Although PASH typically manifests as a localized lesion, diffuse and multifocal involvement have also been reported.[4,5] Clinically, it is a firm, palpable, painless breast mass that may have a diameter of up to 15 cm. It may be misdiagnosed as a fibroadenoma or phyllodes tumor based on clinical, mammographic, and ultrasonographic features.[5-7] The recommended course of treatment for tumor-forming PASH is local surgical excision with sufficient margins when it is growing, or exhibits suspicious imaging findings. The likelihood of recurrence is low, and the prognosis is favorable.

In this study, we aim to define the radiologic findings of PASH through our institutional experience.

MATERIAL AND METHOD

In this retrospective descriptive study, review of the pathological database of our institutions from 2020 to 2023 revealed 11 cases of PASH of the breast among a total of 2172 tru-cut breast biopsies. All of the patients were female. Nine of these cases had radiological studies available in the picture archiving systems (PACS) systems. These 9 cases make up the study population of this study.

Age, gender, the patient's current symptoms, and the results of the tru-cut biopsy and postoperative pathology reports were noted. All of the available radiological studies were retrieved from PACS. Two breast radiologists (5 and 10 years of experience) reevaluated the images in agreement. The Breast Imaging Reporting and Data System (BI-RADS) 5th edition lexicon was used to categorize imaging findings.[8] The morphological characteristics listed below were examined: shape, margin, density, and associated calcifications on mammography; shape, margin, orientation, echo pattern, posterior acoustic features, vascularity on ultrasonography; and shape, margin, internal enhancement patterns, T2 signal, diffusion characteristics, and kinetic features on magnetic resonance imaging (MRI).

Descriptive statistics (mean, standard deviation, minimum, median, maximum) were used to define continuous variables.

The study was carried out with the permission of Ümraniye Training and Research Hospital Clinical Research Ethics Committee (Date: 21.03.2023, Decision No: B.10.1.TKH.4.34.H.JP.0.01/85), and patient consent was waived.

RESULTS

Among a total of 2172 trucut breast biopsies 11 cases of PASH result in an incidence of 0.5%. All patients were women with a median age of 41 (range 22-53), and all were premenopausal except one. The presenting symptom was and palpable mass in 8 patients, one of which was painful. One lesion was detected on screening. None of the patients had a breast cancer history. Two patients had second-degree family history of breast cancer.

The maximum diameter of the lesions ranged between 14-60 mm (mean 36.3 mm) on ultrasound imaging. Seven of these patients had previous medical records which demonstrated 6-34% enlargement in the largest diameter in 6 of the masses. None of the patients had multifocal lesions. Five patients were treated with simple excision and one patient had a mastectomy. On postoperative pathology reports, five patients had an accompanying fibroadenoma, while one patient had isolated PASH. None of the patients had accompanying ductal carcinoma in situ (DCIS) or invasive cancer on imaging findings or pathology.

Imaging Findings

US images of all 9 lesions were available. Five patients had mammography, and 3 patients underwent dynamic contrast-enhanced MRI. There was no multifocality. A summary of the imaging findings is demonstrated in **Table 1**.

All of the masses could be visualized in the US (**Figures 1,2,3**). The orientation of all the lesions was parallel. The shape was oval in all of them. The margins were circumscribed in 8 and microlobulated in one. There were no posterior acoustic features in any of the lesions. The echogenicity was hypoechoic in all lesions. In one lesion, microcystic changes were present within the mass. On color Doppler imaging, one lesion was avascular, while 8 lesions displayed minimal vascularity. Based on US features, 2 of the masses were categorized as BI-RADS 4B, 6 as BI-RADS 4A, and 1 as BI-RADS 3.

Mammography was available in 5 patients (**Figures 1,2**). Three patients had type C, one had type B and one patient had type D breast parenchymal density. One lesion was not seen due to dense breast parenchyma (type D). The shape was oval in the other 4 lesions. The density of one mass was hyperdense while others were isodense. Margins were circumscribed in 1 and indistinct in 3. None of the cases had spiculated margins. Calcification was not present in any of the masses.

Dynamic contrast-enhanced breast MRI was available in 3 cases (**Figures 1,3**). The shape was oval in all cases. The

margins were circumscribed in one, and indistinct in 2. All masses displayed heterogeneous internal enhancement. None displayed rim enhancement. On T2 weighted images, all masses were isohyperintense or hyperintense. On kinetic analysis, enhancement pattern was persistent or plateau-type, and none demonstrated washout kinetics. Diffusion-weighted imaging (DWI) demonstrated no restricted diffusion.

Table 1. Summary of findings

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
MAMMOGRAPHY									
Breast density type	C	C	C					B	D
Shape	oval	oval	oval					oval	-
Margin	circumscribed	indistinct	indistinct					indistinct	-
density	dense	dense	isodense					isodense	isodense
calcification	none	none	none					none	none
ULTRASOUND									
orientation	parallel	parallel	parallel	parallel	parallel	parallel	parallel	parallel	parallel
shape	oval	oval	oval	oval	oval	oval	oval	oval	oval
margin	circumscribed	circumscribed	circumscribed	circumscribed	circumscribed	circumscribed	microlobulated	circumscribed	circumscribed
Echo pattern	Heterogenous Cystic changes	hypoechoic	hypoechoic	hypoechoic	hypoechoic	hypoechoic	hypoechoic	hypoechoic	hypoechoic
Posterior acoustic features	none	none	none	none	none	none	none	none	none
vascularity	minimal	minimal	minimal	minimal	minimal	avascular	minimal	minimal	minimal
BIRADS category	4B	4A	4A	4A	4A	4A	4B	3	4A
MRI									
shape		oval			oval				oval
Internal enhancement		heterogenous			heterogenous				heterogenous
Kinetics		persistent			persistent				plateau
T2 signal		isohyperintense			hyperintense				hyperintense
DWI		No restriction			No restriction				No restriction
ADC value		2077 mm2/s			1777 mm2/s				1500 mm2/s

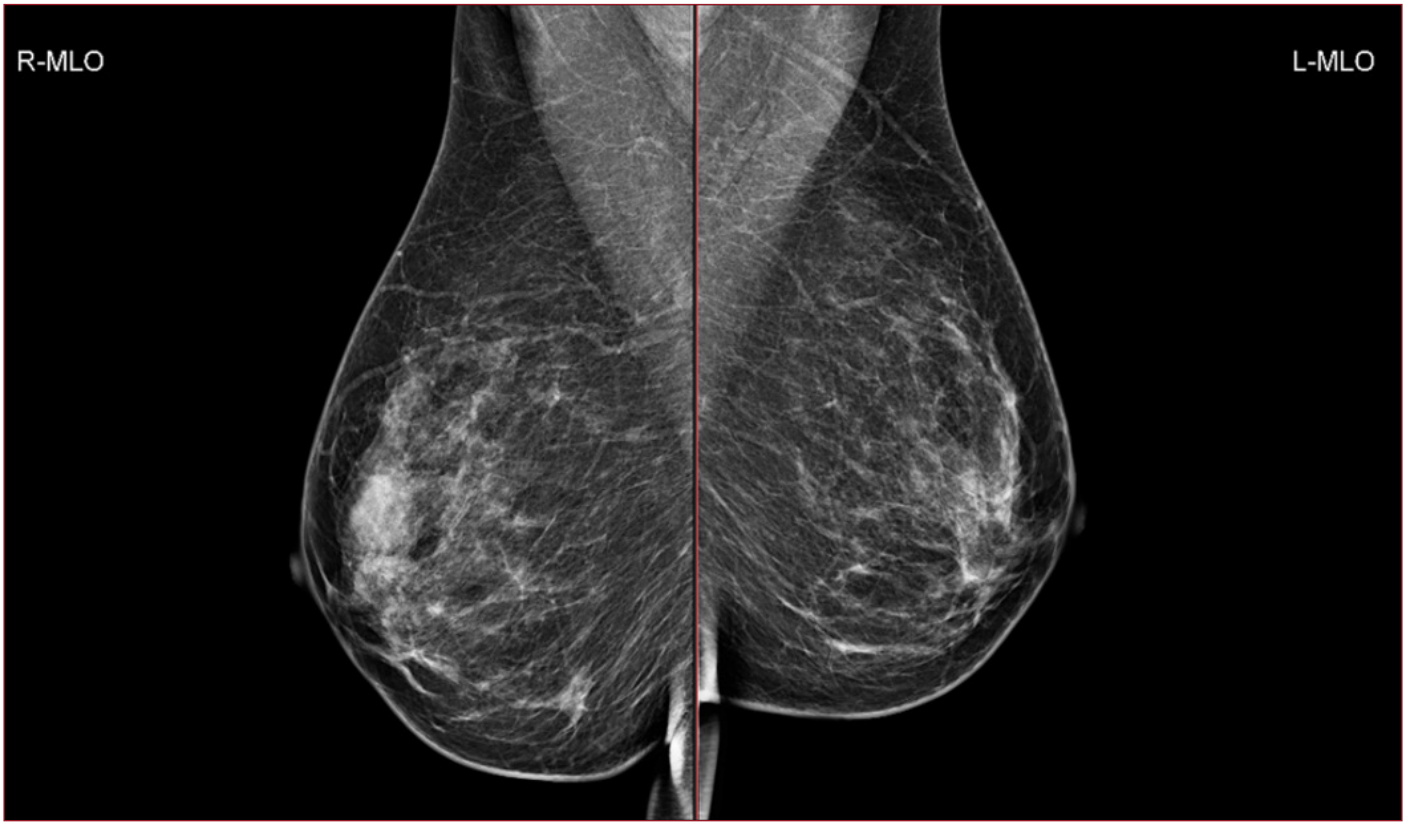

Figure 1a: 42 y/o female patient: Screening mammograms depict an oval mass with indistict margins in the upper outer quadrant of the right breast.

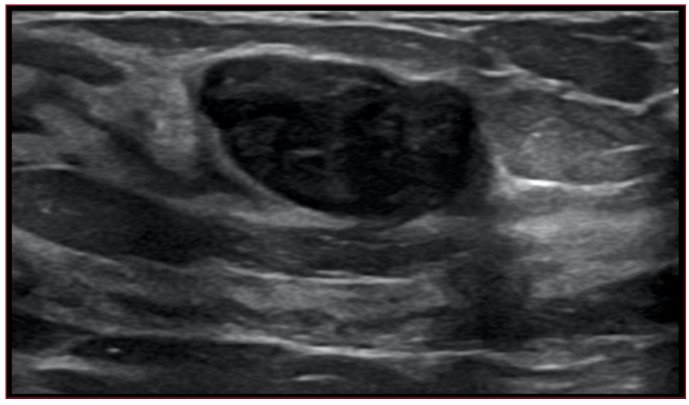

Figure 1b: US image shows a hypoechoic solid mass with circumscribed margins.

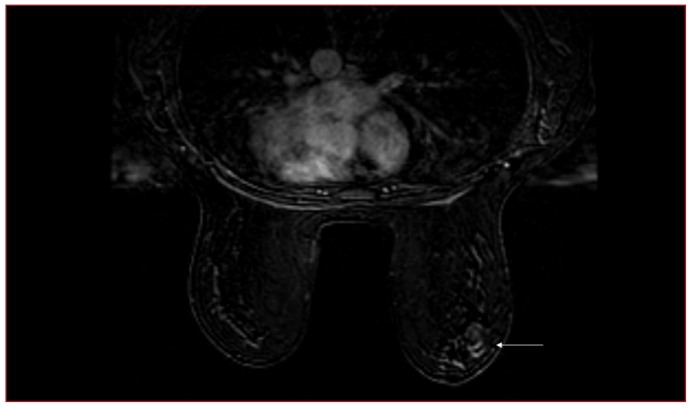

Figure 1g: On contrast-enhanced MR images, the lesion (arrow) shows slight and persistent enhancement.

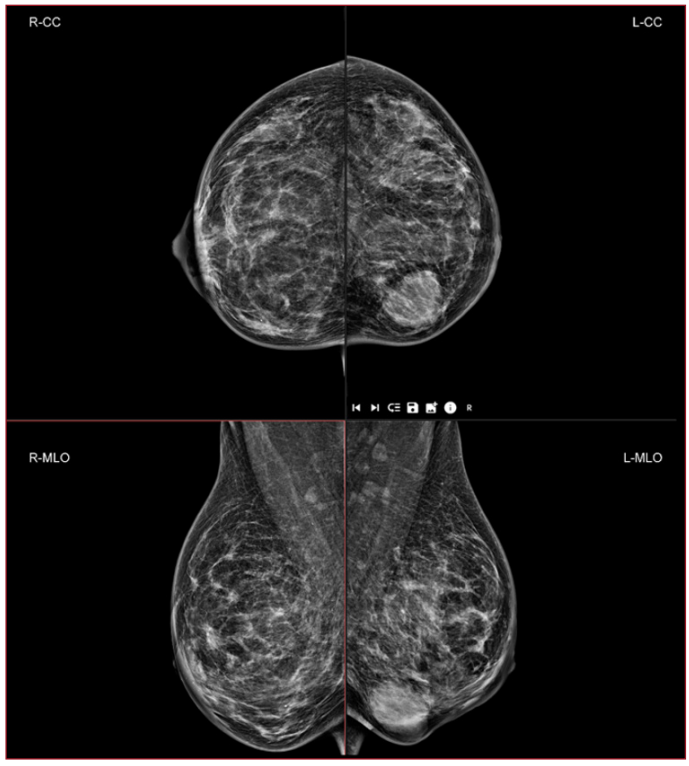

Figure 2a: 41 y/o patient who presented with a palpable mass and tenderness in her left breast. Mammograms of the left breast shows a dense oval mass with circumscribed margins.

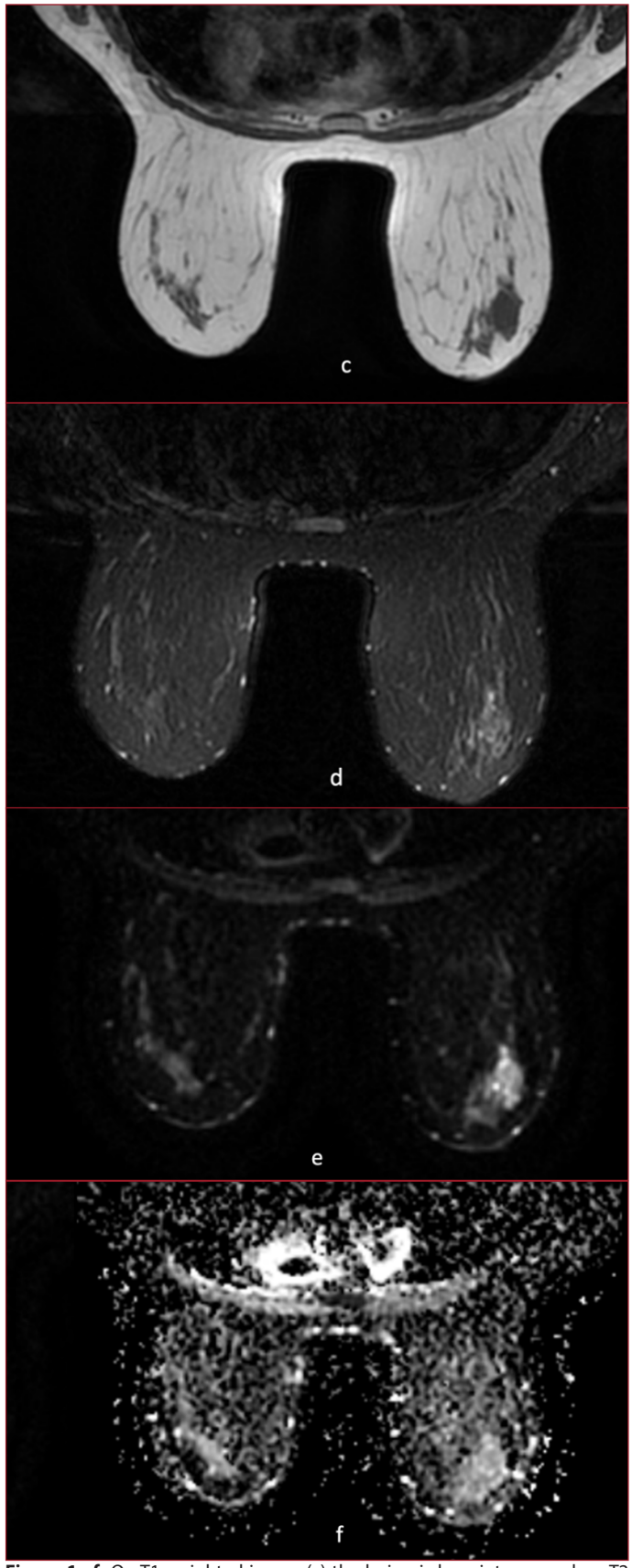

Figure 1c-f: On T1 weighted image (c) the lesion is hypointense and on T2 weighted image (d), the lesion is isohyperintense. On diffusion weighted image (e) slight hyperintensity is due to t2 effect and ADC (f) map indicate that there is no diffusion restriction.

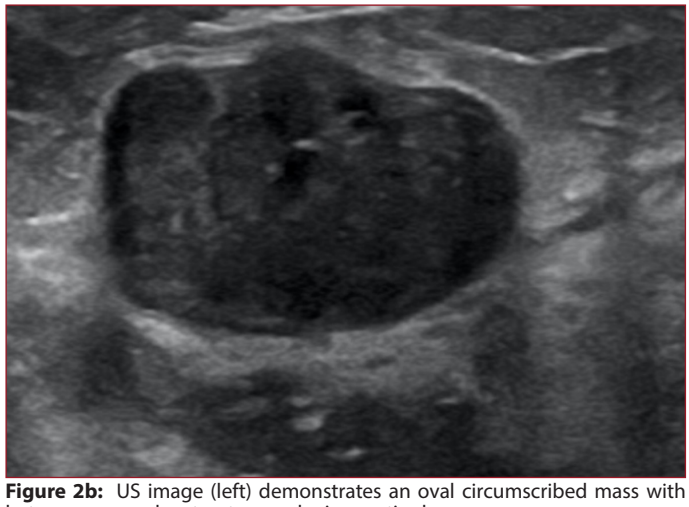

Figure 2b: US image (left) demonstrates an oval circumscribed mass with heterogenous echo structure and microcystic changes

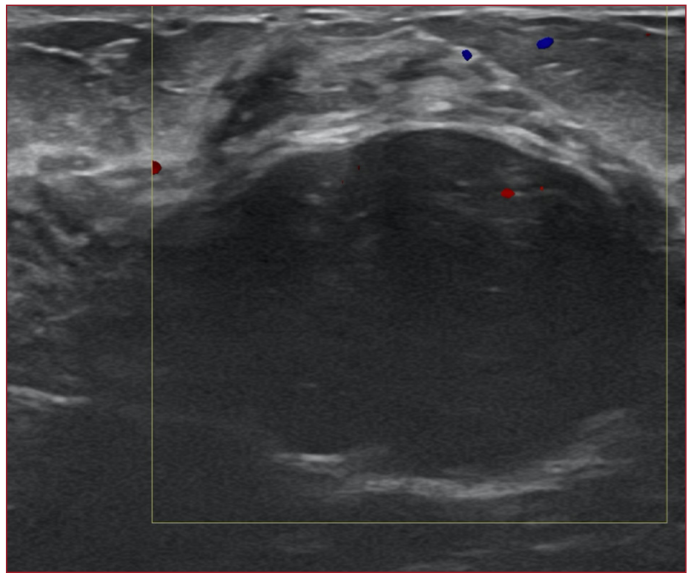

Figure 3a: 38y/o patient who presented with a palpable circumscribed oval solid mass with minimal vascularity on color doppler US image.

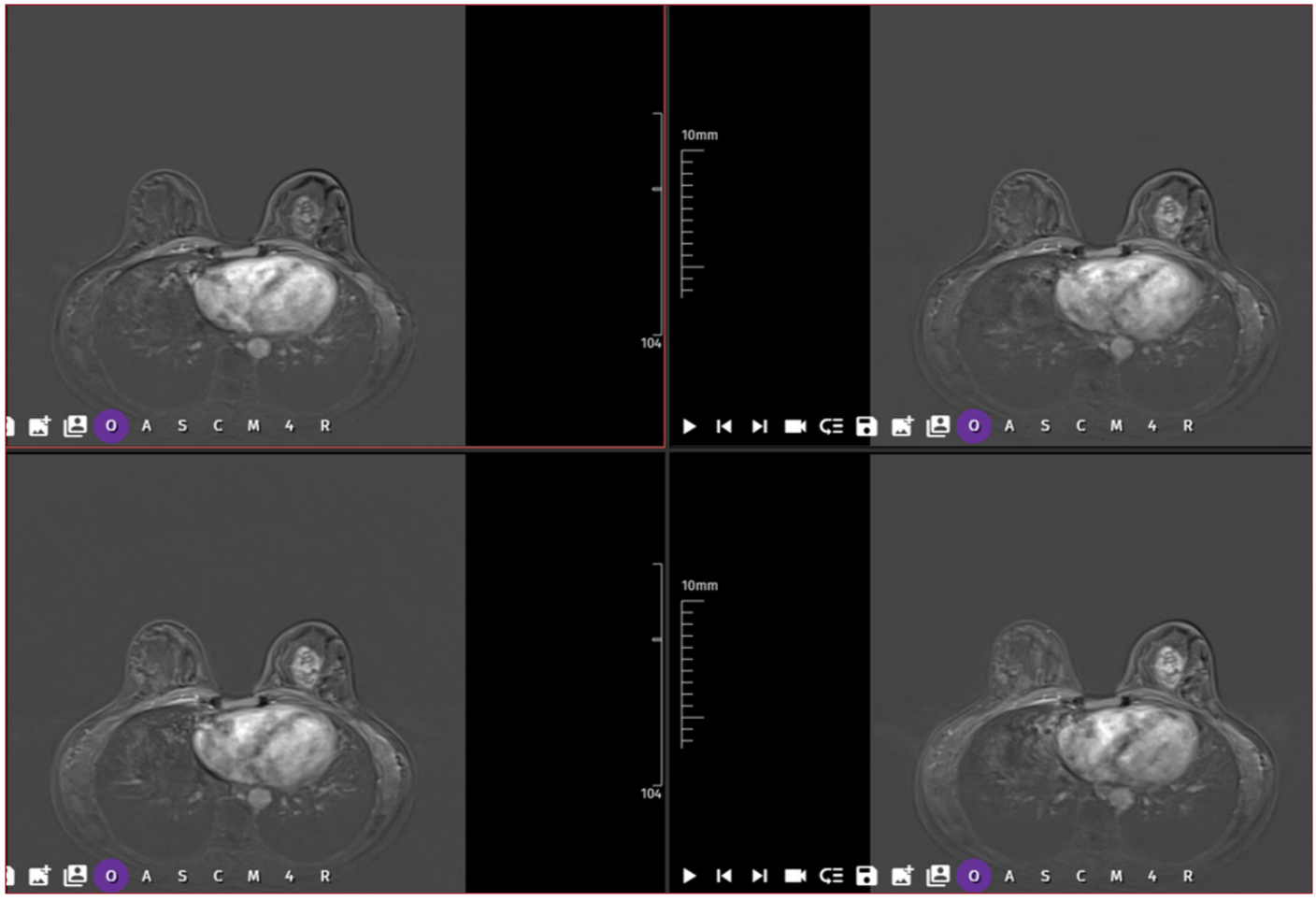

Figure 3b: On contrast-enhanced MR images, the lesion shows heterogenous and persistent enhancement

DISCUSSION

In this retrospective study, we presented the radiological findings of 9 patients with PASH lesions, collected from the databases of our institution between 2020-2023. All patients underwent ultrasound, 5 of them underwent mammography, and 3 of them underwent MRI. Color Doppler imaging was available in all patients. We have reviewed all radiological examinations in detail to determine the most common imaging features.

The radiological characteristics of PASH are not adequately described in the literature. The radiological findings are only briefly discussed in a few studies, the majority of which are case reports. According to the literature, the most common signs of PASH on mammography are non-calcified, round or oval, circumscribed or partially circumscribed masses or an uneven density.[9,10] As their research comprised cases in which PASH was incidentally discovered on histology, Hargaden et al. observed that 69% of patients with PASH did not display any mammographic abnormalities.[5] Only 10 of the 169 cases reported by Hargaden et al. had architectural distortions or calcifications on mammography. In this study, the most common mammographic features were an oval shape, and circumscribed or indistinct margins. Spiculations, microcalcification, or architectural distortion were not present in any of the cases. These findings are consistent with the literature.

On ultrasound, all lesions presented as solid masses in this study. Jones et al. noted that the most typical ultrasonography appearance of PASH was an oval, hypoechoic mass with circumscribed margins.[7] However, there are also suspicious characteristics defined such heterogenous echotexture, high echogenicity, and ill-defined borders.[2] In our study, all the lesions were circumscribed hypoechoic oval masses with circumscribed margins, except one, which was microbulated. Posterior acoustic features were not present in any of the cases in our study. Doppler imaging revealed minimal vascularity in almost all cases. We have categorized the findings as BI-RADS 3-4A in 77% (7/9) of the ultrasound cases. Two lesions, one with microlobulation and the other with heterogeneous echo structure were categorized as BI-RADS 4B. When all imaging findings were taken into account, none of the lesions were considered BI-RADS 4C or 5.

Few studies have defined the appearance of PASH on MRI.[11-13] In this study, T2 hyperintensity and the lack of diffusion restriction are remarkable features on MRI. All three lesions demonstrated type 1 or type 2 contrast enhancement kinetics and washout kinetics were not seen in any of them. Findings on MRI point out the benign nature of the lesion. Alicassi et al. reported a case with multiple masses showing low signal in T1 sequences and high signal in T2 sequences, early homogenous and intense contrast enhancement with all three types of enhancing curves that are more common for persistent kinetics.[13] According to Nia et al.'s analysis of 69 cases, PASH shows in various appereaances on MRI but most frequently as clumped non-mass enhancement with persistent kinetics.[11] Their study group included MRI-guided biopsies, indicating that the lesions were only visible on MRI. Our study differs in way that the lesions are masses which all are also visible on ultrasound.

PASH is primarily present in pre- or perimenopausal women and is thought to be hormone-related.[14,15] In this study, age distribution is in line with the literature data that almost all of them were premenopausal. None of the cases in this study had a breast cancer history or coincidental breast cancer. None of them had first-degree breast cancer family history. To date, PASH associated with malignancy has been rarely reported.[16,17]

Gradual enlargement of PASH masses has been mentioned in mammography.[1,3] We also detected 6-34% enlargement in one year in 6 of the patients who had previous medical records. Although the lesions were benign-appearing, gradual enlargement conveyed a histologic verification.

PASH occurs as a major histological finding in ~6% of surgical breast biopsies[18] and microscopic non-tumor forming PASH is an incidental finding in up to 23% breast biopsies.[3] Cases in our study are the tumor-forming type of PASH. Nodular PASH is a rare entity with an incidence of 0.4% in breast biopsies.[9] Our single-center incidence is 0.5% which is compatible with this literature data. The exact incidence is difficult to estimate as it is related to the awareness of this rare lesion by pathologists.

Limitations

The small number of cases and retrospective design are the main limitations of this study. Although there were more cases with a diagnosis of PASH, not all of them had access to their radiological images. Some cases did not undergo mammography or MRI. Retrospective analysis of radiological data, particularly US findings, can be deceptive.

CONCLUSION

PASH is a benign breast tumor, diagnosed more commonly in premenopausal women. The imaging features suggest a benign lesion in all imaging modalities. In this study tumor forming PASH were generally circumscribed, oval hypoechoic solid masses with minimal vascularity and with no posterior acoustic features on ultrasound. On mammography calcification, architectural distortion or spiculation were not present in any of the cases. MRI findings were t2 hyperintensity, type 1-2 enhancement kinetics, and no diffusion restriction. Although nonspecific, these imaging features of PASH suggest a benign process. Despite the fact that imaging results properly identified the benign nature of the lesions, biopsy verification may be necessary due to the lesions' size and gradual enlargement over time.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ümraniye Training and Research Hospital Clinical Research Ethics Committee (Date: 21.03.2023, Decision No: B.10.1.TKH.4.34.H.JP.0.01/85).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1343166
J Contemp Med 2023;13(5):809-813

Original Article / Orijinal Araştırma

Evaluation of HBV Reactivation and Antiviral Prophylaxis in Patients Receiving Immunosuppressive Therapy

İmmünsupresif Tedavi Alan Hastalarda HBV Reaktivasyonu ve Antiviral Profilaksinin Değerlendirilmesi

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Abstract

Aim: Patients with chronic hepatitis B and people with a history of hepatitis B (HBV) infection are at risk of HBV reactivation (HBVr) when they receive immunosuppressive therapy. In this study, we aimed to evaluate the hepatitis B serology, risk groups and antiviral prophylaxis of patients receiving various immunosuppressive therapies due to rheumatological diseases.

Material and Method: The study included 375 patients over 18 years of age who received tumor necrosis factor-α (TNF-α) inhibitor, tyrosine kinase inhibitor, steroids, methotrexate or anti-CD20 antibodies due to rheumatic diseases in a training and research hospital between May 2022 and May 2023. Hepatitis B surface antigen (HbsAg), hepatitis B surface antibody (anti-Hbs), hepatitis B core protein antibody (anti-Hbc IgG) serologies, immunosuppressive therapies and oral antivirals were retrospectively analyzed.

Results: The average age of the 375 patients included in the study was 43.77±13.07 years. 193 (51.5%) of the patients were male. 11 (2.9%) patients were HbsAg positive, 150 (40%) patients were anti-Hbs positive, 19 (5.1%) patients were isolated anti-Hbc IgG positive, and 79 (21.1%) patients were both anti-Hbs and anti-Hbc IgG positive. According to serological findings, 109 (29%) patients had HBV exposure. All three test results of 194 (51.7%) patients were negative. A total of 85 (22.7%) patients received oral antiviral prophylaxis due to the use of immunosuppressive agents. In terms of HBVr, 16.5% were evaluated as high risk, 75.3% as moderate risk, and 8.2% as low risk. Out of 85 patients 79 received entecavir, 5 reveived tenofovir disoproxil fumarate (TDF) and 1 received tenofovir alafenamide fumarate (TAF). The mean duration for the immunosuppressive therapy was 6.41±4.20 years. HBVr was not observed in any of our patients.

Conclusion: Before patients receive immunosuppressive therapy, hepatitis B serologies and prophylaxis indication should be evaluated firstly. In addition, as a preventive medicine activity, hepatitis B vaccinations of unvaccinated patients should be completed as quickly as possible.

Keywords: Immunosuppression, hepatitis B, reactivation

Öz

Amaç: Kronik hepatit B'li hastalar ve geçirilmiş hepatit B virüs enfeksiyonu olan kişiler immünsupresif tedavi aldıkları zaman HBV reaktivasyonu riskine maruz kalırlar. Bu çalışmada romatolojik hastalıklar nedeni ile çeşitli immünsupresif tedavileri alan hastaların hepatit B serolojilerini, risk gruplarını ve antiviral profilaksi alma durumlarını sunmayı amaçladık.

Gereç ve Yöntem: Çalışmaya Mayıs 2022 ile Mayıs 2023 tarihleri arasında bir eğitim ve araştırma hastanesinde romatolojik hastalıklar nedeni ile tümör nekroz faktör-α inhibitörü, tirozin kinaz inhibitörü, steroid, metotreksat veya anti-CD20 antikoru alan 18 yaş üstü 375 hasta dahil edildi. Hastaların HbsAg, anti-Hbs ve anti-Hbc IgG serolojileri, immünsupresif tedavileri ve süresi ile almış oldukları oral antiviraller retrospektif olarak incelendi.

Bulgular: Çalışmaya alınan 375 hastanın yaş ortalaması 43.77±13.07 idi. Hastaların 193' ü (%51.5) erkek idi. Hastaların 11' inde (%2.9) HbsAg pozitif, 150' sinde (%40) anti Hbs pozitif, 19' unda (%5.1) izole anti-Hbc IgG pozitif ve 79 (%21.1) hastada ise anti-Hbs ile anti-Hbc IgG beraber pozitif idi. Serolojik bulgulara göre 109 (%29) hastada HBV ile karşılaşma durumu mevcuttu. Hastaların 194' ünde (%51.7) ise her üç tetkik sonucu da negatif idi. Toplamda 85 (%22.7) hasta immünsupresif ajan kullanımı nedeni ile oral antiviral profilaksi almaktaydı. HBV reaktivasyon riski profilaksi başlanan hastaların 14' ünde (%16.5) yüksek, 64' ünde (%75.3) orta, 7' sinde (%8.2) düşük riskliydi. Toplam 79 hasta entekavir, 5 hasta tenofovir disoproksil fumarat ve 1 hasta ise tenofovir alafenamid fumarat almakta idi. Ortalama immünsüpresif tedavi alma süresi 6.41±4.20 yıl idi. HBV reaktivasyonu görülen hasta olmadı.

Sonuç: Hastalar immünsupresif tedavi almadan önce hepatit B serolojileri ve profilaksi durumları öncelikle değerlendirilmelidir. Ayrıca koruyucu hekimlik faaliyeti olarak aşısız hastaların en kısa sürede hepatit B aşıları tamamlanmalıdır.

Anahtar Kelimeler: İmmünsupresyon, hepatit B, reaktivasyon

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Received *(Geliş Tarihi)*: 14.08.2023 **Accepted *(Kabul Tarihi)*:** 29.09.2023

INTRODUCTION

Hepatitis B virus (HBV) infection is a global health problem and is among the main causes of chronic hepatitis, liver failure and hepatocellular carcinoma in our country. It is estimated that approximately 296 million people worldwide suffer from chronic hepatitis B and there are approximately 1.5 million new infection cases each year.[1] Our country is located in a region with intermediate endemic hepatitis B seroprevalence. In the TURHEP study, hepatitis B surface antigen (HbsAg) positivity rate in our country was found to be 4% and hepatitis B core protein antibody (anti-Hbc Ig total) positivity rate was found to be 30.6%.[2]

Reactivation of HBV infection is an important cause of mortality and morbidity in rheumatology patients receiving immunosuppressive therapy. HBV reactivation (HBVr) provides insight into the disturbance of the balance between the host's immune system and viral replication.[3] Reactivation can occur spontaneously or after therapeutic agents adversely affect the host's immune system. Cytotoxic chemotherapies, steroid therapy, monoclonal antibody therapy and many other immunosuppressive agents used in the treatment of solid and hematological malignancies are potential risk factors for reactivation.[4] Patients should be closely monitored to prevent reactivation. Some studies have shown that screening for HBV infection in rheumatology patients receiving immunosuppressive therapy reduces the risk of reactivation.[5,6]

In our study, we aimed to present the hepatitis B virus serology data, prophylaxis receiving status and activities to prevent reactivation of patients who were referred to the infectious diseases outpatient clinic before immunosuppressive treatment due to rheumatological diseases.

MATERIAL AND METHOD

The study was carried out with the permission of Gaziantep Islamic Science and Technology University Noninvasive Clinical Researches Ethics Committee (Date: 16.06.2023, Decision No: 265.26.21). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 375 patients over 18 years of age who received tumor necrosis factor-α (TNF-α) inhibitor (adalimumab, infliximab, golimumab, etanercept, secukinumab, certolizumab, risankizumab, ixekizumab...), tyrosine kinase inhibitors (baricitinib, tofacitinib...), steroid, methotrexate or anti-CD20 antibodies (rituximab) due to rheumatological diseases in a training and research hospital between May 2022 and May 2023. Age, gender, type of rheumatological diseases of the patients, their HbsAg, hepatitis B surface antibody (anti-Hbs), anti-Hbc IgG serologies, immunosuppressive treatments / durations and type of oral antivirals were retrospectively analyzed. Those who received prior oral antiviral therapy for chronic hepatitis B disease, those who received immunosuppressive therapy for anything other than rheumatological diseases, and patients under 18 years of age were excluded from the study. Patients who received oral antiviral prophylaxis were followed for at least six months for reactivation. In the analyzes, continuous variables that fit the normal distribution, mean and standard deviation, continuous variables that do not fit the normal distribution, median value and minimum-maximum categorical variables were presented as numbers and percentages. Patients receiving immunosuppressive therapy were evaluated in terms of HBVr risk by dividing them into three categories according to the American Gastroenterological Association (AGA) risk classification. These are: high risk (>10%), moderate risk (1-10%) and low risk (<1%) categories.[4]

Statistical Analysis

Statistical analysis was performed using IBM SPSS 22.0 version (IBM SPSS, Chicago, IL). Of the patients quantitative values, mean (standard deviation), number of patients, serological/virological distribution characteristics, and antiviral prophylaxis were shown as frequency and ratio (n and %).

RESULTS

Of the 375 patients included in the study, 349 were receiving TNF-α inhibitor/steroid/methotrexate, 19 were taking tyrosine kinase inhibitors, and 7 were taking anti-CD20 antibodies. The average age of the patients was 43.77±13.07 years. 193 (51.5%) patients were male and 182 (48.5%) were female. The average duration of immunosuppressive therapy was 6.23±4.14 years. The results of HBsAg, anti-Hbs and anti-Hbc IgG were evaluated. 11 patients were HbsAg positive, 150 patients were anti-Hbs positive, 19 patients were isolated anti-Hbc IgG positive and 79 patients were both anti-Hbs and anti-Hbc IgG positive.

According to serological findings, 109 (29%) patients were exposed to HBV and 64 (17%) patients were found to be immune to HBV by vaccination. All three serology results of 194 (51.7%) patients were negative. A total of 85 (22.7%) patients reveived oral antiviral prophylaxis due to the use of immunosuppressive agents (**Table 1**). When the patients were evaluated in terms of HBVr, 14 (16.5%) patients were high risk, 64 (75.3%) moderate risk and 7 (8.2%) low risk. According to the distribution of prophylaxis, 79 patients were using entecavir, 5 patients were using tenofovir disoproxil fumarate (TDF) and 1 patient was using tenofovir alafenamide fumarate (TAF). Of the 85 patients receiving antiviral prophylaxis, 44 were men and 41 were women. The mean duration for the immunosuppressive therapy was 6.41±4.20 years. According to the distribution of patients who received antiviral prophylaxis for immunosuppressive therapy, 34 patients (40%) had rheumatoid arthritis, 29 patients (34.1%) had ankylosing spondylitis, 10 patients (11.7%) had psoriatic arthritis, 6 patients (7.1%) had Behcet's disease, and 6 (7.1%) patients had systemic lupus erythematosus (**Figure 1**). HBVr was not observed in any of our patients.

Table 1. Demographic and laboratory data of the patients

	All patients, n(%) or (min-max)	Patients receiving antiviral prophylaxis n(%) or (min-max)
Number of patients	375 (100)	85 (22.7)
Mean age ± SD	43.77±13.07	48.3±11.8
Male	193 (51.5)	44 (51.8)
ALT	23.7 (5-108)	25.8 (8-108)
HBsAg positive	11 (2.9)	11 (12.9)
Isolated anti-HBc positive	19 (5.1)	17 (20)
Both anti-HBs and anti-HBc Ig G positive	79 (21.1)	57 (67.1)

SD: Standart deviation, ALT: Alanine transaminase, HbsAg: Hepatitis B surface antigen, Anti-Hbs: Hepatitis B surface antibody, Anti-Hbc IgG: Hepatitis B core protein antibody

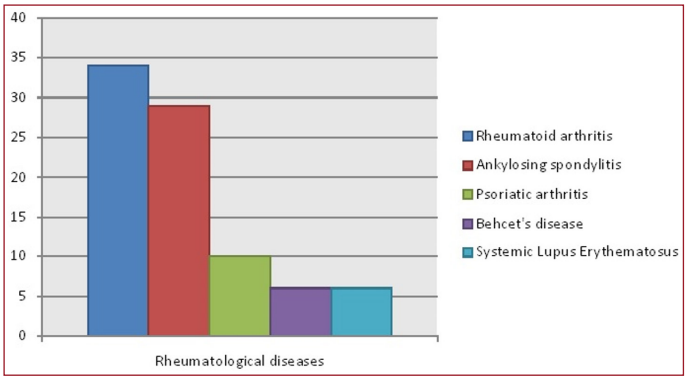

Figure 1. Distribution of patients receiving antiviral prophylaxis

DISCUSSION

HBVr remains an important cause of morbidity and mortality in patients with chronic hepatitis B or resolved HBV infection receiving immunosuppressive therapy. However, according to the risk status of the patients, it is a preventable condition with various options such as close follow-up, preemptive treatment or antiviral prophylaxis.[7,8] HBVr is seen at a rate of 12% in HbsAg-positive and 3-5% in HbsAg-negative / anti-Hbc Ig G-positive patients with rheumatological disease who do not receive antiviral prophylaxis.[9] In a study in which 278 patients receiving TNF-α inhibitor were evaluated in the study of Karadağ et al., 29 patients had a history of HBV infection or isolated anti-HBc total positivity, HBV reactivation was found in 5 (17.2%) patients.[10] In the study of Çabalak et al. Hbs Ag positivity was 4.1%, but no reactivation was observed.[11] We think that the absence of HBVr in our study is due to the low number of high risk patients.

Patients at risk of HBVr were divided into three groups according to AGA risk classification, depending on HBV serology (HbsAg and/or anti-Hbc IgG positivity) and the type of immunosuppressive agent used. These are high risk (>10%), moderate risk (1-10%) and low risk (<1%) patients.[4] Although there are some differences between the guidelines for the follow-up of these patients, the common feature of these guidelines is that it is definitely recommended to start antiviral prophylaxis in high risk patients. On the other hand, in low and moderate risk patients, it varies according to the type of immunosuppressive agent received and HBV serology status, initiation of antiviral prophylaxis with follow-up is left to the physician's decision for these group.[4,12-14] In our study, the majority of patients who received HBVr preventive prophylaxis were in the moderate risk group (75.3%). In the study of Ceylan et al., 35% of the patients were in the high risk group, 49% in the moderate risk group, and 16% in the low risk group.[15] In the study of Durak and Coşar 24.5% were at high risk, 42.6% were at moderate risk and 33% of patients were at low risk.[16]

Entecavir, TDF and TAF used in the treatment of chronic hepatitis B are effective and safe drugs. Guidelines recommend entecavir, TDF or TAF for prophylactic antiviral treatment because of their high genetic barriers and efficacy.[17] However drug interaction, renal dysfunction, osteoporosis are factors that should be considered in the selection of antiviral drugs.[18,19] In one meta-analysis study, initiation of any of these antivirals was shown to inhibit reactivation.[20] In comparative studies with lamivudine, Picardi et al. and Yang et al. showed that the risk of HBVr were lower in patients using TDF and entecavir, respectively.[21,22] In our study, entecavir was the most commonly used antiviral for prophylaxis purposes (92.9%). It was observed that different antivirals were used in different proportions in the literature. The initiation rate of entecavir was 67% in Ceylan et al. study for prophylaxis.[15] Starting entecavir, TDF or TAF varies on the clinician's decision, the patient's condition, and the underlying disease.

It is recommended that antiviral prophylaxis be started 1-3 weeks before or at least concomitantly with immunosuppressive therapy.[12,14] In our study, 27 (31.8%) patients were started concomitantly, while the remaining patients were started later on. No reactivation was observed in these patients. In their study of 2334 rheumatoid arthritis patients, Chen et al. followed up 123 HbsAg positive/high-risk patients without antiviral prophylaxis and reactivation was observed among 30 of them (24.4%).[23] In a multicenter and retrospective study, reactivation was not detected after initiation of prophylaxis in the moderate risk patient group.[24] In another prospective study, among 234 high risk patients, there had been 3 (two chronic HBV, one resolved HBV) reactivation cases.[25] In the study by Harigai et al., reactivation was observed in 14.8% after immunosuppressive treatment.[26] HBVr was 12.3% in the study of Lee et al.[27] which included HbsAg positive patients, and 5% in Urata's study of HBsAg-negative/anti-HBc-positive patients.[28] Studies in the literature also show that strict follow-up is required in terms of HBVr, especially in the high risk group.

In the literature, HbsAg or anti-Hbc Ig G positivity shows regional differences. In our study, HbsAg positivity was 2.9% and HBV exposure was 29% in the rheumatologic patient group. In a study conducted in Italy in which 292 rheumatology patients were included, HbsAg was found to be 2% and HBV exposure was 24%.[29] In another study in

Iran in which 93 systemic lupus erythematosus patients were included, HbsAg positivity was 3.2% and HBV exposure was 8.7%.[30] There was no HBsAg positivity in the study in Turkey, but HBV exposure screening was insufficient.[31]

In our study, our negative patient rate was 51.7% in all three HbsAg, anti-Hbc IgG and anti-Hbs tests. About half of our patients were susceptible to HBV infection. HBV infection is a vaccine-preventable viral infection. The increase of comorbid diseases among immunosuppressive patients negatively affects their quality of life. In addition to the 0-1-6 calendar, which is the most commonly used in HBV vaccination, there are also different hepatitis B vaccination schedules such as 0-1-2-6, 0-1-12, 0-1-2-12.[32] However, in a study comparing a single dose of the vaccine and a double dose among immunosuppressive patients, a higher anti-Hbs titer was detected in those who received a double dose of hepatitis B vaccine.[33] In our study, we recommended a double dose of hepatitis B vaccine on a 0-1-6 schedule, for HBV-susceptible patients to prevent chronic hepatitis B.

There are some limitations of our study. First, this was a single-center, retrospective design study with a sample size. Second, our patients were receiving immunosuppressive therapy only for rheumatological diseases. Cytotoxic chemotherapies and other immunosuppressive agents may also be included. Third, while it is recommended to start oral antiviral therapy in patients according to the risk classification, in our study, the AGA 2015 guideline was used instead of APASL 2021 in terms of HBV reactivation risk and the content of immunosuppressive agents was not specified. These issues should be considered in future studies.

CONCLUSION

The available data suggest that due to the increasing use of TNF-α inhibitor and other biologic immunosuppressive agents, patients should be screened for hepatitis before treatment and regular follow-up should be performed afterwards. The risk of HBVr associated with the ever increasing new immunosuppressive agents is not clear. More comprehensive studies are needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gaziantep Islamic Science and Technology University Noninvasive Clinical Researches Ethics Committee (Date: 16.06.2023, Decision No: 265.26.21).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1342910
J Contemp Med 2023;13(5):814-819

Original Article / Orijinal Araştırma

Bibliometric Analysis of Scientific Literature on Acanthamoeba Keratitis

Acanthamoeba Keratitinin Bibliyometrik Analiz Yöntemiyle Değerlendirilmesi

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Abstract

Aim: Our research aimed to assess Acanthamoeba keratitis research trends and compare contributions from various nations, institutions, journals, and authors.

Material and Method: A bibliometric design was used. We used the Web of Science database to extract all Acanthamoeba keratitis articles from 1970 to 2021. To collect publishing data, analyze publication trends, and visualize relevant data, Microsoft Excel and VOSviewer were used.

Results: 171 (31.784 %) of them were published as open Access. 92.751% of them were published in Science Citation Index Expanded indexed journals. The mean number of citations was 13733, with a median of 25.53, and the H index was 63. 77.32 % of the articles were published since 2000. University of Texas in the United States had the highest number of publications (78, 14.499%), followed by the University of London in the UK (63,11.71%). The United States (USA) ranked first in the number of publications (151, 28.067%), followed by the United Kingdom (49, 9.108%) and Germany (31, 5.762%). Publications from the USA were cited 6,344 times (42.01/ median per publication), while publications from the UK were cited 2,949 times (60.18/median per publication). Acanthamoeba keratitis research has increased significantly in the last 15 years.

Conclusion: With the use of information visualization analysis, we were able to gain a wide understanding of the state of affairs, recognize trends, and identify hotspots. It is a more effective way to learn the literature and could give future researchers summarized data.

Keywords: Bibliometric studies, Acanthamoeba, keratitis, publications, contact lens

Öz

Amaç: Çalışma, Acanthamoeba keratitinin araştırma eğilimlerini değerlendirmeyi ve çeşitli ulusların, kurumların, dergilerin ve yazarların katkılarını karşılaştırmayı amaçlamaktadır.

Gereç ve Yöntem: Bibliyometrik bir analiz yapıldı. 1970'den 2021'e kadar tüm Acanthamoeba keratiti makalelerini değerlendirmek için Web of Science veritabanı kullanıldı. Yayın verilerinin toplamak, yayın eğilimlerini analiz etmek ve ilgili verileri görselleştirmek için Microsoft Excel ve VOSviewer kullanıldı.

Bulgular: Yukarıda ayrıntıları verilen metodolojiye göre 538 makaleye ulaşıldı. 171 tanesi (%31.784) açık erişim olarak yayınlandı. Bunların %92.751'i Science Citation Index Expanded indeksli dergilerde yayınlandı. Ortalama atıf sayısı 13733, medyan değeri 25,53, H indeksi ise 63 idi. Makalelerin %77,32'si 2000 yılından sonra yayınlanmıştır. En fazla yayın Amerika Birleşik Devletleri'ndeki Texas Üniversitesi'nde yapılmış olup (78, %14,499) onu İngiltere'deki Londra Üniversitesi (%63,11,71) izledi. Yayın sayısında Amerika Birleşik Devletleri (ABD) ilk sırada yer alırken (%151, 28.067), onu Birleşik Krallık (%49, 9.108) ve Almanya (%31, 5.762) izledi. ABD'den yayınlara 6.344 kez (yayın başına 42.01/medyan), Birleşik Krallık'tan yayınlara 2.949 kez (yayın başına 60.18/medyan) atıf yapıldı. Acanthamoeba keratit araştırmaları son 15 yılda önemli ölçüde artmıştır.

Sonuç: Bilgi görselleştirme analizini kullanarak, Acanthamoeba keratiti hakkında geniş bir bakış açısı sunulmuştur. Yapılan çalışmaların eğilimleri ve önemli noktoları belirlenmiştir. Bu çalışma, Acanthamoeba keratiti ile ilgili yapılan çalışmaları öğrenmenin etkili yollarından biridir ve araştırmacılar için özetlenmiş bilgiler sağlamaktadır.

Anahtar Kelimeler: Bibliyometrik çalışmalar, Acanthamoeba, keratit, yayınlar, kontakt lens

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Received *(Geliş Tarihi)*: 14.08.2023 **Accepted *(Kabul Tarihi)*:** 11.09.2023

INTRODUCTION

Acanthamoeba amoeba is globally seen as organisms that may thrive as free-living organisms as well as parasites within the host tissue. Acanthamoeba infections pose a significant danger to human health and are associated with a high fatality rate, particularly in immunocompromised patients.[1] Because of their worldwide spread, these amoebas are among the most numerous protozoa in nature, and they can live in a wide, range of environments and severe settings by forming structures known as cysts.[2] Acanthamoeba spp. can be found in lakes, swimming pools, tap water, and heating and cooling equipment. Acanthamoeba species linked to human illness include A. culbertsoni, A. polyphagia, A. castellanii, A. astronyxis, A. hatchetti, A. rhysodes, A. divionensis, A. lugdunensis, and A. lenticulata.[3]

These protozoa are responsible for the etiology of granulomatous amoebic encephalitis (GAE) and Acanthamoeba keratitis (AK).[1] It has been reported that 8 species and five genotypic classes of Acanthamoeba cause keratitis.[4] AK is an uncommon but severe eye inflammation of the lining, permanent vision impairment, or blindness. [5] Furthermore, the number of reported cases globally is growing year after year, primarily in contact lens wearers, however, cases have been documented in non-contact lens wearers as well. Symptoms and signs of AK are pain with photophobia, stromal ring-shaped infiltrates, epithelial defect, and lid edema. Interestingly, despite breakthroughs in antimicrobial treatment and supportive care, Acanthamoeba keratitis has remained prevalent. This is partly due to a lack of understanding of the disease's origin and pathophysiology, as well as diagnostic delays and issues associated with chemotherapeutic therapies.[6]

In this study, we conducted a quantitative evaluation of the existing literature on Acanthamoeba keratitis. Based on Web of Science (WOS) data, the report presents a broad overview of the current state of global Acanthamoeba keratitis research. The bibliometric method was used to find trends in Acanthamoeba keratitis research and explore possible hotspots.

MATERIALS AND METHODS

Research Model: A bibliometric analysis study

Data Collection: To retrieve the research publications, the Web of Science Core Collection (previously known as the Web of Knowledge) database (Clarivate Analytics, Philadelphia, PA, USA) was used. Data were obtained from the database on April 15, 2022.

The titles, document types, years of publication, names of authors, affiliations, keywords, group authors, names of publishing journals, abstracts of each record, and citations within the WOS publications were saved as TXT files and were imported into Microsoft Office Excel 2019 (Los Angeles, CA, USA).

We utilized the Hirsch equation (H-index) for qualitative analysis, which is the most extensively used measurement to quantify both the quality and quantity of a publication group. The H-index was calculated using the Web of Knowledge's Citation Report.

Overview of the output from the WoS database: The WoS database was used to identify the publishing year, country or nation, study category, authors, and citation numbers of the retrieved publications. As a timeline, only articles published between 1971 and 2021 were considered, as we aimed to analyze the 50 years situation. Since 2022 has not been completed yet, publications in this period were excluded from the study.

Microsoft Excel 2013 for Windows was used to transfer the data (Microsoft Corp., Redmond, WA, United States of America, USA). The citations were analyzed using the Wos database. The Hirsch-Index (h-Index) was utilized as a measure of research output quality, and the number of publications was used as a metric of research quantity. The total number of citations as well as the average number of citations per item were computed for each publication (citation rate). The findings' bibliometric data was kept in a separate database and displayed in tables as visualizations.

The following search technique was implemented:

Title: Acanthamoeba keratitis

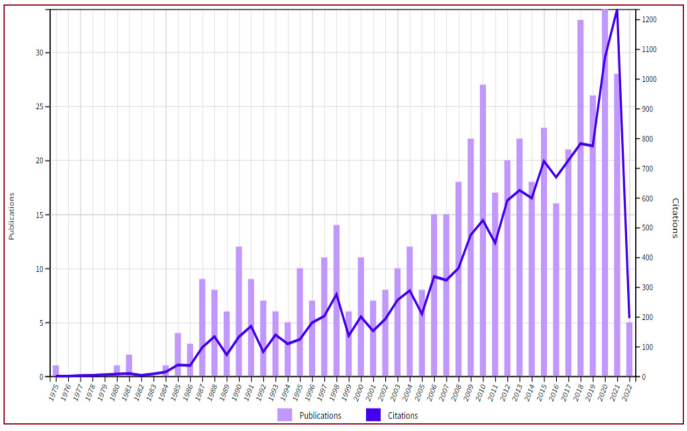
Document Type: Article. Other manuscript formats such as case reports, editorials, and letters were eliminated from the search because they were not peer-reviewed articles.

Timespan: 1970–2021.

Mapping: To visualize country collaboration networks and keywords, the VOSviewer 1.6.18 for Microsoft Windows systems program was used. We created co-occurrence networks from the obtained publications' bibliographic metadata (e.g., nations, citations, and keywords).

RESULTS

According to the methodology detailed above, we retrieved 538 articles. 171 (31.784%) of them were published as Open Access (OA) and 92.379% of them were in the English language. Other rarely preferred languages were German (3.903%), French (2.788%), and other languages (Spanish, Korean and Malay). 499 (92.751%) of them were published in Science Citation Index Expanded (SCI-EXPANDED) indexed journals. The mean number of citations was 13733, with a median of 25.53, and the H index was 63. The number of citations and published articles has increased over the years. 416 (77.32%) of the articles were published since 2000. 2020 was the year with the most publications in terms of the number of publications per year (34, 6.320 %) (**Graphic 1**).



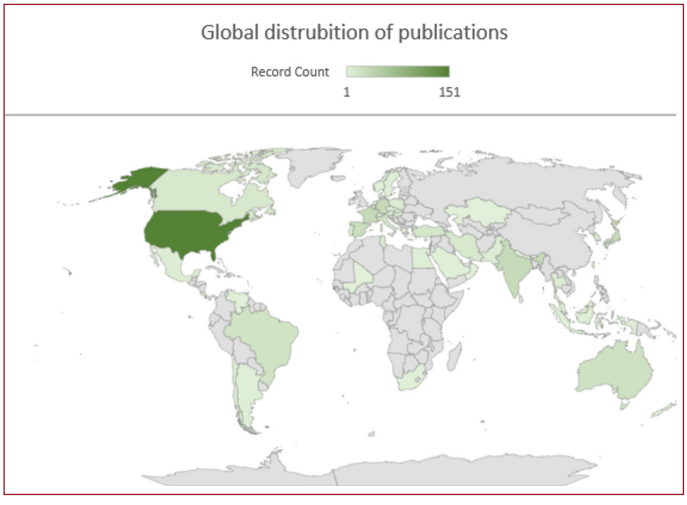
Graphic 1. The number of published articles and citations on Acanthamoeba keratitis.

The United States (USA) ranked first in the number of publications (151, 28.067%), followed by the United Kingdom (49, 9.108%) and Germany (31, 5.762%) (**Table 1**) (**Graphic 2**). Publications from the USA were cited 6,344 times (42.01/median per publication), while publications from the UK were cited 2,949 times (60.18/median per publication).

Table 1. Top 10 countries on publications.

Countries/ Regions	Record Count, %	Number of citations	H indexes	Number of citations average per publication
The USA	151(28.067)	6350	47	42.05
United Kingdom	49(9.108)	2952	26	60.24
Germany	31(5.762)	319	10	10.29
Japan	31(5.762)	477	13	15.39
France	29(5.390)	253	9	8.72
India	29(5.390)	667	11	23
Spain	26(4.833)	407	12	15.65
China	25(4.647)	561	12	22.44
Australia	21(3.903)	423	12	20.14
Brazil	19(3.532)	280	10	14.74

Total 56 countries, 4 record(s) (0.743%) do not contain data in the field being analyzed



Graphic 2. Global distribution of publications

The University of Texas in the United States had the highest number of publications (78, 14.499%) followed by the university of London in the UK (63,11.71%) on Acanthamoeba keratitis (**Table 2**).

Table 2. Publications from the top 20 organizations Acanthamoeba keratitis research.

Organizations	Record Count	% of 538
University of Texas	78	14.499
University of London	63	11.71
University of Illinois Chicago	39	7.248
Moorfields Eye Hospital NHS Foundation Trust	28	5.204
Centers for Disease Control Prevention USA	17	3.160
League of European Research Universities Leru	16	2.974
Udice French Research Universities	13	2.416
Universidad de La Laguna	13	2.416
University of California System	13	2.416
L V Prasad Eye Institute	11	2.045
Baylor College of Medicine	10	1.859
Chno Des Quinze Vingts	10	1.859
Harvard University	10	1.859
Ohio State University	10	1.859
Sorbonne University	10	1.859
Universitatsklinikum Des Saarlandes	10	1.859
Tehran University of Medical Sciences	9	1.673
University of Iowa	9	1.673
Capital Medical University	8	1.487
Jefferson University	8	1.487

*Showing 20 out of 701 entries; 4 record(s) (0.743%) do not contain data in the field being analyzed

Most of the articles were from Ophthalmology (65.985%), Parasitology (9.294%), and Microbiology (8.364%) research areas (**Table 3**).

Table 3. Number of articles according to the research areas.

Research Areas	Record Count	% of 538
Ophthalmology	355	65.985
Parasitology	50	9.294
Microbiology	45	8.364
Infectious Diseases	24	4.461
General Internal Medicine	21	3.903
Immunology	18	3.346
Public Environmental Occupational Health	17	3.160
Tropical Medicine	13	2.416
Pharmacology Pharmacy	10	1.859
Science Technology Other Topics	10	1.859

*Showing 10 out of 29 entries

Cornea journal published most of the articles (**Table 4**).

Table 4. The list of journals published more than five articles.

Publication Titles	Record Count	% of 538
Cornea	68	12.639
American Journal of Ophthalmology	33	6.134
Ophthalmology	31	5.762
Parasitology Research	21	3.903
Archives of Ophthalmology	19	3.532
British Journal of Ophthalmology	18	3.346
Investigative Ophthalmology Visual Science	15	2.788
Eye Contact Lens Science and Clinical Practice	14	2.602
Journal of Clinical Microbiology	13	2.416
Experimental Parasitology	11	2.045
Klinsche Monatsblatter Fur Augenheilkunde	11	2.045
Journal Francais D Ophtalmologie	10	1.859
Ophthalmologe	9	1.673
Current Eye Research	8	1.487
Eye	8	1.487
Contact Lens Anterior Eye	7	1.301
Acta Ophthalmologica	6	1.115
Canadian Journal of Ophthalmology	6	1.115
Clinical Ophthalmology	6	1.115
Clinical and Experimental Ophthalmology	5	0.929

*total 159 entries

Mapping

The network analysis and mapping from the obtained publications' bibliographic metadata (e.g., nations, citations, and keywords) were given in **Figures 1-3**.

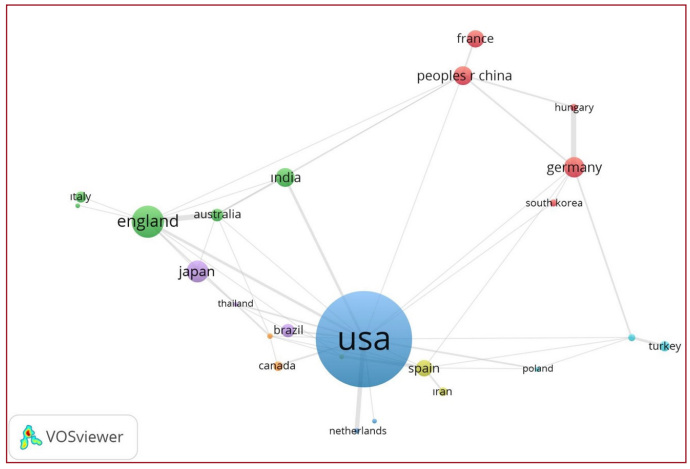


Figure 2. Number of articles from countries and co-authorship analysis

DISCUSSION

Although bibliometrics studies on a variety of topics have been used in the field of ophthalmology,[7-16] none of them have focused on Acanthamoeba keratitis. The use of scientometrics in the field of ophthalmology makes it easier to investigate the productivity of local medical facilities, which aids in the right allocation of future research funds. Because of advances in health informatics, scientometrics can now assess the impact of publications using citation reports, knowledge mapping tools, and other quantitative bibliometrics characteristics.[17]

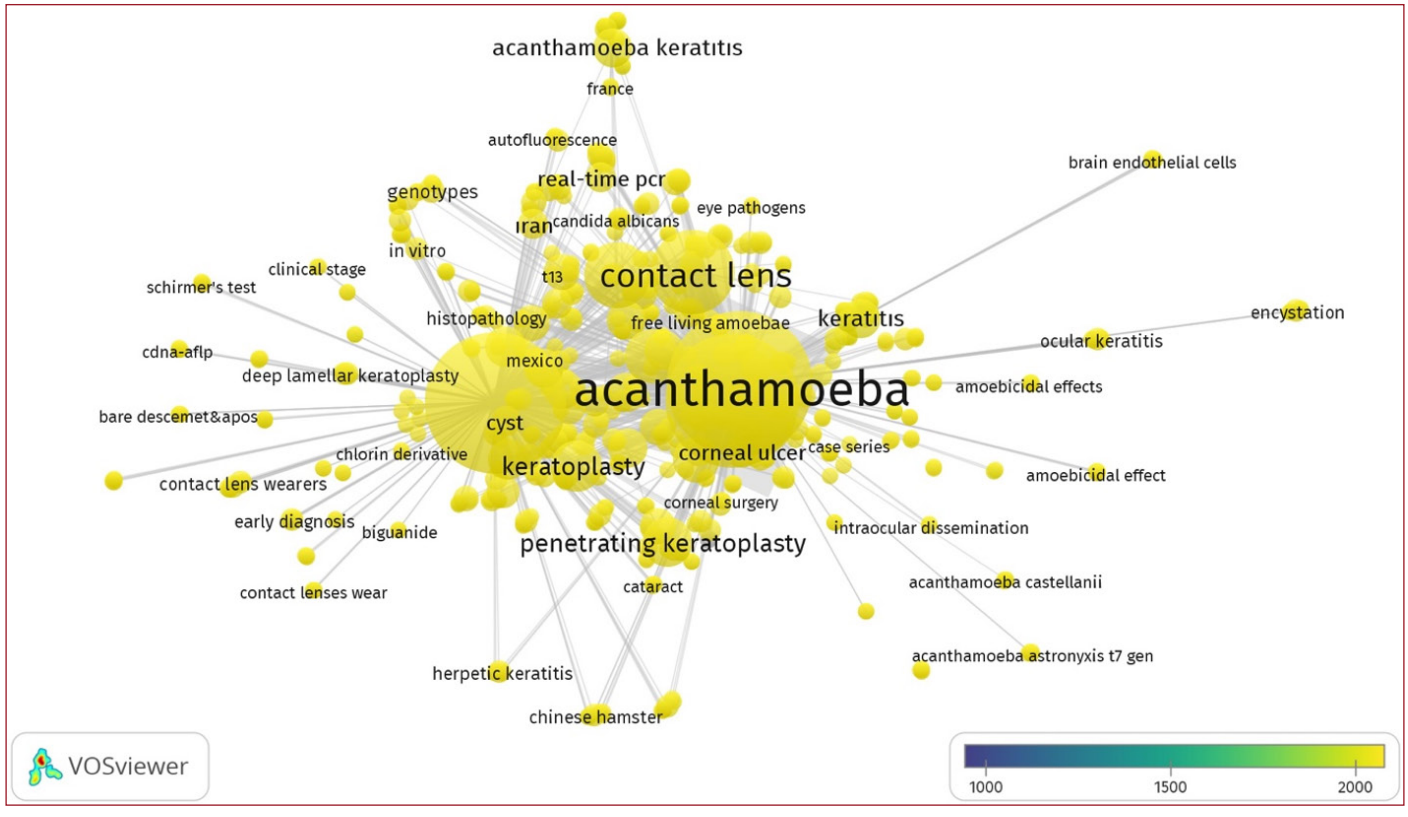


Figure 1. Keyword analysis

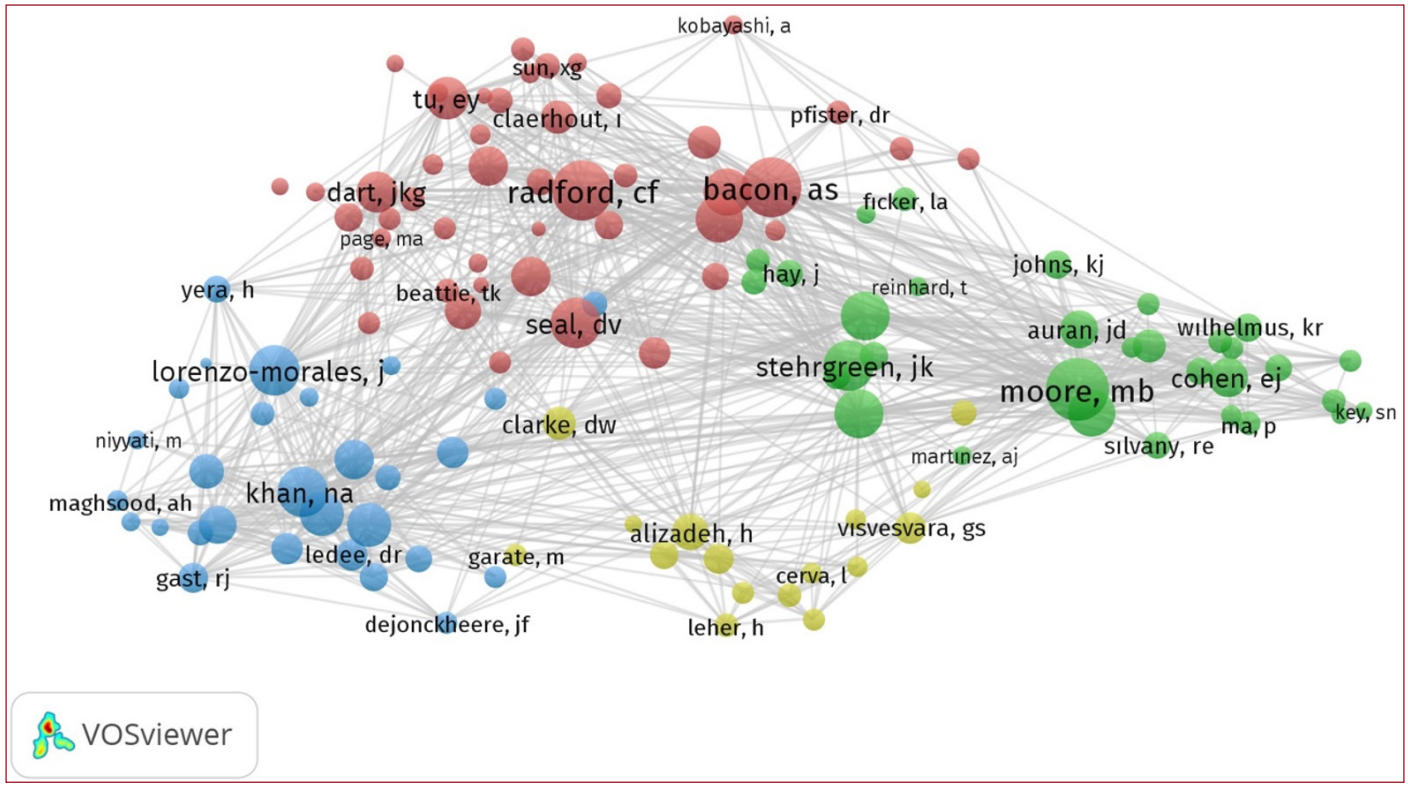


Figure 3. Citations analysis between authors.

This visualized scientometric method was used to determine the general state and trends, as well as hot spots in the Acanthamoeba keratitis research topic. We retrieved 538 articles in the WoS database after carrying out a detailed search. The USA, UK, Germany, Japan, and France were the five most productive countries. The USA also dominated this area in terms of the number of published articles. After the 2000s, the rising trend in the contribution rate was at a level that could not be ignored. According to journal analysis, ophthalmologists and parasitologists are the researchers most interested in Acanthamoeba keratitis research.

As the study becomes more collaborative, it is critical to investigate the relationships between researchers from various countries. We used VOSviewer to analyze the co-occurrence to identify the top authors, nations, institutions, and journals. Each cluster indicated an object in the network map generated by this software, such as authors or nations; the size of clusters represented occurrence frequencies, and the color of clusters reflected which cluster the node belonged to based on a co-occurrence analysis. Meanwhile, the connections between neighboring points indicated that the two components were working together (such as authors or institutions). The connecting lines become thicker as the frequency of collaboration increases (**Figures 1-3**). The publications from the USA were cited 42.01/median per publication, and the publications from the UK were 60.18/median citations per publication. In summary, although the publications from the UK were numerically less than the USA, they were cited more than the publications in the USA.

Before the investigation, similar studies in the literature were examined, and the methodology was developed based on those studies.[15-17] WoS is a respected and trustworthy scientific database that is frequently utilized in academia. On WoS, users might quickly access all of the article data and scientific impact metrics used in the bibliometric study. As a result, it has been frequently utilized in comparable bibliometric research.[7-14,18] We used the WoS advanced search engine to conduct the quantitative search because it provides a standard dataset for analyzing and tracking bibliographical criteria such as author names, keywords, affiliation, country, journal title, number of citations, and broad subject areas.

To our knowledge, this is the first article on Acanthamoeba keratitis to use visualized bibliometrics analysis. In comparison to traditional reviews, VOSviewer-based analyses display data and provide a more complete picture of the history, current state, and research priorities in Acanthamoeba keratitis. However, there are some restrictions. The author of the article only developed the first three names, so the correspondence author information may be omitted at times. Researchers had to read the source material themselves because bibliometrics software was unable to distinguish between fundamental author contributions in extensive collaboration. We excluded articles that were not in the WoS database and non-English literature, which limited the scope of our study.

CONCLUSION

Acanthamoeba keratitis research has increased significantly in the last 15 years. Using information visualization analysis, we were able to obtain a broad picture of the current state and trend of this study field, as well as identify hot spots. It is a more efficient way of learning the literature and may provide summary data for future studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: Because the data were obtained from publicly available studies, no ethical approval was required.

Informed Consent: Informed consent was not required.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1343574
J Contemp Med 2023;13(5):820-823

Original Article / Orijinal Araştırma

Investigation of Variants In SARS-CoV-2 Infections after Three Doses of COVID-19 Vaccine

Üç Doz COVID-19 Aşı Sonrası Oluşan SARS-CoV-2 Enfeksiyonlarında Varyantların Araştırılması

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Abstract

Aim: Our study focused on retrospectively assessing variant of concern, specified by the World Health Organization (WHO), with one-step reverse transcription and real-time polymerase chain reaction (RT-PCR) test in SARS-CoV-2 positive patients after three doses of attenuated COVID-19 vaccine.

Material and Method: 8.520 samples transported with viral nucleic acid buffer (vNAT) tubes between June 2021 and January 31, 2022, were tested and included in the study. All the patients whose samples were included in our research had 3 doses of CoronaVac (Sinovac Life Science Co, Ltd, Beijing, China). Gender distribution was 4686 (55%) female and 3834 (45%) males. Variant specific genome regions only found in B.1.351, P.1 and B.1.1.7 as well as ORF1ab and N gene regions are investigated by the Bio-Speedy® Emerging Plus kit (Bioeksen AR-GE Technologies, Turkey) used to identify the variants in the study.

Results: All 8.520 samples were SARS-CoV-2 RT-PCR positive. Our study detected alpha and delta variants in 1460 (17.14%) and 3570 (41.9%) patients respectively. 2570 (30.16%) patients did not have any variants according to test results. It was observed that the spread of beta, gamma and other suspicious variants remained at relatively low rates.

Conclusion: The delta variant became dominant from July until to the end of the year. Declining delta variant rates and increasing cases of suspected variants towards the beginning of December 2021 suggest the omicron variant. Therefore, molecular surveillance studies that are planned to take epidemiological data into consideration and to examine the prevalence and gene-based analysis of local and worldwide variants are required.

Keywords: SARS-CoV-2, variants take concern, variant B.1.1.7, variant B.1.351, variant P.1, variant B.1.617.2

Öz

Amaç: Çalışmamızda, üç doz atenüe COVID-19 aşısı sonrası SARS-CoV-2 polimeraz zincir reaksiyonu (PCR) testi pozitif saptanan hastalarda Dünya Sağlık Örgütü (DSÖ) tarafından endişe verici varyantların ("variants of concern – VOCs") dağılımının geriye dönük olarak değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Haziran 2021-31 Ocak 2022 tarihleri arasında laboratuvara rutin çalışma kapsamında viral nükleik asit tamponu (vNAT) tüpü ile gelen ve SARS-CoV-2 RT-PCR testi istenen 8520 örnek çalışmaya dahil edildi. Örneklerin hepsi, 3 doz CoronaVac (Sinovac Life Science Co, Ltd, Beijing, China) aşı geçmişine sahip ve son doz aşıdan en az 28 gün geçtikten sonra alınmış, cinsiyet dağılımı 4686 (%55)'sı kadın 3834 (%45)'ü erkektir. SARS-CoV-2 varyantları; ORF1ab ve N gen bölgelerinin yanı sıra yalnızca B.1.1.7, B.1.351 ve P.1'de bulunan varyant spesifik genom bölgelerini de hedefleyen Bio-Speedy® SARS- CoV-2 Emerging Plus kiti (Bioeksen AR-GE Teknolojileri, Türkiye) ile saptandı.

Bulgular: 8.520 numunenin tamamı SARS-CoV-2 RT-PCR pozitifti. Çalışmamızda sırasıyla 1460 (%17,14) ve 3570 (%41,9) hastada alfa ve delta varyantları saptandı. 2570 (%30,16) hastanın test sonuçlarında göre herhangi bir varyantı yoktu. Beta, gama ve diğer şüpheli varyantların yayılımının nispeten düşük oranlarda kaldığı gözlemlendi.

Sonuç: Çalışmamızda, Temmuz ayından yıl sonuna kadar ise delta varyantının baskın hale geldiği tespit edildi. Bu bağlamda epidemiyolojik veriler ışığında planlanmış, bölgesel ve küresel çapta varyantların sıklığını ve genomik analizlerini irdeleyen moleküler sürveyans çalışmalarının yapılması gerekmektedir.

Anahtar Kelimeler: Sars-CoV-2, SARS-CoV-2, endişe verici varyantlar, varyant B.1.1.7, varyant B.1.351, varyant P.1, varyant B.1.617.2

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Received *(Geliş Tarihi)*: 15.08.2023 **Accepted *(Kabul Tarihi)*:** 11.09.2023

INTRODUCTION

The COVID-19 is a significantly infectious disease that initially emerged in China at the very end of 2019. Acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) from the coronavirus family was responsible from the illness. WHO specified the disease as a pandemic on March 11, 2020, after it severely affected almost all countries within weeks.[1] 6.9 million deaths out of approximately 770 million COVID-19 cases have been globally confirmed as of May 2023 according to WHO data.[2] The original strain has mutated since the onset of the pandemic and evolved into several variants. This situation has created threats that may adversely affect the course of the pandemic such as increased risk of transmission, escape from immune response, risk of reinfection, decreased effectiveness of vaccines, and worsening of the clinical picture. WHO primarily categorized mutations as "Variants of Interest (VOIs)", "Variants Under Monitoring (VUMs)" and "Variants of Concern (VOCs)". Alpha (B.1.1.7, UK), Beta (B.1.351, South Africa), Gamma (P.1, Brazil), Delta (B.1.617.2, India), and Omicron (B.1.1.529)[3] are the five concerning variants have emerged so far. Many vaccine studies and subsequent vaccination campaigns against SARS-CoV-2 have started against the pandemic but all the worrying variants have caused a new wave in pandemics resulted in thousands of more deaths worldwide. Therefore, it is critical to identify SARS-CoV-2 variants and follow the mutations as they undergo to eliminate actor of the COVID-19 pandemic.[4] Protection obtained through proper two dose of vaccination gradually declines in severe COVID-19 cases and hospitalization. However, booster vaccination with any of the common mRNA-based vaccines significantly is reported by other research scaling down the reinfection possibility and even if the patient is reinfection and yet the disease can be mildly recovered.[5] Our study aimed to retrospectively examine the distribution of variants in SARS-CoV-2 VOCs positive individuals with one-step reverse transcription and real-time polymerase chain reaction (RT-PCR) after they received 3 doses CoronaVac 600 U/0.5 mL (Sinovac Life Science Co, Ltd, Beijing, China) vaccine and the last dose is at least 28 days before the test.

MATERIAL AND METHOD

The study was carried out with the permission of Yıldırım Beyazit University Yenimahalle Training and Research Hospital Scientific Research Ethics Committee (Date: 11.05.2022, Decision No: 2022-29). All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

The study was carried out retrospectively by covering between June 2021 and January 31, 2022. The study included 8520 samples evaluated as COVID-19 SARS-CoV-2 infection contact follow-up, epidemic management, home patient follow-up and filiation guide as a Scientific Advisory Board study in Ankara Provincial Health Directorate Sample Campus Molecular Diagnosis Laboratory. These samples were transported with a viral nucleic acid buffer (vNAT) tube as routine work by the filiation teams and their test results were positive. All samples obtained from patients who had CoronaVac 600 U/0.5 mL (Sinovac Life Science Co, Ltd, Beijing, China) vaccine (3 doses) and sample collection was at least 28 days after the last dose. Gender distribution was 4686 (55%) females and 3834 (45%) males. Variants was detected with the Bio-Speedy® SARS-CoV-2 Emerging Plus kit (Bioeksen AR-GE Technologies, Turkey). This kit investigates distinct genome regions belonging to the variants with E484K (Gamma and Mu) and L452R (Delta) mutations in the S region and the Nucleocapsid region with D3L (Alfa) mutations in addition to the ORF1ab and N gene regions. Studies were performed on CFX96 DX Real-Time PCR systems (Bio-Rad Laboratories, USA).

Statistical Analysis

Statistical analysis was performed with SPSS 22.0 program (IBM Corp., Armonk, NY, USA). Frequency (n), percentage (%) and mean values were determined in the data analysis.

RESULTS

The average age of 8520 patients was 42.62±14.98 years. 4686 (55%) of them were female and 3834 (45%) were males. 2570 (30.16%) patients did not have any variants while alpha was found in 1460 (17.14%) and delta in 3570 (41.9%). It was observed that the spread of beta, gamma and other suspicious variants remained at relatively low rates (**Table 1**).

Table 1. Distribution of SARS-CoV-2 Variant Types

	SARS-CoV-2 (No variant) n (%)	Alfa Variant n (%)	Delta Variant n (%)	Beta / Gamma Suspicious n (%)	Other Variant Suspicious n (%)
Positive	2570 (30.16%)	1460 (17.14%)	3570 (41.9%)	270 (3.17%)	650 (7.63%)

DISCUSSION

The still ongoing pandemic has started to slow down thanks to the vaccines that emerged because of effective and rapid vaccination studies that were approved for immediate use. It becomes more important whether the vaccines used are effective against variants or not as the strains responsible for overall COVID-19 picture that occurs in vaccinated individuals are frequently variants (VOC)[6] with SARS-CoV-2 variants becoming more common all over the world. Many COVID-19 vaccines have proven to be safe and effective as a booster dose. 7 different vaccines were scrutinized as booster doses in the Cov-Boost trial afer two doses of AstraZeneca or Pfizer vaccines. They are Curevac, AstraZeneca, Moderna, Johnson & Johnson, Novavax, Pfizer and Valneva. The trial showed that all of them enhanced the immunological response.[7]

Vaccination history of positive test subjects (cases) among symptomatic individuals who requested SARS-CoV-2 testing was compared with the vaccination history of negative test

subjects (controls) in a negative case-control study carried out in Alaska. It has been shown that people who have not received the mRNA COVID-19 vaccine reminder dose have an approximately three times higher risk of contracting symptomatic COVID-19 infection compared to people who have received the reminder dose. This analysis also found that reminder dose increased the protection against a COVID-19 reinfection. It has been reported that once-positive patients without a reminder dose have a re-infection risk of 1.6 times compared to those with a reminder dose.[8]

It is known that the immune response of inactivated Sinovac and Sinopharm vaccines is reduced after a certain period like other inactivated vaccines.[9] It seems reasonable to apply a third dose of vaccine to strengthen the immune response for this type vaccines. Moreover, this will support the hypothesis of a third dose vaccine requirement given that it is supported by studies that it is effective against emerging variant viruses.[10] It is thought that China which has received approximately 1.69 billion doses of inactivated vaccines, may change its attitude towards mRNA-based vaccines since she has been keeping a distance from until now due to the low efficacy of these vaccines against new variants (especially the Delta variant) and the increasing number of cases.[11] It is determined that there is a very common SARS-CoV-2 variant positivity in individuals vaccinated with 3 doses of inactivated vaccine in our study similar to this data. Mutations are a natural part of the viruses' life cycle and their adverse effects on the course of epidemics are rare and limited. It is suggested that mutations may help managing existing epidemics and understanding new epidemics.[12] Cellular immune response mediated by T lymphocytes and Natural killer (NK) cells plays a key role in infection control even though spike protein mutations in variant viruses cause evading neutralization.[13] Therefore, vaccines continue to be the greatest arsenal to control variant viruses.

A microneutralization assay was conducted in Israel using Wild-type virus, Beta, Delta and Omicron variant isolates and serum samples from two groups of 20 healthcare professionals. The first group consisted of participants who received two doses of BioNTech vaccine, and the second group consisted of those who received three doses of BioNTech vaccine. Three doses of vaccine resulted in better neutralization of wild-type virus and three variants. Low neutralization efficacy against Wild-type virus and Delta variant was found in an evaluation five months after the second dose. Neutralization against the Omicron variant was four times lower than against the Delta variant even with three vaccine doses. The persistence of the effect of the third vaccine dose against COVID-19 has not yet been determined.[14] We observed that the alpha variant was outweighing in June 2021 while the delta variant became preeminent in July in our study. It has been reported that the infection rate of the delta variant which is defined as one of the VOCs by WHO is approximately twice that of the original virus and that the delta (B.1.617.2) variant is more contagious than previous variants by suppressing globally circulating variants.[15,16] It was observed that the delta variant became dominant in our country as of July 2021 in our study.

Emerging new variants are not only associated with increased contagiousness, distress, and death toll but also, they may deceive diagnostic testing, develop reduced susceptibility to antiviral treatments and have the capacity to cause reinfection in previously vaccinated and surviving individuals. The longer the virus spreads, the higher its probability of mutation increases.[17] Suppression of viral replication through both public health measures along with a fair and widespread vaccine application is critical in reducing the risk of emergence of new variants.[18] In our study, the number of suspected cases of other variants increased in the beginning of December 2021 suggesting the omicron variant which is widely distributed in most countries by the end of the alpha and delta variants' dominance.

CONCLUSION

As far as we know, our study is the first published study on variant prevalence in individuals who are positive after 3 doses of inactivated vaccine. Molecular surveillance studies planned in consideration epidemiological data examining the prevalence and genome-based analysis of local and global variants are required. Pandemic continues due to the fluctuation of incidences with different restrictions applied globally, the risk of reinfection, the fact that the virus is susceptible to new mutations and the acceleration and deceleration in vaccinations. Studies on the spread and genomic analysis of existing variants will allow us to be better prepared for potential outbreaks in addition to the experience we have gained during the COVID-19 pandemic.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Yıldırım Beyazit University Yenimahalle Training and Research Hospital Scientific Research Ethics Committee (Date: 11.05.2022, Decision No: 2022-29).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1345215
J Contemp Med 2023;13(5):824-829

Original Article / Orijinal Araştırma

Assessment of DNA Damage Induced by Velum® Prime in Human Lymphocytes

Velum® Prime Kaynaklı DNA Hasarının İnsan Lenfositlerinde Değerlendirilmesi

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Abstract

Aim: Fluopyram is a mitochondrial complex II inhibitor with low water solubility and a relatively long half-life in soil. So it may also be dangerous for humans. It is very likely to reach humans with its widespread use and long-term stay in nature. Therefore, its genotoxicity should be fully demonstrated.

Material and Method: The effect of fluopyram on DNA damage was evaluated in human lymphocytes using the comet assay. Lymphocytes of eight volunteers were isolated using histopaque-1077. Fluopyram was administered at doses of 0.05, 0.25, and 1.00 mg/mL for 1, 2, and 4 h. The comet assay was applied, and photographs of the slides were taken under a fluorescence microscope. 50 cells per slide were analyzed using the OpenComet software. The obtained results were statistically evaluated using one-way ANOVA.

Results: Fluopyram treatments at 1.00 mg/mL for 1 h and 0.05, 0.25, and 1.00 mg/mL for 2 and 4 h resulted in a statistically significant increase in DNA damage compared to the internal control groups ($p<0.05$). When comparing groups with the same treatment time but different doses, the increase in DNA damage observed after a 1-h treatment of 1.00 mg/mL fluopyram was higher than the increase observed after a 1-h treatment of 0.05 mg/mL fluopyram ($p<0.05$). When comparing groups with different treatment times but the same dose, the increase in DNA damage after a 4-h treatment of 0.25 mg/mL fluopyram was higher than the increase observed after a 1-h treatment of 0.25 mg/mL fluopyram ($p<0.05$).

Conclusion: The results suggest that fluopyram causes an increase in DNA damage in a dose- and time-dependent manner. It is essential to investigate these findings in vivo as well.

Keywords: Comet assay, fluopyram, genotoxicity, pesticide

Öz

Amaç: Fluopyram mitokondriyal kompleks II inhibitörü, suda çözünürlüğü düşük ve topraktaki yarılanma ömrü oldukça uzun bir pestisittir. Yaygın kullanımı ve doğada uzun süreli kalabilmesi ile insanlara ulaşması oldukça muhtemeldir. Dolayısı ile genotoksisite riski tam olarak ortaya konmalıdır.

Gereç ve Yöntem: Fluopyramın DNA hasarı üzerindeki etkisi insan lenfosit hücrelerinde comet metodu ile değerlendirilmiştir. 8 gönüllüden histopak-1077 kullanılarak lenfositler elde edilmiştir. 0,05, 0,25 ve 1,00 mg/mL olmak üzere 3 dozda ve 1, 2 ve 4 saat fluopyram uygulaması yapılmıştır. Comet metodu uygulanmış ve hazırlanan preperatların floresan mikroskop altında fotoğrafları çekilmiştir. Preperat başına 50 hücre OpenComet programı ile değerlendirilmiş ve sonuçlar tek yönlü anova ile istatistiksel olarak değerlendirilmiştir.

Bulgular: 1,00 mg/mL 1 saat ve 0,05, 0,25, 1,00 mg/mL 2 ve 4 saat fluopyram uygulamaları internal kontrol gruplarına kıyasla DNA hasarında istatiksel olarak anlamlı artışa sebep olmuştur ($p<0,05$). Aynı uygulama süresine ve farklı doza sahip gruplar kendi arasında karşılaştırıldığında, 1 saat 1,00 mg/mL fluopyram uygulaması sonucunda DNA hasarında meydana gelen artış, 1 saat 0,05 mg/mL fluopyram uygulaması sonucunda meydana gelen artıştan daha yüksektir ($p<0,05$). Farklı uygulama süresine ve aynı doza sahip gruplar kendi arasında karşılaştırıldığında 4 saat 0,25 mg/mL fluopyram uygulaması sonucunda DNA hasarında meydana gelen artış, 1 saat 0,25 mg/mL fluopyram uygulaması sonucunda meydana gelen artıştan daha yüksektir ($p<0,05$).

Sonuç: Bu sonuçlara göre fluopyramın doz ve zaman bağımlı şekilde DNA hasarında artışa sebep olduğu tespit edilmiştir. Sonuçların in vivo olarak da araştırılması gerekmektedir.

Anahtar Kelimeler: Comet metodu, fluopyram, genotoksisite, pestisit

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Received *(Geliş Tarihi)*: 17.08.2023 **Accepted *(Kabul Tarihi)*:** 13.09.2023

INTRODUCTION

DNA damage is a significant concern that can play a role in the development of cancer and many other chronic diseases.[1] Furthermore, it also plays a role in certain vital intracellular physiological events, such as p53-mediated apoptosis.[2] Therefore, understanding potential DNA damage is crucial for preventing various problems. DNA damage can be caused by various endogenous or exogenous reasons, with chemicals being one of these exogenous sources.[3] Pesticides, which we frequently encounter in our daily lives, are among the harmful chemicals and may cause DNA damage.[4-9] While pesticides are essential for efficient agricultural production, they have been implicated as possible factors behind the rising incidence of certain diseases.[10] With the rapid increase in pesticide use, health issues have also escalated.[11] Pesticide production is a dynamic process, and new formulations or pesticides are continuously introduced to the market. Each pesticide must be investigated individually, and its potential harm to human health must be identified. This includes the adverse effects they might cause on DNA.

Fluopyram, (FL, 396.72 g/mol, C16H11ClF6N2O, CAS Number: 658066-35-4), initially developed by Bayer as a fungicide[12] is a relatively new pesticide currently employed as a nematicide.[13] It comes in various formulations containing different amounts of the active ingredient and is also available in combined formulations with other pesticides. It gained widespread use due to its lack of cross-resistance with previous fungicide families[14] FL functions by inhibiting succinate dehydrogenase (SDH, Complex II) in the mitochondrial respiratory chain, making it a member of the succinate-dehydrogenase inhibitors (SDHI) class of fungicides.[12] SDH is composed of four protein subunits (SDHA-D). The succinate binding region resides within SDHA, and the Ubiquinone (coenzyme Q) binding site formed by the other subunits is blocked by FL.[15] Inhibition of succinate dehydrogenase halts ATP production, ultimately leading to cell death.[15]

The water solubility of FL is low, and its half-life in soil reaches up to two years, which is relatively longer compared to similar pesticides.[16] Therefore, it is highly likely to affect humans after application. However, studies on the genotoxicity of FL are almost non-existent, and there has been no investigation conducted to evaluate DNA damage in human lymphocytes. In conclusion, the objective of this study is to examine the impact of FL on DNA damage, considering its widespread use and potential for long-term environmental persistence, which makes it highly likely to affect humans. For this purpose, the effects of Velum® Prime, a product exclusively containing FL as the active ingredient and manufactured by Bayer, on DNA were investigated in vitro using the comet assay[17] a method capable of rapidly and accurately measuring DNA damage.

MATERIAL AND METHOD

The study was carried out with the permission of Süleyman Demirel University Faculty of Medicine Clinical Researches Ethics Committee (Date: 10.10.2022, Decision No: 285). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

The volunteers included in the study were selected based on various exclusion criteria. Accordingly, the study included four female and four male volunteers aged between 18 and 45, who had no chronic illnesses or continuous medication use, had not undergone any examination or radiation treatment in the last six months, and were non-smokers. The study was conducted in accordance with the principles of the "Helsinki Declaration," and informed consent was obtained from the volunteers. A total of 15 mL of blood was collected from each volunteer, and the blood samples from all volunteers were utilized separately for 15 different groups. The groups are presented in **Table 1**. The doses applied were selected based on the findings of previous studies.[18] The Velum® Prime (Bayer AG, Suspension concentrate, 400 g/l FL) used in the research was obtained from local vendors. All chemicals mentioned as used in the study were obtained through local vendors from Sigma (St. Louis, MO, US) or Merck (Darmstadt, Germany). The manufacturers of chemicals not obtained from these companies are given in parentheses.

Table 1. Groups and doses in the study

Groups	n	Duration	Application
1	8	1 h	None
2			0.05 mg/mL FL
3			0.25 mg/mL FL
4			1.00 mg/mL FL
5			100 µM H_2O_2
6	8	2 h	None
7			0.05 mg/mL FL
8			0.25 mg/mL FL
9			1.00 mg/mL FL
10			100 µM H_2O_2
11	8	4 h	None
12			0.05 mg/mL FL
13			0.25 mg/mL FL
14			1.00 mg/mL FL
15			100 µM H_2O_2

Comet Assay

The assay was performed in accordance with the "OECD In Vivo Mammalian Alkaline Comet Assay Guideline".[19] Blood was drawn from the volunteers, and the comet assay procedure was initiated immediately. Blood samples were mixed in a 1:1 ratio with Histopaque-1077 and centrifuged at 2000 RPM for 20 min, allowing the separation of lymphocytes. These lymphocytes were mixed in a separate tube at a 1:1 ratio with PBS and then centrifuged at 2500 RPM for 10 min. Subsequently, the PBS was

removed, and the lymphocytes were supplemented with RPMI 1640 containing 10% FBS, adjusting the final volume to 1 mL before proceeding to the FL treatment. In accordance with the doses specified in **Table 1**, the FL treatment was conducted at three different time intervals (1, 2, and 4 h) in an incubator at 37°C. For each time interval, separate internal negative and positive control groups were established. 100 µM H_2O_2 was used as the positive control. Following the incubations, the cells were centrifuged at 2500 RPM for 10 min to separate and then washed with PBS and centrifuged again at 2500 RPM for another 10 min. Subsequently, all groups were incubated for an additional 1 h at 37°C in an incubator. For the detection of DNA damage, 20 µL of cells were mixed with 100 µL of low melting point agarose (0.7%, Fisher Scientific, Massachusetts, USA) and spread onto slides pre-coated with normal melting point agarose (1%, Serva Electrophoresis, Germany). The slides were incubated in cold lysis solution (pH: 10, 2.5 M NaCl, 100 mM Na_2-EDTA, 10 mM Tris, 10% DMSO, and 1% Triton X-100) in the dark at +4°C for 90 min. Following this procedure, samples were incubated in ice-cold electrophoresis solution (pH: 13, 300 M NaOH, 1 mM EDTA) in the dark at +4°C for 30 min. Subsequently, an electrophoresis procedure was carried out at 25 V (1.02 V/cm) and +4°C for 25 min. After the designated time, the slides were carefully removed from the electrophoresis tank, rinsed three times with neutralization solution, and then left to dry. During the imaging phase, the slides were stained with 20 µL of fluorescent dye (ethidium bromide) and examined under a microscope (Zeiss Imager A1 fluorescence microscope). Two preparations were prepared from each sample and photographs of 50 cells per slide were taken randomly with a camera (Axiocam Icc 1). The photographs were analyzed using the OpenComet software.[20] The Tail DNA Percentage (TDNAP) parameter was used as an indicator of DNA damage.

Statistical Analysis

The obtained results were statistically evaluated using one-way ANOVA (posthoc Tukey) in SPSS v29.[21] software. Results are presented as mean±standard error, and a p-value of <0.05 was considered statistically significant.

RESULTS

Groups treated with different doses of FL and 100 µM H_2O_2 (positive control) have shown an increase in DNA damage compared to internal negative control groups. When statistically compared, significant results were obtained for some groups (**Figure 1**). Despite more DNA damage was detected compared to the negative control groups, the DNA damage observed in the FL-treated groups is significantly lower than the DNA damage observed in the internal positive control groups.

As expected, the positive control groups caused significantly higher levels of DNA damage compared to all groups with the same time interval ($p<0.05$).

When the groups 2, 3, and 4, subjected to 1-h/0.05-0.25-1.00 mg/mL FL treatments respectively, are compared to internal negative control group an increase in DNA damage is observed. However, this increase in groups 2 and 3; is not statistically significant ($p>0.05$). The increase in DNA damage observed in group 4, on the other hand, is statistically significant ($p<0.05$). When groups 2, 3, and 4 are compared among themselves, it is determined that the group subjected to 1-h/1.00 mg/mL FL treatment causes statistically significantly more DNA damage than the group subjected to 1-h/0.05 mg/mL FL treatment ($p<0.05$). Accordingly, a dose-dependent increase in DNA damage is observed in the 1-h FL treatments.

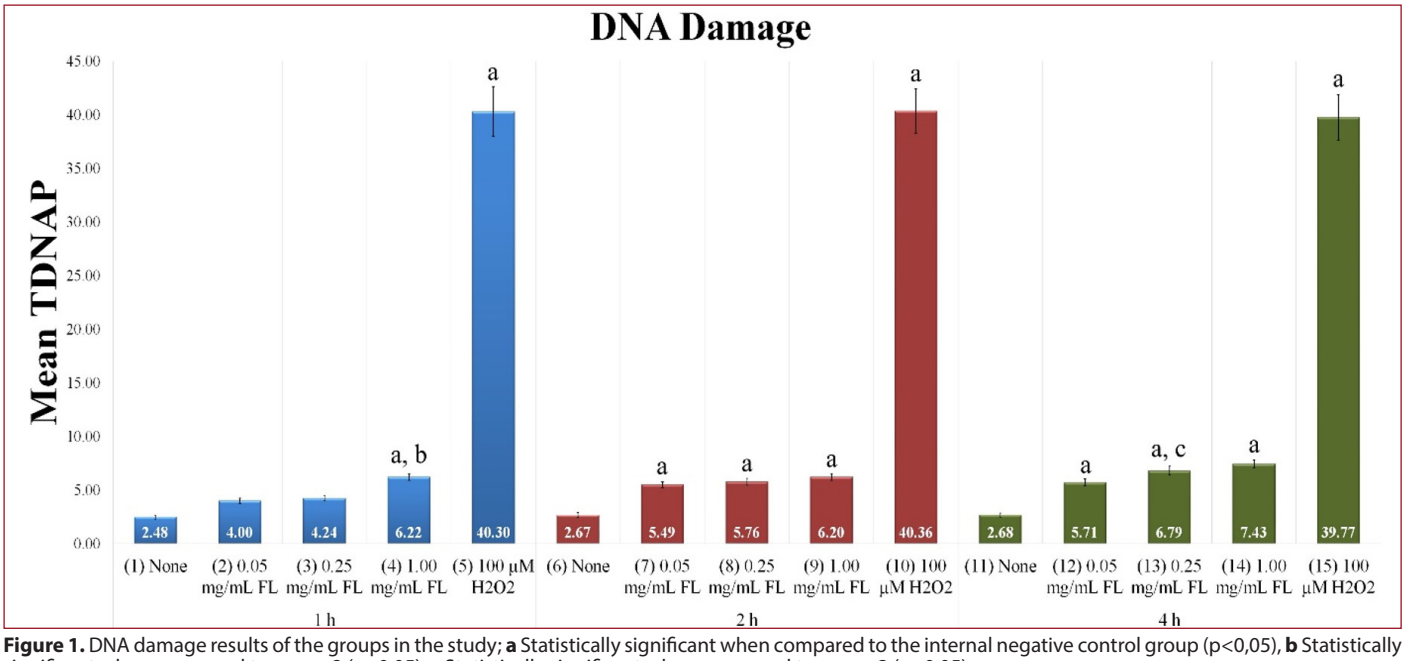

Figure 1. DNA damage results of the groups in the study; **a** Statistically significant when compared to the internal negative control group ($p<0,05$), **b** Statistically significant when compared to group 2 ($p<0,05$), **c** Statistically significant when compared to group 3 ($p<0,05$)

When the groups 7, 8, and 9, subjected to 2-h/0.05-0.25-1.00 mg/mL FL treatments respectively, compared to internal negative control group, an increase in DNA damage is observed for all three groups ($p<0.05$). When groups 7, 8, and 9 are compared among themselves, it is observed that DNA damage increases as the dose increases; however, this increase is not statistically significant ($p>0.05$). Accordingly, a dose-independent increase in DNA damage has been observed in the 2-h FL treatments.

When the groups 12, 13, and 14, subjected to 4-h FL/0.05-0.25-1.00 mg/mL treatments respectively, compared to internal negative control group, an increase in DNA damage is observed for all three groups ($p<0.05$). When groups 12, 13, and 14 are compared among themselves, it is observed that DNA damage increases as the dose increases; however, this increase is not statistically significant ($p>0.05$). Accordingly, a dose-independent increase in DNA damage has been observed in the 4-h FL treatments.

Groups with varying time intervals but identical FL doses were also compared among themselves. When compared the groups 2, 7, and 12, which subjected to 0.05 mg/mL/1, 2 or 4-h FL treatment respectively, it was observed that as the time increased, DNA damage increased; however, this increase was not statistically significant ($p>0.05$). When compared the groups 3, 8, and 13, which subjected to 0.25 mg/mL FL/1, 2 or 4-h treatment respectively, it was observed that as the time increased, DNA damage increased. When comparing the 1-h and 2-h treatments, no significant difference was observed ($p>0.05$). Similarly, when comparing the 2-h and 4-h treatments, no significant difference was observed ($p>0.05$). However, when comparing 4-h/0.25 mg/mL treatment with 1-h/0.25 mg/mL treatment, it was determined that the increase in DNA damage was statistically higher ($p<0.05$). Moreover, when compared the groups 4, 9, and 14, which subjected to 1.00 mg/mL/1, 2 or 4-h FL treatment respectively, it was observed that as the time increased (4 h), DNA damage increased; however, this increase was not statistically significant ($p>0.05$).

According to these results, it can be concluded that FL causes an increase in DNA damage in a dose and time-dependent manner.

DISCUSSION

Among the over 200 fungicides listed by the Fungicide Resistance Action Committee, succinate dehydrogenase inhibitors constitute the most rapidly expanding class in terms of newly synthesized and introduced compounds,[22] with FL being one of the most extensively employed active substances among these pesticides owing to its utilization as a nematicide. Nevertheless, the number of studies addressing the health impacts of FL is quite limited. Apart from Complex II inhibition, its mode of action, side effects in various organisms, and cumulative effects remain uncertain. Its widespread use leads to contamination in both soil and water. In a study conducted in Denmark, the presence of chemicals such as pesticides and pharmaceuticals was investigated in various freshwater systems, and among 83 chemicals examined, FL emerged as one of the most prevalent and widespread substances.[23] In a study published in 2023 and conducted in Austria, the feed of dairy cattle was analyzed for over 700 pesticides and pharmaceuticals, resulting in the identification of a total of 16 compounds. Among these compounds, FL emerged as the most prevalent, accounting for 62% of the total findings. Moreover, FL has been identified as the pesticide that most frequently exceeds the Maximum Residue Level (MRL) limits set by the European Union. In the study, it was found that the widespread presence of pesticides at low doses in the food/feed chain could have implications for animal, human, and environmental health.[24] In light of these results, there have been emerging concerns about the ecotoxicological implications of FL.[18]

Besides its SDH inhibition, it has been determined that FL also induces oxidative stress in nematodes and leads to an increase in reactive oxygen species (ROS).[18] As is well-known, one of the primary causes of DNA damage is oxidative stress.[25] In a study conducted with Luna® Experience, which contains 200 g/L FL and 200 g/L tebuconazole as active ingredients, rats were administered pesticide doses of 5, 10, and 20 mg/kg. Subsequently, oxidative stress markers in the liver and blood, as well as DNA damage, were examined. Both in the blood and the liver, a decrease in catalase enzyme activity and an increase in DNA damage were observed. It was concluded that this DNA damage arose from oxidative stress.[26] In another study published by the same team, using the same experimental design, the cytotoxicity and genotoxicity of Luna® Experience at doses of 5, 10, and 20 mg/kg were evaluated in rat bone marrow. The pesticide demonstrated both cytotoxic and genotoxic properties across all administered doses.[27] In our study, FL was identified as genotoxic, and existing research, albeit in its preliminary stages, suggests that this toxicity may be attributed to oxidative stress. In another study, the effect of FL on tumor formation in the liver was investigated. In female rats exposed to FL for 3, 7, or 28 days at doses of 30, 75, 150, 600, or 1500 ppm, hepatocellular adenoma and carcinoma formation mediated by constitutive androstane receptor/pregnane X receptor activation was observed at the 1500 ppm dose. In the study, the pathway involving DNA damage, which contributes to the formation of liver tumors, was not investigated, given that FL had not been previously reported as genotoxic. FL has been identified as a potential carcinogen for liver tumors.[12]

In addition to these limited studies, there are also researches conducted with pesticides belonging to the same class as FL (complex II inhibitors). The genotoxic and cytotoxic effects of the fungicide Signum and its active constituents (boscalid and pyraclostrobin) on human peripheral blood lymphocytes were investigated using the micronucleus test. The investigation included the evaluation of micronuclei, nucleoplasmic bridges, nuclear bud formations, and

the cytokinesis-block proliferation index. Micronucleus formation statistically increased at doses of 0.5 and 2 µg/mL boscalid, 0.5, 1.5, and 2 µg/mL pyraclostrobin, and 2, 6, and 25 µg/mL signum, while nucleoplasmic bridges increased at a dose of 0.25 µg/mL pyraclostrobin. Although there is no statistically significant increase in nuclear budding formation, it has been determined that cytotoxicity rises in correlation with concentration. It has been concluded that Signum, boscalid, and pyraclostrobin may exhibit genotoxic and cytotoxic effects in lymphocytes.[28] In a study evaluating bixafen, similar to FL, it was determined that bixafen is genotoxic at low doses in the human neuroblastoma cell line (SH-SY5Y) and T-cell leukemia cell line (Jurkat), and it has been suggested that the mechanism could be oxidative stress-induced DNA damage due to increased ROS activity.[29] Benzovindiflupyr also operates through the SDHI mechanism. The toxicity on earthworms (*Eisenia fetida*) has been assessed at doses of 0.1, 1, 5, and 10 mg/kg. It has been found that at high doses, it significantly inhibits mitochondrial complex II and concurrently leads to a substantial increase in ROS and lipid peroxidation. It has also been observed that it causes an increase in DNA damage in a dose and time-dependent manner.[30] The potential cytotoxic/genotoxic effects of another SDH inhibitor, benodanil, were evaluated in onion root meristem cells using the mitotic index and in vitro human peripheral blood lymphocytes using the micronucleus test. At concentrations of 12.5, 25, and 50 ppm, the mitotic index and prophase index decreased compared to the control group in the presence of benodanil. Besides, benodanil significantly reduced the nuclear division index.[31] In a study investigating the toxic effects of the SDH inhibitor penthiopyrad on zebrafish, it was determined that there is an increase in oxidative stress in the liver tissue. Additionally, disruptions were observed in mitochondrial respiratory complexes, mtDNA synthesis, lipid metabolism, and alterations were detected in the expression of genes associated with apoptosis. It was concluded that penthiopyrad toxicity leads to disruptions in lipid metabolism, mitochondrial dysfunction, apoptosis, and DNA damage.[32] In another study conducted on zebrafish, the fish were exposed to 0.25, 50, and 1000 µg/L of flutolanil for 60 days. The research findings reveal that there is a noteworthy reduction in catalase activity in the liver across all groups, coupled with an elevation in malondialdehyde levels, and a dose-dependent increase in DNA damage has been observed as well. Following chronic exposure to flutolanil, alterations in the transcription levels of genes involved in apoptosis and the immune system have been reported, along with an increase in caspase-3 enzyme activity.[33]

According to European Food Safety Authority (EFSA) 2023 report about permitted maximum residue levels (MRL) of FL in different fruits and vegetables, recommended MRL levels of FL range from 0.01 to 40 mg/kg.[34] In a study published in 2023, the FL residues in different fruits and vegetables was investigated. Except for the high value in one tomato sample, all residue amounts were detected in accordance with EFSA MRL levels.[35] In our study, doses between these ranges were used and the genotoxicity of FL was evaluated. Although doses were administered directly to lymphocytes, it could mean that even permitted/suggested MRL doses of FL in the long term are likely to be genotoxic.

Considering the studies indicating the potential genotoxicity of other pesticides acting as SDH inhibitors, it is evident that further comprehensive investigations are necessary for FL, a member of the SDHI group. The findings of our study can serve as a precursor to more advanced mechanistic research; however, it is important to acknowledge certain limitations. One of these limitations is the fact that our study was conducted within a lymphocyte culture. Hence, it has not been possible to determine the specific impact of FL within a metabolism on DNA damage. Secondly, our research evaluated short-term exposures. However, the cumulative effects that may arise from longer, sub-chronic, or chronic exposures should also be taken into account and evaluated.

CONCLUSION

With respect to the results of our study, FL leads to an increase in DNA damage in a dose and time-dependent manner. Even after short-term and low-dose exposures, there has been an increase in DNA damage, although not always statistically significant. The increase in DNA damage becomes more significant with higher doses or longer exposure times. The DNA damage observed may not necessarily result in diseases or cell death and could be effectively repaired by DNA repair mechanisms. Therefore, before arriving at a definitive judgment that FL is unequivocally genotoxic, more comprehensive in vitro and in vivo studies are needed. Nonetheless, results obtained from the lymphocyte culture medium indicate that FL might pose a risk in terms of DNA damage.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Süleyman Demirel University Faculty of Medicine Clinical Researches Ethics Committee (Date: 10.10.2022, Decision No: 285).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1345383
J Contemp Med 2023;13(5):830-835

Original Article / Orijinal Araştırma

Survival Outcomes and Factors Affecting Prognosis in Patients with Head and Neck Region Mucoepidermoid Carcinoma Treated with Adjuvant Radiotherapy

Adjuvan Radyoterapi ile Tedavi Edilen Baş-Boyun Bölgesi Mukoepidermoid Karsinomlu Hastalarda Sağkalım Sonuçları ve Prognozu Etkileyen Faktörler

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Abstract

Aim: This study aims to ascertain the clinical and pathological factors linked to the outcomes of patients subjected to surgical intervention and postoperative radiotherapy for mucoepidermoid carcinoma (MEC) originating from both major and minor salivary glands in the head and neck region.

Material and Method: In this retrospective review, medical records of 42 patients who underwent surgery and subsequent radiotherapy for localized MEC in the major and minor salivary glands of the head and neck were analyzed to identify clinicopathological determinants of overall survival. Secondary endpoints encompassed local-regional control, distant metastasis-free survival, and disease-free survival.

Results: The median age of the patient cohort was 56 years, comprising 52.4% males and 47.6% females. The median follow-up period spanned 36 months, with a range of 6 to 88 months. All patients underwent curative surgery, followed by adjuvant radiotherapy. The 2-year and 5-year rates for overall survival (OS), local-regional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and disease-free survival (DFS) were 92% and 72.6%, 92.2% and 85.6%, 84.8% and 73%, 82% and 67.3%, respectively. Notably, only histologic grade emerged as a statistically significant prognostic factor, influencing both OS (p=0.019), DMFS (p=0.014), and DFS (p=0.044).

Conclusion: The histologic grade of the tumor is the foremost determinant impacting the outcomes of MEC cases. Adjuvant radiotherapy is recommended for high-grade tumors, while its application for low-grade and intermediate-grade tumors should be individualized based on the anticipated risk of recurrence. This underscores the significance of tailoring treatment approaches according to histologic characteristics.

Keywords: Mucoepidermoid carcinoma, Salivary glands, Head and neck cancer, Histological grade, Radiotherapy

Öz

Amaç: Bu çalışmanın amacı, baş ve boyun bölgesi yerleşimli majör ve minör tükürük bezlerinden kaynaklanan mukoepidermoid karsinom (MEC) nedeniyle cerrahi olan ve ameliyat sonrası radyoterapi uygulanan hastaların sonuçlarıyla bağlantılı klinik ve patolojik faktörleri belirlemekti.

Gereç ve Yöntem: Bu retrospektif çalışmada, baş ve boyundaki majör ve minör tükürük bezlerinde MEC nedeniyle cerrahi ve ardından radyoterapi uygulanan 42 hastanın tıbbi kayıtları, genel sağkalımın klinikopatolojik belirleyicilerini tanımlamak için analiz edildi. İkincil sonlanım noktaları lokal-bölgesel kontrol, uzak metastazsız sağkalım ve hastalıksız sağkalımı kapsamaktaydı.

Bulgular: Hasta kohortunun medyan yaşı 56 olup, %52,4'ü erkek ve %47,6'sı kadındı. Ortanca takip süresi 36 ay olup, aralık 6 ila 88 ay arasındaydı. Tüm hastalara küratif cerrahi ve ardından adjuvan radyoterapi uygulandı. Genel sağkalım (OS), lokal-bölgesel nükssüz sağkalım (LRFS), uzak metastazsız sağkalım (DMFS) ve hastalıksız sağkalım (DFS) için 2 yıllık ve 5 yıllık oranlar sırasıyla %92 ve %72,6, %92,2 ve %85,6, %84,8 ve %73, %82 ve %67,3 idi. Sadece histolojik grade istatistiksel olarak anlamlı bir prognostik faktör olarak bulundu ve hem OS (p=0.019), hem DMFS (p=0.014), hem de DFS'yi (p=0.044) etkiledi.

Sonuç: Tümörün histolojik derecesi MEC olgularının sonuçlarını etkileyen en önemli belirleyicidir. Adjuvan radyoterapi yüksek dereceli tümörler için önerilirken, düşük dereceli ve orta dereceli tümörler için uygulanması beklenen nüks riskine göre bireyselleştirilmelidir. Bu durum, tedavi yaklaşımlarının histolojik özelliklere göre uyarlanmasının önemini vurgulamaktadır.

Anahtar Kelimeler: Mukoepidermoid karsinom, Tükürük bezleri, Baş ve boyun kanseri, Histolojik derece, Radyoterapi

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Received *(Geliş Tarihi)*: 17.08.2023 **Accepted *(Kabul Tarihi)*:** 18.09.2023

INTRODUCTION

Mucoepidermoid carcinoma (MEC) stands as an infrequent presence within the realm of head and neck malignancies. Nonetheless, it commands the title of being the most prevalent form of salivary gland malignancy, contributing to 10% of various tumor types, both benign and malign, and encompassing a substantial 30%-35% of malignant tumors.[1,2] The primary salivary glands are accountable for approximately 60% of MEC occurrences, with the parotid gland reigning as the predominant site.[3-5] These growths traverse a spectrum of clinical trajectories, spanning from slow-burning to markedly aggressive locally and highly prone to metastasis. As the cornerstone of managing salivary gland MEC, surgical intervention has historically held the forefront, and in recent times, postoperative radiotherapy has found application in cases of T3–4 tumors, neck node metastases, narrow margins, or positive resection margins, and high-grade tumors. However, the existing repository of knowledge concerning clinicopathologic prognosticators for patients undergoing both surgery and postoperative radiotherapy remains constrained.[3,6-8] In light of this, our study delves into the treatment outcomes of individuals afflicted by salivary gland MEC who have undergone a combined regimen of surgical intervention and postoperative radiotherapy. Our inquiry encompasses aspects of local tumor control, survival rates, and the identification of prognostic determinants.

MATERIAL AND METHOD

Ethical Approval

The study protocol was reviewed and approved by the Selçuk University Local Ethics Committee (Date: 15/03/2022, Decision No: 2022/144). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by a local human research committee. Written informed consent forms were read by each patient and signed consent was obtained prior to their treatment.

Patient Characteristics

Between 2010 and 2020, 42 individuals diagnosed with primary MEC originating from the salivary glands in the head and neck region underwent a combined treatment regimen of surgery followed by postoperative radiotherapy at both Selcuk University Medicine Faculty and Balikesir Ataturk City Hospital. Following a meticulous assessment of pathological findings, 42 patients were included in the study cohort. Within our evaluation, we closely scrutinized a range of clinicopathological variables, encompassing attributes such as age, gender, tumor grade, anatomical site of the disease, T stage, and N stage. The categorization of disease stage for all patients was carried out in accordance with the 8th edition of the staging system devised by the American Joint Committee on Cancer (AJCC).

Inclusion and Exclusion Criteria

Inclusion criteria:

- Who diagnosed with MEC in head and neck region,
- Patients were> 18 years of age
- Who underwent a curative surgery,
- Who received adjuvant RT,
- Cases without a postoperative macroscopic residual mass (R0 and R1 cases were included)
- Cases who have not received neoadjuvant, adjuvant or concurrent chemotherapy

Exclusion criteria:

- Relapsed disease prior to adjuvant RT,
- Cases with no surgery for curative intent,
- Cases with a previous history of another malignant disease,
- Who developed a second primary malignancy during follow-up period,
- Cases with metastases prior to RT,
- Cases with postoperative macroscopic residual mass (R2 resection),
- Cases with immunosuppressive disease.

Radiotherapy and Follow-up

As a standard procedure, postoperative radiotherapy was administered to address particular situations, which included stage T3–4 tumors, cases with positive resection margins, presence of perineural invasion, positive neck node status, or the presence of high-grade tumors. The treatment target was delineated based on individual cases; for tumors devoid of lymph node involvement, the focus centered on the surgical site itself. On the other hand, high-grade tumors and those with lymph node involvement required a wider treatment approach that included the surgical site, the implicated nodal stations, and the ipsilateral neck nodes in levels I through IV. By and large, a radiation dose of 60 Gy was methodically delivered to the surgical site using conventional fractionation techniques via a linear accelerator. If the surgical margin was positive, higher doses of 66-70 Gy were applied to the tumor bed. It is worth noting that none of the patients received adjuvant chemotherapy as the part of their treatment regimen.

After the conclusion of the therapeutic course, patients underwent a post-treatment evaluation within a timeframe of 4–6 weeks. Following this initial assessment, subsequent follow-ups were scheduled at 3-month intervals for the initial 2-year period, followed by a transition to biannual monitoring. Every follow-up visit includes a thorough physical examination as well as, if required, a head and neck or thoracal CT scan.

Statistical Analysis

Study data were analyzed using the statistical package program Statistical Package for the Social Sciences version 25.1 (SPSS, Inc., Chicago, IL, ABD). Numeric, percentage,

standard deviation, mean, minimum and maximum values were used as descriptive statistics. Locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS) were estimated using the Kaplan-Meier method. To identify prognostic factors that might affect survival, log rank tests were performed to examine univariate relationships between survival and parameters of interest. A value of p<0,05 was considered statistically significant.

RESULTS

Patient Characteristics

The median patient age was 56 years (range, 19 to 86 years). Twenty-two (52.4%) were male and 20 (47.6%) were female. Median follow-up was 36 months (range, 6-88). Four (9.5%) were in T1, 8 (19%) in T2, 15 (35.7%) in T3 and 15 (35.7%) in T4 at the time of diagnosis. In all cohort, 16 (38.1%) of them had lymph node metastasis. During the analysis, T1 and T2, T3 and T4 were placed together in two groups, and lymph node status were divided into two groups according to the presence of metastasis or not. T4A and T4B tumours were grouped together as T4. Twenty-eight (66.7%) patients had tumor-free surgical margins, and 14 (33.3%) had positive margins. Grade was recorded for all patients. They were divided into three groups as being either low-grade (18 cases), intermediate-grade (13 cases), or high-grade (11 cases). For perineural invasion (PNI), 12 (28.6%) were positive, 30 (71.4%) were negative. For lymphovascular invasion (LVI), 9 (21.4%) were positive, 33 (78.6%) were negative. All patients underwent a curative surgery. Among 31 patients with parotid MEC, 5 of them underwent total parotidectomy, 3 of them had superficial parotidectomy, 23 of them had total parotidectomy with neck dissection. In cases of submandibular or sublingual MEC, surgery with a wide excision with neck dissection was performed for 7 patients, and mass excision was performed for 1 patient. In cases of minor salivary gland MEC, surgery with a wide excision was performed for 3 patients. All patients underwent postoperative radiotherapy. For 21 (50%) patients, RT was applied only to the postoperative tumor bed, and for 21 (50%) patients, the neck region was also included in the RT treatment area. An average of 50 Gy (46-66 Gy) delivered to the neck region and 60 Gy (50-70 Gy) for the tumor bed (**Table 1**).

The treatments were generally well tolerated by the patients. Two patients completed their radiation treatments with a five- and seven-day break, respectively, due to Grade 3 acute side effects. One patient experienced trismus and another experienced an esophageal stricture that required treatment as chronic, serious adverse effects.

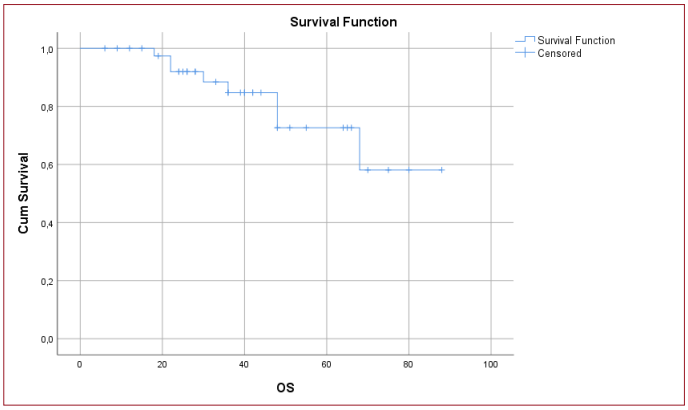
Table 1. Patient characteristics and histopathological features

Characteristic	No. of patients (%)
Age (year)	56 (range, 19-86)
Sex	
Male	22 (52.4%)
Female	20 (47.6%)
Tumor location	
Parotid	31 (73.8%)
Submandibular-Sublingual	8 (19%)
Minor	3 (7.1%)
Pathologic T stage	
T1	4 (9.5%)
T2	8 (19%)
T3	15 (35.7%)
T4	15 (35.7%)
Pathologic N stage	
N0	26 (61.9%)
N1	5 (11.9%)
N2	11 (26.1%)
Overall stage	
I	1 (2.3%)
II	2 (4.7%)
III	5 (11.9%)
IV	34 (80.9%)
Surgery	
Total parotidectomy	5 (11.9%)
Superficial parotidectomy	3 (7.1%)
Total parotidectomy with neck dissection	23 (54.7%)
Wide excision with neck dissection	7 16.6%)
Wide excision	3 (7.1%)
Mass excision	1 (2.3%)
Neck dissection	
No	12 (28.6%)
Yes	30 (71.4%)
Histologic grade	
Low	18 (42.8%)
Intermediate	13 (30.9%)
High	11 (26.1%)
Lymphovascular invasion	
No	33 (78.6%)
Yes	9 (21.4%)
Perineural invasion	
No	30 (71.5%)
Yes	12 (28.5%)
Resection margin	
Negative	28 (66.7%)
Positive	14 (33.3%)
Anatomic location	
Parotid	31 (73.8%)
Submandibular/Sublingual	8 (19%)
Minor	3 (7.2%)

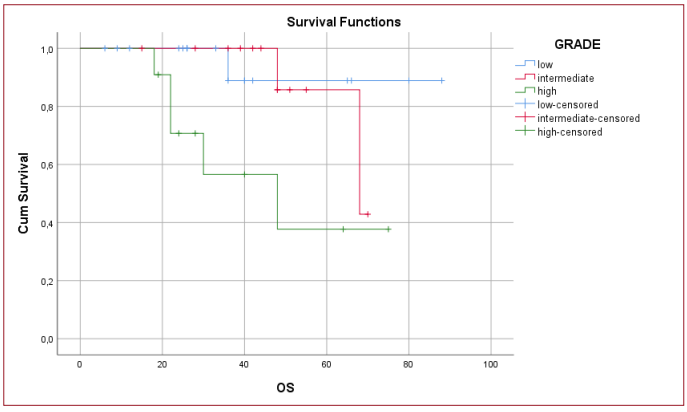
Survival Outcomes and Prognostic Factors

The 2-year and 5-year OS, LRFS, DMFS, and DFS rates were 92% and 72.6%, 92.2% and 85.6%, 84.8% and 73%, 82% and 67.3%, respectively (**Graphic 1**). Eight patients died due to their disease. Distant recurrences occurred in 5 patients. Locoregional recurrences occurred in 2 patients. Additional to that, both distant and locoregional recurrences occurred in 3 patients. Of 8 patients who developed distant metastases, 7 had lung metastases and one had brain metastases.

Age, gender, histological grade, T stage, N stage, surgical margin, extraglandular extension, anatomical location, LVI, PNI were analyzed for their effect on prognosis. None of them had any effect on prognosis except one. Univariate analysis showed that only histologic grade was a prognostic factor for both OS (p=0.019)(**Graphic 2**), DMFS (p=0.014) and DFS (p=0.044). Since only one variable affecting prognosis was found to be significant in univariate analysis, multivariate analysis was not performed.



Graphic 1. Overall survival curve



Graphic 2. Overall survival curve by histologic grade

DISCUSSION

Although there is a male gender predominance in head and neck cancers,[9] there seems to be a slight female gender predominance for MEC.[10] In our study, as in some studies[8] there was a slight male (52.4%) predominance.

MEC can be observed in a wide age range. Although it is mostly seen in the 5th decades,[7] it can also be seen in adult and even childhood and the prognosis of MEC detected in children seems to be better.[11,12] The median age of the patients in our study was 56 years with a wide age range from 19 to 86 years.

According to some studies results, the prognosis of MEC patients is intricately tied to their ethnicity, age, and gender. Notably, Russell et al.[13] conducted an extensive study encompassing salivary gland cancers, revealing that individuals of black ethnicity faced a heightened risk for inferior disease-specific survival in comparison to Hispanics or Caucasians. Particularly, this applied to patients diagnosed with MEC or squamous cell carcinoma. In the current study, we did not find age or gender as a factor affecting prognosis. Similar to our results, Baddour et al. presented findings that contradicted this notion. Their investigation observed no discernible disparities in 5 and 10-year survival rates concerning factors like race/ethnicity, gender, year of diagnosis, or socioeconomic status.[14]

The management of MEC in head and neck region is intricately tailored to factors like tumor location, stage, and operability. The mainstay of the therapeutic strategy is surgery. Adjuvant radiotherapy is generally applied in cases of one or a combination of one or more of the following conditions that are considered to be risky in terms of recurrence: T3-T4 stage, node positivity, high-grade, LVI positivity, PNI positivity, positive surgical margin. The emergence of undesirable effects during and after treatment, especially in the context of combined treatment strategies, underscores significant challenges. The nature of resulting adverse effects is contingent upon various factors such as the cumulative dose, fractionated dosing, treatment volume, treatment duration, tumor stage (early or advanced), sequence of RT and surgical intervention, surgical techniques, and the specifics of the RT protocol. Patients undergoing RT for HNC are susceptible to a spectrum of side effects encompassing mucositis, nutritional deficiencies, alterations in taste perception, diminished saliva production, early-stage skin surface erythema, as well as long-term skin and mucosal atrophies, edema within the treatment region, telangiectasia, trismus, and eventual dental cavities.[15] In our study, two radiation patients finished their full course of treatment by halting it for five and seven days, respectively, due to Grade 3 acute adverse effects. One patient experienced trismus and another experienced an esophageal stricture that required treatment as chronic, serious adverse effects.

According to the findings of studies on MEC in the literature, while low-intermediate- and high-grade patients have high survival rates when analyzed together, survival rates decrease dramatically when high-grade tumors are analyzed separately. In low-grade disease, 5-year survival rates of 80-90% and above are often reported, whereas in high-grade disease these rates fall below 50-60%. A noteworthy study conducted by Chen et al. in 2014 examined a substantial cohort of 2400 MEC patients. Their analysis divulged distinct 5-year survival

rates: 98.8% for low-grade cases, 97.4% for intermediate-grade cases, and 67.0% for high-grade cases. Beyond survival rates, their findings unveiled another significant aspect. Specifically, patients classified as high grade were significantly more likely to have lymph node metastases at levels I to III (34.0%) compared with patients with low grade (3.3%) and intermediate grade (8.1%).[16] Drawing parallels, a research effort documented in 2005 and involving an assessment of 42 MEC patients, led by Kokemueller et al., disclosed notable survival rates. Specifically, the 5-year survival rate for low-grade cases stood at 89.9%, followed by a 10-year rate of 81.5%. Contrasting starkly, the high-grade cohort exhibited a substantially lower 5-year survival rate of 37.5%, which regrettably diminished to 0% at the 10-year mark.[17] An insightful exploration unfolded at the MD Anderson Cancer Center, encompassing a cohort of 125 MEC patients. Over a 5-year span, the overall survival rate and disease-free survival rate stood at 79.3% (Low-grade 92.8%, intermediate-grade 95.1% and high-grade 51%) and 76.5% respectively. This study spotlighted a significant disparity in outcomes based on disease grade. Low- and moderate-grade disease cohorts demonstrated notably improved overall survival and disease-free survival, whereas high-grade disease patients faced a bleaker outlook. However, when contrasting low and moderate-grade disease cohorts, no discernible difference in survival rates emerged. Delving deeper into the findings, several pathologic indicators bore prognostic significance. Positive lymph node results, extracapsular lymph node spread, and perineural invasion each exhibited a correlation with unfavorable prognoses. Through a multivariate analysis, two pivotal prognostic factors emerged: advanced disease stage and perineural invasion. These facets held particular prominence in shaping the prognostic landscape for MEC patients.[18] Similar themes emerged from a Greek study that involved 18 MEC patients. In this cohort, all individuals underwent surgery with curative intentions, and radiotherapy bolstered treatment in 11 cases. The 5-year overall disease-specific survival rate stood at a commendable 85%. Notably, high-grade tumors displayed an average survival of 38 months, intermediate-grade tumors saw this extend to 75 months, and low-grade tumors exhibited an even more promising mean survival of 110 months.[6]

A noteworthy investigation spearheaded by Ghosh-Laskar et al. in 2011 involved 113 MEC patients, yielding valuable insights into disease-free survival (DFS) and overall survival over 5 and 10-year intervals. Across 5 years, DFS percentages were as follows: 84.6% for low-grade tumors, 80.7% for intermediate-grade tumors, and 52.5% for high-grade tumors. A parallel trend emerged for the 10-year mark, showing consistency with 84.6% for low-grade, 67.3% for intermediate-grade, and 35.0% for high-grade tumors. Turning to overall survival, the study unveiled that over 5 years, rates were 96.8% for low-grade tumors, 94.1% for intermediate-grade tumors, and 73.3% for high-grade tumors. Extending the window to 10 years, the numbers shifted slightly, settling at 82.4% for intermediate-grade tumors and 35.0% for high-grade tumors. The study's observations underscored the predictive power of high-grade tumors and lymph node-positive neck tumors in forecasting compromised locoregional control and DFS. Furthermore, the study noted that close or positive surgical margins exhibited a trend indicative of inferior outcomes. The research concluded by highlighting the pivotal role of histologic grade in shaping outcomes for parotid MEC. As a key recommendation, the study advocated for adjuvant radiotherapy in cases of high-grade tumors, while emphasizing the need to tailor treatment plans based on the projected risk of recurrence for low-grade and intermediate-grade tumors.[19]

In a study orchestrated by Chen et al. and published in 2013, a cohort of 61 patients who underwent post-surgery radiotherapy came under scrutiny. Their outcomes were meticulously assessed, yielding substantial insights into overall survival estimates. Over a 3-year span, the overall survival estimate stood at 85%, while spanning 5 years, this rate amounted to 79%. Employing multivariate analysis, distinct factors were discerned as independent predictors of diminished survival. Notably, high tumor grade emerged with a hazard ratio (HR) of 7.92, while T4 disease bore a HR of 3.35. These two factors not only predicted decreased survival but also held additional implications. High-grade tumor histology was indicative of an elevated risk for distant metastasis, whereas T4 disease signaled a heightened potential for local-regional recurrence. Remarkably, patients with non-high-grade tumors displayed a promising 5-year overall survival estimate of 83%, contrasting with the 52% figure attributed to those with high-grade histology ($P = 0.001$). In summation, the study underscored the heightened risk of treatment failure for high-grade tumors and T4 disease following surgery and postoperative radiation therapy for mucoepidermoid carcinoma of the parotid gland. The findings precipitated a recommendation for future investigative strategies aimed at enhancing outcomes for these specific patient subsets.[8]

Consistent with well-established emphasis in the existing literature, our study reinforced the central role of histologic grade as a pivotal prognostic factor. Remarkably, histologic grade emerged as a potent prognostic indicator not only for overall survival (OS) but also for distant metastasis-free survival (DMFS) and disease-free survival (DFS). The survival outcomes underscored the compelling impact of histologic grade: over a 2-year duration, survival rates were an impressive 100% for low-grade cases, 100% for intermediate-grade cases, and 70.7% for high-grade cases. Extending to the 5-year mark, survival rates remained noteworthy, registering at 88.9%, 85.7%, and 37.7%, respectively. In alignment with these trends, instances of disease-related mortality were observed within our studied groups. Specifically, the low-grade group experienced the loss of one patient, while two patients within the intermediate-grade cohort and five patients within the high-grade cohort succumbed to the disease.

CONCLUSION

While our study is not exempt from the inherent limitations of retrospective investigations, our current series has significantly identified a noteworthy prognostic factor: high-grade histology. This attribute, when observed in patients subjected to surgery and postoperative radiation therapy for mucoepidermoid carcinoma, emerged as an indicator of less favorable outcomes. To augment future outcomes, targeted strategies should prioritize patients featuring this specific characteristic.

Notably, avenues to potentially enhance results warrant exploration. One such avenue involves the potential escalation of radiation dosage, perhaps coupled with the incorporation of biological and chemical modifiers. However, the precise implications of these strategies remain to be ascertained.

The prevalence of distant metastases, particularly prevalent among those with high-grade tumors, draws attention to the pressing need for efficacious systemic therapies. This underscores the urgency of developing interventions capable of addressing metastatic progression.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University Local Ethics Committee (Date: 15/03/2022, Decision No: 2022/144).

Informed Consent: Written informed consent forms were read by each patient and signed consent was obtained prior to their treatment.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1345680
J Contemp Med 2023;13(5):836-844

Original Article / Orijinal Araştırma

Evaluation of the Effect of Pelvic Types on Trans-Sacral Screw Corridor Diameter (Retrospective Analysis Using Computerized Tomography Data)

Pelvis Tiplerinin Trans-Sakral Vida Koridor Çapına Etkisinin Değerlendirilmesi (Bilgisayarlı Tomografi Verilerinin Retrospektif Analizi)

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Abstract

Aim: The aim of this study was to investigate the effect of pelvis type on the trans-sacral (TS) screw corridor diameter.

Material and Method: Pelvis computed tomography (CT) scans between 2017 and 2020 were retrospectively reviewed. Age, gender, height, weight and body mass index (BMI) of the patients were determined during the CT examination. Pelvic CT scans were examined using the imaging system's multi-plane reconstruction (MPR) mode, and the TS screw corridor was measured for both the upper and second sacral segments. In addition, pelvic incidence (PI), sacral tilt (SS), and pelvic tilt (PT) values were measured. Pelvis typing was performed using the large transverse diameter, anteroposterior diameter, interspinous, intertuberocytosis, transverse outlet diameter, sagittal mid-pelvic diameter, and sagittal outlet values.

Results: 81(38%) male and 132(62%) female patients were included in the study. Gynecoid pelvis type was more common in females and android pelvis in males ($p < 0.001$). The largest diameters in the TS screw corridor at the S1 level belonged to the anthropoid pelvis type. However, in the TS corridor at the S2 level, there was a significant difference between the pelvis-type groups in the mean values of AP and CC ($p < 0.001$). The effect of gender difference on the TS screw corridor width at the S1 and S2 levels was significant. An adequate corridor width for the TS screw corridor was detected in 50.8% of females and 67.9% of males at the S1 level, while in 21.2% of females and 70.4% of males at the S2 level.

Conclusion: There is a significant difference in the dimensions of the trans-sacral screw corridor according to the pelvis type and gender, with the largest diameter observed in the anthropoid pelvis type and males. In critical situations, especially in males and individuals with android-anthropoid pelvis, the trans-sacral screw option can be considered primarily not only for the S1 trans-sacral corridor but also for the S2 trans-sacral corridor in pelvic posterior ring injuries.

Keywords: Trans-sacral screw corridor, pelvis type, android pelvis, sacrum fracture

Öz

Amaç: Bu çalışmanın amacı, pelvik tipin trans-sakral (TS) vida koridor çapı üzerindeki etkisini araştırmaktır.

Gereç ve Yöntem: 2017 ile 2020 yılları arasında elde edilen pelvik bilgisayarlı tomografi (BT) taramaları retrospektif olarak incelendi. Hastaların yaş, cinsiyet, boy, kilo ve vücut kitle indeksi (VKİ) bilgileri BT muayenesi sırasında belirlendi. Pelvik BT taramaları görüntüleme sisteminin çoklu düzlem rekonstrüksiyon (MPR) modu kullanılarak incelendi ve üst ve ikinci sakral segmentler için TS vida koridoru ölçüldü. Ayrıca, pelvik inklinasyon (PI), sakral eğim (SS) ve pelvik eğim (PT) değerleri ölçüldü. Pelvik tiplemesi büyük çap, anteroposterior çap, interspinöz, intertüberokitoz, çapraz çıkış çapı, sagittal orta pelvik çap ve sagittal çıkış değerleri kullanılarak yapıldı.

Bulgular: Çalışmaya 81 (%38) erkek ve 132 (%62) kadın hasta dahil edildi. Ginekoid pelvik tip kadınlarda daha yaygınken, erkeklerde android pelvis daha yaygındı ($p < 0.001$). S1 düzeyinde TS vida koridorundaki en büyük çaplar antropoid pelvik tipine aitti. Bununla birlikte, S2 düzeyinde TS koridorunda, pelvik tip grupları arasında AP ve CC ortalama değerleri bakımından anlamlı fark vardı ($p < 0.001$). Cinsiyet farkının S1 ve S2 düzeylerinde TS vida koridor genişliği üzerindeki etkisi önemliydi. S1 düzeyinde uygun bir koridor genişliği, kadınların %50.8'inde ve erkeklerin %67.9'unda tespit edildi, S2 düzeyinde ise kadınların %21.2'sinde ve erkeklerin %70.4'ünde görüldü.

Sonuç: Trans-sakral vida koridorunun boyutlarında pelvik tip ve cinsiyet açısından önemli bir fark vardır; en büyük çap antropoid pelvik tipinde ve erkeklerde gözlemlenir. Özellikle erkeklerde ve android-antropoid pelvisli bireylerde kritik durumlarda, pelvik posterior halka yaralanmalarında sadece S1 trans-sakral koridor için değil, aynı zamanda S2 trans-sakral koridor için de trans-sakral vida seçeneği öncelikli olarak düşünülebilir.

Anahtar Kelimeler: Trans-sakral vida koridoru, pelvis tipi, android pelvis, sakrum kırığı

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Received *(Geliş Tarihi)*: 18.08.2023 **Accepted *(Kabul Tarihi)*:** 20.09.2023

INTRODUCTION

The incidence of unilateral or bilateral U or H-shaped sacral fractures and pelvic ring fractures due to high-energy traumas has increased in parallel with the development of high technology.[1,2] Additionally, due to the increase in the elderly population, the frequency of sacral fractures caused by osteoporosis, posterior pelvic ring injuries, sacroiliac joint dislocation, and sacrum and pelvis insufficiency fractures is also increasing.[3,4] Some studies in the literature indicate that iliosacral screw fixation may not yield sufficient stability, whereas the placement of transiliac-trans sacral screws could offer an alternative fixation opportunity and provide more effective stability by allowing cortical fixation on the distal side of the injury and a much longer implant.[5,6]

Trans-sacral (TS) screw fixation has recently been routinely used to treat pelvis posterior stabilization.[7] However, despite its clinical importance, applying trans-sacral implants with minimally invasive techniques is challenging due to anatomical variations in the pelvis and sacral regions and dysmorphism. Moreover, the individual variability of sacrum morphological characteristics makes this procedure even more difficult.[8] Therefore, this is a technically complex procedure that requires performers to fully understand the anatomy of the pelvis, pelvic osseous fixation pathways, and their fluoroscopic imaging to ensure safe iliosacral screw placement. The procedure's safe and effective placement of these screws is also essential.[9]

Biomorphometric data on how the TS corridor can change due to changes in pelvic inlet anatomy and how the PI value can affect bone corridors are relatively scarce. In the general population, performing pelvic measurements to describe the feasibility rates of trans-sacral screw placement of android, gynecoid, anthropoid, and platypelloid pelvis morphologies in females and males, and identifying pelvis type-specific differences in trans-sacral corridor dimensions and the impact of pelvis type on the trans-sacral corridor, could improve understanding of patient-specific differences in terms of risks and motivate the development of treatment strategies that take into account anatomical pelvic differences. For this reason, the present study aimed to evaluate pelvic types using CT anatomical scans to determine the feasibility rates of trans-sacral screw fixation in men and women and investigate the effect of pelvis type on TS corridors and PI values.

MATERIAL AND METHOD

The study was designed as a retrospective cohort study in accordance with the World Medical Association Declaration of Helsinki guidelines, after obtaining local institutional ethics committee approval (No: 21-KAEK-236). Pelvic CT images with 1 mm cross-section width taken for diagnosis in trauma patients over the age of 18 who applied to the university hospital emergency department between 2017 and 2020 were examined. Images were analyzed using the PACS (Patient Archiving Computer System, Sectra) system. The exclusion criteria comprised diseases that disrupt proximal femur anatomy, such as spinal deformity, coxarthrosis, developmental dysplasia of the hip, and a history of recent or past fractures of the sacrum, lumbar, pelvis, acetabulum, and proximal femur. The patients' age, gender, height, weight and BMI measurements for both the upper and second sacral segments were retrospectively reviewed.

Four study groups were constituted according to pelvis types: android, anthropoid, platypelloid and gynecoid pelvis. Caldwell et al. described four main pelvis types, each with distinctive anatomical features.[10] The Android pelvis has a larger transverse diameter than the AP diameter and a heart-shaped pelvic inlet. The Gynecoid pelvis has a slightly larger inlet transverse diameter than the AP diameter and a round or slightly oval inlet. The Platypelloid pelvis has a significantly larger transverse diameter than the AP diameter and a slightly flattened kidney-shaped inlet. The Anthropoid pelvis has a larger AP diameter than the transverse diameter and a divergent pelvic inlet (**Figure 1**).

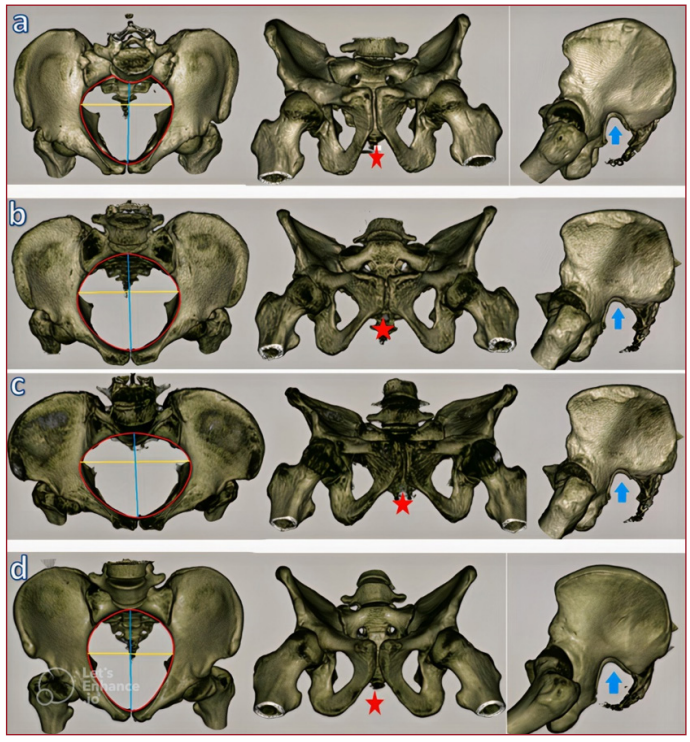

Figure1: Pelvis Types;
a)Android pelvis type, b) Gynecoid pelvis type, c) Platylloid pelvis type, d) Andropoid pelvis type

Pelvis typing was performed on images obtained by multi-planar reconstructions (MPR) and 3D imaging modes of CT scans with the utilization of measurement techniques used in previous studies.[11,12] The pelvic structures that did not exactly match one of the four main pelvis types were included in the pelvis type having the closest similarity. The obstetric conjugate, transverse diameter, interspinous distance, sagittal midpelvic diameter, intertuberous distance and sagittal outlet diameter to be used for pelvis typing were measured using 1 mm MPR images (**Figure 2**).

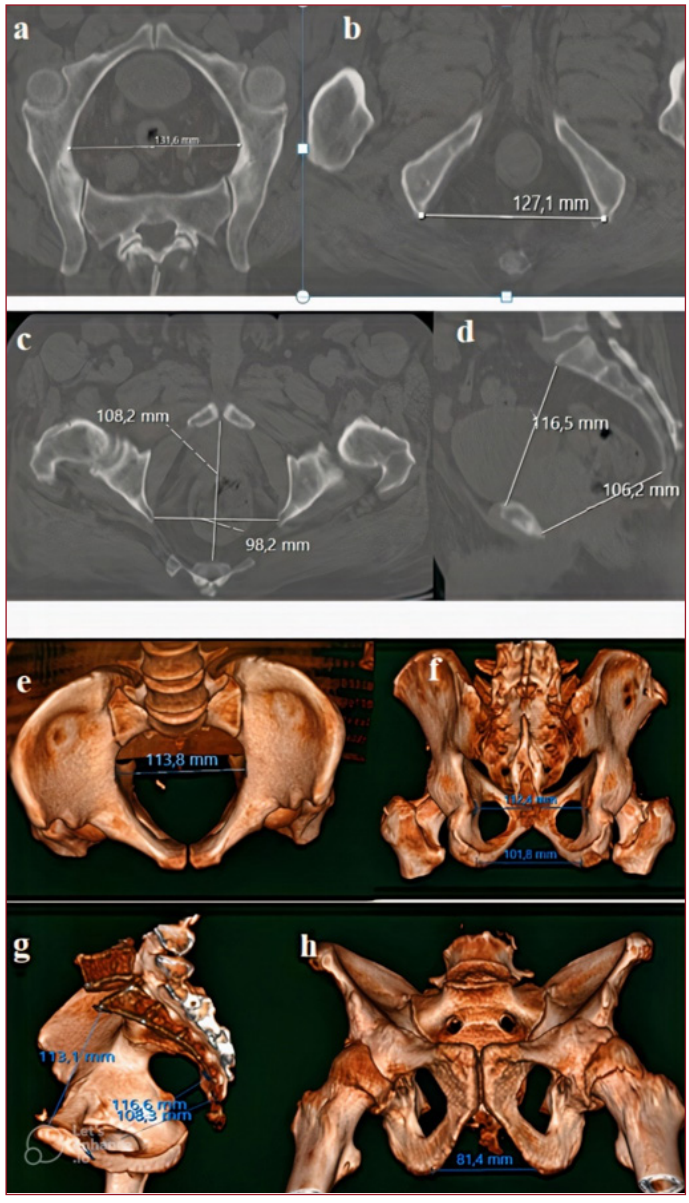

Figure 2: Pelvis typing;
a) Para-axial reconstruction showing the pelvic inlet.Widest transverse diameter of inlet view.
b) Axial slice showing ischial tuberosities and the corresponding measurement.
c)Para-axialreconstruction showing ischial spines, the caudalend of the symphysis and the sacrum so that inter spinal distance and sagittal midpelvic diameter can be measured.
d) Sagittal reconstruction showing the symphysis and the sacrum. Obstetric conjugate and Sagittal outlet distance measurement.
e) Volume-rendered reconstruction in a superior–anteriorview. Measurement of the transverse diameter of the inner pelvis.
f) Posterior view, with lines showing interspinous and intertuberous measurements.
g) Right lateral view of the pelvis split in half in a sagittal plane. Measurement of Obstetric Conjugate, Sagittal Outlet Distance, and Midpelvic Sagittal Distance.
h) Subpubik arc and transvers diamater of outlet

Corridor Measurement Using CT Images

The true coronal (outlet view) and true axial (inlet view) planes of CT images, obtained by manually acquired MPRs, were used to measure trans-sacral corridors in the upper and second sacral segments of pelvic CT images. These images resemble the fluoroscopic outlet (pubic symphysis superimposed on the S2 body) and inlet (anterior cortices of S1 and S2 superimposed) images previously described in the literature and used for trans-sacral corridor measurement. A corridor width of 10 mm or more was considered adequate in both the true coronal and axial planes.[11,12]

First, the midsagittal image was obtained by using the pubic symphysis and sacral median crest as references to identify the midsagittal line in the sagittal CT image. True coronal and axial sacral planes were manually created by reconstructing the standard axis of pelvic CT, which was aligned to be parallel with the anterior cortex according to sacral inclination at the S1 level. Afterwards, the widest corridors were identified for S1 craniocaudal diameter (S1 CC), S2 craniocaudal diameter (S2 CC), S1 anteroposterior diameter (S1 AP), and S2 anteroposterior diameter (S2 AP) while avoiding screw penetration outside the intraosseous corridor (**Figure 3a-d**).

The sagittal tomographic sections were used to determine the pelvic incidence. For this purpose, a line was drawn from the midpoint of the upper endplate of S1 to the midpoint of the line connecting the femoral heads. Similarly, a second line was formed at an angle of 90 degrees downwards from the midpoint of the upper end plate of S1. Then the angle calculated between these two lines was taken as pelvic incidence (**Figure 3e**).

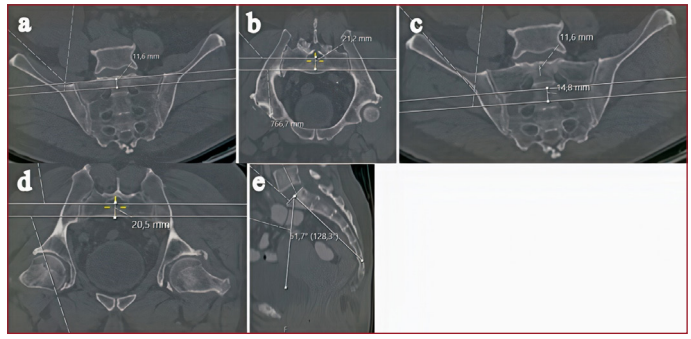

Figure3: Measurement of the horizontal corridor in the S1 sacral segment on reconstructed CT images. A) S1 CC measurement true coronal (outlet view) B) S1 AP measurement true axial (inlet view) C) S2 CC measurement true coronal (outlet view) D) S2 AP measurement true axial (inlet view) E) Pelvic incidence angle

Two specialist surgeons took all measurements with at least ten years of experience in orthopedic trauma surgery. They were trained to increase measurement precision before taking the measurements. The surgeons performed the measurements separately to minimize errors, and the mean values were computed. One of the surgeons repeated all measurements to determine inter-observer variability and confirm measurement validity. After repeated measurements, intra- and inter-observer agreements regarding the measured parameters were calculated.

Statistical Analysis

Interobserver agreement was found to be strong in terms of S1 CC, S1 AP, S2 CC, S2 AP diameters and pelvic incidence, sacral slope and pelvic tilt values (r values:

0.89, 0.88, 0.87, 0,81, 0.84, 0.85 and 0.80 respectively). Regarding the orthopedist who performed the same measurements for the second time one month later, it was detected that intraobserver agreement was very strong for S1 CC, S2 CC and pelvic incidence (r values:0.97, 0.96 and 0.93, respectively), or strong for S1 AP, S2 AP, sacral slope and pelvic tilt (r values: 0.88, 0.85, 0.81 and 0.80, respectively).

The data analysis was conducted using the IBM SPSS statistical analysis software (Version: 23.0). The Kolmogorov-Smirnov test was employed to examine the normality distribution of the variables. The statistical comparison of three or more groups was conducted according to whether the data conformed to the normality distribution. For normally distributed data, the one-way analysis of Variance method was utilized, and multiple comparisons were analyzed with the Duncan and Tamhane's T2 tests, whereas, for non-normally distributed data, the Kruskal Wallis H test was used and multiple comparisons were analyzed with the Dunn test. The Pearson chi-square test was applied to compare categorical variables between the groups, and the Bonferroni corrected z test was performed for multiple comparisons. The analysis results were presented as mean±standard deviation and median (minimum – maximum) for quantitative variables, and frequency (percent) for categorical variables. A p-value less than 0.05 was regarded to be statistically significant in all tests.

RESULTS

Of the CT scans, 132 (62%) belonged to females and 81 (38%) belonged to males. The conducted pelvis typing revealed that there were 98 (46%) android, 80 (37.6%) gynecoid, 7 (3.3%) platypelloid, and 28 (13.1%) anthropoid pelvis types. In the groups created based on pelvis type, there was a significant difference in terms of age distribution between the groups when the patients in the anthropoid group were included, but no difference when they were excluded. No significant difference was detected between the groups in terms of BMI (p=0.848). The sociodemographic data of the study are summarized in **Table 1**.

There was a statistically significant difference between the pelvis type groups in terms of gender distribution ($p < 0.001$). This difference is due to the fact that the rates of android, gynecoid, platypelloid, and anthropoid pelvis types vary according to gender; in this respect, the highest rate in females was obtained in the gynecoid and platypelloid groups, and the highest rate in males was in the android group (**Table 2**).

The largest AP and CC diameters in the TS corridor at the S1 level (p=0.925 and p=0.123, respectively) belonged to the anthropoid pelvis type. In the TS corridor at the S2 level, on the other hand, there was a significant difference between the pelvis type groups in the mean values of AP and CC ($p < 0.001$). The largest corridor was observed in the CT scans belonging to the group with anthropoid pelvis type at the S1 level, whereas the smallest corridor diameter was in the pelvic CT scans of the platypelloid group (**Table 1**).

Table 1: Comparison of quantitative data by pelvis types

		Pelvis Type				Test Statistics	p
		Android Type	Gynecoid Type	Platypelloid Type	Andropoid Type		
Age (year)	Mean±SD	58.2±19.76	58.18±20.33	58.86±17.53	42.61±21.05	13.090	0.004*
	Median (Min.-Max.)	62 (21-86)[a]	61.5 (20-89)[a]	58 (24-80)[ab]	29 (20-84)[b]		
Height (m)	Mean±SD	1.68±0.04	1.66±0.02	1.65±0.02	1.68±0.06	21.945	<0.001*
	Median (Min.-Max.)	1.67 (1.63-1.87)[a]	1.65 (1.6-1.73)[b]	1.64 (1.63-1.67)[b]	1.68 (1.63-1.98)[ab]		
Weight (kg)	Mean±SD	74.21±6.61	72.21±6.45	70.86±7.76	72.75±8.75	2.999	0.392*
	Median (Min.-Max.)	74 (58-93)	72 (55-88)	73 (57-79)	72 (56-92)		
BMI (kg/m²)	Mean±SD	26.34±2.44	26.3±2.44	26.07±2.89	25.72±2.68	0.805	0.848*
	Median (Min.-Max.)	26.61 (19.45-31.99)	26.45 (20.05-30.86)	26.18 (21.19-29.73)	25.73 (20.57-29.76)		
S1 AP (mm)	Mean±SD	11.14±4.61	10.69±5.08	10.77±5.6	11.2±4.76	0.156	0.925**
	Median (Min.-Max.)	10.6 (0-23)	10 (3.8-34.5)	7.7 (5.1-16.7)	11.65 (1.3-20.9)		
S1 Axial (mm)	Mean±SD	16.9±4.51	15.7±3.97	15.16±3.77	17.85±4.15	5.771	0.123*
	Median (Min.-Max.)	16.85 (0-26.9)	15.8 (6.7-26.8)	15.9 (7.3-17.9)	17.6 (10.7-24.9)		
S2 AP(mm)	Mean±SD	10.78±3.4	9.05±2.44	8.46±2.99	10.34±3.27	16.668	0.001*
	Median (Min.-Max.)	11 (2.5-24.7)[a]	9.1 (4.5-16.6)[b]	7.8 (4.6-12.1)[ab]	10 (5.5-16.9)[ab]		
S2 Axial (mm)	Mean±SD	12.33±3.66[a]	10.67±2.93[b]	11.29±6.85[ab]	12.58±3.57s[b]	4.442	0.012**
	Median (Min.-Max.)	12.3 (5.5-26.9)	10.2 (6-20.2)	8.3 (4.6-20.9)	12.15 (6-24.9)		
Pelvic Tilt (°)	Mean±SD	17.74±14.63	19.2±16.76	30.77±10.83	15.08±12.8	2.135	0.097**
	Median (Min.-Max.)	16.55 (-22-58)	20.1 (-23.5-60.3)	29.3 (17.2-52.5)	16 (-12.7-39)		
Sacral Slope (°)	Mean±SD	32.7±9.64	40.46±67.43	28.86±8.82	33.09±7.77	0.663	0.663*
	Median (Min.-Max.)	35 (10-57)	34.5 (10-629)	28 (17-45)	34 (17-48)		
Pelvic Incidence(°)	Mean±SD	50.45±10.32	52.58±12.44	59.63±4.87	48.17±7.38	8.688	0.034*
	Median (Min.-Max.)	48.4 (31.2-82.6)[a]	52.7 (31.2-82.6)[ab]	58.3 (55.9-69.5)[b]	48.6 (34.3-59.8)[ab]		

*Kruskal Wallis H test; **One-way Variance Analysis (ANOVA), a-c No significant difference between pelvic types with the same letter. m:meter, mm:millimeter, kg:kilogram, (°):degree

Table 2: Distribution of pelvis types based on gender.

	Android Type		Gynecoid Type		Platypelloid Type		Andropoid Type		Test Statistics	p*
	n	%	n	%	n	%	n	%		
Gender										
Female	30	30.6[a]	80	100.0[b]	7	100.0[bc]	15	53.6[ac]	95.119	<0.001
Male	68	69.4[a]	0	0.0[b]	0	0.0[bc]	13	46.4[ac]		

*Pearson chi-square test; a-cNo significant difference between pelvic types with the same letter.

TS corridors with a diameter of over 10 mm existed in 122 (57.3%) pelvic CTs at the S1 level and 85 (39.9%) at the S2 level. The TS corridor was over 10 mm in both AP and CC planes at the S1 level in 67.9% of the anthropoid pelvis group, 57.1% of the platypelloid pelvis group, 52.5% of the gynecoid pelvis group, and 58.2% of the android pelvis group(p=0,560). At the S2 level, 46.4% of the anthropoid pelvis group, 28.6% of the platypelloid pelvis group, 22.5% of the gynecoid pelvis group, and 53.1% of the android pelvis group had adequate corridor width in the AP and CC planes(p<0,001) (**Table 3** and **Figure 4-6**).

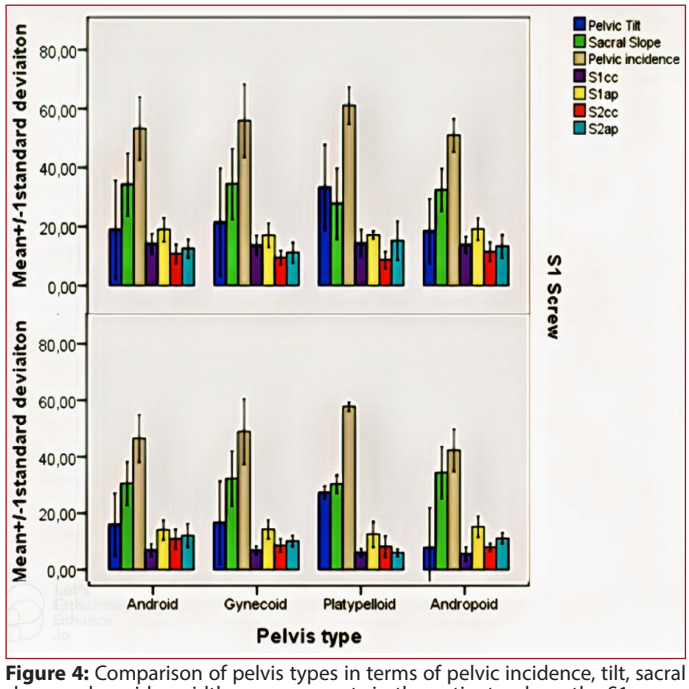

Figure 4: Comparison of pelvis types in terms of pelvic incidence, tilt, sacral slope and corridor width measurements in the patients whom the S1 screw can/cannot be inserted. Bar graph with +/-1 standard deviaiton of variables

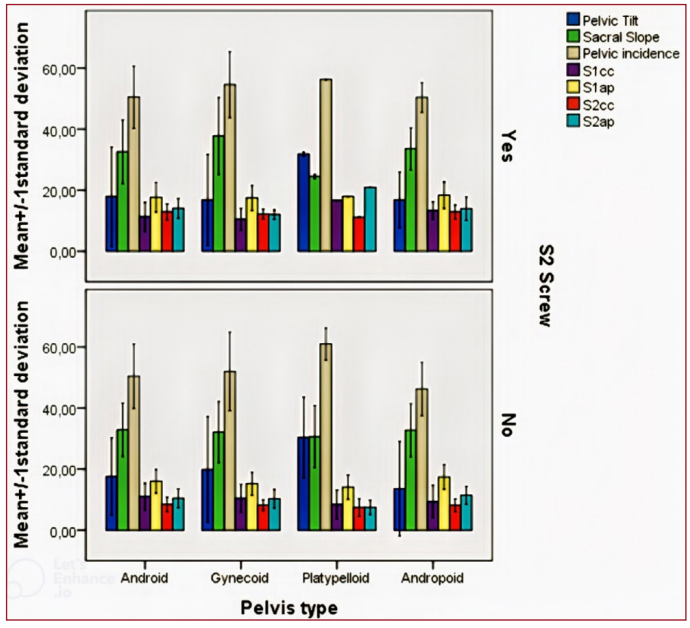

Figure 5: Comparison of pelvis types in terms of pelvic incidence, tilt, sacral slope and corridor width measurements in the patients whom the S2 screw can/cannot be inserted. Bar graph with +/-1 standard deviaiton of variables

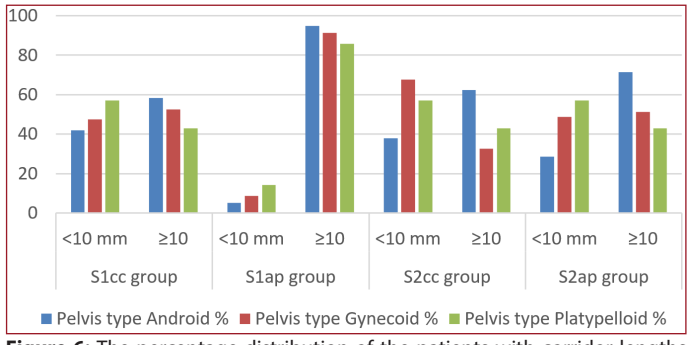

Figure 6: The percentage distribution of the patients with corridor lengths (in axial and frontal CT planes) over 10 mm and below 10 mm according to pelvis types.

Table 3: Distribution of qualitative variables by pelvis types

Variables		Total	Pelvis Type				p
			Android	Gynecoid	Platypelloid	Andropoid	
Gender	Female	132(62)	30(30,6)[a]	80(100)[b]	7(100)[bc]	15(53,6)[ac]	<0,001
	Male	81(38)	68(69,4)[a]	0(0)[b]	0(0)[bc]	13(46,4)[ac]	
S1_Screw	≥10 mm	122(57,3)	57(58,2)	42(52,5)	4(57,1)	19(67,9)	0,560
	<10 mm	91(42,7)	41(41,8)	38(47,5)	3(42,9)	9(32,1)	
S2_Screw	≥10 mm	85(39,9)	52(53,1)[a]	18(22,5)[b]	2(28,6)[ab]	13(46,4)[ab]	<0,001
	<10 mm	128(60,1)	46(46,9)[a]	62(77,5)[b]	5(71,4)[ab]	15(53,6)[ab]	

Pearson chi-square test was used. (ab): In same row, common letter indicates statistical insignificance. mm:millimeter

The effect of gender difference on the TS corridor width at the S1 and S2 levels was significant(p<0,001). An adequate corridor width for the TS screw was detected in 50.8% of females and 67.9% of males at the S1 level, while in 21.2% of females and 70.4% of males at the S2 level (**Figure 7**).

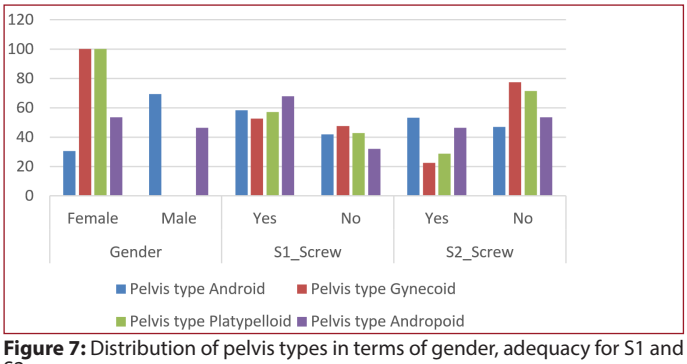

Figure 7: Distribution of pelvis types in terms of gender, adequacy for S1 and S2 screws

No significant difference was determined in terms of the mean values of the pelvic tilt and sacral slope according to the pelvis types (p=0.097 and p=0.663, respectively). It was found that there was a statistical difference in terms of the median values of the pelvic incidence with respect to pelvis types (p=0.034). The median values were determined to be 48.4° in the android group, 52.7° in the gynecoid group, 58.3° in the platypelloid group and 48.6° in the anthropoid group (**Table 1** and **Figure 8**).

DISCUSSION

In summary, according to the results obtained in this study, the anthropoid pelvis has wider S1 and S2 anteroposterior diameters and the largest S1 craniocaudal diameter among other pelvis types. In addition, the android pelvis type was more common in males and was more suitable for TS screw placement with wider TS bone corridors in the CC and AP planes at the S2 level. In the gynecoid pelvis type, which is more common in females, the diameter of the TS bone corridor was narrower at the S2 level in the CC and AP planes. Furthermore, an adequate corridor width for the TS screw was detected in 50.8% of females and 67.9% of males at the S1 level, while 21.2% of females and 70.4% of males at the S2 level.

Since we were unable to find any studies in the literature investigating the relationship between the pelvic inlet type and trans-sacral corridor, we could not directly compare our results with other studies. As well as gender-specific distinctions in the human pelvis can lead to differences in the shape and dimensions of the pelvic, the pelvic characteristics also differ within the same gender due to various external factors. Because of the complicated anatomical structure of the sacrum and the distinctions in the sacral morphology among individuals, performing a safe screw insertion requires this anatomical variability to be well understood.[13,14] It is known that the male pelvis is thick and heavy.[15] In general, gynecoid pelvis with a rounded shape corresponds to a normal female variant and android pelvis to a male variant.[15] Anatomical variances and diversions from the gender-specific characteristics can be observed in the pelvis.[15] The female sacrum is considered to be shorter, wider, and less forward-inclined than the male sacrum, which creates a larger, more oval pelvic inlet.[16] The sacral region has generally been found to be wider than the promontorium in females and narrower in males.[17] It has been stated that in comparison with males, females have a smaller sacral corridor,[18] are more likely to have a sacral dysmorphism.[18,19] On the contrary, in the literature, a study states that sacral dysmorphism is independent of gender despite significant differences in sacral morphology.[20] Although the prevalence of dysmorphic sacra varies between 28% and 53% as reported by Kaiser,

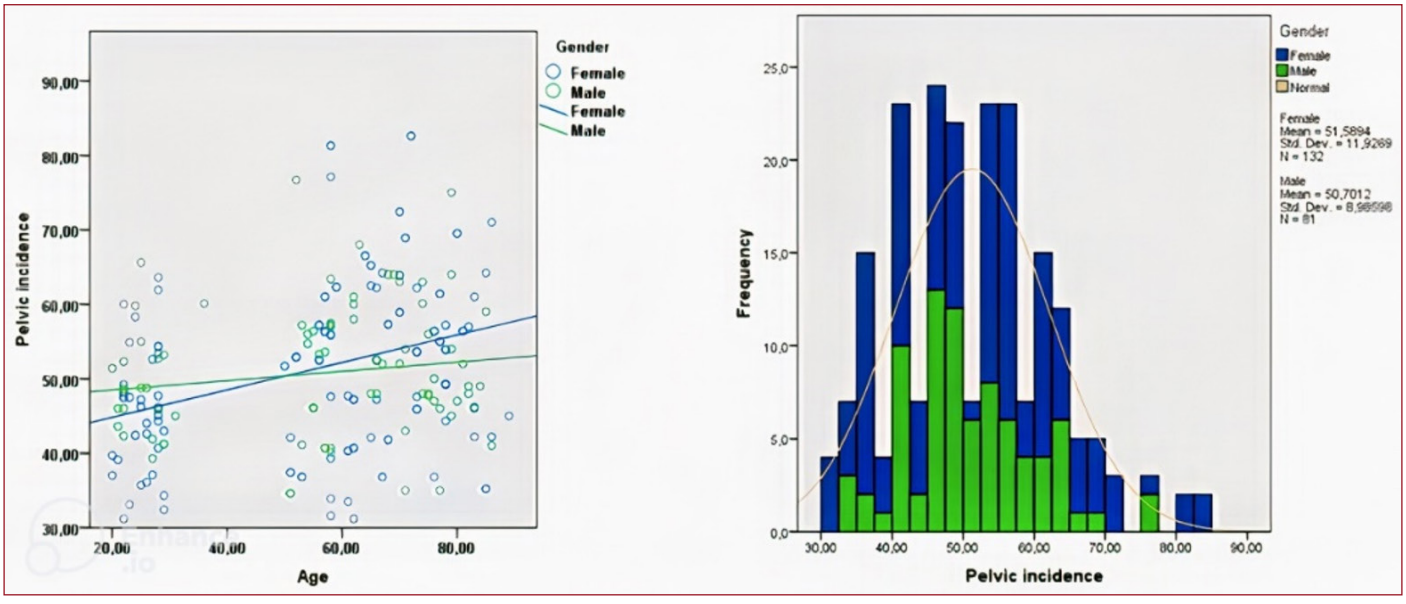

Figure 8: Pelvic incidence values slightly increased with age in both females and males

there are no studies revealing the relationship between pelvis type and sacral dysmorphism and adequate corridor width in patients with sacral dysmorphism.[7] Mendel et al.[22] detected that the S1 trans-sacral corridor in females was narrower than in males. Similarly, König et al.[19] reported significantly larger trans-sacral S2 corridor diameters in males compared to females. The study conducted by Gras et al.[18] revealed more dysmorphism in the female pelvis. In addition, they noted that trans-sacral corridor diameters of the male pelvis were larger than those of the female pelvis.[18] It has been stated in the literature that the corpus of the primary sacral portion of the first sacral vertebra in females is relatively smaller, and the lateral portion, on the other hand, is relatively larger.[23] Our results, which indicated that trans-sacral corridors at the S1 and S2 levels in females are consistent with these studies mentioned above as well as other previous relevant studies.[18,24] In the present research, the android pelvis type was seen in 46% of the study population regardless of gender. The S1 screw could be inserted to 57% of the patients. In the anthropoid pelvis, the rate of the patients with an S1 AP diameter of ≥ 10 mm was 100%, those with an S2 AP diameter of ≥ 10 mm was 89.3% and those with an S1 CC diameter of ≥ 10 mm was 67.9%. Of the patients having anthropoid pelvis type, 53.6% were female and 46.6% were male. In terms of the anatomy of transsacral osseous corridor, anthropoid and android pelvis types were more appropriate for screw insertion.

Determining the appropriate sacra for performing trans-sacral screw insertion procedure is important, however, the highly varied anatomy of the upper sacrum complicates the insertion of an implant at S1. In the literature, the threshold values for the minimal trans-sacral safe zone diameter differ from study to study.[13,25,26] In our study, we regarded that the safe trans-sacral region diameter should be 10 mm and above in both frontal and axial tomographic reconstructions in order not to damage the neurovascular structures and to ensure that the screws remain in the intraosseous corridor. The dissimilarity in the prevalence of trans-sacral S1 corridor in the literature may depend on geographical differences, the distinction of the measured sacral zones for safe zones and the disparity of cut-off values taken for adequate trans-sacral corridor. The adequate corridor width were determined by 8 mm by Gras et al.[18] and 10 mm by Gardner et al.[26] Gras et al.[18] reported that 64% of patients had the adequate S1 corridor and 88% had the adequate S2 corridor. In similar studies, König et al.[19] and Gardner et al.[26] detected that the adequate S1 corridor were present in 68% and 42% of patients, respectively, and the adequate S1 corridor were present in 68% and 72% of patients, respectively. On the other hand, Wagner et al.[27] stated that trans-sacral screws cannot be inserted into the S1 corridor in 26% of patients, whereas the S2 corridor always allows the safe insertion such screws. Another study conducted by Lee et al.[13] indicated that the trans-sacral S2 corridors cannot accommodate two screws due to their small dimensions. In our study, it was found that of the male patients, inserting the S1 screw in 67.9% and the S2 screw in 70.4% were possible.

In the study by Gardner et al.[26] there were adequate S1 and S2 horizontal corridors in 42% and 72% of patients, respectively. In the present study, while 57.3% of the patients had the S1 corridor of 10 mm or more in both planes, 39.9% of the patients had the S2 corridor of 10 mm or more in both planes. We detected that all four pelvis types were present in the female patients. However, there were no male patients with the gynecoid and platypelloid pelvis types. Fischer et al.[28] determined that the shape of the human pelvis is associated with body height. There are also studies indicating that the pelvic inlet of taller people is more oval and that of shorter people is more rounded.[28] In our study, the patients in the gynecoid and platypelloid pelvic groups were shorter.

The pelvic incidence not only shows the width of the pelvis and the balance of entire spine, but also assists us to get acquainted what kind of pelvis to encounter when the pelvis and the sagittal balance of the spine are impaired. In a study conducted by Abola et al.[29] it was shown that there is a relation between an increased pelvic incidence value and a more inclined sacrum, lower sacral-ala width and a SI joint with higher linearity. Inside the pelvis, a large PI value refers to an anteriourly positioned horizontal sacrum; a small PI value, on the other hand, refers to a posteriorly positioned and high vertical sacrum.[30] The results of the present study confirm this difference by revealing that the PI values changed depending on the pelvis type. The PI, which is the link between spinal and pelvic parameters, reflects the orientation of the sacrum within the pelvis, not that of the entire pelvis. Although pelvic incidence is of great significance in the assessment of sagittal parameters in the spinal surgery, the causes of the said large variability in pelvic incidence in the normal population have yet to be discovered. The mean PI values have been reported to be in the range of 41° and 54°. Mehta et al.[31] found that the mean values of pelvic incidence was 48°-55°, the sacral slope was 36°-42°, and the pelvic tilt was 12° and 18°. It has been indicated that the normative value of PI In the Caucasian population is 50°–55° , whereas this value is lower in the Asian population.[32] In the assessments made according to the gender difference, it has been observed that females have higher PI values than males. Likewise, we detected that the pelvic incidence values in females (51.5°) were higher than in males (50.7°). In the present study, the pelvic incidence varied in a wide range from 31.2° to 82.6°. It is considered that the PI gradually increases with the development of gait in childhood.[30] It was seen in our study that the PI values slightly increased with age in both females and males. We also detected that the pelvic incidence was higher in the gynecoid and platypelloid groups.

Our study included certain limitations. First of all, the CT scans examined had been taken with the patient supine and for other medical indications. There were no patients with pelvic ring injury in the study cohort. Therefore, these results do not reflect the condition of patients with prior pelvic injury, or who

underwent pelvic surgery. However, the cohort represents a normal population with a broad age range (20-89), except for the group of patients with CT pelvic ring fractures.

When a screw-like cylindrical shaped volume is not used when measuring trans-sacral corridor diameters, the measured diameter does not exactly complies with the screw application and therefore represents only the maximum osseous corridor height. In our study, the cut-off value was taken as 10 mm. In the studies in the literature, different cut-off values such as 7.5 mm, 8 mm, 10 mm and 12 mm have been used, which restricts the comparison of results between studies. Additionally, the frequency of dysmorphic sacral was not discussed in our study. Sacral dysmorphism and narrow sacral corridors complicate the trans-sacral implant insertion.[26,33] It has been stated that the number of patients with inadequate corridor at the s1 level in dysmorphic sacra is higher than normal.[12] Even in sacra that have been classified as non-dysmorphic, a horizontal corridor that can accommodate a screw may be absent in 25% of cases. However, the sacrum which does not allow the trans-sacral insertion of screws with specific sizes is regarded as dysmorphic. There are also studies in which the absence of a trans-sacral corridor at the S1 vertebra is described as sacral dysmorphism.[18,34] Since we assessed the corridor diameter in our study after all, we regarded that the patients with corridors that do not allow trans-sacral screw fixation as dysmorphic, as in the literature. However, it is not clear whether this would have any real value in clinical practice, because the use of navigation systems has provided trans-sacral screw technique to evolve considerably. On the other hand, navigation systems that help to avoid the problem of sacral dysmorphism in almost all cases, are not yet in use in most countries and centers.

CONCLUSION

There is a significant difference in the dimensions of the trans-sacral screw corridor according to the pelvis type and gender, with the largest diameter observed in the anthropoid pelvis type and males. In critical situations, especially in males and individuals with android-anthropoid pelvis, the trans-sacral screw option can be considered primarily not only for the S1 trans-sacral corridor but also for the S2 trans-sacral corridor in pelvic posterior ring injuries.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Researches Ethics Committee (Date: 04.11.2021, Decision No: 21-KAEK-236).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1346174
J Contemp Med 2023;13(5):845-848

Original Article / Orijinal Araştırma

Dynamic Thiol/Disulphide Homeostasis and Ischemic Modified Albumin Levels in Idiopathic Polyhydramnios

İdiyopatik Polihidramniyoz Olgularında Dinamik Tiyol/Disülfit Homeostazı ve İskemik Modifiye Albümin Seviyeleri

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Abstract

Aim: The aim of study was to determine whether idiopathic polyhydramnios is in relation with dynamic thiol-disulfide homeostasis and ischemia modified albumin levels or not.

Material and Method: In this prospective case- control study, a total of 126 participants were included. The patient group consisted of 56 patients who were diagnosed idiopathic polyhydramnios, and the control group consisted of 56 healthy normal pregnant. Native thiol (-SH), total thiol (-SH. -SS), dynamic disulfide (-SS), values from maternal serum were measured and compared between groups.

Results: 112 patients aged between 18-35 years, consisting of 56 idiopathic polyhydramnios and 56 control groups were included in the study. Maternal serum native and total thiol values were significantly higher in study group compared to control group (382.2±78.5 mmol/L vs. 331.8±43.9 mmol/L, p <0.001 and 435.2±76.2 mmol/L vs. 368.2±47.2 mmol/L, p<0.001). Disulphide / native thiol ratio and disulphide / total thiol ratio ratio was found to be statistically significantly higher (7.3±2.2 vs 5.5±0.9, p<0.001 and 6.3±1.7 vs 5.0±0.7, p<0.001), and native thiol/total thiol ratio ratio was significantly lower (87.4±3.4 vs 90.1±1.4, p<0.001) in control group. Mean cord blood ischemia modified albumin (IMA) was 0.69±0.02 Absorbance Unit, cord blood native thiol (SH) level 410.2±80.2, and cord blood total thiol level was 461.1±82.1 µmol/l in study group. All parameters except IMA and Native thiol / total thiol ratio were higher in cord blood samples of study group compared to control group.

Conclusion: The thiol/disulfide balance shifted towards anti-oxidative status in pregnancies complicated with idiopathic polyhydramnios compared to control group.

Keywords: IMA, polyhydramnios, thiol/disulphide homeostasis

Öz

Amaç: Bu çalışmanın amacı, idiyopatik polihidramniosun dinamik tiyol-disülfit homeostazı ve iskemi modifiye albümin düzeyleri ile ilişkisinin olup olmadığını belirlemektir.

Gereç ve Yöntem: Bu prospektif vaka kontrol çalışmasına toplam 126 katılımcı dahil edildi. Hasta grubunu idiyopatik polihidramnios tanısı alan 56 hasta ve kontrol grubunu 56 sağlıklı normal gebe oluşturdu. Native tiyol (-SH), total tiyol (-SH.-SS), dinamik disülfid (-SS), maternal serum değerleri ölçüldü ve gruplar arasında karşılaştırıldı.

Bulgular: Çalışmaya 56 idiyopatik polihidramnios ve 56 kontrol grubu olmak üzere 18-35 yaş arası 112 hasta dahil edildi. Maternal serum nativ ve total tiyol değerleri çalışma grubunda kontrol grubuna göre anlamlı derecede yüksekti (382,2±78,5 mmol/L - 331,8±43,9 mmol/L, p <0,001 ve 435,2±76,2 mmol/L - 368,2±47,2 mmol/ L, p<0.001). Disülfit/doğal tiyol oranı ve disülfür/toplam tiyol oranı istatistiksel olarak anlamlı derecede yüksek bulundu (7,3±2,2'ye karşı 5,5±0,9, p<0,001 ve 6,3±1,7'ye karşı 5,0±0,7, p<0,001) ve doğal tiyol/toplam tiol oranı oranı kontrol grubunda anlamlı olarak daha düşüktü (87,4±3,4'e karşılık 90,1±1,4, p<0,001). Çalışma grubunda ortalama kordon kanı iskemi modifiye albümin (İMA) 0,69±0,02 Absorbans Birimi, kordon kanı nativ tiyol (SH) düzeyi 410,2±80,2 ve kordon kanı total tiyol düzeyi 461,1±82,1 µmol/l idi. Çalışma grubunun kordon kanı örneklerinde İMA ve Native tiyol/toplam tiyol oranı dışındaki tüm parametreler kontrol grubuna göre daha yüksekti.

Sonuç: Kontrol grubu ile karşılaştırıldığında idiyopatik polihidramnios ile komplike olan gebeliklerde tiyol/disülfür dengesi anti-oksidatif duruma doğru kaymıştır.

Anahtar Kelimeler: İMA, polihidramnios, tiyol/disülfit homeostazı

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Received *(Geliş Tarihi)*: 19.08.2023 **Accepted *(Kabul Tarihi)*:** 20.09.2023

INTRODUCTION

Polyhydramnios prevalence ranges from 0.2% to 2.0%.[1] It is defined by either an amniotic fluid index (AFI) greater than 24 cm or a deep vertical pocket (DVP) greater than 8 cm.[2] Maternal diabetes mellitus, rhesus iso-immunization, congenital and chromosomal abnormalities and multiple gestation are the main maternal, fetal and placental conditions associated with polyhydramnios.[2] Idiopathic polyhydramnios, in as many as 70.0%, is the entity that is not associated with any etiological factor.[2]

Oxidation is a normal and necessary process that occurs in human metabolism. If there is an imbalance between reactive oxygen species (Oxygen-containing molecules with an unequal number of electrons) and antioxidants, metabolism can be complicated by lipid peroxidation, protein peroxidation and DNA damage.[3] Dynamic thiol-disulfide homeostasis (TDH) is reversal of thiol oxidation in proteins and represents the levels of thiols and disulfides. It is an important parameter associated with regulation of protein function, stabilization of protein structure, protection of proteins against irreversible oxidation of cysteine residues, chaperon function, regulation of enzyme functions and transcription.[4-6] Although, TDH has been studied in many hot topic of women's health, such as reproductive, gynecological pathologies, and obstetric pathologies. A growing body of evidence has demonstrated that TDH is involved in obstetric pathologies with unknown etiology such as preeclampsia, intrauterine growth restriction, oligohydramnios, abortus imminens, hyperemesis gravidarum and gestational diabetes.[7-10]

In this study, we aimed to measure serum dynamic thiol/disulfide hemostasis of third trimester idiopathic polyhydramnios cases whose etiology is unclear and to compare them with healthy pregnancies. This study is the first in the literature to examine the relationship of idiopathic polyhydramnios with thiol/ disulphide hemostasis.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 12.10.2022, Decision No: E2-22-2591). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of one-hundred and twelve, term, single pregnancies, who were followed up in our hospital were enrolled in this prospective case- control study. All of the pregnant women who participated in the study were given detailed information about the study and their informed consent was obtained.

Sample size of our study was calculated as 112 (56 patients in study and 56 patients in control group) with 80% confidence interval and $p<0.05$ significance level. 56 term pregnancies with amniotic fluid >8 cm in the deepest pocket or 24 cm quadrants in ultrasonography were included as the study group. The control group consisted of 56 term pregnancies with normal amniotic index (2-8 cm in one pocket or 5-24 cm in four quadrants). Patients with fetal intrauterine growth retardation, had an abnormality in chromosome screening tests or second trimester obstetric ultrasonography, with a history of maternal systemic disease, smoking, alcohol use, had a membrane rupture and/or a labor pain were not included in the study. Absence of fetal anomaly, absence of intrauterine growth retardation, no history of oligohydramnios and absence of pathology in doppler ultrasonography (patients with umbilical artery doppler systolic/ diastolic ratio >3) during the antenatal follow-up period were accepted as indicators that the fetus was not under chronic stress and chronic hypoxia.

2 ml blood samples were taken from the antecubital vein and 2 ml blood samples were taken from umbilical cord under sterile conditions through a vacutainer to an Ethylenediamine tetra acetic acid (EDTA)-free biochemistry tube at the time of delivery. Samples centrifuged at 4000 rpm for 10 minutes and stored stored at -80 C0 until the analyzing time.

Native thiol (SH), total thiol and disulfide (SS) levels in plasma were measured by a new and automatic method developed by Erel and Neşelioğlu[11] This method is the reduction of dynamic disulfide bonds to functional thiol groups with sodium borohydride (NaBH4). Formaldehyde was used to remove all unused NaBH4. This prevents further reduction of 5,5-dithiobis-2-nitrobenzoic acid (DTNB) and reduction of disulfide bonds formed by the DTNB reaction. Total thiol content was measured with a modified Ellman reagent. Native thiol content was separated from total thiol content and it was observed that half of the difference obtained gave the amount of disulfide bond. In addition, disulfide/native thiol, disulfide/total thiol and native thiol/total thiol ratios were also calculated automatically.[11]

Albumin Cobalt Binding Test was used to detect the presence of Ischemia Modified Albumin (IMA). Measurement of IMA levels was obtained using venous blood samples on admittance within 1 hour. Specimens were stored for 30 minutes at room temperature and then centrifuged at 3500 rpm for 5 minutes. Latter samples were transferred to Eppendorf tubes and stored at -80°C until analysis. This test was performed by adding 50 mL 0.1% cobalt (II) chloride ($CoCl_2,6H_2O$) (Sigma-Aldrich Chemie GmbH Riedstrasse 2, Steinheim, Germany) to the patient serum. After mixing, followed by 10 minutes of incubation to allow for albumin cobalt binding, 50 mL 1.5 mg/mL dithiothreitol was added. After mixing followed by 2 minutes of incubation, 1.0 mL of a 0.9% sodium chloride solution was added in order to reduce the binding capacity. The absorbance of samples was measured at 470 nm using a spectrophotometer. The results were expressed as absorbance units (ABSU).[12]

SPSS (Statistical Package for Social Sciences) for Windows version 22.0 software was used for the statistical analysis of the data obtained in our study. Distrubition was checked

by using the Shapiro Wilk and Kolmogorov-Smirnov test. Comparisons between groups of demographic and laboratory data of all participants in those with normal distribution were made with Student's t test. Non-normally distributed data were compared between groups using the Mann-Whitney U test. Categorical data were presented as numbers and percentages and compared with the Chi-square test. Pearson correlation analysis was used to determine the relationship between native and total thiol and some other continuous variables. Data are presented as mean±standard deviation and median (minimum-maximum) or number (percentage). The statistical significance level was accepted as p<0.05.

RESULTS

112 patients aged between 18-35 years, consisting of 56 idiopathic polyhydramnios and 56 control groups were included in the study. The mean age of 56 pregnant women in our study was 30.7±5.3 in the patient group and 27.8±4.9 in the control group. 17(31%) of patients in study group and 16(29.6%) of patients in control group were nulliparous (p=0.835). Total weight gained during pregnancy was 12.3±3.9 kg in the patient group; 11.1±3.2 kg in the control group (p=0.069). The characteristic features of the patients were shown in **Table 1**.

Table 1. Demographic characteristics of the subjects

	Polihidramnios (n=54)	Control group (n=54)	p
Maternal age	30.7±5.3	27.8±4.9	0.003
Nulliparity (n, %)	17 (31.5)	16 (29.6)	0.835
Maternal BMI (kg/m²)	31.2±4.7	26.6±4.2	<0.001
Gestational weight gain (kg)	12.3±3.9	11.1±3.2	0.069
Deepest vertical pocket (mm)	91±14	58±16	<0.001
Total AFI (mm)	275±37	164±52	<0.001
Gastational weeks at delivery	37.9±1.3	39.1±1.0	<0.001
Birthweight (g)	3503±575	3416±365	0.351
Apgar score 1st min <7 (n, %)	4 (7.4)	0	
Apgar score 5st min <7 (n, %)	0	0	

Maternal serum native and total thiol values were significantly higher in the idiopathic polyhydramnios group than control group (382.2±78.5 mmol/L vs. 331.8±43.9 mmol/L, p <0.001 and 435.2±76.2 mmol/L vs. 368.2±47.2 mmol/L, p<0.001). In the idiopathic polyhydramnios group when disulphide / native thiol ratio and disulphide / total thiol ratio ratio was found to be statistically significantly higher (7.3±2.2 vs 5.5±0.9, p<0.001 and 6.3±1.7 vs 5.0±0.7, p<0.001), native thiol / total thiol ratio ratio was significantly lower (87.4±3.4 vs 90.1±1.4, p<0.001). Maternal serum disulphide level in polyhydramnios group were higher compared to control group (26.5±6.1 vs 18.2±3.1, p<0.001). The IMA value was significantly lower in the IO group than control group (0.76±0.10 ABSU vs 0.68±0.06, p < 0.01) (**Table 2**).

Mean cord blood IMA was 0.69±0.02 Absorbance Unit (ABSU), cord blood native thiol (SH) level 410.2±80.2, and cord blood total thiol level was 461.1±82.1 µmol/l in study group. In the control group, cord blood IMA was 1.04±0.14 ABSU, cord blood native thiol (SH) level was 359.4±54.5 µmol/l and cord blood total thiol level was 397.6±57.9 µmol/l. All parameters except IMA and Native thiol / total thiol ratio were higher in cord blood samples of study group compared to control group (**Table 2**).

DISCUSSION

In this prospective case-control study, we examined the patients with idiopathic polyhydramnios who were in third trimester of pregnancy whether the etiology is in relation with TDH or not. The results of study revealed that the thiol/ disulfide balance shifted towards anti-oxidative status in cases with idiopathic polyhydramnios compared to healthy pregnant women with normal AFI. The high levels of antioxidant markers (native and total thiol) and low levels of oxidative markers (-SS/-SH and -SS/-SH, -SS and IMA levels) prove the presence of compensator mechanisms in idiopathic polyhydramnios. This is the first study which evaluates the thiol/ disulphide homeostasis in pregnancies complicated with idiopathic polyhydramnios.

Pregnancy itself is a state of oxidative stress. Increased metabolic activity, increased placental mitochondrial activity, and increased production of ROS during fetal growth can be listed as the main causative factors of oxidative status in normal pregnancy.[13] Superoxide anions produced by placental mitochondria are the most important source of ROS and lipid peroxidation.[14] Free

Table 2. Oxidative/ anti-oxidative markers in maternal serum and cord blood

	Maternal serum			Cord blood		
	Polyhydramnios (n= 54)	Control group (n= 54)	p	Polyhydramnios (n= 46)	Control group (n= 54)	p
Native Thiol (mean±SD)	382.2±78.5	331.8±43.9	<0.001	410.2±80.2	359.4±54.5	<0.001
Total Thiol (mean±SD)	435.2±76.2	368.2±47.2	<0.001	461.1±82.1	397.6±57.9	<0.001
Disulphide (mean±SD)	26.5±6.1	18.2±3.1	<0.001	25.5±4.2	19.1±3.1	<0.001
Native thiol / total thiol ratio	87.4±3.4	90.1±1.4	<0.001	88.7±2.5	90.3±1.4	<0.001
Disulphide / native thiol ratio	7.3±2.2	5.5±0.9	<0.001	6.4±1.6	5.4±0.8	<0.001
Disulphide / total thiol ratio	6.3±1.7	5.0±0.7	<0.001	5.7±1.2	4.8±0.7	<0.001
Ischemia modified albumin (mean±SD)	0.71±0.03	1.06±0.13	<0.001	0.69±0.02	1.04±0.14	<0.001

radicals originating from the placenta pass into the mother's circulation and undergo detoxification, and if there is not enough antioxidant activity, the placental ROS level rises. ROS amount rising in the placenta causes lipid, protein and DNA destruction, causing placental cell death and placental insufficiency. As a result of endothelial insufficiency induced by oxidative stress, pre-eclampsia, IUGR, preterm delivery, and recurrent pregnancy loss are more common.[15]

Antioxidant capacity, which increases as the gestational week increases, reaches its highest level in the third trimester. However, intense and continuous exposure to oxidative stress affects the placental antioxidation capacity and causes the consumption and reduction of antioxidants.[15] Oxidative stress is an important factor in many complications during the second and third trimester of pregnancy. Oxidative stress in pregnancy complicated with oligohydramnios has been explained based on two main mechanisms. According to the first hypothesis, inadequate extravillous trophoblast invasion could result in an imbalance of oxidant/antioxidant activity when antioxidant capacity does not keep pace with increased oxygen tension leading to a chronic state of oxidative stress. Second hypothesis explains the oxidative stress by intermittent maternal blood flow in the intervillous space resulting in ischemic-reperfusion damage. An extensive production of ROS leads to irreversible cellular dysfunction and tissue damage.[16] Intrestingly, TDH homeostasis in cases complicated with polyhydramnios without any etiological factor has not been questioned to date.

Our results showed clearly that the thiol/disulfide balance shifted towards anti-oxidative status in pregnancies complicated with idiopathic polyhydramnios compared to cases with normal AFI. The results raise the following question The principal theoretical implication of this study is that because of the predominance of antioxidants at the end of the 3rd trimester can be a result of regeneration phase following placental damage, and fetal renal perfusion switching to the compensatory polyuric/diuretic phase.

The generalisability of these results is subject to certain limitations. For instance, current study was limited by its sample size and designed in a single center. Randomised controlled trials with larger sample sizes could provide more definitive evidence.

CONCLUSION

All TDH parameters except disulphide levels and native thiol/total thiol ratio were higher in cases with idiopathic polyhydramnios. The evidence so far has proposed that thiol-disulfide homeostasis is an important issue and needs to be elucidated wholly. More research with larger sample sizes is needed to better understand the dynamic thiol/disulphide homeostasis and its role in pathophysiology of idiopathic polyhydramnios.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 12.10.2022, Decision No: E2-22-2591).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1345944
J Contemp Med 2023;13(5):849-854

Original Article / Orijinal Araştırma

Evaluation of Caregiver Burdens of Caregivers to Individuals with Chronic Heart Failure

Kronik Kalp Yetmezliği Olan Bireylere Bakım Verenlerin Bakım Verme Yüklerinin Değerlendirilmesi

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Abstract

Aim: In this study we aimed to determine the burden of caregiving and the factors affecting the burden of caregiving among caregivers of patients with chronic heart failure (HF).

Material and Method: In this prospective study, the Zarit Care Burden Scale (ZCBS) was applied face-to-face to caregivers of 178 HF patients. On the scale scoring, 0-20 points indicate "no care burden", 21-40 points indicate "light care burden", 41-60 points indicate "moderate care burden" and 61-88 points indicate "heavy care burden".

Results: The burden of caregivers over 65 years of age with HF was higher ($p<0.01$). Caregivers with a heavy burden of care were those who had a bad economic situation, did not receive support from family members, had other caregivers, and had a high number of children ($p<0.001$). There was no significant relationship between the caregiver's age, occupation, education level, place of residence, proximity and ZCBS ($p>0.05$). Depression was the most common psychiatric problem in both HF patients and caregivers.

Conclusion: Especially family, psychological, and economic support should be provided to patients with chronic HF and their caregivers. As the living standards of patients with HF improve, the burden of caregivers decreases.

Keywords: Heart failure, caregiving,depression

Öz

Amaç: Bu çalışmada kronik kalp yetmezliği (KY) olan hastalara bakım verenlerin bakım verme yükünü ve bakım verme yükünü etkileyen faktörleri belirlemeyi amaçladık.

Gereç ve Yöntem: Bu prospektif çalışmada 178 kalp yetmezlikli hastaya bakım verenlere zarit bakım yükü skalası (BYÖ) yüzyüze uygulandı. Ölçek puanlamasında 0-20 puan "bakım yükü yok", 21-40 puan "hafif bakım yükü", 41-60 puan "orta bakım yükü" ve 61-88 puan "ağır bakım yükü" anlamına gelmektedir.

Bulgular: 65 yaşın üzerindeki kalp yetmezlikli kişilere bakım verenlerin yükü daha fazlaydı ($p<0.01$). Bakım yükü ağır olan kişiler ekonomik durumu kötü, aile bireylerinden destek almayan, başka baktığı kişi olan ve fazla çocuk sayısın sahip olan kişilerdi ($p<0,001$). Bakım verenin yaş, meslek, eğitim durumu, yaşadığı yer, yakınlık durumu ile BYÖ arasında anlamlı bir ilişki tespit edilmedi ($p>0,05$). Hem KY'li hastalarda hem bakım vericilerde ortaya çıkan en sık psikiyatrik problem depresyondu.

Sonuç: Kronik KY'li hastalara ve onlara bakım verenlere özellikle ailevi, psikolojik ve ekonomik yönden destek sağlanmalıdır. KY'li kişilerin yaşam standartları iyileştikçe bakım verenlerin yükü de azalmaktadır.

Anahtar Kelimeler: Kalp yetmezliği, bakım verme, depresyon

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Received *(Geliş Tarihi)*: 18.08.2023 **Accepted *(Kabul Tarihi)*:** 20.09.2023

INTRODUCTION

Heart failure (HF) is a complex condition in which the heart cannot pump enough blood to meet the metabolic needs of the body due to a structural or functional defect.[1] As a result of the advancement of science and technology, the population is aging, chronic patients can live longer, and the mortality rate in acute coronary events is decreasing. As a result of these developments, the prevalence and incidence of HF are increasing. The prevalence of HF exceeds 40 million worldwide, with approximately 6 million in the United States and 6.5 million in Europe. In Turkey, approximately 3-4 million people have HF.[2]

In a patient with HF, dyspnea, fatigue, edema, and activity limitation are among the primary symptoms. In these patients, deterioration in quality of life is observed due to dietary restrictions, difficulties in normal work performance, difficulties in sexual intercourse, progressive loss of self-confidence, side effects of drug treatment, and rehospitalizations.[3] The goal of HF treatment is to reduce mortality and unnecessary hospitalizations, eliminate symptoms (dyspnea, fatigue, depression, anxiety, and cognitive disorders), and provide quality of life. Since HF requires a long care process starting from the diagnosis stage, it affects the families of caregivers as well as patients physically, psychologically, socially, economically, and spiritually, and creates a heavy economic burden with intense stress. As a result of all these problems, the search for new service models such as home care for patients with chronic diseases such as HF is on the agenda.[4]

Although caregiving is not limited to a single type of assistance, it includes the coordinated execution of many tasks such as providing emotional, physical, or financial support, coordinating health care, carrying out routine health care, personal care, transportation, shopping, doing small household chores, and money management in addition to providing the patient's care needs.[5]

Care burden includes negative objective or subjective results, such as problems in many areas, including psychological, economic, social, physical, and health; deterioration in family relationships; and the feeling that the caregiver is not in control .This multidimensional and complicated care-giving process may cause the caregiver to feel burdened and experience psychosocial problems as a result of being forced at times. The transformation of caregiving into a one-way, dependent, intensive, and long-lasting obligation that puts the individual's life in distress causes the caregiver to experience problems of harmony between family relations, work, entertainment, social life roles, and care roles and to perceive care as a burden. The burden of caregivers should be determined, the factors affecting them should be revealed, and the degree to which their quality of life is affected should be determined.[4-6]

In this study, it was aimed to determine the burden of caregiving and the factors affecting the burden of caregiving among caregivers of patients with chronic HF.

MATERIAL AND METHOD

The study was carried out with the permission of Kayseri City Hospital Ethics Committee (Date: 14.05.2020, Decision No: 66). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The population of this prospective study was the primary caregivers of patients with chronic HF admitted to the cardiology outpatient clinic of a district state hospital. Among the caregivers included in the study, 178 caregivers and 178 care recipients were included in accordance with the principle of voluntary participation. The criteria for inclusion in the study were that the caregiver cared for the patient at home and in the hospital, was over 18 years of age, the caregiver had no perception, hearing, speech, and mental problems, was literate, and agreed to participate in the study. Exclusion criteria were illiteracy, being younger than 18 years of age, caring for the patient for less than 6 months, caregivers for financial gain, and those who did not accept participation in the study were excluded from the study. The demographic data form, including the descriptive characteristics of the caregivers and the care burden scale, was used to collect the data. Data collection tools were prepared by the researchers in line with the literature, with a form including descriptive characteristics of caregivers and descriptive information about the disabled person. The caregiver information form and Zarit Caregiver Burden Scale (ZCBS) were used to evaluate the stress experienced by caregivers of elderly individuals in need of care.[7] The scale, which can be completed by the caregivers themselves or by the researcher, consists of 22 statements that determine the impact of caregiving on the individual's life. With this scale, the caregiver/patient relationship, the caregiver's health status, psychological comfort, social life, and economic burden can be evaluated. The evaluation of the ZCBS, in which all items are expressed in plain language, is based on the total score. The higher the score, the higher the burden of care, and a maximum score of 88 points can be obtained from the scale. The relevant forms were applied by the researchers to the caregivers who agreed to participate in the study by face-to-face interview technique in an empty patient room, and each interview lasted approximately 15-20 minutes. The scale has a Likert-type evaluation ranging from 0 to 4 as (0) "Never", (1) "Rarely", (2) "Sometimes", (3) "Quite Often", (4) "Almost Always". A minimum score of 0 and a maximum score of 88 can be obtained from the scale. In scoring, 0-20 points indicate "no care burden", 21-40 points indicate "light care burden", 41-60 points indicate "moderate care burden" and 61-88 points indicate "heavy care burden". The validity and reliability study of the adaptation of the ZCBS to the Turkish population was conducted in 2006.[7-9]

Statistical Analysis

Mean, standard deviation, median, minimum, minimum, maximum, frequency, and ratio values were used in the descriptive statistics of the data. The Mann-Whitney U test and Kruskall-Wallis Test were used to analyze quantitative

independent data. The chi-square test was used in the analysis of qualitative independent data, and the Fischer test was used when the chi-square test conditions were not met. The SPSS 26.0 program was used in the analysis.

RESULTS

The study included 178 caregivers and 178 care recipients of HF patients. The mean age of caregivers was 44.5±10.2 years, and the mean age of care recipients was 63.1±7.35 years. 59% of care recipients were female, and 77.5% of caregivers were female. 58.4% of the caregivers were the daughters of the patients receiving care, 92.1% were married, and 23.6% had an additional disease. Of the comorbidities, 57.1% had depressive disorders and 42.9% had chronic diseases (HT, DM). Depression in patients with HF occurred during the caregiving process. Psychiatric problems experienced by caregivers occurred during the caregiving process. Caregivers had no previous education in caregiving. 59% of the caregivers were housewives, 60.1% were high school graduates, and 55.1% lived in the district. The proportion of caregivers who had no other patients was 88.2% and the proportion of caregivers whose expenses were higher than their income was 46.6%. The CBM was administered to 78.1% of caregivers before the pandemic and 21.9% during the pandemic. In the care burden grading, 44.7% had a light burden, 43.6% had a moderate burden, and 5.8% had a heavy burden. 51.7% of caregivers provided both treatment and care (**Table 1**).

Table 1.

		Caregiver (n) ZCBS	p value
Gender	Male (40) Female (138)	49.5 (22-86) 41.5 (22-86)	0.107
Marital Status	Married (164) Single (14)	44.5 (22-86) 35 (22-84)	0.236
Job	Housewife (105) Civil servants (31) Self-employed (30) Unemployed (12)	44 (22-86) 40 (22-84) 40 (22-54) 52 (22-86)	0.051
Education	Primer education(27) High School(107) University (44)	50 (22-84) 44 (22-86) 40 (22-86)	0.351
Living stage	County (98) Village (61) Town center (19)	45 (22-86) 40 (22-85) 49 (22-54)	0.566
Care	Treatment and care (92) Treatment (86)	49 (22-86) 40 (22-86)	0.044
Other caregiver	No Yes	0 (22-86) 52 (48-86)	<0.001
Economical situation	Expense Excess (83) Income-Expense (72) Equal Income more (23)	51 (24-86) 35.3 (22-85) 22 (22-44)	<0.001
Child	Yes No	45 (22-86) 23 (22-25)	0.001
Relationship	Wife/husband Daughter Son Sister	40 (22-86) 48 (22-85) 50 (22-86) 38 (22-50)	0.234

ManN Whitney U testi ve Kruskall Wallis Testi. p<0.05 was considered statistically significant. ZCBS: Zarit Caregiver Burden Scale

The care burden scale of caregivers was similar in terms of gender, marital status, occupation, educational status, place of residence, and degree of closeness (p:0.107, p:0.236, p:0.051, p:0.351, p:0.566, p:0.234, respectively). Participants who both helped in the treatment of the patient and provided care had higher ZCBS (p:0.044). Patients who also cared for patients other than HF patients had a higher ZCBS (p:0,000). Caregivers who had children had a significantly higher ZCBS (p<0,001). There was a significant difference between the groups in terms of economic status (p:0,000). The group with higher expenses had a higher CBS than the group with equal income and expenses (p:0,000). The group with more expenses had a higher ZCBS than the group with more income (p:0,000). The ZCBS of the group with equal income and expenses was higher than that of the group with more income (p:0,003). According to the age groups of the patients being cared for, the ZCBS of the caregivers was statistically different. Participants who provided care to patients over the age of 65 years had a higher ZCBS (p:0.000). However, according to the gender of the patient being cared for, caregivers' ZCBS scales were similar (p:0.320) (**Table 2**).

Table 2. Caregiver burden by age and gender of caregiver

		ZCBS	P
Patient Gender	Male Female	40 (22-86) 48 (22-84)	0.320
Age	<65 >65	40 (22-55) 50 (22-86)	<0.01

p<0.05 was considered statistically significant.

There was a very weak positive correlation between the caregiver's ZCBS and the age of the caregiver (r:0.157, p:0.037), a moderate positive correlation with the age of the care recipient (r:0.459, p:0.000), and a weak positive correlation with the duration of caregiving (r:0.367, p:0.000) (**Table 3**).

DISCUSSION

In our study, we found that caregivers experienced the most psychological and economic problems, and that patients with heart failure also had problems in terms of psychological and familial support. Taking care of an individual with a chronic disease such as HF, meeting his/her needs, and helping him/her causes physical, psychological, social, and economic difficulties for his/her family and relatives, and the role of the caregiver may worsen as the course of the disease worsens.[10] In recent years, many new treatment technologies, such as implantable defibrillators (ICD), biventricular pacemakers, and left ventricular assist devices, have been developed.[11] As a result of these developments, the life expectancy of patients is prolonged, and the parameters of care (such as treatment, follow-up, nutrition, and cleaning) are increased.[4] Given the central role of caregivers for patients with HF, it is important to understand the burden of caregiving responsibilities on these individuals in order to meet their needs and promote their continuous and effective support.

Many factors such as age, gender, cultural characteristics, socioeconomic status, educational level, health status, family dynamics, closeness to the patient, willingness to provide care, presence or absence of disease, coping skills, beliefs, and the presence of social support may affect the caregiving role of caregivers.[5,12]

In studies, the effect of age and gender on caregiving burden varies. Şahin et al. reported that there was no significant difference between age groups and caregiving burden scale scores (p>0.05).[13] In a study conducted by Yüksel et al. with the caregivers of Parkinson's patients, they stated that when they made an evaluation according to the age and gender of the caregiver, they found that women and older people were under more burden, although there was no statistical significance.[14] Şahin et al. determined that the burden of care decreased with increasing age.[15] In our study, there was a very weak positive correlation (r:0.157, p:0.037) between the caregiver's ZCBS and the caregiver's age. In a study conducted by Tülüce, it was found that women experienced more care burden than men.[16] The fact that women experience more care burden than men may be due to their inability to cope effectively with the caregiving function, having other responsibilities other than caregiving, and not having adequate and effective support systems. In our study, the majority of caregivers were women, but there was no significant difference in terms of ZCBS in terms of gender. Participants caring for patients over the age of 65 years had significantly higher ZCBSs, but the ZCBS scales of the caregivers did not differ according to the gender of the patient being cared for. In previous studies, it was determined that the care burden of married caregivers was higher than that of single caregivers.[17] It is thought that married caregivers experience more care burden than single caregivers because they have more responsibilities in daily life (housework, child care, etc.). In our study, there was no difference between married and single caregivers in terms of care burden. We believe that these results were obtained according to the sociocultural situation in which the studies were conducted.

The primary caregivers of chronically ill people are wives, daughters, and daughters-in-law. In our country, the care of the elderly is carried out by family members, especially women and spouses. In another study conducted with caregivers of patients with HF, it was determined that 20% of the participants were the patient's spouse.[16,17] In the literature, it is stated that caregivers for chronic diseases requiring physical or psychological long-term care are mostly women from the family who do not have a job and are often the mother, sister, or wife of the patient. Since unemployed individuals are responsible for caregiving, economic problems may arise. In our study, in line with the literature, the majority of caregivers were daughters and spouses. The unemployed caregivers had poor economic status and a moderate to heavy care burden. According to this information, which overlaps with the study findings, it was thought that caregiving is a social role assigned to women in different cultures, and this view was effective in this result.[5,18]

Education level is also one of the factors affecting care burden. Iconomou et al. reported that caregivers with lower educational levels experienced more emotional stress, had more impact on their lives, and had worse physical health than those with higher educational levels.[19] In our study, there was no difference in terms of care burden in terms of educational status and occupation. Different results were obtained between care burden and number of children according to the socio-demographic data of the caregiver. In the study of Özdemir, the burden of caregiving was found to be higher in mothers with three or more children, but it was not found to be significant.[20] In our study, the care burden of caregivers with children was significantly higher. This may be attributed to the increase in stress and fatigue experienced by the caregiver with the increase in workload. In our study, a weak positive correlation was found between the duration of caregiving and care burden scores (p<0.001). Yüksel et al. found that there was a significant direct correlation between the duration of caregiving and care burden (p=0.032) and that the burden of the caregiver increased as the duration of caregiving increased.[14] In a study that the burden perception of caregivers who provided care for 13-24 months was higher than that of those who provided care for 24 months or more.[21]

Psychological problems may also occur in caregivers of patients with HF. The most common conditions that occur or worsen are stress, anxiety, sleep problems, migraine/headache, and depression.[22] Physical problems also arise as caregivers limit their physical activities. Therefore, perceived care burden negatively affects not only the care given to the patient but also the lives of caregivers. As a result of the study conducted by Balaban, it was found that there was a significant relationship between care burden and anxiety and depression levels of caregivers, and as the care burden increased, anxiety and depression levels increased.[23] In a study conducted by Zincir et al., it was found that caregivers of patients with HF experienced high levels of care burden and anxiety, and female caregivers experienced more care burden and anxiety than male caregivers.[24] As a result of the study to determine the care stress of family caregivers, it was found that HT , weakening of the immune system, depression, and anxiety were observed in caregivers. In a study conducted by Peter et al., it was found that caregivers of patients with HF experienced high rates of depressive symptoms and care burden, and their quality of life decreased in parallel. In a study conducted by Harkness, it was found that 48% of caregivers of patients with HF experienced anxiety.[25-27] In our study, depression, sleep problems, and HT were present in patients with heavy care burdens, in accordance with the literature.

There is an important relationship between the prognosis of patients with HF and social relationships. Social support given to patients with HF has beneficial effects on the prognosis of

the disease. As the quality of life of patients with HF increases, the prognosis of the disease is better and caregivers are less needed. Depression was present in 16% of the patients in our study, and caregivers of depressed HF patients were mostly non-nuclear family members. Research clearly demonstrates the importance of the support of family members, especially spouses, in disease management and self-care. There is evidence that spousal support has a positive effect on the outcomes of patients with HF and other heart diseases.[28,29]

In order to reduce caregiver burden, the first step is to identify the experienced burden. Knowing and revealing the burden contributes to improving the quality of life of both caregivers and recipients. Therefore, approaches to reducing the burden of care are important in terms of maintaining the well-being of both the patient and the caregiver. In our country, providing psychological support training to both family members and patients may be a healthier health practice. In our study, caregivers did not receive any training, etc., on this subject. Reducing the burden of caregiving causes the HF patient receiving care to receive better quality care and to have a better quality of life.[6,29]

CONCLUSION

Caregivers of patients with HF should receive more support and training from healthcare providers to develop their coping and resilience skills in a way that decreases their care burden and improves their quality of care and self-confidence. Especially economic and psychological problems arise in caregivers, so they also need economic and psychological support. In addition, the number of studies on the difficulties and needs of caregivers in our country is not sufficient. It is thought that there is a need for more comprehensive and qualitative studies on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kayseri City Hospital Ethics Committee (Date: 14.05.2020, Decision No: 66).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1348296
J Contemp Med 2023;13(5):855-860

Original Article / Orijinal Araştırma

Surgical Management of Acute Complications Arising from Endovascular Interventions in Peripheral Arterial Disease of the Lower Extremities: Everlasting Novel

Alt Ekstremite Periferik Arter Hastalığında Endovasküler Girişimlerden Kaynaklanan Akut Komplikasyonların Cerrahi Yönetimi: Eskimeyen Yeni

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Abstract

Aim: The importance of endovascular procedures in the diagnosis and treatment of peripheral vascular diseases has seen a notable rise in recent years. Nevertheless, this surge has resulted in a corresponding rise in iatrogenic vascular complications and subsequent interventions associated with peripheral endovascular procedures. This study involved a retrospective evaluation of acute complications associated with endovascular treatments performed for lower limb peripheral artery diseases as well as a closer look at the related therapeutic strategies for these challenges.

Material and Method: A retrospective evaluation was conducted on a cohort of 400 patients who received endovascular intervention for lower extremity peripheral artery disease at our clinic. The study included 27 patients (6.7%) from this cohort who received surgical or endovascular treatment for acute complications following endovascular intervention. Our preference for endovascular or surgical treatments was chosen based on the type and localization of the complications.

Results: The mean age of patients who experienced complications was 63.7±6 years. The complications were as follows in order of frequency: dissection in 14 (51.9%) patients, arterial perforation in 5 (18.5%) patients, major hematoma in 3 (11.1%) patients, pseudoaneurysm in 2 (7.4%) patients, distal embolism in 2 (7.4%) patients and arterio-venous fistula in 1 (3.7%) patient. In the treatment of complications, endovascular methods were preferred in 19 (4.7%) patients and surgical approaches were used in 8 (2%) patients. Following endovascular intervention, a minor amputation was performed in one patient.

Conclusion: The rapid and effective management of complications related to peripheral endovascular procedures in the lower extremities is of utmost importance. Despite the notable advancements in endovascular procedures in recent years, there are scenarios where these interventions may be insufficient for dealing with complications. The management of such problems may necessitate surgical intervention. Hence, the integration of well-established and validated vascular surgical techniques with endovascular interventions is believed to yield optimal outcomes.

Keywords: Endovascular treatment, complications, peripheral artery disease, vascular surgery

Öz

Amaç: Son yıllarda periferik vasküler hastalıkların tanı ve tedavisinde endovasküler işlemlerin önemi artmıştır. Ancak bu artış, periferik endovasküler işlemlere bağlı iyatrojenik damar yaralanmalarının ve buna bağlı girişimlerin artmasına neden olmuştur. Bu çalışmada, alt ekstremite periferik arter hastalıklarında gerçekleştirilen endovasküler işlemlere bağlı akut komplikasyonlar ve bu komplikasyonların yönetimi retrospektif olarak değerlendirilmektedir.

Gereç ve Yöntem: Kliniğimizde alt ekstremite periferik arter hastalığı nedeniyle endovasküler girişim yapılan 400 hasta retrospektif olarak değerlendirildi. Bu gruptan, endovasküler müdahale sonrası akut komplikasyonlarına cerrahi veya endovasküler tedavi uygulanan 27 (%6.7) hasta çalışmaya dahil edildi. Komplikasyonların tipi ve lokalizasyonuna bağlı olarak endovasküler veya cerrahi müdahale tercihimizi belirledik.

Bulgular: Komplikasyon gelişen hastaların yaş ortalaması 63.7±6 yıl olarak belirlendi. Görülen komplikasyonlar sıklık sırasına göre şu şekildeydi: diseksiyon 14 (%51.9) hasta, arteriyel perforasyon 5 (%18.5) hasta, majör hematom 3 (%11.1) hasta, psödoanevrizma 2 (%7.4) hasta, distal emboli 2 (%7.4) hasta ve arteriyo-venöz fistül 1 (%3.7) hasta. Komplikasyonların tedavisinde, 19 (%4.7) hastada endovasküler yöntemler tercih edilirken 8 (%2) hastada ise cerrahi yaklaşımlara başvuruldu. Endovasküler girişimi takiben, bir hastada minör amputasyon gerçekleştirilmiştir.

Sonuç: Alt ekstremite periferik endovasküler işlemlere bağlı komplikasyonlara hızlı ve etkili müdahale önemlidir. Endovasküler teknikler son yıllarda önemli ilerlemeler kaydetmiş olsa da, bazı durumlarda komplikasyonların tedavisinde yetersiz kalabilmektedir. Bu tür komplikasyonların yönetimi için cerrahi müdahale kaçınılmaz olabilir. Dolayısıyla, uzun yıllara dayanan ve etkinliği kanıtlanmış damar cerrahisi yaklaşımlarının endovasküler tedavilerle birleştirilmesinin, en etkili sonuçların elde edilmesini sağlayacağı düşünülmektedir.

Anahtar Kelimeler: Endovasküler tedavi, komplikasyon, periferik arter hastalığı, vasküler cerrahi

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Received *(Geliş Tarihi)*: 23.08.2023 **Accepted *(Kabul Tarihi)*:** 20.09.2023

INTRODUCTION

The introduction of peripheral angioplasty throughout the 1960s marked a significant milestone in the management of peripheral artery diseases.[1] As a result of the rapid development of balloon and catheter technology, these endovascular procedures are now commonly used in the treatment of peripheral artery disorders. The utilization of endovascular therapies in the treatment of lower extremity peripheral arterial disease during the past five decades, particularly atherosclerotic disease affecting the iliac and distal arteries, has resulted in a substantial rise in complications. The aforementioned challenges may potentially arise due to complications with vascular access or the use of guidewires, catheters, balloons, or stents. The most common acute complications associated with peripheral endovascular procedures include residual stenosis, dissection, arterial perforation (AP), hematoma, pseudoaneurysm (PA), arterio-venous fistula (AVF), and distal embolism (DE).[2] These kinds of complications, which could develop in peripheral endovascular treatments, can typically be addressed by endovascular techniques, although in certain cases, urgent surgical interventions may be warranted. The crucial aspect to consider is carrying out timely and appropriate interventions for these types of issues.

The objective of this study is to provide a retrospective assessment of the acute complications linked to endovascular procedures for peripheral artery disease in the lower extremities as well as the strategies employed to address these issues.

MATERIAL AND METHOD

The study was approved by the KTO Karatay University Faculty of Medicine, Pharmaceutical and Non-Medical Device Research Ethics Committee (Date: 17.06.2022, Decision No: 2022/034). The study was conducted in accordance with the principles of the Declaration of Helsinki. We retrospectively evaluated 400 adult (≥18 years) patients who underwent endovascular intervention for lower extremity peripheral arterial disease. Among these patients, 27 patients who developed acute complications after the endovascular procedure and underwent surgical or endovascular treatment for these complications were included in the study.

Demographic data, preoperative, intraoperative, and postoperative records, as well as follow-up outcomes of the patients, were acquired from the hospital's data system. Data included age, gender, comorbidities, endovascular procedure-associated complications and their anatomical locations, interventions used to treat these complications using surgical and/or endovascular approaches, amputations, mortality rates, length of stay in the intensive care unit, and length of hospitalization.

Individuals presenting with lower extremity claudication, rest pain, or acute ischemia underwent a thorough assessment employing arterial Doppler ultrasonography, computed tomography angiography, or magnetic resonance angiography. Those displaying morphological lesions in alignment with the TASC II classification and concurrently falling under the clinical classification of Rutherford classes 3 to 6 were deemed eligible for inclusion in the endovascular intervention.

All patients underwent a physical examination, routine blood tests, echocardiography (ECHO), and electrocardiography before the endovascular procedure. All endovascular procedures were performed under local anesthesia in the hybrid cardiovascular surgery room. Percutaneous transluminal angioplasty (PTA), stent implantation, and mechanical thrombectomy were performed as peripheral endovascular procedures. Subsequent to the intervention, meticulous post-procedural monitoring was executed within the intensive care unit and ward settings.

We determined our preference for endovascular or surgical intervention based on the nature and location of the complication that occurs during the procedure or follow-up. Complications that may arise from the endovascular procedure of lower limb arteries that necessitate rapid action to preserve the extremities or the patient include dissection, arterial perforation (AP), hematoma, pseudoaneurysm (PA), arteriovenous fistula (AVF), and distal embolism (DE). In instances of pseudoaneurysm necessitating surgical consideration, primary attention was accorded to its symptomatic manifestation, unsuitability for alternative treatments, progressive enlargement, and dimensions exceeding 3 cm. For dissection, arterial perforation, and AVF cases, a preference was extended to percutaneous transluminal angioplasty (PTA) as the initial approach. Open or covered stent implantation was entertained, with recourse to surgical intervention if endovascular approaches proved insufficient. Urgent surgical intervention was reserved for hematomas characterized by rapid and pronounced diameter increase at the intervention site, substantial hematocrit value reduction demanding blood transfusion, and in cases of complications engendering limb-threatening ischemia or severe hemorrhage. Moreover, immediate emergency intervention was executed in instances where complications induced limb-threatening ischemia or severe hemorrhage. Conversely, for other patients, the intervention was planned on an elective basis, guided by their clinical condition and laboratory findings. Predominantly, surgical procedures were conducted under local anesthesia, with only a handful performed under general anesthesia. Postoperative monitoring of lower extremity blood flow was standard practice, encompassing manual distal pulse evaluation and hand Doppler assessment immediately following the surgical procedure.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA) software. Nominal variables were expressed as numbers and percentages. The distribution of continuous variables was evaluated by the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean±standard deviation.

RESULTS

This study examined a cohort of 400 patients who received endovascular intervention for lower extremity peripheral artery disease. Among this group, a subset of 27 patients (6.7%) who experienced complications related to endovascular procedures either during the intervention or while in their hospital stay were included in the analysis. Of these, 11 (40.7%) were female and 16 (59.3%) were male. The mean age of the patients was 63.7±6 years. When the patients' preoperative comorbidities and risk factors were analyzed, smoking (16, 59.3%), hypertension (18, 66.7%), diabetes mellitus (12, 44.4%), and coronary artery disease (10, 37%) were found to be the most prevalent comorbidities. **Table 1** displays the patients' demographic information.

Table 1. Demographic information and comorbid diseases of the patients

Variables	Mean	Standard deviation	Number (n=27)	Percentage (%)
Age (years)	63.7	6		
Female / Male			11 / 16	40.7 / 59.3
Smoking			16	59.3
HT			18	66.7
DM			12	44.4
CAD			10	37

HT: Hypertension; DM: Diabetes mellitus; CAD: Coronary artery disease

The complications associated with the endovascular treatment were categorized based on their location of occurrence. Out of the total complications, 1 (3.7%) took place in the iliac region, 21 (77.8%) in the femoropopliteal region, and 5 (18.5%) in the infrapopliteal region, as seen in **Figure 1**.

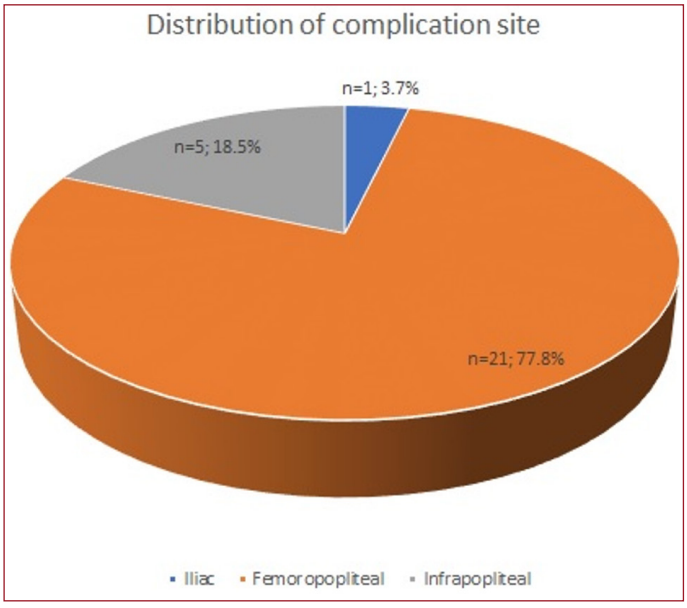

Figure 1: illustrates the classification of complications linked to endovascular treatment according to the site of their occurrence.

The prevailing major complication observed in the study was dissection, accounting for a substantial proportion of cases (n=14, 51.9%). Among these dissections, their distribution across different anatomical regions indicated that 1 case (7.1%) was located in the iliac region, while the femoropopliteal region saw a significantly higher incidence with 11 cases (78.6%), and 2 cases (14.3%) were documented in the infrapopliteal region. In all cases, the management approach for dissections involved ballooning or stenting. Specifically, 11 cases (78.6%) underwent treatment through ballooning, while the remaining 3 cases (21.4%) received stenting. Notably, percutaneous methods took precedence in addressing dissections that arose during the course of endovascular intervention, with surgical intervention being considered as a secondary option. Other complications were as follows: arterial perforation in 5 (18.5%) patients; major hematoma in 3 (11.1%) patients; pseudoaneurysm in 2 (7.4%) patients; distal embolism in 2 (7.4%) patients; and arterio-venous fistula in 1 (3.7%) patient.

Arterial perforation emerged as the prevailing complication subsequent to dissection. Among the cases of perforation, two (40%) were localized in the anterior tibial artery (TA), and three (60%) were situated in the superficial femoral artery (SFA). An instance of rupture in the SFA necessitated primary repair of the femoral artery, while endovascular techniques were employed to address the other instances of perforation.

Subsequent to the endovascular intervention, three patients encountered significant hematomas that necessitated blood transfusion. The femoral region was the site of detection for all major hematomas. Surgical intervention under general anesthesia was the chosen approach for all hematoma cases. The procedure included hematoma evacuation and primary repair of the catheter access site.

Following the endovascular procedures, pseudoaneurysms were identified in two patients. In cases where a pulsatile and dilatation tendency was observed, surgical interventions were carried out. The mean diameter of the pseudoaneurysms was 44.4±13.8 mm. All two surgeries were performed under local anesthesia. The pseudoaneurysms were located in the femoral artery, and both cases underwent primary repair of the femoral artery.

Two instances of DE were identified within the femoropopliteal artery territory. Embolectomy was deemed appropriate for these cases. Moreover, a single patient experienced the formation of an AVF between the anterior tibial artery and vein subsequent to the endovascular procedure. In this particular instance, successful closure of the AVF was achieved through prolonged balloon inflation. A comprehensive depiction of major complications and their corresponding treatments is outlined in **Table 2**.

Table 2. Major complications and treatments

Variables	Surgical treatment (n=8)	Endovascular treatment (n=19)	Total (n=27)
Dissection		14	14 (51.9%)
Arterial perforation	1	4	5 (18.5%)
Major hematoma	3		3 (11.1%)
Pseudoaneurysm	2		2 (7.4%)
Distal embolism	2		2 (7.4%)
Arterio-venous fistula		1	1 (3.7%)

Within the cohort of patients considered for this study, endovascular techniques were primarily favored for addressing complications (19 patients, 4.7%), while surgical interventions were employed in the remaining cases (8 patients, 2%). The mean duration of stay in the intensive care unit was calculated at 0.63±0.49 days, with a mean hospitalization period of 2.48±1.58 days. Notably, in 26 out of 27 cases (96.3%) where complications emerged, critical amputations were prevented, resulting in the preservation of the extremities. Only one case, which underwent embolectomy, necessitated a minor amputation during the follow-up period. The ischemia of the patient's finger did not resolve despite all medical treatments, including ilomedin therapy, and amputation was necessitated. Regrettably, the study observed a single case of mortality during hospital stay.

DISCUSSION

The first successful attempt of percutaneous dilatation of the stenotic vessel was accomplished by Charles Theodore Dotter in 1964. The balloon angioplasty catheter was then introduced by Grüntzig and Hopff in 1974, which marked a substantial advancement in catheter-mediated therapy. Over the past 50 years, endovascular procedures have become widely used in both the diagnosis and treatment of peripheral vascular disease.[2] However, this increase in the number of peripheral endovascular procedures has led to a rise in iatrogenic vascular injuries and related surgical interventions. In the literature, it has been reported that 2.7% of patients who underwent peripheral endovascular interventional procedures developed complications requiring surgical intervention.[3] The incidence of vascular complications necessitating surgical intervention was determined to be 2% in our study, which is consistent with the literature.

The majority of patients with peripheral artery disease have comorbid conditions including diabetes, hypertension, renal dysfunction, and coronary artery disease. The management and outcome of endovascular procedures are significantly influenced by these comorbid situations. Therefore, a detailed patient assessment should be performed before endovascular interventions, and precautions should be taken against possible complications. Furthermore, it is imperative to develop personalized treatment strategies that consider several characteristics influencing the likelihood of challenges, including but not limited to advanced age, obesity, atherosclerosis, gender, and smoking behavior.[2,4] By employing this approach, the efficacy of endovascular procedures can be improved, leading to a notable enhancement in patients' quality of life. The age, gender distribution, and presence of concomitant conditions among the patients in our study group were consistent with the existing literature.[5,6]

There are several important factors that can significantly affect the rate of complications following peripheral endovascular treatments. These factors include the size of the catheter used, the characteristics of the arteries being treated, the patient's previous experiences with catheterization, the specific anticoagulation regimen being employed, the severity of the underlying medical condition, and the administration of thrombolytic agents.[2] In the study conducted by Dariushnia et al.[7] 1% was considered an acceptable rate for all major complications that may develop in patients undergoing diagnostic angiography. However, Singh et al.[8] reported that the total rate of complications following balloon angioplasty should not exceed 10%, while the rate of severe complications should not exceed 5%. These findings suggest that endovascular procedures, particularly PTA, increase the risk of vascular complications. We attribute the relatively elevated rate of complications associated with endovascular interventions in our patient cohort (6.7%) in comparison to existing literature due to the extensive application of balloon-stent procedures within our patient group. Moreover, the inclusion of patients necessitating more complex interventions, a characteristic of our vascular surgery clinic, could also contribute to this observed variance.

In the existing literature, dissection has been consistently documented as the prevailing complication associated with endovascular procedures.[9,10] Remarkably, our study's observed incidence of dissection, which aligns with this trend, corroborates the literature's findings. The SFA became the primary site of dissection, with balloon intervention emerging as the prevailing approach. In cases where the dissection extended over a vessel segment exceeding 5 cm and successful flow restoration wasn't achieved through ballooning alone, stenting was subsequently employed. Importantly, within our dissection cases, surgical intervention wasn't necessary, and favorable outcomes were achieved exclusively through endovascular modalities.

Arterial perforation was another complication we experienced in our patient population. Five patients (18.5%) developed perforation, of which two were localized in the TA and three in the SFA. In one of the three patients with SFA rupture, primary repair was performed, while covered stents were preferred in the other two cases. All instances of TA perforations were effectively managed through the application of prolonged, low-pressure balloon inflation over the affected lesion. Upon comparing our findings with those

reported in the existing literature, we observed similarities in both our complication rates and the cases necessitating surgical approach.[11] Despite the typically elevated risk of mortality in such cases, it is noteworthy that our timely and appropriate actions have resulted in a complete absence of operative and interventional mortality. However, it is important to note that these ruptures may arise in individuals who have calcified plaques, vasculitis, or when utilizing big diameter balloons that are not appropriate for angioplasty.[2] Hence, it is imperative to pay attention to the selection of catheter, balloon, and stent diameters, as well as the conduct of procedures, in order to mitigate the occurrence of complications and to enable the development of successful therapeutic approaches in the context of endovascular interventions.

Significant hematomas at the intervention site were one of the complications we observed. All hematomas requiring transfusion were found in the femoral region. All of the hematoma cases underwent surgical treatment under general anesthesia, and all of these patients required primary repair with hematoma evacuation as an additional procedure because of active bleeding at the catheter entry site in the femoral artery. The results of the hematoma cases in our study were successful and consistent with the series in the literature.[12] The causes of intervention site-related major hematomas, a serious complication of peripheral endovascular procedures, depend on various factors. Potential causes of hematomas include damage to the vessel wall during catheter insertion, the use of large-diameter catheters or balloons, and severe vascular calcification.[2] These factors may increase the likelihood of hematoma formation during peripheral endovascular procedures. Preventing and effectively treating such complications is a crucial step in ensuring the efficacy and safety of peripheral endovascular interventions. Accordingly, experienced healthcare professionals with the appropriate training to improve the outcomes of peripheral vascular interventions, particularly cardiovascular surgeons with the ability to make prompt decisions and switch to open surgery when necessary, will play a crucial role in addressing these complications.

Pseudoaneurysm was another complication associated with the site of peripheral endovascular intervention. In our study, two cases of femoral pseudoaneurysms necessitating surgical intervention were detected. Primary repair was performed under local anesthesia in both cases. The incidence of pseudoaneurysms after percutaneous intervention in the femoral artery is approximately 1.2%.[13] Risk factors in such cases include female gender, advanced age, hypertension, arterial calcification, large arterial catheters, and anticoagulation use. Pseudoaneurysms can lead to distal embolization, arterial and venous occlusion, compression of adjacent nerve structures, and even rupture. Treatment is determined depending on the size of the pseudoaneurysm, the diameter of the neck, and the patient's coagulation status. Pseudoaneurysms, usually smaller than 2 mm, tend to thrombose spontaneously and can therefore be monitored by serial ultrasonography follow-up.[2,14] The occurrence of pseudoaneurysms following peripheral endovascular interventions can have devastating effects on mortality and morbidity. Therefore, careful patient assessment, close follow-up, and appropriate precautions should be taken to prevent such complications. Especially following the procedure, the arterial access site should be kept under compression with a certain force and duration.

In our study, we observed two cases of distal embolism requiring urgent surgical intervention. Both patients developed distal embolism in the femoropopliteal region, leading to critical leg ischemia. An embolectomy was performed under emergency conditions. Distal flow was maintained in both cases, and one of the patients required minor amputation during the follow-up period. Our distal embolism results related to endovascular procedures are similar to the literature.[15] Distal embolism is a rare but serious complication following endovascular procedures. Embolism occurs when plaques or thrombi are carried into the distal vessels during the endovascular intervention. Distal embolism typically remains asymptomatic when involving small emboli; however, a significant thrombus can prompt acute limb ischemia, eliciting intense leg pain and other associated symptoms. In such cases, it is critical that the thrombus be removed as quickly as possible. To reduce the risk of distal embolism, it is important that appropriate techniques are used and procedures are performed by experienced professionals. Close monitoring of patients and timely action to deal with distal embolism and other complications are of vital importance.

In our study, AVF, a rare but potentially serious complication during endovascular interventions, was seen in one of our patients. The localization of the AVF was between the anterior tibial artery and vein. The fistula was successfully repaired with prolonged PTA balloon inflation. Neither the implementation of covered stents nor surgical closure were deemed necessary. Both the incidence of complications and the type of interventions administered aligned closely with existing literature findings.[14] AVF is more common in patients with hypertension, female gender, and high-dose anticoagulants. AVF usually affects the SFA and profunda femoral arteries and less frequently involves the main femoral artery. AVF may present with symptoms including pain, pulsatile mass, distal ischemia, limb swelling, dermatitis, skin ulceration, or congestive heart failure. Balloon-stenting may be used for the closure of short-segment AVFs. However, placement of a covered stent at the bifurcation of the CFA is contraindicated because it may lead to the occlusion of the PFA.[14] In such cases, surgical repair should be considered first. During endovascular interventions, caution should be taken against the possibility of AVF complications, and appropriate treatment methods should be utilized if they occur.

There are several noteworthy limitations associated with our study that warrant discussion. First and foremost, our research design is retrospective in nature. Furthermore, our study was conducted at a single medical center, which may limit the generalizability of our findings to a broader population. Another limitation pertains to the size of our patient cohort. While we analyzed a substantial number of cases, it is important to acknowledge that a larger sample size would provide greater statistical power and potentially more robust conclusions. Lastly, the absence of a control group is a limitation that should be acknowledged. Comparative studies with control groups are valuable for drawing stronger causal inferences and assessing the true impact of interventions. In light of these limitations, the interpretation of our findings should be made with caution, and future research, ideally employing prospective designs and larger, more diverse patient populations, is warranted to further investigate and validate the outcomes observed in our study.

CONCLUSION

In contemporary medical practice, peripheral endovascular treatments have gained significant prominence, often rivaling conventional surgical approaches. Undoubtedly, this surge in popularity has introduced its own set of associated complications. When treating serious complications arising from peripheral endovascular procedures, prompt and effective surgical intervention is essential. Healthcare professionals in this field must possess the necessary knowledge, expertise, and clinical experience to effectively manage these severe complications. Since cardiovascular surgeons have adequate training and expertise in the natural course of peripheral arterial diseases and their response to treatment, we believe they are able to assess medical, surgical, and endovascular approaches holistically when evaluating lower extremity peripheral arterial diseases and decide on the most appropriate approach for primary treatment and emergency complications. Although endovascular techniques have made significant advances in recent years, they have the potential to be inadequate in some cases when dealing with complications. As our study shows, surgical intervention may become inevitable for the management of such complications. The enduring importance of traditional vascular surgical techniques is well recognized, as they are believed to yield the best results when combined with modern endovascular methods.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the KTO Karatay University Faculty of Medicine, Pharmaceutical and Non-Medical Device Research Ethics Committee (Date: 17.06.2022, Decision No: 2022/034)

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1346500
J Contemp Med 2023;13(5):861-865

Original Article / Orijinal Araştırma

Knowledge Level of High School Students about Crimean Congo Hemorrhagic Fever

Lise Öğrencilerinin Kırım Kongo Kanamalı Ateşi Hakkında Bilgi Düzeyleri

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Abstract

Aim: The aim of this study is to determine the knowledge level of high school students about CCHF disease.

Material and Method: The population of the study, which was planned in descriptive type, consisted of 530 students in the first, second, third and fourth grades of high school, and 54.9% (n: 291) of the students were reached. Verbal consent was obtained from the students and they were asked to fill out the questionnaire consisting of 15 questions. Data were calculated using mean, frequency and percentage in SPSS database.

Results: In the study, although the students knew that the transmission was by tick contact, they did not have enough information about how the transmission was, what to do in case of tick contact and the symptoms of the disease

Conclusion: It is necessary to increase the knowledge level of students in order to prevent contagion. In order to increase the level of knowledge, the deficiencies of the students should be determined and the necessary training should be planned.

Keywords: Tick, Crimean Congo hemorrhagic fever, knowledge level, Bunyaviridae

Öz

Amaç: Bu çalışmanın amacı Lise öğrencilerinin KKKA hastalığı hakkındaki bilgi düzeyini belirlemektir.

Gereç ve Yöntem: Tanımlayıcı tipte planlanan çalışmanın evrenini, Lise birinci, ikinci, üçüncü ve dördüncü sınıfta bulunan 530 öğrenci oluşturdu ve öğrencilerin %54,9 (n: 291)'una ulaşıldı. Öğrencilerden sözlü onam alınarak 15 sorudan oluşan anketi doldurmaları istendi. Veriler SPSS veri tabanında ortalama, frekans, yüzde kullanılarak hesaplandı.

Bulgular: Çalışmada öğrenciler bulaşmanın kene teması ile olduğunu bilmelerine rağmen bulaşmanın nasıl olduğu, kene teması durumunda yapılması gerekenler ve hastalığın belirtileri hakkında yeterli bilgiye sahip değillerdi.

Sonuç: Bulaşmanın önlenmesi için öğrencilerin bilgi düzeylerinin arttırılması gerekmektedir. Bilgi düzeyini artırmak için öğrencilerin eksiklikleri belirlenerek gerekli eğitimler planlanmalıdır.

Anahtar Kelimeler: Kene, Kırım Kongo kanamalı ateş, bilgi düzeyi, Bunyaviridae

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Received *(Geliş Tarihi)*: 21.08.2023 **Accepted *(Kabul Tarihi)*:** 21.09.2023

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) virus is a negative-stranded, enveloped RNA virus belonging to the genus Nairovirus of the Bunyaviridae family. It is carried by arthropods and transmitted to humans through tick bites. The clinical course ranges from asymptomatic to hemorrhagic fever, which can be fatal. Prevention is important due to the lack of specific treatment and the risk of mortality. The virus is resistant to the external environment and cannot survive outside the host. Geographically, the disease is found in Asia, Europe and Africa and can be transported to distant regions by birds. In our country, it can be encountered in all regions, being common in Eastern Black Sea, Central Anatolia and Eastern Anatolia. The disease, which starts to be seen in the spring months with the warming of the weather, decreases and ends in the fall. People who stay indoors during the winter are more likely to visit open areas in the spring, which increases the risk of contact with ticks and the associated CCHF virus transmission. Young people are more at risk because they are more likely to be in these are as due to their dynamic nature. In this study, it was planned to measure the level of knowledge of young people to guide the trainings to be given in terms of prevention.

MATERIAL AND METHOD

The study was approved by Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 16/11/2022, Decision no: E1-22-.3019). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The population of the descriptive study consisted of first, second, third and fourth grade high school students attending Science High School and Girls Vocational High School in Giresun City. The number of all high school students is 530. The sample was not selected and it was aimed to reach the whole population.

Verbal consent was obtained from the students and they were asked to fill out the questionnaire consisting of 15 questions. Data were calculated using mean, frequency and percentage in SPSS database.

RESULTS

The study was conducted in December 2022 with 291 students at Science High School and Girls Vocational High School in Bulancak district of Giresun province. While 79.4% (n:231) of the students knew correctly that tick bites transmit the disease, almost half of them did not know that the blood and secretions of animals and humans were infectious (43.3% (n:126) from animal sand 49.5% (n:144) from humans) (**Table 1**).

Table 1:Students' level of knowledge about the transmission routes of CCHF disease (n=291)

	n	%
CCHF can be transmitted by tick attachment, picking, crushing or bursting the tick with bare hands		
That'sright	231	79.4
Wrong	12	4.1
I don'tknow	48	16.5
CCHF can be transmitted to humans by contact with bodily fluids such as blood, urine and feces of animals with ticks on them.		
That'sright	132	45.4
Wrong	33	11.3
I don'tknow	126	43.3
CCHF can be transmitted to other people through contact with the blood, urine and other excretions of people infected with the disease.		
That's right	105	36.1
Wrong	42	14.4
I don't know	144	49.5

88.7% (n:258) students knew that they should wear closed clothes in the field, vineyard, garden or picnic to protect themselves from the disease, 85.2% (n:248) students knew that they should check their body for ticks every time they return from a rural or picnic, and 70.1% (n:204) students knew where the tick can be found in the body most (**Table 2**).

Table 2: Students' level of knowledge about ways of protection against CCHF disease (n=291)

	n	%
In order to prevent CCHF, tucking trouser cuffs into socks, wearing closed clothes and wearing boots in the field, vineyard, garden or on a picnic are the most important methods to prevent the tick from attaching to humans?		
That's right	258	88.7
Wrong	6	2.1
I don't know	27	9.3
In order to prevent CCHF, it is absolutely necessary to check our bodies for ticks every time were turn from a picnic or a picnic?		
That's right	248	85.2
Wrong	10	3.4
I don't know	33	11.3
Ticks most commonly attach to the back of the ears, armpits, groin and back of the knees?		
That's right	204	70.1
Wrong	18	6.2
I don't know	69	23.7

The level of knowledge on how to intervene when a tick is attached was low. 71.1% (n:207) knew how to remove the tick, 14.4% (n:42) knew what to do before removing the tick and 79.7% (n:232) knew that they could remove the tick themselves. 59.8% (n:174) did not know what to do for the disposal of there moved tick. 69.4% (n:202) knew incorrectly when to apply to the health institution after removing the tick. (**Table 3**)

74.9% (n:218) correctly recognized the clinical symptoms and 79.4% (n:231) correctly recognized the risk of death (**Table 4**).

Table 3: Students' level of knowledge on what to do after tick attachment (n=291)

	n	%
If we have a tick attached to our body, were move it ourselves with a cloth, a piece of paper or a pair of tweezers?		
That's right	51	17.5
Wrong	207	71.1
I don't know	33	11.3
If we have a tick attached to our body, we remove the tick ourselves, but before removing it, we pour cologne, alcohol or press a cigarette on it to make it come out of the skin more easily?		
That's right	42	14.4
Wrong	198	68.0
I don't know	51	17.5
If there is a tick attached to our body, there is no need to go to a doctor to remove the tick, there is no harm in removing the tick ourselves?		
That's right	28	9.6
Wrong	232	79.7
I don'tknow	31	10.7
In the disposal of a tick attached to your body after removing it from the body,		
The tick is crushed by hand or destroyed by bursting	24	8.2
The tick is thrown to the ground and crushed with the foot	12	4.1
The tick is put in a small bottle or jar with bleach and thrown in.	81	27.8
I don't know anything about his	174	59.8
A person with a tick attached after removing the tick from their body		
Go to the doctor immediately, at least the same day	149	51.2
Even if he/she does not have any complaints, he/she should definitely see a doctor within 10 days	53	18.2
Within 10 days, if you have complaints, you should definitely go to the doctor	53	18.2
I don't know anything about this	36	12.4

Table 4: Students' level of knowledge about the clinic of CCHF disease (n=291)

	n	%
The most important complaints when a tick-borne person becomes ill		
Cough, runny nose	14	4.8
Fever, malaise, body pain	218	74.9
Ear pain, itching on the body	26	8.9
I don't have any information on this	33	11.3
Is Crimean-Congo hemorrhagic fever a fatal disease?		
That's right	231	79.4
Wrong	15	5.2
I don't know	45	15.5

DISCUSSION

CCHF is an infectious disease and there is nospecific treatment available. Prevention of transmission is important due to the risk of mortality. This can be achieved by raising awareness about the disease. Although the disease is more common in the northern parts of our country, it occurs in all regions, especially in rural areas during the summer season. It is important to raise awareness of people living in these regions as they are at risk.

Young people are in a period when they transition from childhood to adolescence and participate in many activities due to their dynamic nature. As they gain their own identity, they isolate themselves from their families and try to spend time with their circle of friends. Due to their inquisitive and curious nature, they often spend time in environments where they can come into contact with ticks, especially in a long period starting in spring and lasting until fall. In addition, since we live in a patriarchal society, young people in farming families take part in the fields and among the animals to help the family during the summer periods. Families are weak in warning their children about the risks in these environments, and do not feel the need to provide extra education because they receive education at school. Despite education, young people are selective about information on many issues because their perceptions are variable. Due to the risk of CCHF, which is a mortal disease, knowing the level of knowledge of young people on this subject will direct the education to be given.

Warming weather causes ticks to multiply and increase their numbers in open areas. With the effect of animal transportation and migratory birds, these ticks spread to many regions and cause the disease to be seen in wider areas.[1,2] In their study, Alkan-çeviker et al. Emphasized that the patients who were hospitalized between 2010 and 2018 showed a clustering in the summer months.[2] In our country, there are reports from many cities, more frequently in Eastern Black Sea, Central Anatolia and Eastern Anatolia.[4] Increasing awareness of this disease, which is a public health problem, is an effective method to prevent transmission.

Transmission of the disease is most commonly caused by tickbites or crushing ticks with bare fingers.[2] 16.5% of the students did not know this route of transmission and 4.1% knew it incorrectly. Since transmission can also ocur through direct contact with blood or other bodily fluids of farm animals, CCHF is frequently encountered as an occupational disease among veterinarians, butchers and farmers who have contact with animals. Since human blood and body secretions also play a role in transmission, healthcare workers constitute another risk group.[1,5-8] However, the fact that it is transmitted in this way causes individual sotherthan healthcare workers to be at risk. However, transmission is not seen in other contacts such as hugging and shaking hands with the patient where blood and secretions are not present.[9] In our study, about half of the students did not have sufficient information about the high potential for transmission through blood and body fluids. In this situation, uninformed young people may not pay the necessary attention to protect themselves in contact with sick animals and people.

The spectrum of clinical manifestations ranges from subclinical disease to acute infection with bleeding and multiple organ failure. Clinical manifestations of CCHF include nonspecific symptoms such as sudden onset of fever, headache, weakness, myalgia, photophobia, abdominal pain, nausea and vomiting. In severe cases, hemorrhagic symptoms are observed; petechiae, ecchymosis, epistaxis, nose bleeds, bleeding gums, melena, hematuria can cause

severe consequences. In this direction, 13.7% (n:40) of the students knew the symptoms of the disease incorrectly and 15.5% (n:45) did not know that it could be fatal.

CCHF has no effective treatment, so prevention of transmission of the disease comes to the fore. This is best achieved by preventing contact with ticks and animal body fluids. People living and traveling in endemic areas should be aware of personal protective measures against tick bites. Ticks can settle on allparts of the human body, including the trunk, extremities, head and neck.[10] Therefore, when going to risky areas, it is absolutely necessary to check the body for ticks on return. Wearing light-colored clothes allows ticks to be easily detected. Intertwining clothes so that there is no open space minimizes tick exposure. In the questions asked to the students, 9.3% (n: 27) did not know the necessity of wearing closed clothes, 11.3% (n: 33) did not know the necessity of checking the body forticks, and 23.7% (n: 69) did not know the places on the body that must be checked.

Prevention of tick contact against the disease is as important as the actions to be taken after tick attachment in preventing transmission. In case of tick attachment, the tick should not be held, crushed or squeezed with bare hands. Ticks should be removed with tweezers, the skin should be cleaned with antiseptic after removal and hand hygiene should be followed. In case of possible transmission of the disease, the person who comes into contact with the tick should monitör himself/herself for CCHF symptoms such as fever and bleeding for 10-14 days. As a result of the answers given by the students, it was seen that they misunderstood what they should do before and after the removal of the tick.

Although CCHF disease is subclinical in 88% of cases, it is mortal in 10-40% of cases. In the study, it was observed that students' awareness of the disease was insufficient.

CONCLUSION

Increasing the level of knowledge of people at risk of contact with this disease, especially in endemic areas, will reduce the morbidity and mortality rate of the disease. Young people spend more time in environments where the disease can be transmitted due to their active nature. Therefore, it is necessary to increase the awareness of students in terms of prevention of CCHF transmission and what to do in case of infection. Organizing trainings in schools in this direction will be effective.[11]

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 16/11/2022, Decision no: E1-22-.3019).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1347443
J Contemp Med 2023;13(5):866-870

Original Article / Orijinal Araştırma

Investigation of Thought Control and Obsessive Beliefs in Generalised Anxiety Disorder and Panic Disorder

Yaygın Anksiyete Bozukluğu ve Panik Bozuklukta Düşünce Kontrolü ve Obsesif İnanışların İncelenmesi

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Abstract

Aim: Obsessive Beliefs and Thought Control are often thought to be associated with Obsessive Compulsive Disorder. However, the relationship with Anxiety Disorders has recently been investigated in the literature. In this study, Obsessive Beliefs and Thought Control levels in patients diagnosed with Generalised Anxiety Disorder and Panic Disorder were investigated. It is aimed to contribute to the literature on the cognitive aspects of anxiety disorders.

Material and Method: According to DSM-5 diagnostic criteria, 71 patients diagnosed with Generalised Anxiety Disorder, 63 patients diagnosed with Panic Disorder and 63 healthy controls were included in the study. The participants were applied the Thought Control Questionnaire and Obsessive Beliefs Questionnaire. In addition, Beck Anxiety Scale was applied to patients diagnosed with Generalised Anxiety Disorder and Panic Agoraphobia Scale was applied to patients diagnosed with Panic Disorder.

Results: A statistically significant difference was found between the groups in Distraction (F=11.383; p=<0.01; η2=0.105), Social Control (F=9.517; p=<0.01; η2=0.089), Worry (F=5.589; p=0.004; η2=0.054), Self-Punishment (F=4.879; p=0.009; η2=0.048), and Reappraisal (F=3.916; p=0.021; η2=0.039) sub-dimensions. There was a statistically significant difference between the groups in the sub-dimensions of Responsibility/Threat Estimation (F=9.268; p=<0.01; η2=0.087) and Perfectionism/Certainty (F=18.557; p=<0.01; η2=0.161), but there was no statistically significant difference in the subdimension Importance/Control of Thoughts (F=0.300; p=0.741; η2=0.003).

Conclusion: In our study, Obsessive Beliefs and Thought Control levels of patients with Generalised Anxiety Disorder and Panic Disorder were higher than healthy control group. These dysfunctional thoughts may be a risk factor in the development of Anxiety Disorders. Research on the aetiology of Anxiety Disorders will contribute to the literature.

Keywords: obsessive beliefs, thought control, anxiety disorder, panic disorder

Öz

Amaç: Obsesif İnanışlar ve Düşünce Kontrolü çoğunlukla Obsesif Kompulsif Bozuklukla ilişkilendirilmiştir. Ancak son zamanlarda literatürde Anksiyete Bozuklukları ile ilişkisi de araştırılmaktadır. Bu araştırmada Yaygın Anksiyete Bozukluğu ve Panik Bozukluk tanılı hastalarda Obsesif İnanışlar ve Düşünce Kontrolü düzeyleri incelenmiştir. Anksiyete Bozukluklarının bilişsel temeli ile ilgili literatüre katkı sağlanması amaçlanmıştır.

Gereç ve Yöntem: Araştırmaya DSM-5 tanı kriterlerine göre Yaygın Anksiyete Bozukluğu tanısı alan 71 hasta, Panik Bozukluk tanısı alan 63 hasta ve 63 sağlıklı kontrol grubu dahil edilmiştir. Katılımcılara Düşünce Kontrol Ölçeği ve Obsesif İnanışlar Ölçeği uygulanmıştır. Ayrıca Yaygın Anksiyete Bozukluğu tanısı alan hastalara Beck Anksiyete Ölçeği, Panik Bozukluk tanısı alan hastalara ise Panik Agorafobi Ölçeği uygulanmıştır.

Bulgular: Dikkat Dağıtma (F=11.383; p=<0.01; η2=0.105), Sosyal Kontrol (F=9.517; p=<0.01; η2=0.089), Endişe (F=5.589; p=0.004; η2=0.054), Kendini Cezalandırma (F=4.879; p=0.009; η2=0.048) ve Yeniden Değerlendirme (F=3.916; p=0.021; η2=0.039) alt boyutlarında gruplar arasında istatistiksel olarak anlamlı fark saptanmıştır. Gruplar arasında Sorumluluk/Tehlike Beklentisi (F=9.268; p=<0.01; η2=0.087) ve Mükemmeliyetçilik/ Kesinlik (F=18.557; p=<0.01; η2=0.161) alt boyutlarında istatistiksel olarak anlamlı fark saptanırken Önem Verme/ Düşünceleri Kontrol Etme (F=0.300; p=0.741; η2=0.003) alt boyutunda istatistiksel olarak anlamlı fark saptanmamıştır.

Sonuç: Araştırmamızda Yaygın Ankisiyete Bozukluğu ve Panik Bozukluk tanısı olan hastaların Obsesif İnanışlar ve Düşünce Kontrolü düzeyleri sağlıklı kontrollerden yüksek bulunmuştur. İşlevsel olmayan bu düşünceler Anksiyete Bozukluklarının gelişiminde risk faktörü olabilir. Anksiyete Bozukluklarının etyolojisine yönelik yapılacak araştırmalar literatüre katkı sağlayacaktır.

Anahtar Kelimeler: Obsesif inanışlar, düşünce kontrolü, anksiyete bozukluğu, panik bozukluk

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Received *(Geliş Tarihi)*: 21.08.2023 **Accepted *(Kabul Tarihi)*:** 20.09.2023

INTRODUCTION

Obsessive beliefs (OB) were defined by the Obsessive Compulsive Cognitions Working Group to describe the cognitive component of Obsessive Compulsive Disorder (OCD). Three different ways of thinking were identified as inflated responsibility / overestimation of threat, perfectionism/ intolerance of uncertainty, overimportance of thoughts / excessive concern about the importance of controlling one's thoughts. With the identification of OB, scales were developed in this subject and a new perspective on the cognitive component of OCD was developed.[1] Similarly, many studies support that these false and compulsive thoughts may play a role in the development of OCD. With these dysfunctional and false thoughts, the person may think that the world is more threatening or that his/her thoughts are real. This may lead to increased obsessive thoughts.[2,3]

Thought control (TC) is a control strategy developed against the thoughts that develop in one's mind about the negative situations. In fact, most people may have unwanted thoughts. People may be disturbed by these thoughts and may endeavour to reduce them. However, if the strategies to get rid of the thought are unsuccessful, this can lead to negative consequences. The person uses more TC strategies and may develop anxiety. In addition, the thoughts can increase even more with the increasing striving for control. All these TC strategies can have a negative effect.[4] Wells and Davies defined TC strategies as distraction, worrying about the thought, controlling with social environment, reevaluating the thought and self-punishment about the thought. In fact, these TC strategies, which are thought to have a positive effect from time to time, can cause psychological pathologies when used excessively or inappropriately.[5]

OB and TC are often associated with OCD. However, when these wrong thinking methods are used excessively and inappropriately, they can lead to anxiety and worry. There are studies in the literature mostly related to OCD. Comorbidity rates of OCD and Anxiety Disorders are high and studies have shown common etiological factors. In this case it can be thought that the thoughts underlying OCD may be a risk factor for Anxiety Disorders.[6] In our study, based on this idea, the levels of OB and TC in Generalised Anxiety Disorder (GAD) and Panic Disorder (PD) were analysed. In the literature, there are studies investigating OB and TC in Anxiety Disorders and OCD, but they are more limited compared to OCD. In addition, Anxiety Disorders were not analysed in separate diagnoses in these studies. In our study, Anxiety Disorders were analysed separately as GAD and PD. It is aimed to contribute to the literature on the importance of thoughts in the development of Anxiety Disorders. In this respect, our research will provide a new perspective on the cognitive basis of GAD and PD.

MATERIAL AND METHOD

The study was conducted in Psychiatry Outpatient Clinic between 12/2022 and 08/2023. The study included 71 patients diagnosed with GAD and 63 patients diagnosed with PD according to DSM-5 diagnostic criteria and 63 healthy controls. People with a comorbid mental illness, alcohol-substance use disorder, chronic internal disease and chronic drug use for chronic disease were not included in the study. Firstly, the participants were informed about the study and their written and verbal consent was obtained. Thought Control Questionnaire (TCQ) and Obsessive Beliefs Questionnaire (OBQ) were applied to the participants who agreed to participate in the study. In addition, Beck Anxiety Scale (BAS) was applied to patients diagnosed with GAD and Panic Agoraphobia Scale (PAS) was applied to patients diagnosed with PD. The ethics committee approval of the study was obtained. In addition, all practices in the research were carried out in accordance with the ethical standards of the institution and the 1964 Helsinki Declaration and its later amndments.

Data Collection Tools

Beck Anxiety Scale (BAS): The scale was developed by Beck to assess anxiety levels and it is frequently used in the clinic to measure the level of anxiety. It consists of 21 questions and increasing scores are associated with increasing levels of anxiety.[7] The Turkish validity and reliability of the scale was conducted by Ulusoy et al.. The scale was found to have a high internal consistency in the Turkish sample and Cronbach's alpha value was calculated as 0.93. In our research sample, the cronbach alpha value of the scale was calculated as 0.86.[8]

Panic Agoraphobia Scale (PAS): It was developed by Bandelow to measure disease severity in patients with PD. It is a Likert-type scale and increasing scores are associated with increasing disease severity.[9] The scale has both a self-report section and an observer section. In our study, only the self-report part of the scale was used to assess the severity of illness. Turkish validity and reliability of the scale was performed by Tural et al.[10] The cronbach alpha value for the observer subsection was calculated as 0.86. In our study, the cronbach alpha value was 0.81.

Thought Control Questionnaire (TCQ): It is a scale developed by Wells to assess strategies for controlling unwanted thoughts. The scale has five subdimensions as Distraction (D), Worrying (W), Social Control (SC), Reappraisal (RE) and Self-Punishment (SP). Each sub-dimension is assessed by scoring separately and the total score of the scale is calculated with the total of all sub-dimensions. Whichever sub-dimension has a higher score, it is considered that the thought strategy is used more.[5] The Turkish validity and reliability of the scale was conducted by Yorulmaz et al. The scale was found to have high internal consistency in the Turkish sample. Cronbach's alpha value was found as 0.72 for D, 0.79 for SC, 0.71 for W, 0.64 for SP and 0.67 for RE.[11] For our sample, these values were calculated as 0.71, 0.76, 0.78, 0.74 and 0.71, respectively. In our study, the subdimensions of the scale were calculated separately and evaluated as separate subdimensions.

Obsessive Beliefs Questionnaire (OBQ): It was developed by the Obsessive Compulsive Cognitions Working Group to

evaluate OB. There are three subdimensions as Responsibility/ Threat Estimation (RT), Perfectionism/Certainty (PC), and Importance/Control of Thoughts (IC). Each three subdimensions of the scale are calculated separately and the total score of the scale is calculated with the sum of all subdimensions. Increased scores are considered as increased levels of OB.[12] The Turkish validity and reliability of the scale was conducted by Boysan et al. The cronbach alpha value of the scale, which had sufficient internal consistency in the Turkish sample, was calculated as 0.95.[13] In our sample, it was calculated as 0.84 for RT subdimension, 0.78 for PC subdimension and 0.76 for IC subdimension.

Statistical Analysis

The research data were analyzed with the SPSS (Statistical package for social sciences) Version 25th. Descriptive statistics of the participants were presented as mean, standard deviation, number and percentage. Normality of data was evaluated by Kolmogorov Smirnov test, kurtosis and skewness values and histogram. One way ANOVA was used to analyzed the difference between the means of continuous data with normal distribution in more than two independent groups. In cases with more than one dependent variable, one way MANOVA was used. The difference of categorical data was calculated by Pearson chi square test. Pearson correlation test was used in the correlation of normally distributed data. In addition, the effect of each variable seperately was evaluated by partial correlation. Statistical significance was accepted as p value <0.05.

RESULTS

The study included 71 GAD, 63 PD and 63 healthy controls. The mean age of the participants was 33.14±10.732 in the GAD group, 32.02±9.268 in the PD group and 33.24±10.503 in the control group. There was no statistically significant difference between the mean ages of the groups (p=0.754). In the GAD group 49 (69%) were female and 22 (31%) were male, in the PD group 40 (63.5%) were female and 23 (36.5%) were male, in the control group 31 (49.2%) were female and 32 (50.8%) were male. There was no statistically significant difference between the genders of the groups (p=0.560). Other sociodemographic data of the participants and comparisons between groups were presented in **Table 1**. When we examined the differences between the groups in the subdimensions of the scales of the TCQ and OBQ scales, we found a difference between groups D (F=11.383; p=<0.01; η2=0.105), SC (F=9.517; p=<0.01; η2=0.089), W (F=5. 589; p=0.004; η2=0.054), SP (F=4.879; p=0.009; η2=0.048), and RE (F=3.916; p=0.021; η2=0.039). While a statistically significant difference was found between the groups in the RT (F=9.268; p=<0.01; η2=0.087) and PC (F=18.557; p=<0.01; η2=0.161) subdimensions of the OBQ scale, no statistically significant difference was found in the IC (F=0.300; p=0.741; η2=0.003) subdimension (**Table 2**). When the difference between the groups was analysed, there was no difference between the D, SC, RT and PC scores of the GAD and PD group, but it was higher than the control group. In the GAD group, W and RE scores were higher than the control group, whereas there was no difference between PD and control group and between GAD and PD. While the SP scores in the PD group were higher than the control group, there was no difference between PD and GAD and between GAD and control group. There was no difference between all groups in the IC scores (**Table 3**). Correlations were analysed between the subdimensions of the TCQ and OBQ, and the PAS and BAS. A significant positive correlation was found between PAS and SC (r=0.397, p=0.001), SP (r=0.477, p<0.01), RT (r=0.488, p<0.01), PC (r=0.427, p<0.01), and IC (r=0.409, p=0.001). However, when the effect of other variables was eliminated and all variables were analyzed by partial correlation, a significant positive correlation was found only between PAS and SP (r=0.357, p=0.007). No significant correlation was found between other variables and PAS. A significant positive correlation was found between the BAS and W (r=0.385, p=0.001) and SP (r=0.326, p=0.005). When all variables were analyzed by partial correlation, a significant positive correlation was found between BAS and W (r=0.310, p=0.013) and SP (r=0.300, p=0.016) (**Table 4**).

Table 1: Sociodemographic data of the patient and control group

	GAD (n=71)	PD (n=63)	Control (n=63)	test st.	p
Age	33.14 [10.732]	32.02 [9.268]	33.24 [10.503]	0.283	0.754
Gender				5.759	0.560
Female	49 (69)	40 (63.5)	31 (49.2)		
Male	22 (31)	23 (36.5)	32 (50.8)		
Education				4.827	0.306
Primary school	52 (73.2)	48 (76.2)	43 (68.3)		
High school	13 (18.3)	5 (7.9)	11 (17.5)		
University	6 (8.5)	10 (15.9)	9 (14.3)		
Marriage status				1.192	0.551
Married	58 (81.7)	51 (81)	47 (74.6)		
Single	13 (18.3)	12 (19)	16 (25.4)		
Occupation				11.283	0.024*
Unemployed	36 (50.7)[b]	46 (73)[a]	43 (68.3)[a,b]		
Officer	10 (14.1)[a]	9 (14.3)[a]	5 (7.9)[a]		
Worker	25 (35.2)[b]	8 (12.7)[a]	15 (23.8)[a,b]		

One way ANOVA, chi square,* p<0.05, mean [SD], n(%), GAD: Generalized anxiety disorder, PD:Panic disorder

Table 2: Comparison of scale scores between groups (generalized anxiety disorder, panic disorder, control)

Group	F	p	partial eta square
D[1]	11.383	0.000**	0.105
SC[2]	9.517	0.000**	0.089
W[3]	5.589	0.004**	0.054
SP[4]	4.879	0.009**	0.048
RE[5]	3.916	0.021*	0.039
RT[6]	9.268	0.000**	0.087
PC[7]	18.557	0.000**	0.161
IC[8]	0.300	0.741	0.003

1R2=0.096,2R2=0.080,3R2=0.045,4R2=0.38,5R2=0.029,6R2=0.78,7R2=0.152,8R2=-0.007, *p<0.05,**p<0.01, one way MANOVA, Pillai's Trace p value=<0.001, D: distraction, SC:social control W: worry SP: self-punishment, RE: reappraisal, RT: Responsibility/threat estimation, PC: Perfectionism/ Certainty , IC: Importance/Control of Thoughts

Table 3: Descriptive statistics of the scale scores of the groups

	D	SC	W	SP	RE	RT	PC	IC
GAD	13.6±3.8[a]	11.7±3.1[a]	11.3±2.8[a]	10.2±2.3[a,b]	13±3.4[a]	59.2±15.9[a]	75.3±16.1[a]	35.2±12.7[a]
PD	13.6±3.4[a]	12±3[a]	10.7±2.9[a,b]	11.1±2.8[a]	12.8±4.1[a,b]	58.4±23.6[a]	72.1±30.2[a]	33.6±13.5[a]
Control	11.1±2.8[b]	9.9±2.5[b]	9.7±2.7[b]	9.8±2[b]	11.4±3.4[b]	46.7±14.5[b]	53.5±17.7[b]	34.1±10.6[a]

D: distraction, SC: social control W:worry SP: self-punishment, RE: reappraisal, RT: Responsibility/threat estimation, PC: Perfectionism/Certainty, IC: Importance/Control of Thoughts, GAD: generalized anxiety disorder, PD:panic disorder, mean±SD

Table 4: The correlation between scale scores in patients with Panic Disorder and Generalized Anxiety Disorder

	PD(n=63) PAS				GAD(n=71) BAS			
	r¹	p	r²	p	r¹	p	r²	P
D	0.193	0.129	0.007	0.961	0.133	0.270	0.021	0.868
SC	0.397	0.001**	0.134	0.326	0.025	0.838	-0.101	0.429
W	0.174	0.173	-0.106	0.438	0.385	0.001**	0.310	0.013*
SP	0.477	0.000**	0.357	0.007**	0.326	0.005**	0.300	0.016*
RE	0.094	0.465	0.059	0.663	-0.078	0.520	0.024	0.849
RT	0.488	0.000**	0.122	0.372	0.161	0.179	0.106	0.404
PC	0.427	0.000**	0.076	0.576	0.219	0.066	0.066	0.606
IC	0.409	0.001**	-0.053	0.697	0.072	0.549	-0.236	0.061

r1:pearson correlation r2:partial correlation, *p<0.05,**p<0.01, D: distraction, SC:social control W: worry SP:self-punishment, RE: reappraisal, RT: Responsibility/threat estimation, PC:Perfectionism/ Certainty, IC: Importance/Control of Thoughts, GAD: generalized anxiety disorder, PD:panic disorder, PAS: panic Agoraphobia Scale, BAS: beck anxiety scale

DISCUSSION

In our study, TC and OB levels in patients with GAD and PD were analysed. When the results of our study were analysed, no significant difference was observed between the groups in all sub-dimensions of TCQ and OBQ in GAD and PD patients. In both patient groups, D, SC, RT and PC subdimensions were higher than the control group. While the SP subdimension was higher only in the PD group than in the control group, the RE and W were higher only in the GAD group than in the control group. TC and OB have been mostly associated with OCD until this time. It was thought to be involved in the cognitive basis of OCD and was considered as a predictor in the development of the disease. In a study by Rhéaume et al., OB levels were found to be high in OCD. Similarly, there are studies that found OB to be higher in OCD patients.[14-16] In a study conducted by Fergus et al., it was shown that the TC sub-dimension W was higher in OCD patients.[17] In another study, the SP and W subscales of TC were found to be higher in OCD patients compared to the control group.[18] Considering the common aetiologies of OCD and Anxiety Disorders, it may be considered that OB and TC may also be related to Anxiety Disorders. In addition, dysfunctional thought patterns such as TC and OB may lead to anxiety, restlessness, negative thoughts about the future and negative perception of the world. In this case, it is likely that OB and TC are not only related to OCD but also to other mental disorders, especially Anxiety Disorders related to worry.[4,6] The results of research on Anxiety Disorders in the literature are inconsistent.[19] In a study conducted by Coles et al. with patients diagnosed with GAD, W and SP were found to be high in the patient group.[20] In another study, similar OB levels were found in PD patients as in OCD patients.[21] In our study, OB and TC levels were higher in patients with GAD and PD than in the healthy control group, in accordance with the literature. In the light of all this information, it can be considered that OB and TC are not only related to OCD. OB are intrusive and unpleasant thoughts. People with more of these unpleasant thoughts can be expected to experience more symptoms such as anxiety and worry. Although TC is sometimes considered a good strategy, increased TC can increase anxiety levels.[4,22] The cognitive background of Anxiety Disorders is based on negative thoughts. Especially, anxiety about the future and intolerance of uncertainty, constant negative thoughts or inadequate efforts to control thoughts increase anxiety. Patients can try to use more TC strategies to try to control uncertain situations more. On the other hand, these strategies can be used to control symptoms. However, increased thoughts lead to increased anxiety.[23] In our study, W and RE scores were higher in GAD and SP scores were higher in PD. The main clinical finding of GAD is restlessness and anxiety and it is possible that GAD is observed more frequently in an person who uses W thought control strategies. Although RE is sometimes considered as a positive TC strategy, it can be considered that it can increase anxiety when used too much.[11] Another finding of our study is that SP is high in PD patients. It is possible that PD is more likely to be seen in people who use SP thought control strategy. A person who is constantly punishing himself or herself may have a panic attack with unbearably severe anxiety. Although thoughts can be considered as just thoughts, they can actually lead to many of the disease symptoms.[20,24]

In our study, the relationship of OB and TC with disease symptom severity was also analysed. A significant positive correlation was found between PAS levels and SP, and between BAS levels and W and SP. In other words, while SP and W increase anxiety levels, SP increases the severity of panic attacks. SP and W may have inappropriate TC strategies and when patients have excessive worry and constant self-blaming thoughts, their level of illness may also increase. Many studies were shown the relationship between PD and worry.[25] Similarly, negative thoughts underlie the cognitive basis of GAD. In particular, anxiety about the future and intolerance of uncertainty, constant negative thoughts or inadequate control efforts of thoughts increase anxiety. GAD patients can try to control uncertain situations more, they can try to use more TC strategies. On the one hand, these strategies can be used to control symptoms. However, increased thoughts lead to increased anxiety.[23,26] This is an issue that should be emphasised in the treatment process,

especially in therapies. In OCD, there are researches on the therapy strategies of OB and TC. However, there is limited data on therapy models for TC or OB in Anxiety Disorders. The evaluation of OB and TC in the therapy process may lead to positive progress in the treatment of diseases.[20,27,28]

Our research is a single-centre study. Therefore, it is not appropriate to generalise the results of the research. It would be appropriate to extend the findings with multicentre studies. In addition, other factors affecting anxiety were not analysed in the study.

CONCLUSION

TC and OB were generally higher in GAD and PD patients in our study. In addition, especially W and SP were found to be associated with symptom severity. To our knowledge, this is the first study investigating TC and OB in both patient groups. Any research on the treatment and recovery of both diseases, which are frequently observed in the society and are an important public health problem in patients, is very valuable. For this reason, there are need for more research that will be effective both in the pathogenesis and treatment of diseases.

ETHICAL DECLARATIONS

Ethics Committee Approval: The ethics committee approval of the study was obtained from Recep Tayyip Erdoğan University Non-Interventional Ethics Committee (Date 28.11.2022, Decision No: 2022/213).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1347057
J Contemp Med 2023;13(5):871-878

Original Article / Orijinal Araştırma

A Systematic Review and Meta-Analysis: Acute Migraine Treatment in Pediatric and Adolescent Populations

Sistematik Bir İnceleme ve Meta-Analiz: Pediatrik ve Ergen Popülasyonlarda Akut Migren Tedavisi

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Abstract

Aim: The array of medications used to treat acute migraine in adults is extensive, with several now authorized for use in children and adolescents in outpatient settings. The aim of this meta-analysis was to evaluate the impact of pharmacological interventions, regardless of the method of delivery, compared to placebo, in treating migraine among individuals aged 18 years or younger.

Material and Method: We searched PubMed, EMBASE, and Cochrane Library for comparative RCTs published 30 years before May 2023. We included prospective randomized controlled clinical trials of children and adolescents with migraine, comparing acute symptom-relieving migraine medications with a placebo.

Results: Twelve clinical trials were included in this meta-analysis. The migraine treatment choice and the proportion of patients with complete pain relief at 2 hours post-treatment were analyzed. Ibuprofen (n=2), sumatriptan (n=3), zolmitriptan (n=3), and rizatriptan (n=4) were used for the analysis. Notably, sumatriptan did not exhibit significant differences compared to placebo, despite mixed individual study outcomes (OR:1.35; 95% CI 0.81, 2.27). Rizatriptan displayed varying efficacies across age groups, showing no significant difference in adolescents aged 12-17 years (p>0.05). Zolmitriptan showed dose-dependent effectiveness, with higher doses yielding better outcomes (OR:2.18; 95% CI 1.45,3.28). Ibuprofen emerged as the sole non-triptan medication to demonstrate efficacy in achieving pain-free status at 2 hours, with a favorable safety profile (OR:2.54; 95% CI 1.20, 5.37).

Conclusion: These findings suggest that ibuprofen, zolmitriptan, and rizatriptan are potential treatment options for rapidly relieving migraine in children and adolescents. However, ibuprofen may have advantages over triptans, owing to its convenience and cost-effectiveness.

Keywords: Acute migraine treatment, adolescent, meta-analysis, pediatric, pharmacological interventions, randomized controlled trials

Öz

Amaç: Yetişkinlerde akut migreni tedavi etmek için kullanılan ilaç çeşitleri oldukça geniştir ve birçoğunun artık ayakta tedavi ortamlarında çocuklarda ve ergenlerde kullanılmasına izin verilmiştir. Bu meta-analizin amacı, 18 yaş ve altındaki bireylerde migren tedavisinde, uygulama yöntemine bakılmaksızın, plaseboya kıyasla farmakolojik müdahalelerin etkisini değerlendirmekti.

Gereç ve Yöntem: Mayıs 2023'ten 30 yıl önce yayınlanan karşılaştırmalı RCT'ler için PubMed, EMBASE ve Cochrane Library'yi araştırdık. Migrenli çocuk ve ergenlerde akut semptomları hafifleten migren ilaçlarını plaseboyla karşılaştıran prospektif randomize kontrollü klinik araştırmaları dahil ettik.

Bulgular: Bu meta-analize 12 klinik çalışma dahil edildi. Migren tedavisi seçimi ve tedaviden 2 saat sonra ağrıları tamamen geçen hastaların oranı analiz edildi. Analizde ibuprofen (n=2), sumatriptan (n=3), zolmitriptan (n=3) ve rizatriptan (n=4) kullanıldı. Karışık bireysel çalışma sonuçlarına rağmen (OR:1,35; %95 CI 0,81, 2,27), sumatriptan plaseboya kıyasla anlamlı farklılıklar sergilemedi. Rizatriptanın etkinliği yaş grupları arasında değişkenlik gösterdi ve 12-17 yaş arası ergenlerde anlamlı bir fark görülmedi (p>0,05). Zolmitriptan doza bağımlı etkinlik gösterdi ve daha yüksek dozlar daha iyi sonuçlar verdi (OR:2,18; %95 CI 1,45,3,28). İbuprofen, olumlu bir güvenlik profiliyle (OR:2,54; %95 CI 1,20, 5,37) 2 saatte ağrısız duruma ulaşmada etkinliğini gösteren, triptan olmayan tek ilaç olarak ortaya çıktı.

Sonuç: Bu bulgular ibuprofen, zolmitriptan ve rizatriptanın çocuk ve ergenlerde migreni hızlı bir şekilde hafifletmek için potansiyel tedavi seçenekleri olduğunu göstermektedir. Ancak ibuprofenin kullanışlılığı ve maliyet etkinliği nedeniyle triptanlara göre avantajları olabilir.

Anahtar Kelimeler: Akut migren tedavisi, ergen, meta-analiz, pediatrik, farmakolojik müdahaleler, randomize kontrollü çalışmalar

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Received *(Geliş Tarihi)*: 21.08.2023 **Accepted *(Kabul Tarihi)*:** 20.09.2023

INTRODUCTION

Migraine is a common primary headache disorder affecting both children and adolescents. According to the International Classification of Headache Disorders (ICHD), the prevalence of headaches ranges from 3% to 11% in this age group. Before puberty, boys are slightly more likely to have migraine than girls; however, after puberty, girls have a higher incidence and prevalence of migraine than boys. By the age of 11, one in every 10 girls suffers from recurrent headaches caused by migraine.[1-5] Migraine is a leading cause of morbidity worldwide and can significantly impair school performance and quality of life. Moreover, most adults with migraine have their first headache during childhood or adolescence.[6] In fact, 18% of patients in the pediatric emergency department are diagnosed with migraine.[7]

Migraine in children and adolescents is clinically diagnosed based on the ICHD criteria. The management of migraine involves behavioral and lifestyle changes as well as acute and preventive treatments. The choice of acute treatment depends on the timing, duration, and severity of the headache as well as the patient's needs and treatment goals. The most common drug treatments for acute migraine in children and adolescents are oral analgesics such as paracetamol and ibuprofen.[8] Other agents such as ergot derivatives (e.g., dihydroergotamine) and serotonin 1b/1d receptor agonists (triptans) have been approved by the US Food and Drug Administration for adolescent migraines and are widely used in adults. However, there is a lack of randomized controlled trials (RCTs) that have evaluated the efficacy and safety of these symptomatic therapies for migraine in children and adolescents.

Objective

We performed a meta-analysis to compare and rank the acceptability, safety, and efficacy of different drugs for the treatment of acute migraine in children and adolescents. This meta-analysis focused exclusively on RCTs that investigated symptomatic migraine treatment in children under 18 years of age.

MATERIALS AND METHODS

We conducted this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.[9] The PICO method was used as follows:

- Population (P) = Children with migraine
- Intervention (I) = Random onset controlled migraine therapy
- Comparison (C) = Conventional initiation controlled migraine therapy
- Outcome (O) = Drugs and outcomes

We searched PubMed, EMBASE, and the Cochrane Library for comparative RCTs published 30 years prior to May 29, 2023. The studies had to diagnose episodic migraine (with or without aura) according to the International Headache Society criteria or use similar criteria for migraine diagnosis. We used a comprehensive set of keywords, such as "acute," "headache," "migraine," "child," "youth," "teenage," "adolescent," " p(a)ediatric," and "treatment," and their spelling variations. We limited our search to human studies and texts in English.

We identified studies that compared acute migraine therapy outcomes between drugs and placebos, and extracted data on the outcomes of interest. **Figure 1** shows the search strategy and included studies.

Data extraction

Two reviewers (E.Ö.K. and İ.K.) independently reviewed the studies identified in the electronic database search. The primary screening was completed by reviewing the titles and abstracts of each study. They then reviewed the full texts of studies that passed the primary screening based on the inclusion criteria. They manually reviewed the reference lists of these studies to identify additional papers. The data extracted from each study included the first author, publication year, country, study design, and study period. They also extracted quantitative evaluation data, such as age, sex, and intervention (type and dosage of medicines) that were used in the treatment. A customized data-extraction form, as described in the Cochrane Handbook for Systematic Reviews of Interventions was used to record the duration of the trial, sample size, dropouts, and effect of interventions. Each study was evaluated according to inclusion and exclusion criteria. Any disputes were resolved through consensus or, if necessary, consultation with a third reviewer (C.A.).

Inclusion and exclusion criteria

We included all comparative RCTs that evaluated drugs for the treatment of children with migraine. The articles had to be full-length English texts. The participants were required to have episodic migraine (with or without aura) diagnosed according to the International Headache Society criteria or similar migraine diagnostic criteria. Studies and case reports that did not compare the drugs used in the treatment were excluded. We also excluded studies with patients older than 18 years, case series, case reports, and trials with patients with migraines associated with other neurological disorders. **Table 1** presents the demographic characteristics of the included studies.

Outcomes of interest

We were interested in the primary outcomes of migraine treatment choice and pain-free status at 2 h after treatment. We were also interested in the secondary outcomes of the treatment choice and pain reduction at 2 hours, the ability to sleep, the relief of other symptoms, and the decrease in pain frequency and intensity.

Table 1. Characteristics of included studies, listed according to year of publication.

	Study design	Study population	Headache severity scale	Interventions	Outcomes	Mean age	% Female
Hämäläinen et al. 1997	Randomized, double-blind, placebo-controlled, 3-way cross-over trial of ibuprofen, paracetamol, and placebo	< 18 years	5-faces pain scale	Each participant treated 1 of 3 migraine attacks with either oral paracetamol (15 mg/kg), oral ibuprofen (10 mg/kg), or placebo.	Headache relief at 2 h	10,7	50
Lewis et al. 2002	Randomized, double-blind, placebo-controlled, parallel-group trial of oral ibuprofen	6-12 years of age	4-point scale	Each participant treated 1 migraine with liquid ibuprofen suspension (7.5 mg/kg) or placebo	Headache relief (defined as a reduction from moderate or severe to mild or no headache) at 2 h	9	ND
Winner et al. 2002	Randomized, double-blind, placebo-controlled, parallel-group trial of oral rizatriptan	12-17 years of age	4-point scale	Each participant was instructed to take the study medication (rizatriptan 5 mg or placebo) within 30 min of onset of a moderate or severe migraine	Pain-free at 2 h	14	54
Ahonen et al. 2004	Randomized, double-blind, placebo-controlled, two-way cross-over trial of sumatriptan nasal spray	8-17 years of age	5-faces pain scale	Sumatriptan nasal spray 10 mg (weight 20 to 39 kg) or 20 mg (>40 kg) versus placebo.	Headache relief at 2 h (defined as severe or moderate (a grade of ^ 3) to at least 2 grades lower or fell asleep during these 2 h and was pain-free on awakening)	12,4	46
Visser et al. 2004	Randomized, double-blind, placebo-controlled, parallel-group single-attack trial of oral rizatriptan	12-17 years of age	4-point scale	Each participant treated 1 migraine with oral rizatriptan (5 mg) or placebo within 30 minutes of onset.	Headache relief at 2 h	14,2	55
Ahonen et al. 2006	Randomized, placebo-controlled, double-blind, 3-way cross-over trial of oral rizatriptan	6 - 17 years of age	5-faces pain scale	Rizatriptan 5 mg (weight 20 to 39 kg) or rizatriptan 10 mg (weight >40 kg) and placebo.	Headache relief at 2 h (defined as severe or moderate (a grade of ^ 3) to at least 2 grades lower or fell asleep during these 2 h and was pain-free on awakening)	12	54
Winner et al. 2006	Randomized, double-blind, placebo-controlled, parallel-group, multicenter, single-attack, outpatient study of intranasal sumatriptan	12-17 years of age	4-point scale	Sumatriptan 5 mg nasal spray; sumatriptan 20 mg nasal spray; or placebo	Headache relief at 2 h	14,3	55
Lewis et al. 2007	Multicenter, randomized, double-blind, placebo-controlled, 2-way, 2-attack, cross-over study of zolmitriptan nasal spray with a single-blind 'placebo challenge' or 'enrichment' phase	12-17 years of age	4-point scale	Each participant treated 1 migraine attack with zolmitriptan 5 mg nasal spray and another with matching placebo within a 12-week period.	Headache relief (decrease from moderate or severe to mild or no headache) at 2 h (1 h was used as the primary outcome in the study)	14,2	57
Ho et al. 2012	Randomized, double-blind, placebo-controlled, parallel group trial of oral rizatriptan with an enrichment design	6 - 17 years of age	4-point scale	Oral-disintegrating tablet of rizatriptan 5 mg (< 40 kg) or 10 mg (> 40 kg) or placebo.	Pain-free at 2 h	ND	44
Fujita et al. 2014	Randomized, double-blind, placebo-controlled, parallel group trial of oral sumatriptan	10 - 17 years of age	5-grade scale	Oral sumatriptan 25 mg (1 tablet and 1 matching placebo), sumatriptan 50 mg (2 tablets), or placebo (2 tablets) taken as soon as possible (within 30 minutes) after the development of a migraine with grade 3 or more pain	Headache relief (reduction of 2 grades) at 2 h	14,1	58
Winner et al. 2016	Randomized, double-blind, placebo-controlled, parallel group trial of zolmitriptan nasal spray	12-17 years of age	4-point scale	Zolmitriptan 0.5, 2.5, 5 mg nasal spray	Pain-free at 2 h	14	ND
Yonker et al. 2022	Randomized, double-blind, placebo-controlled, crossover trial	6 to 11 years of age	4-point scale	Zolmitriptan nasal spray followed by matching placebo	Headache relief at 2 h	11	57

Quality Assessment and Assessing Bias

Critical appraisals of the included studies were conducted using the Cochrane risk-of-bias tool for RCTs.[10] Two reviewers evaluated each study independently. Any conflicts were resolved through consensus or consultation with a third reviewer if necessary.

Statistical analysis

Effect size serves as a critical metric in meta-analysis, quantifying the magnitude of the relationship between variables across multiple studies. A common effect size measure of our study is odds ratio (OR). Consequently, all estimated OR's and corresponding 95% confidence intervals (CI) for a given outcome were pooled. The I^2 statistic and chi-squared test of heterogeneity were used to assess the heterogeneity of treatment effects between studies. The degree of heterogeneity (I^2) was categorized as low (25%), moderate (25–75%), or high (>75%). According to these heterogeneity statistics, we used Random Effects Model which stands out as an approach that accommodates heterogeneity and provides a more comprehensive understanding of the overall effect size. To visualize our results Forest Plots were used which clearly shows the results of individual studies, combining those studies with corresponding confidence intervals (CIs). Sensitivity analyzes and subgroups analyzes are also used to see the changes in the results. Data were analyzed using Review Manager (RevMan) version 5.4.1, and results were regarded as statistically significant if $p<0.05$.

RESULTS

The literature search yielded 138 unique citations, of which 42 full-text articles were assessed for eligibility. Some of our data requests to manufacturers were met with referrals to trial registry websites, or data were not made available. Between 1993 and 2023, a total of 12 randomized placebo-controlled trials of acute drug therapy for migraine met our inclusion criteria.[11-22] **Figure 1** shows the PRISMA flowchart, which illustrates how we selected the studies. There was complete agreement between the two reviewers regarding data extraction. Data on the study population, interventions, controls, and outcomes were extracted. The 2-hour posttreatment endpoint was chosen as this was the only consistent time interval used in the trials. Headache relief is generally quantified based on changes in pain scales. The characteristics of included studies are shown in **Table 1**.

Risk of Bias Included Studies

The risk of bias in the included studies is illustrated in **Figures 2** and **3**.

Allocation

Investigators described all studies as randomized (low risk of bias in random sequence generation), but the method of randomization was unclear in 4 studies (unclear risk of bias). The authors often used vague terms to describe sequence generation, such as 'randomized 1:1' or 'block randomization to two age groups.' Eight studies reported adequate allocation concealment, and we assessed them as having a low risk of bias in allocation concealment.

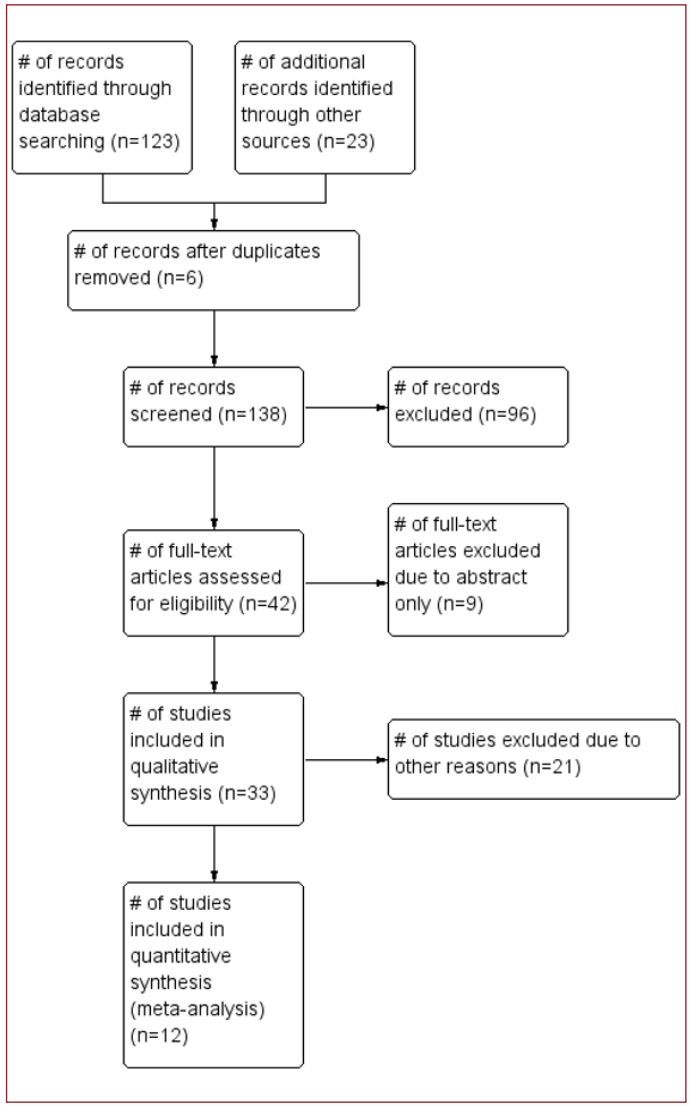

Figure 1. Study flow diagram

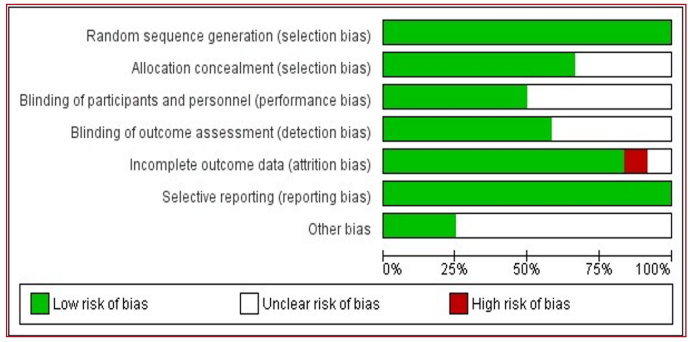

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

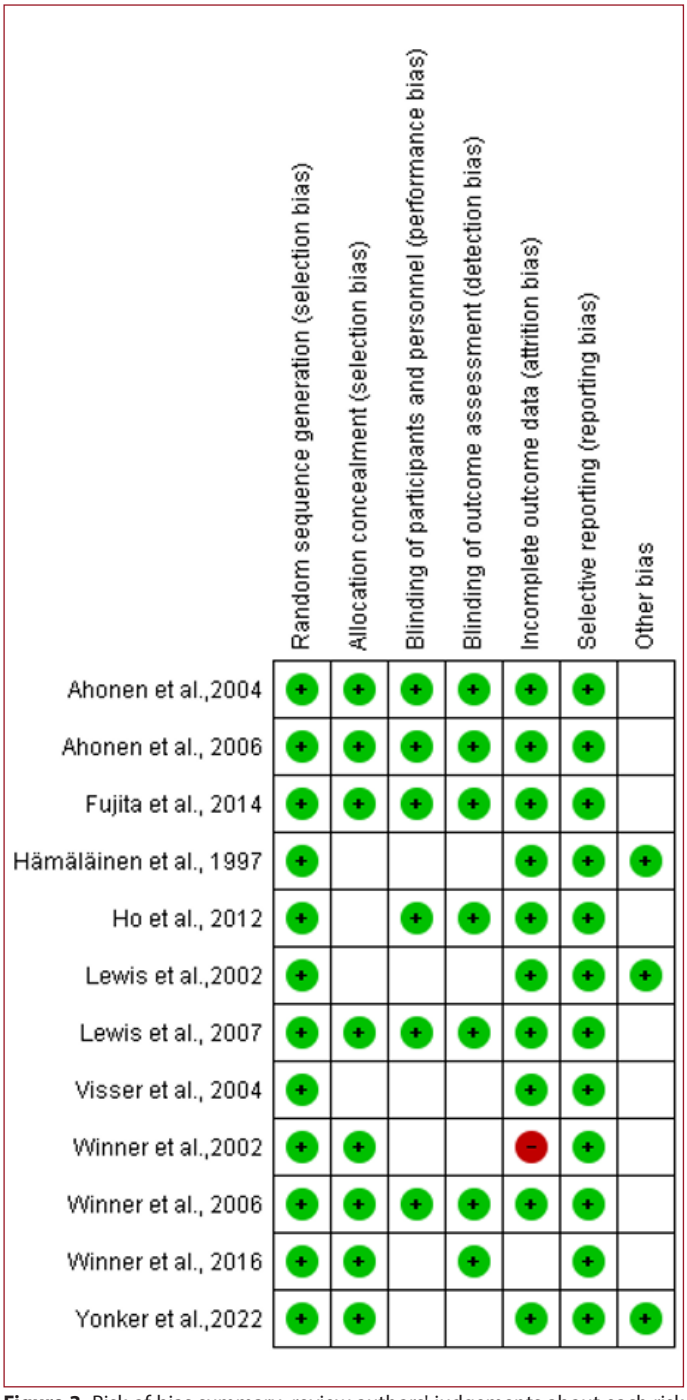

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Blinding

Generally, the authors described all studies as double-blind, but the method for blinding of participants and personnel was unclear in 6 studies (unclear risk of bias). We assessed six studies as having a low risk of bias in blinding the participants and personnel. The method for blinding the outcome assessment was unclear in five studies (unclear risk of bias). Seven studies had a low risk of bias in the blinding outcome assessment.

Incomplete Outcome Data

We rated one study as having a high risk of bias and 1 study as having an unclear risk of bias due to incomplete reporting of outcome data. We rated the remaining 10 studies as low risk.

Selective Reporting

Two studies were accessible only in the sponsors' clinical trial report registry and had no full publications, whereas one study was accessible only in the sponsor's clinical trial report registry. All the included studies reported pain-free primary efficacy outcomes. We considered the remaining studies to be of low risk.

Other Potential Sources of Bias

We evaluated publication bias based on pain-free outcomes for all triptans versus placebo in adolescents, excluding Yonger et al.[21] Although most of the published clinical trial data had low bias, we could not access the unpublished data of 9 studies (unclear risk of bias).

Effects of Interventions

We describe the measures of the effects for each intervention below.

Rizatriptan

Four studies were included in the investigation of rizatriptan's efficacy (5 mg and 10 mg orally) compared with placebo. Two of these RCTs focused on patients aged 12-17 years,[15,16] whereas the other two involved patients aged 6-17 years.[13,14] The rizatriptan dose in patients receiving acute treatment was adjusted based on their weight.

In the analysis, two RCTs,[15,16] examined the efficacy of 5 mg oral rizatriptan compared with placebo in outpatients aged 12-17 years. However, the difference in pain-free status after 2 h of treatment between the rizatriptan and placebo groups was not statistically significant ($p > 0.05$).

In a study involving patients aged 6-17 years,[13] which utilized a three-way crossover design with two doses of rizatriptan and placebo, rizatriptan was more effective than placebo ($p = 0.015$ for rizatriptan first vs. placebo; $p = 0.037$ for rizatriptan second vs. placebo). Another study involving patients of the same age range also found that rizatriptan was more effective than placebo ($p = 0.025$; OR:1.55; 95% CI:1.06 to 2.26).[14]

Upon combining all the studies, the analysis demonstrated that rizatriptan provided relief from headaches after 2 hours (OR: 1.51; 95% CI: 1.22, 1.88) (**Figure 4**). In summary, oral rizatriptan was found to be effective in treating migraine attacks and was well tolerated by patients.

Sumatriptan

This meta-analysis included three RCTs focusing on sumatriptan treatment for pediatric migraine attacks. Among these studies, two utilized nasal sprays, while one involved the oral administration of sumatriptan. The age range of the participants was 8-17 years.

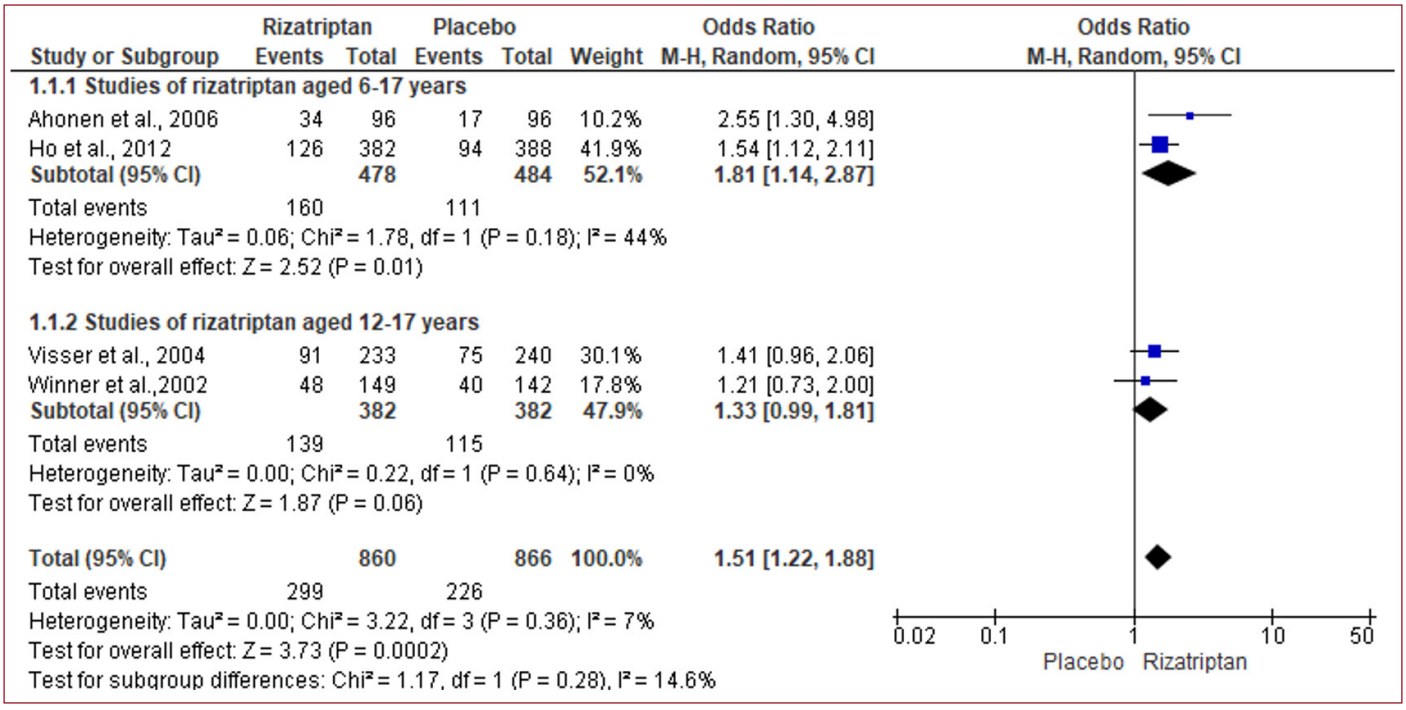

Figure 4. Forest plot of comparison: Rizatriptan vs placebo

In a study where oral sumatriptan was compared to a placebo group, no statistically significant difference was found between the two groups. Therefore, based on the available data, the oral use of sumatriptan did not significantly affect the treatment of pediatric migraine attacks.

In contrast, studies using nasal sumatriptan reported positive results. Nasal sumatriptan has been found to be an effective and well-tolerated treatment for pediatric migraine attacks.[19] However, it is worth noting that one of the studies on nasal sumatriptan had a limited number of patients, which might affect the extent of safety documentation in this specific age group.

Based on the findings from the three RCTs, oral sumatriptan did not show statistically significant efficacy compared to placebo in the treatment of pediatric migraines (OR: 1.35; 95% CI 0.81, 2.27) (**Figure 5**). On the other hand, nasal sumatriptan was demonstrated to be effective and well tolerated, although more research is required to establish its safety in this age group.

Zolmitriptan

Nasal therapy was used as the treatment method in all three zolmitriptan studies. Two of these studies involved patients aged 12-17 years,[20,22] while one study focused on patients aged 6-11 years.[21]

In the study conducted by Winner et al. zolmitriptan nasal therapy proved to be more effective than placebo in achieving a headache response at 2 hours after treatment ($p < 0.001$, OR:2.18; 95% CI 1.40, 3.39). The efficacy was sustained even 3 and 4 h after treatment ($p < 0.001$).

Yonker et al. compared zolmitriptan nasal spray with a placebo in 300 patients. Although the difference in response after 2 hours was not statistically significant ($p = 0.0777$), there was still a trend towards a higher response with zolmitriptan (OR: 1.51; 95% CI: 0.96, 2.38).

In the study conducted by Lewis et al. on the acute treatment of adolescent migraine, zolmitriptan nasal spray was well tolerated and provided rapid relief from migraine symptoms ($p < 0.01$).

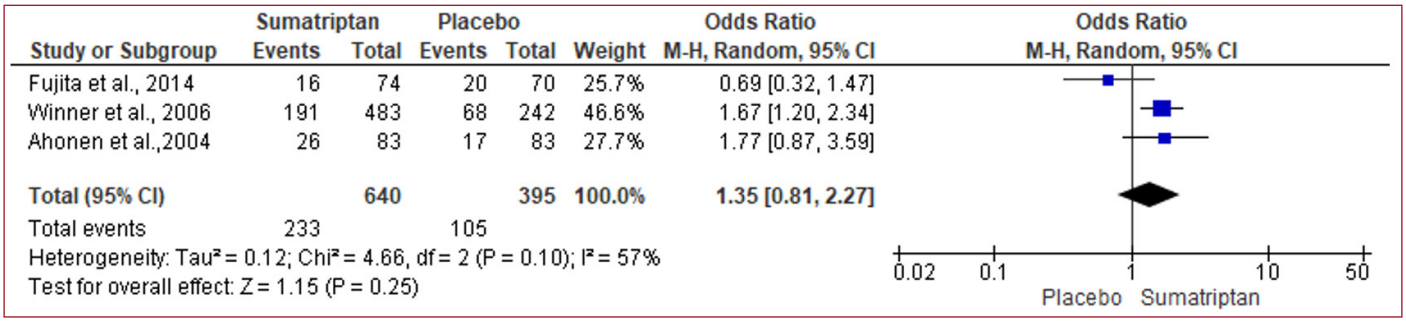

Figure 5. Forest plot of comparison: Sumatriptan vs placebo

Based on the three studies, zolmitriptan nasal therapy demonstrated efficacy in providing effective relief from migraine symptoms in adolescents and was generally well tolerated (OR: 2.18; 95% CI 1.45,3.28) (**Figure 6**).

Ibuprofen

Two RCTs were considered eligible for comparison between ibuprofen and placebo in the acute treatment of pediatric migraine. Alongside the three-way crossover study involving acetaminophen, ibuprofen, and placebo, there was also a smaller RCT that assessed ibuprofen (7.5 mg/kg liquid suspension) versus placebo in children aged 6–12 years, evaluated in a hospital setting.

The summarized data indicated that ibuprofen provided significantly more effective pain-free after 2 hours of migraine treatment compared to placebo, with a OR of 2.54 (95% CI 1.20, 5.37) (**Figure 7**).

DISCUSSION

The acute treatment of pediatric migraine with ibuprofen, triptans (sumatriptan, zolmitriptan, and rizatriptan), and placebo was compared in 12 RCTs. The main outcome was a pain-free status at 2 h post-treatment. The results showed that ibuprofen, rizatriptan, and zolmitriptan were significantly more effective than placebo in achieving this outcome.

Sumatriptan did not differ from placebo in terms of pain-free status at 2 h post-treatment, despite some individual studies showing positive effects. Rizatriptan had inconsistent results across different age groups, with no significant difference compared to placebo in adolescents aged 12-17 years. Zolmitriptan had a dose-dependent effect, with higher doses being more effective than lower ones. Ibuprofen was the only non-triptan medication that showed efficacy in a pain-free status at 2 h post-treatment, and it had a favorable safety profile.

All triptans were generally well tolerated, but some studies were funded by the same company that produced them, which may raise some concerns about bias.

Limitations: This review had some limitations that should be acknowledged. We excluded several studies from the meta-analysis owing to methodological limitations. We also discarded clinical trials that were not available in the full text or that could not be accessed. The final 12 RCTs had heterogeneous population characteristics such as age and sex. Many of the trials had small sample sizes. We pooled the data based on time and an intention-to-treat analysis, which may have increased the strength of the evidence but also introduced some heterogeneity.

CONCLUSION

According to this review, ibuprofen, zolmitriptan, and rizatriptan can help children with migraine relieve their pain quickly. However, ibuprofen may be more convenient and cost-effective than triptans, as it requires fewer doses to achieve the same effect. More research is needed to confirm these findings and explore other aspects of migraine in children, such as how often it comes back, how it affects their daily activities, and how it impacts their well-being. These studies should use larger and more diverse samples of children and adolescents and compare different treatments in a fair and rigorous manner.

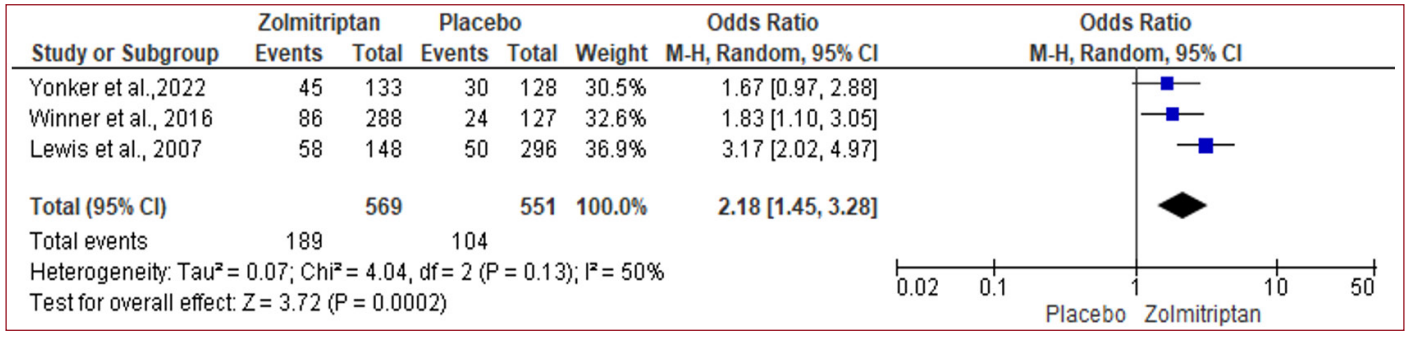

Figure 6. Forest plot of comparison: Zolmitriptan vs placebo

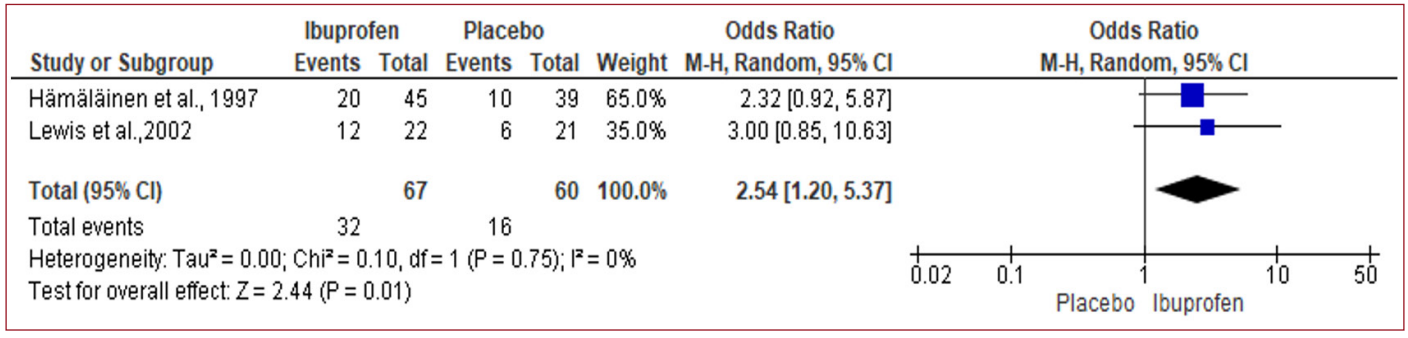

Figure 7. Forest plot of comparison: Ibuprofen vs placebo

Highlights

- Sumatriptan did not show a significant difference from placebo in achieving a pain-free status at 2 hours post-treatment, despite some positive effects observed in individual studies.
- Rizatriptan yielded inconsistent results across different age groups. In adolescents aged 12-17 years, there was no significant difference compared to placebo in terms of effectiveness.
- Zolmitriptan displayed a dose-dependent effect, where higher doses demonstrated greater efficacy in achieving the desired outcome compared to lower doses.
- Among non-triptan medications, only ibuprofen exhibited efficacy in achieving a pain-free status at 2 hours post-treatment. Additionally, ibuprofen demonstrated a favorable safety profile.

Abbreviations

CI: Confidence Interval, ICHD: International Classification of Headache Disorders, OR: Odds Ratio, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses, RCT: Randomized Controlled Trials

ETHICAL DECLARATIONS

Ethics Committee Approval: We conducted this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines. Ethics committee approval was not obtained as this is a meta-analysis.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1347034
J Contemp Med 2023;13(5):879-884

Original Article / Orijinal Araştırma

The Prognostic Value of Systemic Immune Inflammation Index in Children with Carbon Monoxide Poisoning

Karbon Monoksit Zehirlenmesi Olan Çocuklarda Sistemik İmmün İnflamasyon İndeksinin Prognostik Değeri

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Abstract

Aim: Carbon monoxide (CO) is an odorless and colorless gas that forms when organic materials burn incompletely. Children are more susceptible to CO poisoning than adults because their respiratory and immune systems are still developing. The systemic immune inflammation index (SII) is a marker that reflects the balance between inflammation and immunity. In this study, we investigate the relationship between CO poisoning in children and SII.

Material and Method: We conducted a retrospective observational study involving pediatric patients (age <18 years) diagnosed with CO poisoning and treated at Aksaray University Training and Research Hospital, a tertiary medical center, from January 2018 to January 2023. We included consecutive pediatric patients (age <18 years) with CO poisoning who had available clinical and laboratory data and were treated at our hospital.

Results: The study included 393 patients with a mean age of 7.24 (±4.67) years, of whom 184 (46.8%) were male. When comparing COHb groups, significant statistical differences emerged between the groups regarding GCS, pH levels, occurrences of dizziness, confusion, seizures, lethargy, and prognosis ($p<0.05$). When comparing lactate groups, significant differences were observed between the groups concerning GCS, COHb levels, pH levels, occurrences of confusion, lethargy, prognosis, and LOS ($p<0.05$). Upon evaluating the SII, no statistically significant difference was found between the groups in terms of gender, COHb levels, lactate levels, LOS, and prognosis.

Conclusion: SII cannot be considered a reliable predictor of the severity of carbon monoxide poisoning in children. Despite the evident inflammatory response triggered by exposure to carbon monoxide, the SII did not consistently correlate with the varying degrees of poisoning severity.

Keywords: Carbon monoxide poisoning, Inflammatory response, Pediatric patients, Severity assessment, Systemic immune inflammation index (SII)

Öz

Amaç: Karbon monoksit (CO), organik maddelerin eksik yanmasıyla oluşan kokusuz ve renksiz bir gazdır. Çocuklar CO zehirlenmesine yetişkinlerden daha duyarlıdır çünkü solunum ve bağışıklık sistemleri hala gelişmektedir. Sistemik immün inflamasyon indeksi (SII), inflamasyon ve bağışıklık arasındaki dengeyi yansıtan bir belirteçtir. Bu çalışmada, çocuklarda CO zehirlenmesi ile SII arasındaki ilişkiyi araştırdık.

Gereç ve Yöntem: Ocak 2018 - Ocak 2023 tarihleri arasında üçüncü basamak bir tıp merkezi olan Aksaray Üniversitesi Eğitim ve Araştırma Hastanesi'nde CO zehirlenmesi tanısı alan ve tedavi edilen çocuk hastaları (18 yaş altı) içeren retrospektif gözlemsel bir çalışma yürüttük. Klinik ve laboratuvar verileri mevcut olan ve hastanemizde tedavi edilen CO zehirlenmesi olan ardışık çocuk hastaları (yaş <18) dahil ettik.

Bulgular: Çalışmaya yaş ortalaması 7,24 (±4,67) yıl olan ve 184'ü (%46,8) erkek olan 393 hasta dahil edildi. COHb grupları karşılaştırıldığında, GKS, pH düzeyleri, baş dönmesi, konfüzyon, nöbet, letarji ve prognoz açısından gruplar arasında anlamlı istatistiksel farklılıklar ortaya çıktı ($p<0.05$). Laktat grupları karşılaştırıldığında, GKS, COHb seviyeleri, pH seviyeleri, konfüzyon, letarji, prognoz ve hastanede kalış süresi açısından gruplar arasında anlamlı farklılıklar gözlenmiştir ($p<0,05$). SII değerlendirildiğinde, gruplar arasında istatistiksel olarak anlamlı bir fark bulunmamıştır.

Sonuç: SII, çocuklarda karbon monoksit zehirlenmesinin şiddetinin güvenilir bir göstergesi olarak kabul edilemez. Karbon monoksit maruziyetinin tetiklediği bariz inflamatuar tepkiye rağmen SII, değişen derecelerdeki zehirlenme şiddetiyle tutarlı bir şekilde korelasyon göstermedi.

Anahtar Kelimeler: Karbon monoksit zehirlenmesi, İnflamatuvar yanıt, Pediatrik hastalar, Şiddet değerlendirmesi, Sistemik immün inflamasyon indeksi (SII)

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Received *(Geliş Tarihi)*: 20.08.2023 **Accepted *(Kabul Tarihi)*:** 20.09.2023

INTRODUCTION

Carbon monoxide (CO) is an odourless, colourless gas produced by the incomplete combustion of organic matter.[1,2] It is a major cause of illness and death worldwide, particularly in countries where people use wood and coal-burning stoves for heating without proper ventilation.[3] In fact, CO poisoning accounts for 3.6-9.4% of all poisonings in children.[4] Children are more susceptible to CO poisoning than adults because their respiratory and immune systems are still developing. CO has a much higher affinity for haemoglobin than oxygen, preventing oxygen from reaching the tissues and causing hypoxia.[5] CO also interferes with cellular oxidation, binds to myoglobin and cytochromes, and damages lipids.[6] These effects trigger an inflammatory response that can be measured by acute-phase reactants such as leukocytes, neutrophils, lymphocytes, platelets and proteins.[7]

The Systemic Immune Inflammation Index (SII) is a marker that reflects the balance between inflammation and immunity. It is calculated from the absolute numbers of neutrophils, lymphocytes and platelets. High levels of SII indicate a strong inflammatory response in the body and are associated with several diseases, such as cardiovascular disease and infections.[8]

CO poisoning can cause a wide range of symptoms, from mild headaches and dizziness to severe confusion and coma. It can also have long-term effects, such as cognitive impairment and respiratory problems, which can affect children's health and development.[9 10]

In this study, we investigate the relationship between CO poisoning in children and the SII. We aim to determine whether the SII can be used as a predictor of the severity of CO poisoning.

MATERIAL AND METHOD

Study Design

We conducted a retrospective observational study of pediatric patients (age <18 years) diagnosed with CO poisoning and treated at Aksaray University Training and Research Hospital, a tertiary medical center, from January 2018 to January 2023. The study was carried out with the permission of Local Ethics Committee (Decision No: 2021/17-06).

Study Setting and Patient Cohort

Consecutive pediatric patients (age <18 years) with CO poisoning who had available clinical and laboratory data and who were treated at our hospital were included in the study. CO poisoning was defined as exposure to CO emissions and a carboxyhemoglobin (COHb) level above 5% at the time of admission to the pediatric emergency department. Patients with chronic diseases (such as chronic pulmonary, cardiac, renal, hepatic, inflammatory, hematological, rheumatic diseases, or immunosuppression), those for whom information could not be retrieved from the electronic record system, and patients older than 18 years were excluded.

Patients were divided into two groups according to their COHb levels: mild to moderate poisoning (COgroup-1) with levels between 5% and 20%, and severe poisoning (COgroup-2) with COHb levels above 20%. In addition, patients were classified based on their blood lactate levels: mild-moderate (Lgroup-1) if lactate was less than 2.2 mmol/L, and severe poisoning (Lgroup-2) if lactate was 2.2 mmol/L or greater.

Patients were divided into three categories based on length of hospital stay (LOS): 0-24 hours, 24-72 hours, and over 72 hours. Patients were also divided into four groups according to their clinical outcome: discharge after treatment in the emergency department, admission to the hospital's pediatric service, admission to intensive care, and referral to another medical facility.

The SII was calculated using the formula SII =[(platelet count × neutrophil count) / lymphocyte count].[11] Patients' SII levels were evaluated in relation to their CO levels, lactate levels, length of hospital stay, and clinical outcomes.

Data Collection

Data on patient demographic characteristics such as age and sex, symptoms and complaints at the time of application, Glasgow Coma Scale (GCS), LOS, clinical outcomes (discharge/hospitalisation/referral), initial laboratory results; white blood cell (WBC), platelet, neutrophil, lymphocyte, monocyte, and lactate values were retrospectively recorded from the patient's medical records.

Statistical Analysis

Statistical analyses were performed using SPSS 21.0 (IBM Inc, Chicago, IL, USA). Numerical parameters were expressed as median (min-max) or mean±SD, and categorical variables were expressed as frequencies and percentages (%). Kolmogrov-Smirnov test, histogram analysis and skewness/kurtosis data were used to assess the conformity of numerical variables with normal distribution. Levene's test was used to analyse the homogeneity characteristics of numerical parameters between groups. When comparing two independent groups, the independent t-test was used for parameters with normal distribution, while the Mann-Witney U test was used for parameters without normal distribution. Spearman's correlation analysis was used for correlations between numerical parameters. Binary logistic regression analysis was used to determine the predictive factors. The accuracy of binary relations and analyses in the models was confirmed by the Hosmer-Lemeshow test. Chi-squared or Fisher's exact tests were used to analyse the relationship between binary categorical groups. Significant parameters that might influence the severity of poisoning were subjected to ROC analysis and diagnostic data were presented. The type I error rate was set at 5% for the entire study, and $p<0.05$ was considered significant.

RESULTS

In our study, a total of 457 patients with acute CO poisoning were admitted to our pediatric emergency department. After applying the exclusion criteria, 64 patients were considered ineligible, leaving a final inclusion of 393 patients. The mean age of the patients was 7.24 (±4.67) years and 184 (46.8%) were male. The mean GCS score was 13.55 (±1.72), while the mean COHb level was 7.92 (±5.50). Most patients (74%) were admitted 8-24 hours

after CO exposure. Of the patients, 369 (94.1%) had COHb levels between 5% and 20%, while 24 (5.9%) had COHb levels ≥20%.

Regarding lactate levels, 324 (82.4%) patients had lactate levels below 2.2 mmol/L, while 69 (17.6%) had lactate levels of 2.2 mmol/L or higher. The most common symptom on admission was headache (41.7%), followed by dizziness (36.4%) and epileptic seizures (36.1%). Of the patients, 255 (64.9%) were discharged within the first 24 hours after treatment, while 24 (6.1%) were referred to another facility for hyperbaric oxygen requirements or other reasons. To the best of our knowledge from the medical records, no patient succumbed to the disease. Detailed demographic characteristics, laboratory findings, symptoms on admission, length of hospital stay, and follow-up data are shown in **Tables 1** and **2**.

When evaluating the COHb groups, it was observed that COgroup-1 was most frequently associated with headache (n=154; 41.7%), whereas COgroup-2 had a higher incidence of confusion (n=22; 91.7%). The mean GCS score for COgroup-1 was 13.68 (±1.64), whereas COgroup-2 had a mean GCS score of 11.50 (±1.67). In addition, the mean pH was 7.35 (±0.05) for COgroup-1 and 7.28 (±0.06) for COgroup-2. Regarding hospitalization, the majority of COgroup-1 patients were admitted to the hospital pediatric service (n=172; 46.6%), whereas most COgroup-2 patients were transferred to another medical facility (n=22; 91.7%). When the COHb groups were compared, statistically significant differences were found between the groups in terms of GCS, pH levels, incidence of dizziness, confusion, seizures, lethargy, and prognosis ($p<0.05$). Detailed comparisons of group data based on COHb levels are shown in **Tables 3** and **4**.

Table 1. Demographics and laboratory findings of the study population

	Mean	SD	Median	25%	75%
Age (years)	7.24	4.67	6.00	3.00	10.00
GCS[1]	13.55	1.72	14.00	12.00	15.00
WBC[2] (10^3/μL)	12.16	37.45	9.24	7.41	11.77
Lymphocyte (10^3/μL)	2.42	1.23	2.18	1.63	3.01
Monocyte (10^3/μL)	0.62	0.56	0.55	0.41	0.70
Neutrophil (10^3/μL)	6.82	5.05	6.19	4.82	7.67
Platelet (10^3/μL)	255.94	92.41	244.00	197.00	296.00
pH	7.35	0.05	7.35	7.32	7.36
COHb[3] (%)	7.92	5.50	5.00	5.00	8.00
SII[4]	982.47	2459.66	699.39	430.42	1071.23

[1]Glasgow Coma Scale, [2]White Blood Cell, [3]Carboxyhemoglobin, [4]Systemic Immune-Inflammation Index

Table 2. Demographics, symptoms, and prognosis of the study population.

	Count	Column N %
Gender		
Female	209	53.2%
Male	184	46.8%
Application Time		
0-8 Hours	73	18.6%
8-24 Hours	291	74.0%
>24 Hours	29	7.4%
Lactate (mmol/L)		
<2.2	324	82.4%
>2.2	69	17.6%
Headache		
No	318	
Yes	75	
Nausea-Vomiting		
No	318	80.9%
Yes	75	19.1%
Weakness		
No	266	67.7%
Yes	127	32.3%
Dizziness		
No	250	
Yes	143	
Syncope		
No	283	72.0%
Yes	110	28.0%
Confusion		
No	253	
Yes	140	
Seizure		
No	251	63.9%
Yes	142	36.1%
Lethargy		
No	266	67.7%
Yes	127	32.3%
Length of Hospital Stay		
0-24 Hours	256	65.1%
24-72 Hours	122	31.0%
>72 Hours	15	3.8%
Follow-Up		
Discharge after treatment in the E.D.*	88	22.4%
Pediatric service	173	44.0%
Intensive care unit	108	27.5%
Referral	24	6.1%

*Emergency Department

Table 3. Comparisons of COHb groups' demographics and laboratory findings.

	COgroup-1					COgroup-2					p value
	Mean	SD	Median	25%	75%	Mean	SD	Median	25%	75%	
Age (years)	7,23	4,65	6,00	3,00	10,00	7,42	4,99	6,50	3,00	10,00	0,911
GCS[1]	13,68	1,64	15,00	13,00	15,00	11,50	1,67	11,00	11,00	12,50	<0,001
WBC[2] (10^3/μL)	12,33	38,63	9,24	7,42	11,77	9,66	4,01	9,07	6,76	12,14	0,567
Lymphocyte (10^3/μL)	2,42	1,24	2,15	1,58	3,05	2,43	1,07	2,29	1,79	3,00	0,707
Monocyte (10^3/μL)	0,63	0,57	0,55	0,41	0,70	0,53	0,22	0,47	0,39	0,63	0,166
Neutrophil (10^3/μL)	6,83	5,15	6,19	4,82	7,67	6,69	3,10	6,15	4,88	7,65	0,993
Platelet (10^3/μL)	255,98	93,02	245,00	197,00	296,00	255,21	84,30	233,50	206,50	294,50	0,909
pH	7,35	0,05	7,36	7,33	7,36	7,28	0,06	7,28	7,23	7,32	<0,001
SII[3]	985,73	2526,68	704,56	430,86	1071,23	932,44	981,63	589,89	337,19	1041,69	0,687

1Glasgow Coma Scale, 2 White Blood Cell, 3 Systemic Immune-Inflammation Index

Table 4. Comparisons of COHb groups' demographics, symptoms, and prognosis of the study population.

	CO group-1		CO group-2		p value
	n	%	n	%	
Gender					0,345
Female	194	52,6%	15	62,5%	
Male	175	47,4%	9	37,5%	
Application Time					0,501*
0-8 Hours	68	18,4%	5	20,8%	
8-24 Hours	275	74,5%	16	66,7%	
>24 Hours	26	7,0%	3	12,5%	
Headache					0,995
No	215	58,3%	14	58,3%	
Yes	154	41,7%	10	41,7%	
Nausea-Vomiting					0,791*
No	299	81,0%	19	79,2%	
Yes	70	19,0%	5	20,8%	
Weakness					0,429
No	248	67,2%	18	75,0%	
Yes	121	32,8%	6	25,0%	
Dizziness					0,038
No	230	62,3%	20	83,3%	
Yes	139	37,7%	4	16,7%	
Syncope					0,547
No	267	72,4%	16	66,7%	
Yes	102	27,6%	8	33,3%	
Confusion					<0,001
No	251	68,0%	2	8,3%	
Yes	118	32,0%	22	91,7%	
Seizure					<0,001
No	246	66,7%	5	20,8%	
Yes	123	33,3%	19	79,2%	
Lethargy					<0,001
No	261	70,7%	5	20,8%	
Yes	108	29,3%	19	79,2%	
Length of Hospital Stay					0,248*
0-24 Hours	237	64,2%	19	79,2%	
24-72 Hours	118	32,0%	4	16,7%	
>72 Hours	14	3,8%	1	4,2%	
Follow-Up					<0,001*
Discharge after treatment in the E.D.**	88	23,8%	0	0,0%	
Pediatric service	172	46,6%	1	4,2%	
Intensive care unit	107	29,0%	1	4,2%	
Referral	2	0,5%	22	91,7%	

* Fisher's exact test p value and all others Pearson Chi-square test **Emergency Department

Evaluation of the lactate groups showed that the mean GCS scores for Lgroup-1 and Lgroup-2 were 13.88 (±1.51) and 11.99 (±1.79) respectively. Lgroup-2 had a higher mean COHb value compared to Lgroup-1, with values of 10.86 (±8.02) and 7.29 (±4.57), respectively. In addition, the mean pH was 7.36 (±0.05) in L-group-1 and 7.29 (±0.04) in L-group-2. In terms of symptoms, headache was the most common presentation in L-group-1 (n=133; 41%), whereas confusion was the predominant symptom in L-group-2 (n=34; 49.3%). Regarding hospitalization, the majority of L-group-1 patients were admitted to the hospital's pediatric service (n=159; 49.1%), whereas the majority of L-group-2 patients were admitted to the intensive care unit (n=40; 58%). When comparing the lactate groups, statistically significant differences were observed between the groups for GCS, COHb, pH, confusion, lethargy, prognosis, and LOS ($p<0.05$). Detailed comparisons of the data between the lactate groups are shown in **Tables 5** and **6**.

When evaluating the SII, we found no statistically significant difference between groups in terms of gender, COHb levels, lactate levels, LOS, and prognosis. A comprehensive comparison of group data based on SII is presented in **Table 7**.

There were no patient deaths for which records were available.

DISCUSSION

To the best of our knowledge, this study is the first to investigate the relationship between CO poisoning and SII in children in the Central Anatolian region. Contrary to initial expectations, our comprehensive analysis of the relationship between CO poisoning and the SII revealed that the SII is not reliable enough to accurately predict the severity of CO poisoning in children. While CO exposure does induce an inflammatory response, the magnitude of this response does not consistently correlate with the severity of poisoning symptoms.

Table 5. Comparisons of lactate groups' demographics and laboratory findings.

	L group-1					L group-2					p value
	Mean	SD	Median	25%	75%	Mean	SD	Median	25%	75%	
Age (years)	7,30	4,69	6,00	3,00	10,00	6,96	4,61	6,00	3,00	9,00	0,600
GCS[1]	13,88	1,51	15,00	13,00	15,00	11,99	1,79	12,00	11,00	13,00	<0,001
WBC[2] (10^3/µL)	12,49	41,11	9,19	7,42	11,69	10,62	7,34	9,48	7,35	12,22	0,686
Lymphocyte (10^3/µL)	2,43	1,23	2,22	1,63	3,00	2,40	1,23	2,12	1,42	3,07	0,829
Monocyte (10^3/µL)	0,59	0,39	0,55	0,41	0,70	0,77	1,02	0,55	0,42	0,76	0,689
Neutrophil (10^3/µL)	6,96	5,41	6,24	5,04	7,83	6,15	2,66	5,75	4,49	7,11	0,106
Platelet (10^3/µL)	255,68	93,48	244,50	196,00	296,50	257,14	87,87	241,00	203,00	286,00	0,895
pH	7,36	0,05	7,36	7,34	7,36	7,29	0,04	7,31	7,28	7,31	<0,001
SII[3]	1012,91	2693,44	706,90	433,67	1026,24	839,58	625,77	675,38	401,16	1124,41	0,564
COHb[4]	7,29	4,57	5,00	5,00	7,50	10,86	8,02	5,00	5,00	15,00	<0,001

1Glasgow Coma Scale, 2 White Blood Cell, 3 Systemic Immune-Inflammation Index, 4Carboxyhemoglobin

Table 6. Comparisons of lactate groups' demographics, symptoms, and prognosis of the study population.

	Lgroup-1		Lgroup-2		p value
	n	%	n	%	
Gender					0,653
Female	174	53,7%	35	50,7%	
Male	150	46,3%	34	49,3%	
Application Time					0,646
0-8 Hours	58	17,9%	15	21,7%	
8-24 Hours	243	75,0%	48	69,6%	
>24 Hours	23	7,1%	6	8,7%	
Headache					0,553
No	191	59,0%	38	55,1%	
Yes	133	41,0%	31	44,9%	
Nausea-Vomiting					0,103
No	267	82,4%	51	73,9%	
Yes	57	17,6%	18	26,1%	
Weakness					0,629
No	221	68,2%	45	65,2%	
Yes	103	31,8%	24	34,8%	
Dizziness					0,159
No	201	62,0%	49	71,0%	
Yes	123	38,0%	20	29,0%	
Syncope					0,698
No	232	71,6%	51	73,9%	
Yes	92	28,4%	18	26,1%	
Confusion					0,009
No	218	67,3%	35	50,7%	
Yes	106	32,7%	34	49,3%	
Seizure					0,051
No	214	66,0%	37	53,6%	
Yes	110	34,0%	32	46,4%	
Lethargy					0,006
No	229	70,7%	37	53,6%	
Yes	95	29,3%	32	46,4%	
Length of Hospital Stay					0,002*
0-24 Hours	221	68,2%	35	50,7%	
24-72 Hours	95	29,3%	27	39,1%	
>72 Hours	8	2,5%	7	10,1%	
Follow-Up					<0,001*
Discharge after treatment in the E.D.**	87	26,9%	1	1,4%	
Pediatric service	159	49,1%	14	20,3%	
Intensive care unit	68	21,0%	40	58,0%	
Referral	10	3,1%	14	20,3%	

* Fisher's exact test p value and all others Pearson Chi-square test **Emergency Department

Among the key diagnostic and prognostic indicators for carbon monoxide poisoning, CO level stands out as one of the most important. Our results showed that patients with higher CO levels had lower GCS scores and blood pH levels, accompanied by an increased prevalence of symptoms such as dizziness, confusion, seizures, and lethargy. In addition, the need for additional interventions such as hyperbaric oxygen treatment became more apparent as CO levels escalated. These observations are consistent with the existing literature.

Another important prognostic parameter in CO poisoning is the lactate level. In our study, patients with elevated lactate levels had lower GCS scores, lower blood pH levels, and higher COHb levels. In addition, these patients had a higher incidence of confusion and lethargy. As a result, these patients had longer stays in intensive care and longer hospital stays.

Although significant differences were observed between the subgroups categorized by COHb and lactate levels, no corresponding differences were observed in SII levels. Although the SII has recently gained popularity as an index that holistically captures the balance between a patient's immune response and inflammatory state, it did not show sufficient predictive power in determining the severity of poisoning in patients presenting with CO poisoning.

Limitations: This study has certain limitations. Firstly, it has the inherent limitations of a retrospective study and it was not possible to include all patients in the analysis. Second, the single-center design and limited patient population prevent direct extrapolation of the results to all patient groups. Thirdly, the ability of the SII to predict mortality could not be assessed because there were no deaths among the patients. Finally, complete access to data on patients referred to other hospitals was not possible.

Table 7. Comparisons of group data and prognosis based on SII

	SII					p value
	Mean	SD	Median	25%	75%	
Length of Hospital Stay						0,563
0-24 Hours	896,91	784,30	712,05	457,49	1082,94	
24-72 Hours	1179,78	4300,71	638,72	400,75	990,75	
>72 Hours	923,23	691,76	739,02	362,21	1260,12	
Lactate (mmol/L)						0,564
<2.2	1012,91	2693,44	706,90	433,67	1026,24	
>2.2	839,58	625,77	675,38	401,16	1124,41	
Follow-Up						0,941
Discharge after treatment in the E.D.*	883,42	724,11	712,61	478,61	1053,01	
Pediatric service	1102,01	3606,18	685,41	414,82	1025,02	
Intensive care unit	862,45	739,04	698,22	446,98	1090,82	
Referral	1024,15	1059,14	589,89	391,06	1258,97	
COHb**						0,687
COgroup-1	985,73	2526,68	704,56	430,86	1071,23	
COgroup-2	932,44	981,63	589,89	337,19	1041,69	
Gender						0,878
Female	835,81	622,53	684,04	430,86	1071,23	
Male	1149,07	3530,79	708,49	425,77	1074,28	

*Emergency Department **Carboxyhemoglobin

CONCLUSION

In conclusion, based on the results of this study, the SII cannot be considered a reliable predictor of the severity of carbon monoxide poisoning in children. Despite the apparent inflammatory response induced by carbon monoxide exposure, the SII did not consistently correlate with different degrees of poisoning severity. Further research, preferably using prospective and multicentre approaches, is needed to elucidate the complex dynamics between SII and the severity of carbon monoxide poisoning.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Local Ethics Committee (Decision No: 2021/17-06).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1343842
J Contemp Med 2023;13(5):885-890

Original Article / Orijinal Araştırma

Current Status of Global Hysteroscopy and Female Infertility Research: A Web of Science Based Bibliometric Analysis Study

Global Histeroskopi ve Kadın İnfertilitesi Araştırmalarının Mevcut Durumu: Web of Science Tabanlı Bibliyometrik Analiz Çalışması

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Abstract

Aim: The aim of this study was to identify trends in the literature on female infertility and hysteroscopy and to quantitatively evaluate them using various bibliometric parameters.

Material and Method: The study data was taken from the Web of Science electronic database for this bibliometric network analysis. The network analysis and bibliometric analysis were carried out by using the Biblioshiny and VOSviewer bibliometric tools.

Results: A total of 1,023 documents were included in the study. The first article was published in 1977. Until 1990, the annual number of articles was irregular. The quantity of publications published annually significantly increased after 2005, peaking in 2020 and 2021 (68 and 67 articles, respectively). The included articles were published in 67 countries. Among these countries, China (n=299), the United States of America (n=237), Italy (n=235), andTurkey (n=156) had the highest number of publications. Especially after 2012, there has been a significant increase in Chines epublications. In addition, 10.07% of the documents had co-authors from other countries. The keywords 'hysteroscopy (n=422), hysterosalpingography office (n=65), hysteroscopy (n=49), and chronic endometritis (n=45) topped the trending topic list.

Conclusion: It is notable that among international publications, Chinese publications have increased significantly, especially in the last decade. Funding support from Chinese institutions may be responsible for this. This study is the first study published on the current status of global hysteroscopy and female infertility research and its results may give an idea to the related field researchers.

Keywords: Bibliometric analysis, hysteroscopy, infertility

Öz

Amaç: Bu çalışmanın amacı, kadın infertilitesi ve histeroskopi literatüründeki eğilimleri belirlemek ve bunları çeşitli bibliyometrik parametreler kullanarak niceliksel olarak değerlendirmektir.

Gereç ve Yöntem: Bu bibliyometrik ağ analizi için çalışma verileri Web of Science elektronik veri tabanından alınmıştır. Ağ analizi ve bibliyometrik analiz Biblioshiny ve VosViewer bibliyometrik araçları kullanılarak gerçekleştirilmiştir.

Bulgular: Çalışmaya toplam 1023 belge dahil edilmiştir. İlk makale 1977 yılında yayımlanmıştır. 1990 yılına kadar yıllık makale sayısı düzensizdi. Her yıl yayınlanan yayınların sayısı 2005'ten sonra önemli ölçüde artarak 2020 ve 2021'de zirve yapmıştır (sırasıyla 68 ve 67 makale). Dahil edilen makaleler 67 ülkede yayınlanmıştır. Bu ülkeler arasında Çin (n=299), Amerika Birleşik Devletleri (n=237), İtalya (n=235) ve Türkiye (n=156) en fazla yayına sahip ülkelerdir. Özellikle 2012 yılından sonra Çin yayınlarında önemli bir artış olmuştur. Ayrıca, dokümanların %10,07'sinin diğer ülkelerden ortak yazarları bulunmaktadır. 'Histeroskopi (n=422), histerosalpingografi ofisi (n=65), histeroskopi (n= 49) ve kronik endometrit (n= 45) anahtar kelimeleri trend konu listesinin başında yer almıştır.

Sonuç: Uluslararası yayınlar arasında Çin menşeyli yayınlarının özellikle son on yılda önemli ölçüde artmış olması dikkat çekicidir. Çin'deki kurumlarca verilen fon desteği bundan sorumlu olabilir. Bu çalışma, küresel histeroskopi ve kadın infertilitesi araştırmalarının mevcut durumu hakkında yayınlanan ilk çalışmadır ve sonuçları bu alandaki araştırmacılar için fikir sağlayabilir.

Anahtar Kelimeler: Bibliyometrik analiz, histeroskopi, infertilite

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Received *(Geliş Tarihi)*: 15.08.2023 **Accepted *(Kabul Tarihi)*:** 16.09.2023

INTRODUCTION

The term of 'infertility' defined by the World Health Organization (WHO) as the inability to become pregnant after one year (or more) of unprotected sexual activity.[1] Infertility is divided into two subcategories: primary and secondary. Women who have never given birth before are considered to be suffering from primary infertility. At least one conception occurs in secondary infertility, but it doesn't happen again. [2] The most prevalent type of female infertility worldwide is secondary infertility, which is frequently brought on by infections of the reproductive system. The time of undesirable non-conception, the age of the female partner, and disease-related infertility are the three main variables affecting the spontaneous likelihood of conception. The longer you wait before conception, the lower your probability of getting pregnant on your own. In the majority of examined populations with natural fertility, the fall in female fertility already begins at 25–30 years of age, and the median age at last birth is 40–41 years.[3]

Infertility is a global public health issue that has an impact on an individual's personal, social, and economic life as well as the family as a whole.[4] The prevalence of infertility is estimated to be 9% among couples who are of reproductive age, and female variables account for 20–35% of all infertility cases.[4] A recent meta analysis found that the total pooled prevalence for infertility and primary infertility was 46.25% and 51.5%, respectively.[5]

Infertility brought on by a medical condition may affect either or both genders. Hypogonadotropic hypogonadism, hyperprolactinemia, ciliary disorders, cystic fibrosis, infections, systemic diseases, and diseases connected to lifestyle are the factors that impair fertility in both sexes. Female infertility maybe caused by premature ovarian insufficiency, polycystic ovary syndrome, endometriosis, uterine fibroids, uterine malformation, endometrial atrophy, and endometrial polyps, etc..[3,6]

Hysteroscopy has experienced a significant transformation, moving from its traditional function as a diagnostic tool for examining the uterine cavity to an essential modality that allows simultaneous diagnosis, visualization, and treatment of a wide range of intrauterine illnesses. With in specialist medical settings and clinics devoted to there search and care of female reproductive health, this change is especially important.[6]

An interdisciplinary topic called bibliometrics uses mathematical and statistical methods to objectively assess the distribution of knowledge, particularly literature. We can gain importan t insights by conducting thoroughand objective bibliometric analyses of voluminous literature on a given topic, including: a) the roles played by countries/regions, institutions, journals, and authors within the domain; b) the cooperative efforts among countries, institutions, or authors; c) the distribution patterns of journals; and d) the fundamental knowledge reservoir.[7,8]

Information and communication Technologies are evolving quickly and areused in many aspects of the healthcare industry.[9] In the area of medicine[10-14] and obstetrics[13-16] bibliometric analyses are also frequently published, both from Turkey and globally. In addition, female infertility and hysteroscopy-related articles have been published more frequently in recent years. The characteristics and strengths of the published research on hysteroscopy and female infertility are not well understood, nevertheless.

The demand for greater research on healthcare disciplines, as well as for the synthesis and use of such research in practice, has been prompted by the increasing emphasis on evidence-based practice. In this study, the global trend in research on female infertility and hysteroscopy was examined, and the influence and impact of pertinent publications on the scientific community were evaluated. Therefore, this study's goals were to: (1) as certain the growth research trend of journal publications on hysteroscopy and female infertility; (2) quantitatively evaluate the contribution of the most pertinent literature on hysteroscopy and female infertility, using various bibliometric parameters; and (3) pinpoint key themes in hysteroscopy and female infertility research, using keyword co-occurrence analysis.

MATERIAL AND METHOD

Search Strategies and Inclusion Criteria

In order to ensure a trust worthy coverage of pertinent studies, related research articles on hysteroscopy and female infertility were retrieved from the Web of Science for this study, on August 1, 2023. In this study, "hysteroscopy studies" related to the field of gynecology and obstetrics were included.

The keywords hysteroscopy (Topic) AND infertility (Topic) were selected in the Web of Science search engine. The search language was English. There were no time restrictions. All publications published until 1 August 2023 were included. 1303 publications were reached in the first search. Then, the search was narrowed to only 'research articles' as publication type. As a result of this restriction, 1023 publications were reached.

The current study investigated some main bibliometric parameters such as the number of publications, the most-published fields, countries of collaboration, trend keywords, the number of citations, etc.

Exclusion criteria: Other document types besides research articles were excluded.

Bibliometric Tools

For data visualization and analysis, a variety of bibliometric software packages were used, including VOSviewer [19,20], the Bibliometrix R package (version 4.1.2), and Biblioshiny (version 2.0) (https://www.bibliometrix.org/home/index.php/layout/biblioshiny).[21] Building and visualizing bibliometric

maps can be done using the free computer free wareVOS viewer.[19,20]

The first step in conducting analyses using these bibliometric tools was to search the Web of Science database according to inclusion criteria, then download the results in plaintext format onto computer. The relevant bibliometric software package was then used to import the bibliometric data and conduct thorough analyses.

RESULTS

The data set includes 1,023 documents in this temporal context. The data set shows an impressive annual growth rate of 8.17%, indicating a steady growth of the body of knowledge within the subject area. This literature was produced by 3976 authors. 65 publications in the dataset had a single author. The dataset had an average of 4.9 co-authors per document. International co-authorship was identified in approximately 10.07 percent of the documents.

The initial article was published in 1977. In the years that followed, up until 1990, the frequency of published articles showed sporadic patterns, with some years seeing a dearthor complete lack of articles. However, a clear paradigm shift occurred after 2005, when it became clear that the number of articles published each year had significantly increased. Particularly noteworthy are the years 2020 and 2021, which standout for being the peak of publication activity and manifesting an output of 68 and 67 articles, respectively. A corpus of 30 articles has been published as of the current analysis, which covers the year 2023 (**Figure 1**).

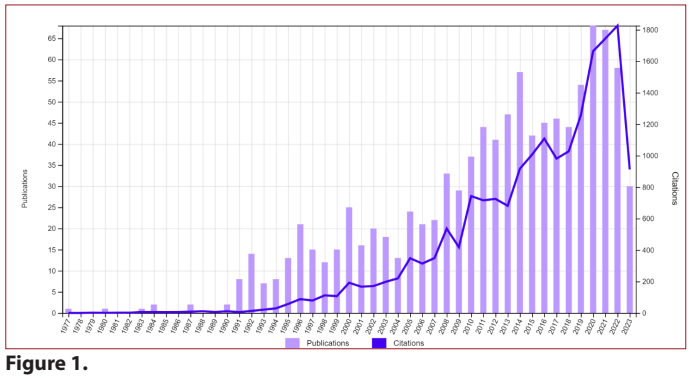

Figure 1.

In order to ruleout any conclusive interpretation of this numerical datum as indicative of a decline in publication frequency, it is essential to recognize that 2023 is still in progress. After removing self-citations, these publications received 15,655 citations out of a total of 18,800. The H-index now stands at 67 and the average number of citations per article is 18.38.

Countries and Affiliations

The entire set of articles under consideration includes contributions from a total of 67 distinct countries. Among them, China had 299 publications, the United States had 237 publications, Italy had 235 publications, Turkey had 156 publications, India had 137 publications, France had 128 publications, Iran had 115 publications, Egypt had 71 publications, Israel had 63 publications, and the United Kingdom had 6 publications. With some countries exhibiting higher levels of research productivity and significant contributions, this distribution highlights the diverse global involvement in scholarly discourse related to the subject.

The United States laid the ground work for later contributions by publishing the first works in the field. However, as time went on after 1990, the range of contributions grew to include contributions from various countries. Beginning in the new millennium, and more specifically after 2000, publications from all participating countries started to show an upward trajectory, which was a sign of a general increase in scholarly output. Notably, the trajectory of Chinese publications underwent a noticeable acceleration after 2012 and reached a notable peak. This quickening growth highlights China's quick rise to prominence in the academic conversation within the targeted field, highlighting the dynamic development of research participation and its impact over time (**Figure 2**).

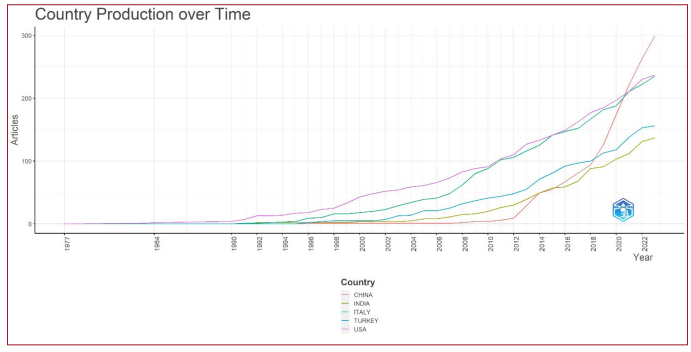

Figure 2.

These publications had 225 funders in total. National Natural Science Foundation of China was the major funder with 22 funds. China National Key Research and Development Programme was the second largest funder with 12 funds.

Leading affiliations in this field of study include Egyptian Knowledge Bank EKB, which has contributed 54 publications (5.279%), UDICE French Research Universities, which has contributed 41 publications (4.008%), Assistance PubliqueHopitaux Paris, which has contributed 31 publications (3.030%), Universite Paris Cite, which has contributed 25 publications (2.444%), Tel Aviv University, which has contributed 22 publications (2.11%), Sackler Faculty of Medicine, which has contributed 21, andAll India Institute of Medical Sciences.

The Word Cloud and Trend Topics

The word cloud diagram that was generated shows how popular particular keywords were within the dataset. Eachword's size and prominence in the diagram reflect how frequently it appears in thedataset. The keyword sand their corresponding frequencies are listed below: (**Figure3 a**)

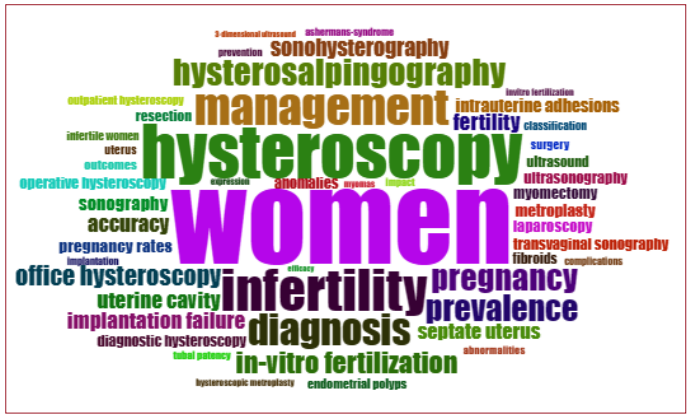

Figure 3a.

"women": 257 occurrences

"hysteroscopy": 154 occurrences

"infertility": 120 occurrences

"management": 105 occurrences

"diagnosis": 90 occurrences

"hysterosalpingography": 78 occurrences

"pregnancy": 75 occurrences

"prevalence": 74 occurrences

"in-vitro fertilization": 63 occurrences

"officehysteroscopy": 57 occurrences

Collectively, these keywords shedlight on the dataset's content and thematic focus. The frequent occurrence of these terms in the dataset's scholarly discourse highlights their importance and relevance. The prevalence of terms like "women," "hysteroscopy," and related terms like "infertility," "pregnancy," and "diagnosis" hints that the research in the dataset may be focused on gynecological and reproductive health, with an emphasis on diagnostic and management strategies.

The keywords 'hysteroscopy (n=422), hysterosalpingography office (n= 65), hysteroscopy (n= 49), and chronic endometritis (n=45) were located at the top of the trending topiclist (**Figure 3b**).

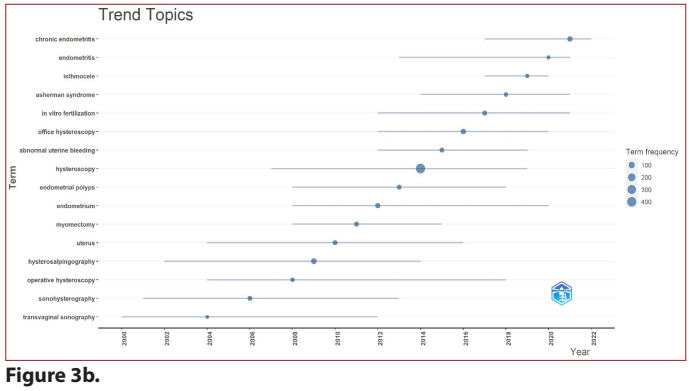

Figure 3b.

In the context of female infertility, the following journals focus exclusively on hysteroscopy: Journal of Minimally Invasive Gynecology (58 papers), Fertility and Sterility (84 articles), and Human Reproduction (50 articles). The number of articles published by the journal Fertility and Sterility on the topic of hysteroscopy in the context of female infertility has quickly increased, especially after 2007. In addition "Fertility and Sterility" journal publications were the most cited publications overall (4461 citations). **Table 1** shows the mostly publishing journals on this topic and also **Figure 4** shows the top sources' production over time.

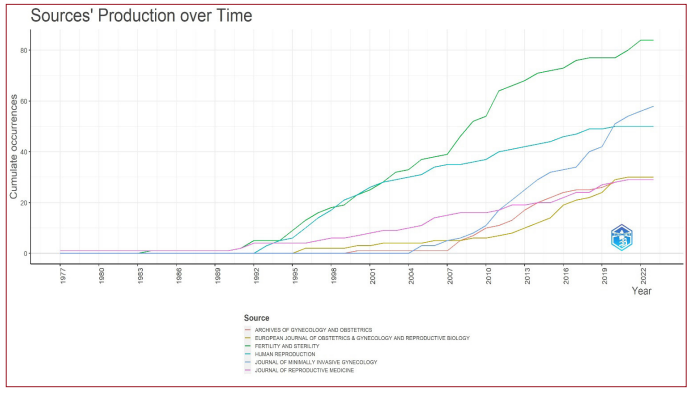

Figure 4.

Table 1. Mostly publishing journals on the topic of hysteroscopy and female infertility and citation number of these articles

Sources	Articles	Number of citations
Fertility and Sterility	84	4461
Journal of Minimally Invasive Gynecology	58	944
Human Reproduction	50	2328
European Journal of Obstetrics & Gynecology and Reproductive Biology	30	651
Archives of Gynecology and Obstetrics	29	337
Journal of Reproductive Medicine	29	393
Journal of Obstetrics and Gynaecology Research	26	202
International Journal of Gynecology & Obstetrics	21	405
Journal of Gynecologic Surgery	20	23
Clinical and Experimental Obstetrics & Gynecology	16	41

Collaboration Mappings

Collaborations between countries and organizations were examined at, according to the analysis done with VOS viewer. As a result, collaboration analys for 67 countries that have worked together on at least 5 publications were shown in **Figure 5a**. Most publications were produced by the nation with the largest circle, while collaborations were denoted by groups of thesamehue. The entire link strength was indicated by the line thickness, which represented the degree of connectivity.

Significant differences in research production and collaboration capacities were discovered through an analysis of countries' intellectual contributions. This data was according to first authorsans the United States had the

most documents (145), citations (4039), and an impressive total link strength (39), all of which were led by the country. With 101 documentsand 1050 citations, Peoples Republic of China displayed a considerably lower total link strength of 12. With 99 documents, 2715 citations, and 49 links overall, Italy displayed a strong scholarly presence. Other notable donors include Egypt (55 papers, 622 citations, total link strength: 8), Turkey (75 documents, 900 citations, total link strength: 5), India (69 documents, 697 citations, total link strength: 7), and France (55 documents, 1120 citations, total link strength: 11).

Figure 5b showed instances of sharedpublications and the linkages between organisations in terms of bibliographic coupling. A noteworthy finding was the existence of 47 groups working together on projects with ten or more publications in common. The information reveals the relationships and cooperative research projects between various organizations. Examples of prominent link strengths with high document counts and citations are Tel Aviv University, Shandong University, and University of Bari, demonstrating strong research collaboration. As a result of strong connections within its constrained scope, Hop Bicetre standsout with a relatively reduced document count but an astonishingly high total link strength.

DISCUSSION

In this study, 1.023 articles on female infertility and hysteroscopy since 1970 using Biblioshiny and VosViewer tools were retrospectively analyzed, and intuitively reflected the publication time distribution, main authors' collaboration network, research points, and development trend of articles in the field of female infertility and hysteroscopy by visual analysis of the knowledge map.

The first publication appeared in 1977, and the years that followed up until 1990 showed erratic article frequencies, with brief intervals when publications were scarceornon existent. After 2005, there was a fundamental change, indicated by a significant increase in annual article outputs. Particularly noteworthy are the years 2020 and 2021, which standout as publication activity peaks and produce, respectively, 68 and 67 articles. The annual growth rate of 8.17%. From the publication trend of articles, it can be seen that the published volume has increased steadily year by year. This shows that the topic of hysteroscopy in female infertility is being paid more and more attention by medical professionals and China has made great contributions in this field. But according to first authors, the intellectual contributions of different nations revealed differences in research production and collaborative qualities. With 145 papers, 4039 citations, and a strong overall link strength of 39, the United States took the top spot. China came in second with 101 documents, 1050 citations, and a weaker link strength of 12. With 99 documents, 2715 citations, and a total link strength of 49, Italy demonstrated a significant scholarly presence. Furthermore, significant contributions came from Egypt (55 papers, 622 citations, link strength: 8), Turkey (75 documents, 900 citations, link strength: 5), India (69 documents, 697 citations, link strength: 7), and France (55 documents, 1120 citations, link strength: 11), revealing distinctive patterns of research productivity and collaboration across countries. In summary, approximately 10.07% of the documents have international co-authorship.

Literature databases (such as PubMed, Scopus, and Web of Science) vary in terms of their scope, emphasis, and tools available. Scopus and Web of Science are multidisciplinary, whereas PubMed concentrate mostly on life sciences and biomedical fields.[22]

Due to its dual characteristics of multidisciplinarity and inclusion of high-quality publications, the Web of Science database was chosen for this study since it was a favor edoption. The Web of Science database is a great option because it integrates with bibliometric tools that can perform both citation analysis and output generation. The desire to eliminate bias and duplication led to the choice to forgochoosing various databases.

The main topics, concepts, ideas, or arguments in a text are condensed into document keywords, which help algorithms find the necessary data quickly and efficiently. They play a crucial part in many activities

Involving documents, including indexing, categorization, grouping, and summarization. Traditional approaches to keyword extraction mostly rely on examining statistical patterns of important phrases included in a document.[23-27] In the current study, the chosen keywords reveal information about the themes and substance of the collection. Their continued inclusion in academic discussions emphasizes how important they are. Notably, wordslike "women," "hysteroscopy," and related wordslike "infertility," "pregnancy," and "diagnosis" point to a potential focus on gynecological and reproductive health research, specifically around diagnostic and management approaches.

The journals that published the most papers were also investigated in this analysis. When choosing journals for publishing, scholars in this discipline can use this information as a reference.

Limitations

Despite its limitations, this study contributed to the bibliometric examination of publications on hysteroscopy and female infertility. Overall, this study's bibliometric and content analysis only touches on a small portion of the scholarly discussion around this issue. The sample does not contain any articles that were published in other databases (such as Pubmed, Scopus, etc.). In addition, only original articles made up the sample. Publications released on or after August 1, 2023, were excluded from the sample. More bibliometric studies are thus necessary to look into the articles in the databases related to hysteroscopy and female infertility.

CONCLUSION

The results of this study will be pertinent to numerous groups of individuals involved in hysteroscopy and female infertility research, including field practitioners, academics, and journal editors. Inparticular, they will inform researchers of the abundance of hysteroscopy and female infertility research worldwide in the hopes of fostering future international research collaborations on the topic. Researchers may find it helpful to know which journals have the best influence when they submit their work on female infertility and hysteroscopy in the future.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study didn't need to be ethically approved as it is free database study.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1347963
J Contemp Med 2023;13(5):891-895

Original Article / Orijinal Araştırma

Evaluation of the Effect of Intraoperative Frozen Section on Overall Timeliness and Survival in Lung Cancer Surgery

Akciğer Kanseri Cerrahisinde İntraoperatif Frozen Section Uygulamasının Genel Zamanlama ve Sağkalım Üzerine Etkisinin Değerlendirilmesi

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Abstract

Aim: We aimed to find out whether there is any delay in the management of the process in patients operated for lung cancer and to understand the effect of intraoperative frozen section on this process.

Material and Method: A total of 176 patients were examined. The dates of admission, diagnosis, operation and postoperative pathology results were noted. Five intervals were defined as time to first evaluation to diagnosis, first evaluation to surgery, diagnosis to surgery, first evaluation to the day of postoperative pathology report and diagnosis to the day of postoperative pathology report.

Results: The majority of patients (81.8%) were male and the median age was 63 years (iqr=11). The median time between the first assessment to final pathological examination result were 62 days (iqr=70). The time from initial presentation to surgery was significantly shorter (p<0.001) and the time from diagnosis to final pathology was also significantly shorter (p<0.001) in patients diagnosed by frozen section. However, there was no significant difference in the time from initial evaluation to diagnosis between the two groups (0.052). There was no significant difference in survival between patients diagnosed by frozen and patients diagnosed by other methods (p=0.508).

Conclusion: Solutions to increase the timeliness of care for patients with lung cancer can be designed with a better understanding of delays. Intraoperative frozen section diagnosis improves overall timeliness but has no effect on survival in lung cancer patients undergoing surgery.

Keywords: Timeliness, lung cancer, thoracic surgery, frozen section

Öz

Amaç: Akciğer kanseri nedeniyle ameliyat edilen hastalarda sürecin yönetiminde herhangi bir gecikme olup olmadığını bulmayı ve intraoperatif frozen incelemenin bu süreçteki etkisini anlamayı hedefledik.

Gereç ve Yöntem: Toplam 176 hasta analiz edildi. Başvuru tarihleri, tanıları, yapılan ameliyatlar ve ameliyat sonrası patoloji sonuçları kaydedildi. İlk başvurudan histopatolojik tanının konulmasına, cerrahi gününe ve ameliyat sonrası patolojinin sonuçlandığı güne kadar olan 3 zaman dilimi, histopatolojik tanının konulduğu günden cerrahiye kadar olan interval ve cerrahi gününden ameliyat sonrası patolojinin sonuçlandığı güne kadar olan gün olmak üzere toplam 5 interval tanımlandı.

Bulgular: Hastaların çoğunluğu (%81,8) erkekti ve ortanca yaş 63 (IQR=11) idi. İlk değerlendirmeden nihai patolojik inceleme sonucuna kadar geçen ortanca süre 62 gündü (iqr=70). İntraoperatif frozen inceleme ile tanı konulan hastalarda ilk başvurudan ameliyata kadar geçen süre anlamlı olarak daha kısaydı (p<0.001) ve tanıdan nihai patolojiye kadar geçen süre de anlamlı olarak daha kısaydı (p<0.001). Ancak, ilk değerlendirmeden tanıya kadar geçen süre açısından iki grup arasında anlamlı bir fark yoktu (0,052). İntraoperatif frozen ile tanı konulan hastalar ile preoperatif diğer yöntemlerle tanı konulan hastalar arasında sağkalım açısından anlamlı bir fark bulunmadı (p=0,508).

Sonuç: Akciğer kanserli hastaların bakımının zamanında yapılmasını sağlayacak planlar ancak gecikmelerin daha iyi anlaşılmasıyla tasarlanabilir. Akciğer kanseri nedeniyle cerrahi uygulanan hastalarda tanının intraoperatif frozen inceleme ile koyulması tüm sürecin hızlanmasına katkı sağlar ancak sağkalım üzerinde bir etkisi yoktur.

Anahtar Kelimeler: Akciğer kanseri, frozen kesit, göğüs cerrahisi, zamanındalık

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Received *(Geliş Tarihi)*: 23.08.2023 **Accepted *(Kabul Tarihi)*:** 24.09.2023

INTRODUCTION

In developed countries, lung cancer is the leading cause of cancer-related deaths because it is often not diagnosed until late stages.[1] In 2018, 52.7% of newly diagnosed lung malignancies in Turkey had distant metastases at the time of diagnosis.[2] It seems that, although there are many factors that directly affect the results, such as the type of cancer, the stage of the malignancy, and the treatment method the most critical step toward effective lung cancer treatment is a reliable early identification.[3] Delays in lung cancer detection and treatment can cause severe emotional anguish, decreased quality of life, higher use of health-care resources, and, arguably, increased costs of care.

A tissue biopsy is the gold standard for confirming the presence of malignancy. Lung tissue biopsy samples must contain enough tissue material to allow histopathology processes to determine the subtype of lung cancer. The initial biopsy is crucial for confirming an early diagnosis and preventing the need for a repeat biopsy, which increases the risk of complications and delays in treatment commencement.[4] There are numerous procedures that are frequently used to diagnose lung cancer, such as fiber optic bronchoscopy with or without transbronchial needle aspiration, endobronchial ultrasound (EBUS), image-guided trans-thoracic needle aspiration, mediastinoscopy, pleural fluid analysis (thoracentesis), thoracoscopy, and other surgical methods.

Despite comprehensive investigations, some patients with suspected lung cancer may undergo surgery without prior histological evidence of malignancy. Intraoperative frozen section is one of the key tools for directing surgical methods for pulmonary nodules since it is an important way for rapid intraoperative assessment of the benignity or malignancy and histological type of pulmonary nodules.[5,6]

Our goal was to find out if there were any delays between the initial presentation and the diagnosis or between the diagnosis and the treatment. Also, if there are delays in patient care, if these delays affect overall survival and what variables contribute to these delays. Our ultimate goal was to determine how the time from admission to the finalization of the postoperative pathologic diagnosis was affected in patients with intraoperative frozen diagnosis.

MATERİAL AND METHOD

In this retrospective study, patients from 1 March 2019 to 30 January 2023 who underwent surgical resection due to non small cell lung cancer were evaluated. The study was approved by Bilkent City Hospital Ethics Committee (Date: 25.06.2020, Decision no: E1-20-817). All participants provided informed consent. All procedures employed in this investigation were in conformity with the appropriate standards and regulations, as well as the Helsinki Declaration.

Patients who underwent more than one surgery, who were metastatic at the time of diagnosis and who were lost to follow-up and those whose records could not be accessed were excluded. Patients with incompatible preoperative and postoperative diagnoses were also excluded (2 patients).

Age, gender, preoperative diagnosis method, operation information, pathologic stage of the patients information was noted. Operative records, survival information and tumor characteristics were accessed through the Hospital and National medical records system. The dates of admission, diagnosis, operation day and the day of postoperative pathology result confirmed were also noted.

Thus 5 time intervals were defined as;

- from date of admission to diagnosis,
- from date of admission to surgery day
- from diagnosis to surgery date of
- from surgery day to postoperative pathology result confirmed
- from date of admission to postoperative pathology result confirmed

The date of admission was based on the day of presentation with the relevant complaint to any of pulmonology, thoracic surgery or medical oncology. Patients hospitalized in other clinics were considered to be admitted on the day of consultation to the same disciplines. For patients with a pathologic diagnosis obtained by any method, the date of the final pathology of the material obtained in the procedure was determined as the date of diagnosis. For patients diagnosed by intraoperative frozen, the date of diagnosis was determined to be the same as the date of operation. Twenty four patients came to our hospital for operation after being diagnosed at an external center. In these patients, unlike the patients diagnosed in our hospital, the date of admission was after the date of diagnosis. The date when the postoperative pathology was confirmed was taken as the date when the treatment plans of the patients were finalized.

Patients were divided into two subgroups: patients with preoperative diagnosis by any method and patients with intraoperative diagnosis by intraoperative frozen section. Those who underwent rebiopsy due to inadequate diagnosis were noted. In addition, the preoperative diagnosis obtained by EBUS, bronchus biopsy or trans thoracic needle biopsy was compared with the postoperative diagnosis.

The Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corp., Armonk, NY, USA) was used for all analyses. The variables were investigated using visual and analytical methods to determine whether or not they are normally distributed. Continuous variable descriptive analysis is expressed as a median (interquartile range [IQR]) for not normally distributed variables and mean (standard deviation), or a number (percentages) for normally distributed variables. Numbers and percentages are used to represent categorical variables. The Mann-Whitney U test was used to compare time invervals and survival between the groups. A p value of less than 0.05 was considered to show a statistically significant result.

RESULTS

In total, we identified 176 patients. The majority of patients (81.8%) were male, the median age was 63 (iqr=11), and squamous cell carsinoma was the most frequent histology (47.1%). The most common comorbidity was chronic obstructive pulmonary disease (n=56, 31.8%). While there were 56 patients (31.8%) diagnosed by bronchus biopsy or EBUS, 64 patients (36.3%) were diagnosed by transthoracic biopsy. There were 54 patients (30.7%) in the frozen group and 122 patients (69.3%) in the non-frozen group. The tumors characteristics are listed in **Table 1**.

Table 1. Tumor Characteristic in 176 patients

	No. of tumors n (%)
Histologic type	
squamous cell	83(47.1%)
adenocarcinoma	55(31.2%)
large cell	11(6.2%)
nos	9(5.1%)
carsinoid	8(4.5%)
adenosquamous	4(2.3%)
malign mesenchimal tumor	3(1.7%)
malign epithelial tumor	1(0.6%)
snovial sarcom	1(0.6%)
karsinosarcoma	1(0.6%)
Stage	
IA1	11(6.3)
IA2	20(11.4%)
IA3	16 (9.1%)
IB	17(9.7%)
IIA	15(8.5%)
IIB	45(25.6%)
IIIA	39(22.2%)
IIIB	7(4%)
IIIC	2(1.1%)
IVA	4(2.3%)

Of the 54 patients in whom the diagnosis was made by intraoperative frozen section, 34 (62.9%) underwent bronchus biopsy or transthoracic needle biopsy as a preoperative diagnostic procedure with negative results (16 bronchus biopsy and 18 transthoracic needle biopsy).

Wedge resection or segmentectomy was performed in 8 cases (4.5%), lobectomy in 99 cases (56.2%), bilobectomy in 12 cases (6.8%), lobectomy plus thoracic wall resection in 9 cases (5.1%), sleeve lobectomy in 8 cases (4.5%), pneumonectomy in 31 cases (17.6%), and extended pneumonectomy in 9 cases (5.1%).

The median time between the first assessment to diagnosis were 19 days (iqr=34.7), first assessment to surgery day were 40 days (iqr=67.2) and first assessment to final pathological examination result were 62 days (iqr=70). The median time between the diagnosis to surgery day were 20 days (iqr=42) and diagnosis to final pathological examination result were 42 days (iqr=40.7). The median time between the surgery day to final pathological examination result were 19 days (iqr=16).

The time from initial presentation to surgery was significantly shorter (p<0.001) and the time from diagnosis to final pathology was also significantly shorter (p<0.001) in patients diagnosed by frozen section. In addition, the whole process progressed faster in patients diagnosed perioperatively by frozen section (p<0.001). However, there was no significant difference in the time from initial evaluation to diagnosis between the two groups (p=0.052). In addition, the time from surgery to the postoperative pathology result was not affected by whether the diagnosis was made by frozen section or not (p=0.464). The timeliness of entire cohort is summarized in **Table 2**.

Table 2. Median time intervals for frozen and non-frozen groups

	frozen median day (iqr)	non-frozen median day (iqr)	p value
	21.5 (30.2)	16(43.5)	0.052
from date of admission to surgery day	21.5 (26.5)	55(75.2)	<0.001
from diagnosis to surgery day	0(0)	31.5(39.7)	<0.001
from diagnosis to the postoperative pathology	19.5(18.2)	53(40.2)	<0.001
from surgery day to the postoperative pathology	19.5(18)	19 (13.2)	0.464
from date of admission to the postoperative pathology	46 (47.7)	73(68.2)	<0.001

Median survival was 15.66 months (min 0.17- max 41.96 months, iqr=22.1). In patients who underwent lung resection, there was no significant difference in survival between patients diagnosed by frozen and patients diagnosed by other methods (p=0.508).

DISCUSSION

Screening for early lung cancer development is essential for early treatment, which can improve the disease's outcome. Because most modern tools and methodologies can only detect cancer in its advanced stages, when therapy may be ineffective in controlling the disease, early diagnosis of lung cancer remains challenging. There are numerous effects that can affect how long it takes to reach a diagnosis and how long it takes for the treatment plan to be finalized. Despite all of the multiple variables, it is possible to argue that decreasing this interval will benefit the sickness. Clinicians can propose measures to speed up the lengthiest phase if they can pinpoint it.

The intersections that patients must pass through between diagnosis and the choice of a treatment plan are described by standardized definitions of time points and intervals, some of which are objective (such as the date of diagnosis or the date of surgery), while others, such as the date of initial presentation, are subjective.[4]

The reliability and applicability of globally applicable approaches to assessing the timing of cancer diagnosis in each center is questionable, as the dates of some decisive

milestones are uncertain and multifactorial. Accurate estimates of the timing of cancer diagnosis and understanding the factors affecting the diagnostic process require methods that are independent of this uncertainty. In this sense, it is important for each center to evaluate its own process and see where it stands and to take delaying measures. Our findings are consistent with those of numerous other research conducted around the world. The time to diagnosis ranged from 1 to 35.5 days in various studies.[7] They commented that there was a higher than average delay, especially in veteran hospitals, but suggested that this may be due to differences in care processes.[7-9] However, the median time to diagnosis in this study was 19 days, which is within the guidelines recommended by the RAND Corporation.[9]

Similarly, there have been numerous studies on the time interval between diagnosis and treatment. Times ranging from 22 to 66 days have been reported.[10,11] In our study, the treatment time was found to be 20 days. Compared to other studies, this short interval may be due to the high number of patients diagnosed with intraoperative frozen section. Because intraoperative frozen section makes it possible to diagnose and treat the patient on the same day.

In the RAND Corporation guideline, it was pointed out that the time until diagnosis should not exceed 42 days.[9] When global data on the subject are analyzed, inter-country variations are noteworthy.[11] Access to timely health treatments is not the same in all nations, and there are variances even within the same country's centers and regions. If the center determines in its own evaluation that the most time loss occurs in the period from diagnosis to surgery, it should not hesitate to diagnose appropriate cases with intraoperative frozen section. In this way, it may be possible to minimize the impact of center-specific factors on patient care. Our study showed that in patients undergoing lung resection, frozen section diagnosed patients were prepared for surgery faster from the first admission. Ultimately, this acceleration, which is due to the fact that diagnosis and treatment are offered on the same day, shortens the time from initial presentation to final pathology in patients undergoing lung resection. In our study, this time was approximately one and a half times between the two groups.

Some studies have reported mixed findings on whether mortality is affected by delays in diagnosis or treatment. While some attributed the decrease in mortality to shorter delays, other studies actually found a statistically significant relationship between shorter delays and increased mortality.[9-11] In our study, in support of these conflicting data, we concluded that this time advantage provided by intraoperative frozen section did not affect survival as a result of the comparison between the groups. Therefore, we think that it is not possible to definitively determine whether the delays experienced have a positive or negative effect on long-term outcomes.

In our study, it was determined that the interval from surgery to the final postoperative pathology report was not affected by whether intraoperative frozen section was performed or not. This interval is independent of surgeons and is pathology managed. It is also the least open to external influence in the entire timeline. In the goal of improving patient care, it would be wise to focus on services that are within the sphere of influence.

Many studies have aimed to identify and correct inefficiencies in all aspects of patient care, from initial contact to final follow-up. Recommendations include creating a dedicated team for each cancer, providing a patient navigator to help schedule appointments, diagnostic and treatment algorithms, and using outpatient care instead of hospitalization for minor diagnostic or treatment procedures.[7,13] We believe that these types of system improvement steps will be the focus of attention in the future. It is critical to continue working toward improving cancer timelines so that we can keep up with developments in lung cancer diagnosis and therapy.

This study has some limitations. First of all, it is a retrospective and single-center study. The facilities of the center may be different in other parts of the country, so generalizing the data to Turkey in general may be misleading. Moreover, the period covered by the study includes the COVID-19 pandemic period when access to hospitals with other complaints was limited. The sample size is small, and larger studies with more centers and cases are required. It was also observed that due to some personal preferences, patients hesitated to reach the center where they could receive treatment despite knowing their diagnosis.

CONCLUSION

In lung cancer, reducing the time between diagnosis and definitive treatment plan provides a survival advantage. From initial evaluation to postoperative pathologic examination of patients, it has been found that the most time lost is the time spent in deciding on and preparing for surgery. Intraoperative frozen section shortens both times but is not effective in achieving a survival advantage.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Bilkent City Hospital Ethics Committee (Date: 25.06.2020, Decision no: E1-20-817).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1349221
J Contemp Med 2023;13(5):896-900

Original Article / Orijinal Araştırma

Arterial Spin Labelling Magnetic Resonance Perfusion Imaging for the Diagnosis of Cerebral Venous Thrombosis

Akut Serebral Venöz Tromboz Tanısında Arteriyel Spin Etiketleme Manyetik Rezonans Perfüzyon Görüntüleme

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Abstract

Aim: Early diagnosis of cerebral venous thrombosis (CVT) is crucial for a favourable prognosis as CVT can lead to severe outcomes. However, certain scenarios, such as during pregnancy, restrict the use of contrast agents, thus rendering conventional magnetic resonance imaging (MRI) methods insufficient for accurate diagnosis. In light of these challenges, our study endeavours to assess the diagnostic potential of the arterial spin labelling magnetic resonance perfusion (ASL-MRP) technique, a contrast-agent–free approach, in the context of CVT diagnosis.

Material and Method: Between 1 March 2022 and 30 May 2022, patients diagnosed with CVT via contrast-enhanced MR venography in the neurology clinic of our hospital were evaluated through ASL-MRP. Patient-specific demographics, including age, gender, presenting symptoms, underlying causes, impacted cortical sinus structures and MRI findings, were documented. Within the framework of ASL-MRP, an elevation in cerebral blood flow (CBF) detected within the affected sinus and/or neighbouring structures was deemed indicative of pathological conditions.

Results: Among the 13 patients included in our study, six were diagnosed with acute CVT, whereas seven were diagnosed with chronic CVT. The assessment of CBF using ASL-MRP revealed CBF elevation in five out of the six cases (83.3%) exhibiting acute CVT. However, no anomalous findings were observed in the ASL-MRP scans of patients presenting with chronic CVT.

Conclusion: The utilisation of ASL-MRP eliminates the need for contrast agent administration. It is a promising technique in facilitating the diagnosis of acute CVT and distinguishing it from chronic CVT cases.

Keywords: Cerebral venous thrombosis, arterial spin labelling magnetic resonance perfusion, pregnancy, diagnosis

Öz

Amaç: Serebral venöz trombozunun (SVT) erken tanısı, SVT'nin ciddi sonuçlara yol açabilmesi nedeniyle iyi prognoz için çok önemlidir. Ancak hamilelik gibi bazı durumlar, kontrast maddelerin kullanımını kısıtlar, bu nedenle de geleneksel manyetik rezonans görüntüleme (MRG) yöntemleri doğru teşhis için yetersiz kalabilir. Bu zorluklar göz önünde bulundurularak çalışmamız, kontrast madde içermeyen bir yaklaşım olan arteriyel spin etiketleme tabanlı manyetik rezonans perfüzyon (ASE-MRP) tekniğinin, SVT teşhis potansiyelini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: 1 Mart 2022 ile 30 Mayıs 2022 tarihleri arasında hastanemiz nöroloji kliniğinde MR venografi ile SVT tanısı konulan hastalar ASE-MRP ile değerlendirildi. Yaş, cinsiyet, başvuru semptomları, risk faktörleri, etkilenen kortikal sinüs yapıları ve MRG bulguları kaydedildi. ASE-MRP tekniğinde, etkilenen sinüs ve/veya komşu yapılardaki serebral kan akımında (SKA) artış, patolojik durumların göstergesi olarak kabul edildi.

Bulgular: Çalışmamıza dahil edilen 13 hastanın altısına akut, yedisine kronik SVT teşhisi kondu. ASE-MRP kullanarak yapılan SKA değerlendirmesinde, akut SVT tanısı alan altı olgudan beşinde (%83,3) SKA artışı saptandı. Ancak kronik SVT ile başvuran hastaların ASE-MRP taramalarında anormal bulgu gözlenmedi.

Sonuç: ASE-MRP'nin kullanılması kontrast madde uygulama ihtiyacını ortadan kaldırır. Akut SVT'nin tanısını kolaylaştırmada ve kronik SVT vakalarından ayırmada umut verici bir tekniktir.

Anahtar Kelimeler: Serebral venöz tromboz, arteriyel spin etiketleme manyetik rezonans perfüzyon görüntüleme, gebelik, tanı

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Received *(Geliş Tarihi)*: 24.08.2023 **Accepted *(Kabul Tarihi)*:** 23.09.2023

INTRODUCTION

Cerebral venous thrombosis (CVT) constitutes a relatively uncommon cause, accounting for approximately 0.5–1% of all stroke cases.[1] Although it often exhibits a favourable prognosis, CVT can still lead to significant rates of disability and mortality.[2,3] Timely and effective treatment has been demonstrated to impact patient outcomes positively.[4] Given the diverse range of clinical presentations and characteristics associated with this condition, the role of imaging modalities in the diagnostic process is crucial.[5] However, the identification of CVT can sometimes face delays or challenges due to atypical clinical manifestations.[6]

Although computed tomography (CT) and magnetic resonance (MR) angiography are recommended diagnostic tools for detecting CVT, these methods have limitations.[7,8] They include issues such as false negatives/positives, susceptibility to motion artefacts, extended examination times and reduced sensitivity in cases where contrast agents cannot be used, particularly in non-contrast-enhanced time-of-flight (TOF) MR venography (MRV).[9,10] Among these limitations, the requirement for contrast agents is particularly significant. Furthermore, circumstances such as pregnancy (a notable risk factor for CVT), drug allergies and renal impairment can limit the use of contrast agents. In situations where contrast agents cannot be administered, the diagnostic sensitivity of the procedure diminishes, exacerbating difficulties in distinguishing between hypoplasia and thrombosis.[11] Digital subtraction angiography, often considered the gold standard for CVT diagnosis, is feasible for only a select group of patients due to its invasive nature.[12]

Arterial spin labelling (ASL) MR perfusion (MRP) has emerged as a non-invasive and reliable technique for evaluating cerebral blood flow (CBF) without the need for intravenous contrast agent administration.[13] Although the existing literature provides limited evidence of its effectiveness in diagnosing acute ischemic stroke and CVT, these studies are based on a few clinical cases.[14-16] Consequently, ASL-MRP has not been integrated into the routine imaging approach for CVT diagnosis thus far.

In the context of our investigation, our primary aim was to assess the diagnostic effectiveness of the ASL-MRP technique in CVT cases.

MATERIAL AND METHOD

Ethics Committee

The study was approved by Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 01.02.2022, Decision no: E1-22-2365). Informed voluntary consent was obtained from all patients included in the study. Our study was conducted in accordance with research and publication ethics following the principles in the Declaration of Helsinki.

This prospectively designed study was conducted between March 2022 and May 2022 at our hospital's neurology clinic. Within this period, patients diagnosed with CVT following MRV were subsequently evaluated using ASL-MRP. The patients' age, gender, comorbidities, risk factors, presenting symptoms, neurological examinations, MRI results, affected venous sinuses and prognoses were recorded. The exclusion criteria for the study included pregnancy, allergy to medications, history of stroke and any diagnosed neurological disorder related to the central nervous system.

MRI and Analysis Protocol

All patients were examined using a 3-T MRI unit (SIGNA™ Pioneer 3T MRI; GE Healthcare, Milwaukee). ASL-MRP imaging was conducted using a pseudocontinuous ASL pulse sequence. The ASL parameters were configured as follows: labelling pulse duration=1.5 s, post-labelling delay=1.5 s, TR=4948 ms, TE=10.9 ms, field-of-view=240 × 240 mm, number of excitations=3, number of interleaved slices=32 and slice thickness=4 mm. A quantitative map of CBF in mL/100 g tissue/min was obtained using the perfusion quantification model. An increase in CBF in the affected sinuses and/or neighbouring structures detected through ASL-MRP was considered pathological. The images were interpreted and reported by a radiology specialist with over 20 years of experience in the field of neuroradiology.

Statistical Analysis

The obtained data were analysed using a statistical software package (SPSS) (Version 17, Chicago IL, USA). Descriptive statistics (mean, standard deviation, median, minimum, maximum, count and percentage) were provided for categorical and continuous variables in the study.

RESULTS

Our study included 13 patients, with a mean age of 32.7±9.7 years and 76.9% (n=10) being female. Among the 13 patients, six were diagnosed with acute CVT, whereas seven exhibited chronic CVT. Within the acute CVT group, five (83.3%) demonstrated an increase in CBF when assessed using the ASL-MRP technique. Conversely, the ASL-MRP sequences for patients diagnosed with chronic CVT showed no pathological findings (Figure and Table).

Among the thrombosed sinuses, the transverse sinuses were the most commonly affected, accounting for 77% of the cases (46.2% and 30.8% on the right and left, respectively). The sigmoid sinuses followed closely at 46.2% (23.1% and 23.1% on the right and left, respectively), whereas the superior sagittal sinus was involved in 30.8% of the cases. In terms of clinical presentation, the most frequent complaint was headache, as reported by 69.2% of the patients. Seizures were observed in 23.1% of the cases, and altered consciousness was noted in 7.7% of the cases.

Table : Characteristics of the Cases and ASL-MRP Results

No	Age	Gender	Presenting symptoms	Possible underlying causes	Impacted cortical sinus	Timeliness	ASL-MRP (+/-)*
1	25	Male	Headache	Drug abuse	Right TS and SS	Acute	+
2	29	Female	Headache	Postpartum period	Right TS and SS	Acute	+
3	57	Female	Altered Consciousness	-	SSS	Acute	+
4	21	Female	Seizure	Steroid use	Right TS and SSS	Acute	-
5	29	Female	Headache	Postpartum period	Right TS and SSs	Acute	+
6	28	Female	Seizure	-	Left TS and SS	Acute	+
7	25	Female	Headache	Postpartum period	Right TS	Acute	-
8	40	Male	Seizure	Thrombophilia	Right TS and SS	Cronic	-
9	32	Male	Headache	-	Bilateral TS	Cronic	-
10	38	Female	Headache	Migraine	SSS	Cronic	-
11	42	Female	Headache	-	Left TS and SS	Cronic	-
12	35	Female	Headache	-	Left TS	Cronic	-
13	28	Female	Headache	-	Right TS	Cronic	-

SS; sigmoid sinus; FAQ; superior sagittal sinus, TS; transverse sinus *In this table ASL-MRP results (+/-) are presented.

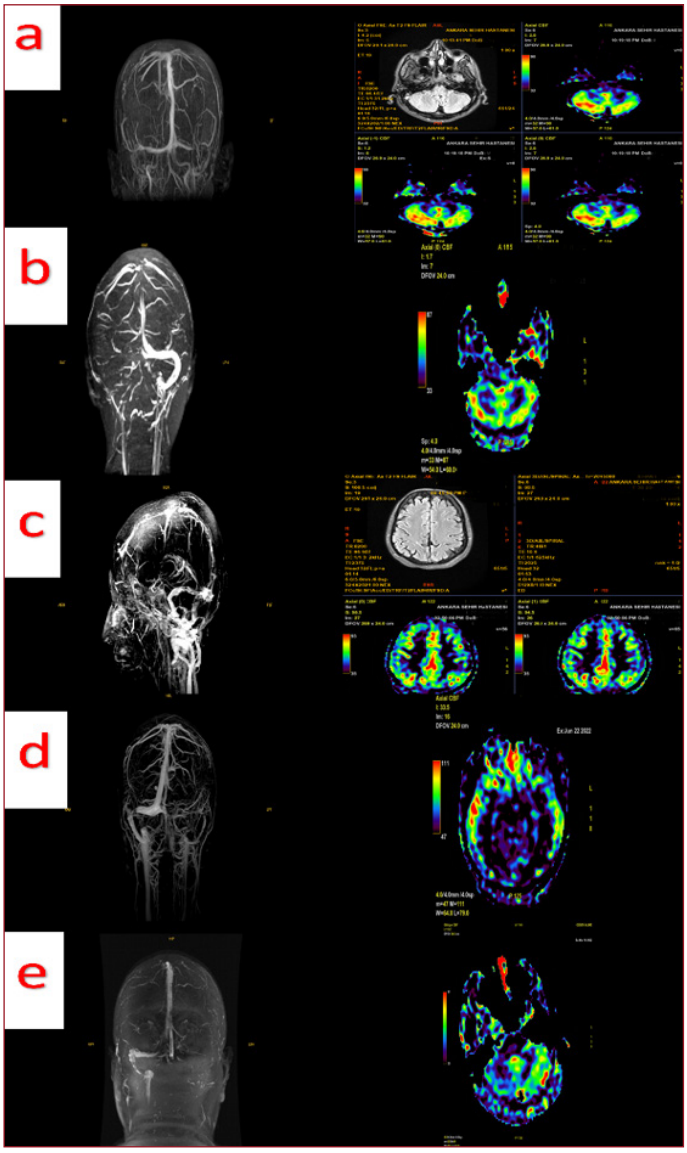

Figure: In cases 1 and 2 with right TS and SS thrombosis (right image), CBF increase in adjacent structures in ASL-MRP images (image on the right, red color) [a and b]. In case 3 with CNS thrombosis (right image), CBF increase in adjacent structures in ASL-MRP images (left image, red color). In case 5, TS and CNS thrombosis on the right, TS hypoplasia on the left (right image), increased CBF in adjacent structures on ASL-MRP images (left image, red color) [d]. CBF increase in adjacent structures in ASL-MRP images in case 6 (right image) with left TS and SS thrombosis (image in left, red color).

DISCUSSION

Diagnosing CVT can be exceptionally challenging due to variability in clinical presentations and imaging findings. When conventional cranial MRI and head CT yield inconclusive results, the possibility of CVT cannot be definitively ruled out, necessitating further assessment through MRV.[6,17] In cases where contrast agents cannot be administered, MRV's sensitivity and specificity diminish, potentially leading to false-negative or false-positive outcomes.[10] In our study aimed at evaluating the impact of the ASL-MRP technique on CVT diagnosis, we observed an increase in CBF in five out of six patients with acute CVT. However, no abnormal CBF findings were detected in the ASL-MRP scans of the seven chronic CVT cases.

Although the annual incidence of CVT is reported to be 1–2 million cases, recent advances in neuroradiology suggest higher rates.[18,19] CVT, commonly observed in young females with a favourable prognosis,[20,21] can result in mortality rates of up to 5%[2] and long-term neurological sequelae of up to 15%.[3] Given that effective treatment can improve prognosis in CVT cases, early diagnosis is crucial.[4] Similar to our findings, multiple venous sinuses are often affected, with the superior sagittal sinus, transverse sinuses and sigmoid sinuses being the most commonly involved.[17] The female gender-specific pregnancy risk factor constituted approximately three-quarters of our study population and may impose limitations on imaging techniques.

The complexity of diagnosing CVT is influenced by various factors. For instance, the use of ionising radiation in CT is contraindicated during pregnancy.[22] Additionally, conditions such as pregnancy, renal insufficiency and drug allergies limit the use of contrast agents, resulting in reduced sensitivity of TOF-MRV images.[9] Moreover, clinical symptoms, particularly changes in consciousness, can lead to motion artefacts during imaging procedures, potentially compromising the accuracy of CVT diagnosis. These complexities underscore the need for a comprehensive approach to CVT diagnosis, considering the limitations of various imaging modalities and the dynamic nature of

disease presentation. Therefore, the sensitivity of different MR techniques in diagnosing CVT has been investigated in the literature. They include FLAIR, echo-planar T2*-weighted susceptibility-weighted imaging and diffusion-weighted images.[23-25]

The ASL-MRP technique operates on the principles of subtracting a 'tag' image acquired through magnetic labelling of blood from a 'control' or 'reference' image obtained without labelling. This approach involves labelling the magnetisation of water protons in the blood using methods such as inversion at the major feeding arteries. In ASL-MRP, an elevation in blood flow within the affected vascular structures is considered indicative of pathology.[26] Previous studies have demonstrated the effectiveness of ASL-MRP in diagnosing acute stroke resulting from arterial occlusion.[14,15] For instance, Knag et al. conducted a study involving 13 CVT patients using ASL-MRP and identifying the bright sinus appearance image in all patients. They also observed hypoperfusion in 77% of the cases. The authors emphasised the potential utility of bright sinus appearance as a diagnostic marker within ASL-MRP assessments.[16] Similarly, our study also evaluated CBF through ASL-MRP, detecting abnormalities in 83.3% of acute cases. This finding suggests that ASL-MRP may offer benefits in diagnosing acute CVT, akin to its utility in acute arterial stroke cases. The ability of ASL-MRP to assess CBF non-invasively presents a promising avenue for enhancing the accuracy and timeliness of acute CVT diagnosis, which could potentially influence treatment decisions and patient outcomes.

Furthermore, the variability in the presentation and progression of CVT cases underscores the need for a multimodal diagnostic approach. Combining ASL-MRP with other imaging techniques, such as conventional MRV and dynamic contrast-enhanced imaging, could enhance diagnostic accuracy and offer a more comprehensive assessment of cerebral haemodynamics.

CONCLUSION

Our study contributes to the growing body of literature providing evidence on the potential of ASL-MRP as a valuable tool for diagnosing CVT, particularly in the acute phase. Assessing CBF non-invasively through ASL-MRP offers a unique advantage in cases where contrast agents cannot be used. However, further research involving larger cohorts and longitudinal follow-up is necessary to validate and refine the diagnostic utility of ASL-MRP in different stages of CVT. As our understanding of neuroimaging techniques continues to evolve, integrating advanced methods such as ASL-MRP into clinical practice holds the promise of improving the accuracy and timeliness of CVT diagnosis, leading to more informed treatment decisions and ultimately better patient outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 01.02.2022, Decision no: E1-22-2365).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1348372
J Contemp Med 2023;13(5):901-906

Original Article / Orijinal Araştırma

Comparison of Results of the sIPOM and the IPOM-Plus Techniques for Small and Medium-Sized Primary Midline Abdominal Wall Hernias

Küçük ve Orta Büyüklükteki Primer Ortahat Karın Duvarı Fıtıklarında sIPOM ve IPOM-Plus Tekniklerinin Sonuçlarının Karşılaştırılması

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Abstract

Aims: To compare the results of the standard intraperitoneal onlay mesh (sIPOM) and intraperitoneal onlay mesh-plus (IPOM-Plus) techniques for the repair of small and medium-sized primary midline abdominal wall hernias (PMAWHs).

Material and Method: A prospectively documented data of 82 patients who underwent the sIPOM and IPOM-Plus approach between January 2016 and December 2021 was retrospectively evaluated. Forty-one patients with PMAWH repaired with sIPOM (18) and IPOM-Plus (23) were included in the study. Median follow-up for the sIPOM and IPOM-Plus was 73 and 51 months (mean 73.83±7.81vs. 47.43±19.22), respectively.

Results: Both groups had no difference in demographics, comorbidities, and smoking habits. The mesh area (MA) and the mesh-to-defect ratio (MDR) were not significant (p=0.083 and p= 0.30, respectively); however, the defect area (DA) was higher in the sIPOM group (p= 0.005). The IPOM-Plus group had a longer operative time and length of hospital stay (LOHS) and higher early postoperative pain than the IPOM group (p=0.002, p=0.049 and p <0.001). Seroma developed in 4 (22.2%) and 2 (8.6%) patients in the sIPOM and IPOM-Plus groups, respectively, with no significant difference (p=0.477). There was two (11.1%) recurrence in the sIPOM group, while no recurrences were observed in the IPOM-Plus group (p=0.196).

Conclusion: The IPOM-Plus approach has similar seroma and recurrence rates to sIPOM in small and medium-sized PMAWH, but with higher postoperative pain and longer LOHS. More randomized controlled studies (RCTs), meta-analyses, and multi-center studies with large samples are needed for more valuable results.

Keywords: sIPOM, IPOM-Plus, Primary abdominal wall hernia, Laparoscopic hernia repair

Öz

Amaç: Küçük ve orta büyüklükteki primer orta hat karın duvarı fıtıklarının (PMAWH) onarımında standart intraperitoneal onlay mesh (sIPOM) ve intraperitoneal onlay mesh-plus (IPOM-Plus) tekniklerinin sonuçlarının karşılaştırılması amaçlandı.

Gereç ve Yöntem: Ocak 2016 ile Aralık 2021 arasında sIPOM ve IPOM-Plus yaklaşımı uygulanan 82 hastanın prospektif olarak belgelenmiş verileri retrospektif olarak değerlendirildi. Çalışmaya sIPOM (18) ve IPOM-Plus (23) ile onarılan 41 PMAWH hastası dahil edildi. sIPOM ve IPOM-Plus için ortanca takip süresi sırasıyla 73 ve 51 (ortalama 73.83±7.81vs. 47.43±19.22) aydı.

Bulgular: Her iki grupta demografik özellikler, eşlik eden hastalıklar ve sigara içme alışkanlığı açısından fark yoktu. Mesh alanı (MA) ve mesh-defekt oranı (MDR) istatistiksel olarak anlamlı değildi (sırasıyla p=0,083 ve p=0,30); ancak defekt alanı (DA) sIPOM grubunda daha yüksekti (p= 0,005). IPOM-Plus grubunda ameliyat süresi ve hastanede kalış süresi (LOHS) daha uzundu ve erken ameliyat sonrası ağrı daha fazlaydı (p=0,002, p=0,049, p <0,001). sIPOM ve IPOM-Plus gruplarında sırasıyla 4 (%22,2) ve 2 (%8,6) hastada seroma gelişti, anlamlı fark yoktu (p=0,477). sIPOM grubunda iki (%11,1) nüks görülürken, IPOM-Plus grubunda nüks gözlenmedi (p=0,196).

Sonuç: IPOM-Plus yaklaşımı, küçük ve orta büyüklükteki PMAWH'de sIPOM ile benzer seroma ve nüks oranlarına sahiptir, ancak ameliyat sonrası ağrı daha yüksek ve LOHS daha uzundur. Daha değerli sonuçlar için daha fazla randomize kontrollü çalışmaya (RKÇ), meta-analizlere ve geniş örneklemli çok merkezli vaka kontrol çalışmalarına ihtiyaç vardır.

Anahtar kelimeler: sIPOM, IPOM-Plus, Primer karın duvarı fıtığı, Laparoskopik fıtık tamiri

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Received *(Geliş Tarihi)*: 23.08.2023 **Accepted *(Kabul Tarihi)*:** 20.09.2023

INTRODUCTION

Until approximately three decades ago, the repair of abdominal wall hernias was executed with open techniques. Following the initial introduction of the laparoscopic ventral and incisional abdominal wall hernia repair (LVIHR) technique in 1993, it began to receive recognition and approval within the surgical community.[1,2] The paramount element of this acceptance is that laparoscopic repair manifests significantly reduced incidences of surgical site complications despite presenting recurrence rates similar to open repairs.[3] The LVIHR technique involves using a large mesh to bridge hernia defects. The mesh is anchored to the abdominal wall with transfascial sutures and permanent staples. Various techniques have been developed for closing defects over the years to prevent issues like seroma formation, postoperative bulging, and recurrences caused by incomplete anatomical restoration of the abdominal wall with bridging.[4–7] As per the IEHS (International Endohernia Society) Guideline, the LVIHR technique accompanied by defect closure has been designated as intraperitoneal onlay mesh-plus (IPOM-plus), and the conventional LVHIR technique has been defined as standard intraperitoneal onlay mesh (sIPOM).[8,9]

Incisional and primary abdominal wall hernias (AWHs) exhibit distinctions in terms of underlying causes, patient characteristics, outcomes of surgical interventions, and potential complications. When writing a scientific report about abdominal wall hernias, it is recommended to analyze and report the results of incisional and primary hernia repairs as separate entities.[10–12] The EHS reported distinct classifications for incisional and primary AWHs.[13] This study aims to present a comparison of the outcomes of the sIPOM and the IPOM-Plus techniques in primary midline abdominal wall hernia repairs. All surgical procedures were performed by the same surgeon. The main hypothesis of this study was that in the IPOM-Plus technique, adding the closing of the defects could decrease the seroma formation and recurrence rates, but the postoperative pain could increase due to the tension on the midline.

MATERIAL AND METHOD

A prospectively documented data emanating from the primary and incisional AWH repairs with laparoscopic IPOM-Plus on 64 patients or sIPOM technique on 18 patients, which were performed by the same surgeon within the timeframe spanning from January 2016 to December 2021 at the Trabzon Kanuni Training and Research Hospital General Surgery Clinic, were retrospectively evaluated. The study protocol received endorsement from the ethics committee of Trabzon Kanuni Training and Research Hospital (11384-2022/22).

Patients over 18 years of age with midline primary ventral hernia and operated with laparoscopic IPOM-Plus or sIPOM technique were included in the study. Exclusion criteria: Ventral and incisional hernia repairs with open or other laparoscopic procedures, incisional hernia repairs, primary lateral AWH repairs, emergency cases, hernias complicated with fistula formation and surgical site infection, and loss of domain (LOD) were determined. All patients underwent preoperative physical examination and routine laboratory tests. In addition, non-contrast abdominal computed tomography (CT) was performed in all cases to evaluate the location and size of AWH defects according to the European Hernia Society Classification. CT-defined features of hernia defects were also measured and verified during the operation. Demographic characteristics of the patients (age, gender, body mass index (BMI), history of previous hernia surgery, comorbidities, smoking habit), American Society of Anesthesiology (ASA) scores, surgical technique, operation times, hernia defect characteristics and mesh area, the type of mesh, mesh fixation methods, complications during and after the operation, postoperative length of hospital stay (LOHS), morbidity, recurrence and reoperations, pain scores (Visual Analogue Scale – VAS, ranging from 0 to 10) were evaluated retrospectively. All patients were examined on the 10th postoperative day, in the first, third, and sixth months, and at the end of the first year. Abdominal CT was included in the first-year controls. Individuals who failed to participate in their clinical appointments were contacted by telephone.

Outcomes of the IPOM-Plus and the sIPOM techniques for PMAWHs were compared. Statistical calculations were made using the SPSS22 program. Chi-square or Fischer's exact test was used for categorical data (presented as n (%)), and the Student-t test or Manny-Whitney U test was used for continuous data (presented as the mean±SD (standard deviation)). A $p < 0.05$ value was considered as significant.

Surgical Technique

The IPOM-Plus and sIPOM techniques share identical steps except for the closure of the defect. A single intravenous dose of 1 g cefazoline was administered to all patients roughly thirty minutes prior to the surgical procedure. The patients were positioned on the operating table in the supine position, with their arms secured on both sides. Following the administration of general anesthesia, carbon dioxide insufflation was initiated by introducing a Veress needle through Palmer's point, progressing until an intra-abdominal pressure of up to 12 mmHg was achieved. Next, the abdominal cavity was entered with the help of an optical trocar through an incision made on the left mid-axillary line, usually at the level of the umbilicus. Two 5 mm working ports were inserted approximately 5 cm above and below the optical trocar. The trocar layout was chosen flexibly according to the location and size of the defects. All trocars were placed lateral to the linea semilunaris (**Figure 1**). A 5 mm working port was entered from the opposite side if there was difficulty on the same side while fixing the mesh. After intra-abdominal exploration, all omental and intestinal adhesions to the anterior abdominal wall, if any, were separated with sharp dissections. The use of energy devices was avoided to prevent thermal injury during adhesiolysis. However, energy devices were kept ready for use when necessary. The omentum or intestines within the hernia

defects were separated with sharp dissection (**Figure 2a**). A plastic ruler was sent into the abdomen, and measurements were made to determine the defect's width and adequate mesh size. The falciform and umbilical ligaments were dissected and separated from the abdominal wall for proper laying and fixation of the mesh (**Figure 2b**). A composite mesh was sent into the abdomen through the optical trocar. Usually, two, sometimes four, cardinal transfascial sutures were used to attach the mesh to the anterior abdominal wall. Next, the mesh was secured in a double-crown style, using either absorbable or titanium staples, with intervals of approximately 2 centimeters (**Figure 2d**). The intra-abdominal pressure was lowered to 8 mmHg during measurement and fixation of the mesh.

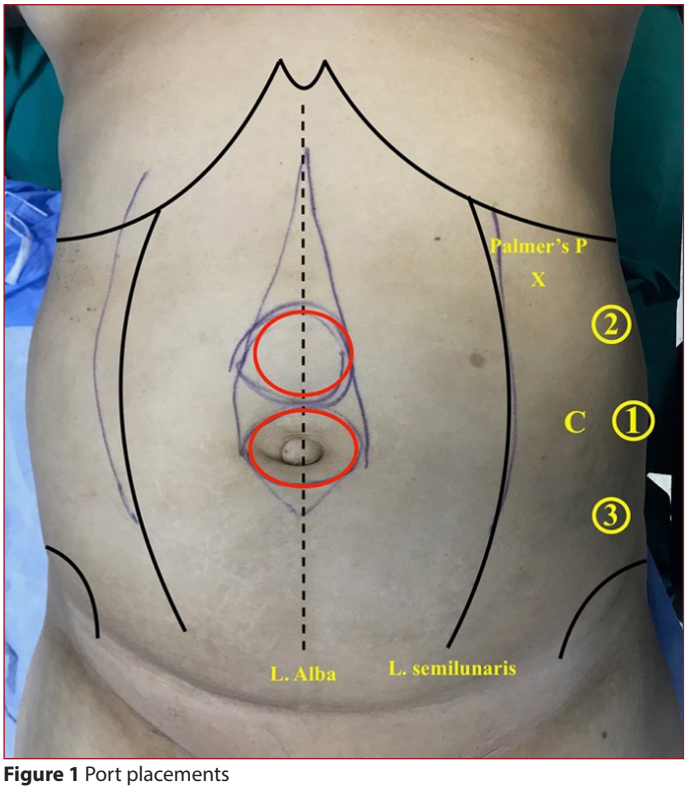

Figure 1 Port placements

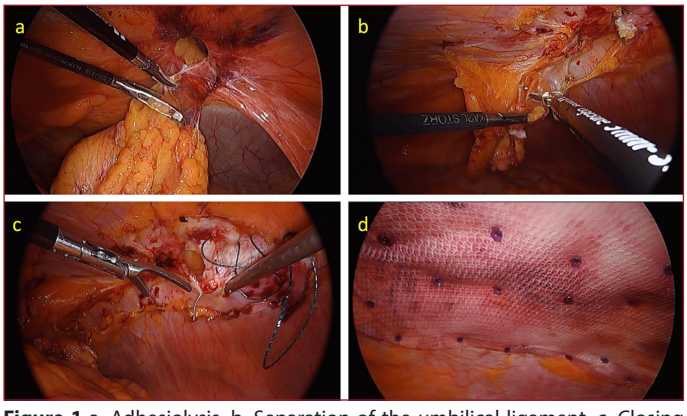

Figure 1 a. Adhesiolysis. b. Separation of the umbilical ligament. c. Closing the defect and plication of linea alba. d. Composite mesh placement with transfascial sutures + double crown style

Various techniques have been described for the closure of the defects in the IPOM-Plus technique. In this study, the defects were closed with extracorporeal interrupted n0 0 or no1 polypropylene sutures, usually with the help of the EndocloseTM. In some cases, closure of the defect was performed with no1 polydioxanone (PDS) or 0 barbed (V-LocTM no0, Medtronic) sutures in a continuous fashion. A linea alba plication was added to the technique for a primary midline hernia concomitant with diastasis (**Figure 2c**). The 10 mm trocar site fascia was routinely closed with a single no0 polypropylene suture.

RESULTS

Data prospectively gathered and documented from 82 patients who underwent the IPOM-Plus and sIPOM procedures for ventral and incisional hernia repairs between January 2016 and December 2021 were retrospectively assessed. Forty-one patients operated on with IPOM-Plus for incisional midline or lateral AWHs were excluded from the current study. However, no incisional or lateral hernia cases underwent the sIPOM technique in this cohort. Ultimately, the study included 23 patients for the IPOM-Plus group and 18 for the sIPOM group. For the IPOM-Plus group, the mean follow-up duration was 73.83±7.81, whereas for the sIPOM group, it was 47.43±19.22.

Both cohorts exhibited no significant disparities concerning gender, age, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) scores, comorbidities, or smoking habits. Both groups had predominantly female patients (77.8% vs. 65.2%, p=0.30), with a mean age of 54.16±11.08 for the sIPOM group and 53.43±9.7 for the IPOM-Plus group (p=0.82). The average BMI was 34.40±8.8 for both groups (p=0.58), and most patients in both groups had an ASA score of 2 (p=0.88). Comorbidities in the sIPOM and IPOM-Plus groups were as follows: hypertension 8 (44.4%) vs. 10 (43.5%), type II diabetes mellitus 4 (22.2%) vs. 6 (26.1%), hyperlipidemia 0 (0.0%) vs. 3 (13%), coronary artery disease (CAD) 3 (16.7%) vs. 2 (8.7%), and chronic obstructive pulmonary disease (COPD) 3 (16.7%) vs. 3 (13%). The number of smoker patients was 4 in each group (22.2% vs. 17.4%, p=0.71). The demographic characteristics are presented in **Table 1**.

Intraoperative and postoperative data of the groups are displayed in **Table 2**. The width of the defects was lower than four centimeters for both groups. The sIPOM group had a higher defect area (DA) of 9.16 cm^2±4.42 compared to the IPOM-Plus group's 6.52 cm^2±3.08 (p=0.005). The sIPOM group's mesh area (MA) was 220.83 cm^2±70.31, while the IPOM-Plus group had an MA of 185.86 cm^2±63.43. The mesh-to-defect ratio (MDR) for the sIPOM group was 27.80 cm^2±10.45, and the IPOM-Plus group's MDR was 33.24 cm^2±16.5. In both groups, the MA and the MDR were found to be statistically insignificant (p =0.083 and p=0.30, respectively). In four patients (22.2%) from the sIPOM group and five patients (21.7%) from the IPOM-Plus group, there was concomitant rectus muscle diastasis, but it was not statistically significant (p=1.0).

Table 1 Demographic characteristics

	IPOM (n=18)	IPOM-Plus (n=23)	p value
Age (years), mean±SD (min-max)	54.16±11.08 (34-71)	53.43±9.7 (37-70)	0.82
Sex			0.38
Female	14 (77.8%)	15 (65.2%)	
Male	4 (22.2%)	8 (34.8%)	
BMI (kg/m²), mean±SD (min-max)	34.40±8.8 (23.4-55.8)	34.59±7.5 (22.4-50.5)	0.58
ASA score			0.88
1	4 (22.2%)	5 (21.7%)	
2	9 (50.0%)	11 (47.8%)	
3	5 (27.8%)	7 (30.5%)	
Hypertension	8 (44.4%)	10 (43.5%)	0.95
Diabetes mellitus	4 (22.2%)	6 (26.1%)	1.00
Hyperlipidemia	0 (0.0%)	3 (13.0%)	0.24
CAD	3 (16.7%)	2 (8.7%)	0.63
COPD	3 (16.7%)	3 (13.0%)	1.0
Smoker	4 (22.2%)	4 (17.4%)	0.71

Continuous and categorical variables are shown as the mean±Standard Deviation (SD) and n (%), respectively. BMI Body mass index, ASA American Society of Anesthesiologists, CAD Coronary artery disease, COPD Chronic obstructive pulmonary disease

Table 2 Intraoperative and postoperative data

	IPOM (n=18)	IPOM-Plus (n=23)	p value
The defect area (cm², mean±SD min-max)	9.16±4.42 (4-18)	6.52±3.08 (4-16)	0.005
The mesh area (cm², mean±SD min-max)	220.83±70.31 (150-300)	185.86±63.43 (150-300)	0.083
Mesh-to-defect ratio (mean±SD min-max)	27.80±10.45 (9.38-50.0)	33.24±16.5 (16.67-75.0)	0.306
Operative time (minutes, mean±SD min-max)	74.16±14.1 (50-100)	94.0±23.9 (55-155)	0.002
Concomitant Diastasis	4 (22.2%)	5 (21.7%)	1.0
LOHS (mean±SD min-max, Median)	3.11±0.90 (2-4) (3)	2.56±1.16 (1-6) (2)	0.049
Complications			
Intraoperative complications	0	0	(-)
Surgical site complications			
Seroma (total)	4 (22.2%)	2 (8.6%)	0.477
Conservative treatment	2 (11.1%)	1 (4.3%)	
Interventional treatment	2 (11.1%)	1 (4.3%)	
Infection	0	0	(-)
Wound dehiscence	0	0	(-)
30-day readmissions	0	0	(-)
Chronic pain	0	0	(-)
Recurrence	2 (11.1%)	0 (0.0%)	0.196
Conversion to open	0	0	(-)

Categorical and continuous variables are presented as n (%) and the mean± Standard Deviation (SD), respectively. LOHS Length of hospital stay

The operative time was shorter in the sIPOM group and was statistically significant (74.16 minutes ±14.1 vs. 94.0 minutes ±23.9, p=0.002). The length of hospital stay (LOHS) was longer in the IPOM-Plus group (3.11 days ±0.90 vs. 2.56 days ±1.16, p=0.04). There were no intraoperative complications and conversion to other techniques in both groups. Postoperative seroma formation occurred in 4 (22.2%) and 2 (8.6%) patients in the sIPOM and IPOM-Plus groups, respectively, with no significant difference (p =0.477). Both groups had no surgical site infection (SSI) and wound dehiscence. The VAS pain scores during periods of rest and throughout daily activities showed improvement on both the first and 10th days postoperatively in both groups. However, the pain scores were significantly higher in the IPOM-Plus group (p <0.001). The early postoperative pain assessment with the VAS is shown in **Table 3**. There was two (11.1%) recurrence in the sIPOM group, while no recurrences were observed in the IPOM-Plus group (p=0.196).

Table 3 The VAS pain scores during at rest and daily activity.

VAS scores (mean±SD, min-max)	IPOM (n=18)	IPOM-Plus (n=23)	p value
Postop day 1 (at rest)	3.33±0.42 (2.5-4)	4.28±0.42 (3.5-5)	<0.001
Postop day 1 (daily activity)	4.13±0.58(3-5)	5.08±0.51 (4-6)	<0.001
Postop day 10 (at rest)	1.91±0.35 (1.5-2.5)	2.95±0.45 (2-3.5)	<0.001
Postop day 10 (daily activity)	2.97±0.55 (2-4)	3.97±0.46 (3-4.5)	<0.001

VAS Visual analog scale

DISCUSSION

The LVIHR technique offers various advantages over open repair, including reduced operative time, shorter LOHS, and lower complication rates. However, it demonstrates comparable postoperative pain and recurrence rates.[3,14,15] As outlined in the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) guideline, the decision to close the defects (the IPOM-Plus) is left to the discretion of the operating surgeon, and its potential benefits have not yet been conclusively established through high-quality research.[14] Conversely, the IEHS guideline recommends defect closure for ventral and incisional hernias with level-3 and level-4 statements.[8] Incisional and primary AWHs differ in terms of pathophysiologic characteristics and possible outcomes of the surgical repair. Several studies comparing the sIPOM and IPOM-Plus approaches have also presented combined findings for repairs of incisional and primary AWHs.[16–20] This article focuses on small and medium-sized PMAWHs and compares the outcomes of the sIPOM and IPOM-Plus techniques.

In the IPOM-Plus group, the surgical time was statistically significantly longer than in the sIPOM group. It is obvious that closure of the defects is the only difference in surgical steps between both techniques and requires more time. Recent studies have indicated that incorporating defect closure into the laparoscopic repair of primary and incisional hernias increases surgery times.[17,19,21] Conversely, Martin-del-Campo et al. found no correlation between defect closure and operating time.[22] Similarly, in their research, no significant difference was noted between the two groups in terms of length of hospital stay.[22] However, Basakula et al. reported an extended LOHS in the IPOM-Plus group.[17] Our study also found significantly longer LOHS in the IPOM-Plus group.

According to the SAGES Guideline, the development of seromas in hernia surgery should be viewed as an anticipated outcome rather than a complication.[14] Closure of defects helps reduce dead space, potentially leading to lower seroma rates in laparoscopic incisional and primary AWH repairs, as reported by several case series, a meta-analysis, and a randomized controlled study (RCT).[21–24] However, not statistically significant, numerically higher seroma rates were found in the sIPOM group in this study.

The VAS-pain scores decreased between the first and 10th postoperative days in both groups; however, pain scores were significantly higher in the IPOM-Plus group. Ahonen-Siirtola et al. reported increased early pain following the IPOM-Plus procedure compared to the sIPOM. In contrast, a randomized controlled study (RCT) declared that closing the hernia defect during laparoscopic ventral hernia repair did not increase postoperative pain.

Two patients in the sIPOM group experienced recurrence at the end of the postoperative first year. There were no recurrences in the IPOM-Plus group. However, the differences between the two groups were statistically insignificant (p=0.196) despite the numerical difference. Numerous articles reported that incorporating the closing of the defects to the sIPOM approach decreased the recurrence rates.[17,21,22]

Low sample numbers and the retrospective nature were the significant limitations of this study. In addition, detailed quality-of-life (QoL) and long-term pain assessments could not be presented despite the long-term follow-up period.

CONCLUSION

In conclusion, despite the increased early-postoperative pain and LOHS, the IPOM-Plus technique has similar seroma and recurrence rates for repairing small to medium-sized primary midline abdominal wall hernias compared to the non-closure technique (despite the numerical difference). The seroma formation and recurrence rates seem higher for the medium-large primary and incisional AWHs repaired with the sIPOM technique versus the IPOM-Plus. More RCTs, meta-analyses, and multi-center case-control studies with large samples are needed for more valuable and definitive results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Trabzon Kanuni Training and Research Hospital Ethics Committee (Date:28.02.2022 Decision no: 11384-2022/22).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1312540
J Contemp Med 2023;13(5):907-913

Original Article / Orijinal Araştırma

Whole Genome Sequence Analysis of Six SARS-CoV-2 Positive Patients Followed in a Tertiary University Hospital

Üçüncü Basamak Üniversite Hastanesinde Takip Edilen Altı SARS-CoV-2 Pozitif Hastanın Tüm Genom Dizi Analizi

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Abstract

Aim: In this study, we aimed to determine mutations in the gene sequence of this virus, by performing whole genome sequence analysis from patient samples found positive by actual RT-PCR for SARS-CoV-2.

Material and Method: The study included six adult patient samples with different clinical manifestations with positive PCR tests for SARS-CoV-2, between June 01, 2020, and March 12, 2021. Sequence knowledge of all samples/testers has been loaded into the GISEAD (Global Initiative on Sharing All Influenza Data) data system. Clade Analysis, Genome Analysis, Variant Analysis, and Phylogenetic Tree Analysis were conducted.

Results: 3 of the patients were women (female), and three were men (male), with the mean age of 42.5 years old (between 20-61). Totally 71 mutations were specified in 6 adult patients. By the Pangolin lineage, three of the patients were B.1.177, two were B.1, one was of B1.36 lineage. By the Pango lineage, two of the patients were B.1.609, one was B.177, one was B.1.36. By the Nexstrain Clade, four of the patients were 20A and two were of 19A lineage. No D614G mutation was detected in any of the patients. While five patients recovered, one patient with metastatic lung adenocarcinoma died.

Conclusion; The patients were detected in the commonly found 'Non-VOC' group. Therefore, variants could not be associated with the clinical status and prognosis of the patients. However, it is thought that the data obtained contribute to both global and national SARS-CoV-2 data.

Keywords: Genome sequence analysis, SARS-CoV-2, Konya, mutation

Öz

Amaç: Bu çalışmada Gerçek RT-PCR ile SARS-CoV-2 için pozitif bulunan hasta örneklerinden tam genom dizi analizi yaparak bu virüsün gen dizisindeki mutasyonları belirlemeyi amaçladık.

Gereç ve Yöntem: Çalışma, 01 Haziran 2020 - 12 Mart 2021 tarihleri arasında SARS-CoV-2 için pozitif PCR testleri olan farklı klinik belirtilere sahip altı yetişkin hasta örneğini içermektedir. Tüm numunelerin/test edicilerin sekans bilgisi, GISEAD (Tüm İnfluenza Verilerini Paylaşma Küresel Girişimi) veri sistemine yüklenmiştir. Clade Analizi, Genom Analizi, Varyant Analizi ve Filogenetik Ağaç Analizi yapılmıştır.

Bulgular: Hastaların 3'ü kadın (kadın), 3'ü erkek (erkek) olup, yaş ortalaması 42,5 (20 - 61 arası) idi. 6 yetişkin hastada toplam 71 mutasyon belirlendi. Pangolin soyuna göre, hastaların üçü B.1.177, ikisi B.1, biri B1.36 soyundandı. Pango soyuna göre hastaların ikisi B.1.609, biri B.177, biri B.1.36 idi. Nexstrain Clade'e göre hastaların dördü 20A ve ikisi 19A soyundandı. Hiçbir hastada D614G mutasyonu saptanmadı. Beş hasta iyileşirken, metastatik akciğer adenokarsinomu olan bir hasta hayatını kaybetti.

Sonuç; Hastalar yaygın olarak bulunan 'VOC olmayan' grupta tespit edildi. Bu nedenle varyantlar, hastaların klinik durumu ve prognozu ile ilişkilendirilememiştir. Ancak elde edilen verilerin hem küresel hem de ulusal SARS-CoV-2 verilerine katkı sağladığı düşünülüyor.

Anahtar Kelimeler: Genom dizi analizi, SARS-CoV-2, Konya, mutasyon

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Received *(Geliş Tarihi)*: 11.06.2023 **Accepted *(Kabul Tarihi)*:** 30.09.2023

INTRODUCTION

In the year December 2019, incidents of pneumonia of obscure origination were determined in the province of Wuhan of Hubei city of Peoples Republics of China, and almost identical incidents outspread to other cities of China and later to all world, causing the pandemic. The causative agent of this outbreak was called SARS-CoV-2 because of its resemblance to the Severe Acute Respiratory Syndrome Agent-Coronavirus (SARS-CoV). The World Health Organization (WHO) named as Coronavirus disease-2019 (COVID-19). On the date January 30, 2020, WHO proclaimed the epidemic as a worldwide emergency situation and a pandemic on 11 March 2020. And the first incident in Turkey was reported on 11 March 2020. Incidents have correspondingly been seen in province Konya and also they are still being seen. SARS-CoV-2 infection characteristically starts with fever, persistent dry cough, fatigue, and progresses to shortness of breath.[1]

Generally the most valid method for the virological diagnosis of active infection is present reverse transcriptase polymerase chain reaction (rRT-PCR) for identifying viral RNA.[2] Genomic sequence analysis can be used to quickly and accurately identify the transmission routes of the pathogen.[3] The first genome analysis on COVID-19 was published on January 10, 2020, by the researchers team directed by Yong-Zhen Zhang.[4] The achievement of COVID-19 diagnostic test kits, antibody tests, and protein-targeted medications likely depends on genomic variants. And for antibody tests, the sensitivity of the test can be greatly reduced if a mutation affects protein recognition. Consequently, mutation profiles of isolates circulating in abundance in the region should be considered in order to adapt these tests.[3]

The phylogenetic characterization of this virus is crucial to contribute to the knowledge of viral variation to identify the most suitable regions to be used as vaccine targets or antivirals. Studies on this subject in our region are limited. Therefore, in this study, by performing gene sequence analysis from patient samples found positive for SARS-CoV-2 PCR (RT-PCR), it was aimed to contribute to the epidemiological data of our country, to compare the studied strains with other strains registered in the gene bank, to add new sequence information to the gene bank, and to provide information about the clonal relationship and origin of the mutations in the gene sequence of this virus, which spread from Wuhan to Konya.

MATERIAL AND METHOD

This academic paper was permitted by the Turkey Health Ministry (Dated 17.06.2020 and numbered 2020-06-12T13_47_55) and the University Ethics Committee (decision no. 2020/2694). Characteristics of the patients, such as age, gender, hematological and biochemical factors, were recorded.

In our hospital's Microbiology laboratory, nasopharyngeal swabs from patients, which is a standard protocol for routine diagnosis, were taken into a viral transport medium, and the existence of SARS-CoV-2 was inspected. Viral RNA extraction from these testers was completed with a nucleic acid isolation equipment (RINATM, Bio Eksen, Turkey) in accordance with the producer's directives. The RT-PCR response was conducted with the commercial equipment (BioSpeedy SARS-CoV-2 dual gene, Bio Eksen, Turkey) using the Rotorgene Q (Qiagen, Germany) heat cycler. Diagnosis with the equipment was made by RT-PCR directing the SARS-CoV-2 particular N and orf1ab gene area. After a test run was completed, the response curves were understood according to the procedures of the equipment procedure process. Values less than the cycle threshold (Ct) 38 ($Ct < 38$) were considered positive.

For further analysis, 6 SARS-CoV-2 positive samples with high virus-related load (cycle threshold < 20) were randomly chosen. RNA samples were saved in a freezing compartment at -80°C till additional processing. At the following phase, sequence study of the whole genome of the virus was executed with next-gen sequencing apparatuses; followed by variant analysis, genome analysis, bioinformatics analysis, clade analysis, and phylogenetic tree analysis.

Sequence Analysis

SARS-CoV-2 virus whole genome sequencing was conducted on Oxford Nanopore Technologies, Cat. #MIN-101B (MinION TM) instrument using Oxford Nanopore Technology. RNA samples with full nucleic acid isolation were transformed to cDNA by contrary transcription. Subsequently the contrary transcription phase, with 2 diverse primer pools in the ARTIC nCoV-2019 V3 panel, ½ minute of first denaturation at 98°C, 15 seconds of denaturation at 98°C with 35 cycles, and 5 minutes of attachment and elongation at 65°C PCR step was performed. Afterwards PCR, the same samples worked with 2 diverse primer pools were gathered in one tube. Agencourt AMPure XP beads equipment (Beckman Coulter, Kat. #A6388) was used for refinement. Concentration measurement was performed with Qubit™ four Fluorometer (Thermo Sciences, Cat. # Q33238) before the tip preparation phase. The NEBNext End Repair/dA-tailing Module (New England Bio-labs, Cat. #E7546) set was used for tip reparation and dA tail generation. After NEBNext Ultra II End Prep enzyme mixture was added, the samples were keept warm (incubation), for 5 min at 20°C and 5 min at 65°C. For barcoding, NEB Blunt/TA Ligase Master (New-England Bio-labs, #M0367) was mixed with nuclease-free water, tipped DNA and native barcodes. The mixed substance was kept warm at 20°C for 20 minutes and at 65°C for 10 minutes. After keeping warm (incubation), all barcoded samples were gathered in a tube. The Agencourt AMPure XP beads equipment (Cat. # A63880, Beckman Coulter) was used for refinement, and the concentration was measured with a Qubit TM-4 Fluorometer (Thermo Science, Cat. #Q33238) before the adapter ligation phase. For the adapter ligation step, NEBNext Quick T4 DNA Ligase (New-England Bio-labs,

Cat. # M0202), AMII (Adapter Mix II), and NEBNext Quick Ligation Reaction Buffer (5X) were added to the pool sample tube. The combination was then kept (incubated) at room heat for 1/3 hour, and purification was completed using Agencourt AMPure XP beads. Finally, the concentration of the DNA library to be loaded was measured with the Qubit TM 4 Fluorometer (Thermo Science, Cat. #Q33238). Afterwards the SpotON Flow Cell (Oxford Nanopore Technologies; Cat. # FLO-MIN106D) was made ready for loading with the mixture of Flush Tether (FLT) and Flush Buffer (FB) in the Flow Cell Priming Equipment (Oxford Nanopore Technologies; Cat. # EXP-FLP002), the arranged DNA archive was loaded into the flow cell, and sequence analysis was started using the MinKNOW program.

Bioinformatics Analysis

This analysis comprises of 2 parts. In the first part, the genome of the virus was removed from the generated FASTQ information. At this stage, mutations in the virus were also identified. At this stage, the FASTQ information were charted to the reference genome with Minimap 2 and the BAM file was produced. The BAM file, after needed quality control and filtering with Medaka, Samtools and Longshot tools, mutation discovery was made and the file containing the mutations in VCF format was produced. Then, the genome of the virus was produced with the BAM and VCF file produced with the help of Bcftools. In the second stage of the analysis, clade analysis was performed for each sample. In these clade analyzes, Nextstrain clade analysis was performed and then Pangolin linage was added. Clade analysis is actually a sequence-based classification.

RESULTS

Three of the patients were women (female) and 3 were men (male), with the mean age of 42.5 years-old (between 20-61). Laboratory values of the patients at the time of admittance are presented in **Table 1**, and genome sequence analysis results are presented in **Table 2**. The numerical values of the laboratory results of the patients at the time of application.

In this study, a total of 71 mutations were detected in six adult patients reported from the Konya region. By the Pangolin lineage, three patients were B.1.177, two were B.1, and one was of B1.36 lineage. By the Pango lineage, two patients were B.1.609, one was B.177, and one was B.1.36. By the Nexstrain Clade, four patients were 20A, and two were of 19A lineage. Different mutations were detected in the N regions of the first, second and third patients. The most common mutation detected in the 1st, 2nd, 3rd, and 6th patients was NSP12 (P323L). NSP12 (M601I) mutation was found in the fourth patient, NSP12 (T739I) mutation was found in the sixth patient, and N501Y mutation was found in the Spike protein in the fifth patient. The first, second, third and fifth patients had mutations in the ORF1a regions; Mutations in ORF1b regions were detected in patients 1, 2, 3, 4 and 6. mutations were detected in the ORF3a regions of the second and fourth patients. Mutations were detected in the ORF8 region of the 1st and 5th patients. No D614G mutation was detected in the patients. While five patients recovered completely, by the pangolin lineage, the fourth patient with metastatic lung adenocarcinoma, descendant of B.1.177, died.

Displaying patient genomes on the global phylogenetic tree is shown in **Figure 1**.

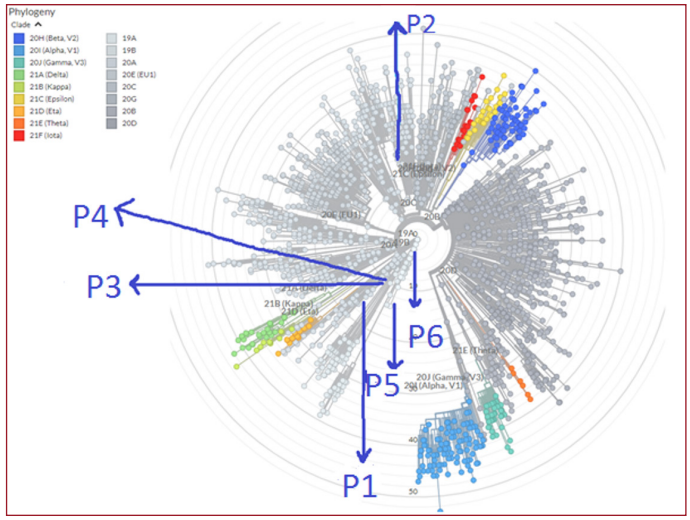

Figure 1. Imaging of the genomes in this study on the global phylogenetic tree (P:Patient). The image was created using the auspice.us website and sample files with json extension.

Table 1. Laboratory Results of the Patients at the Time of Application

Patient number	1	2	3	4	5	6
Hemoglobin (gr/dl)	12.6	13.3	16	10.4	12	16
Leukocytes(/µl)	7040	5950	6170	8980	3030	5920
Neutrophil (/µl)	4680	5230	4530	7220	2210	3030
Lymphocyte(/µl)	1260	590	790	480	180	2360
Platelets (/µl)	320000	233000	172000	156000	148000	147000
C Reactive Protein (mg/L)	8.5	9.2	3.6	170.9	20.9	2.3
Sedimentation (mg/h)		17		56	25	
Procalcitonin (µg /L)		0.032		1.26	0.062	
Fibrinogen (mg/dl)	356	345	175	403	244	309
D Dimer (ng /ml)	86	178	54	2103	695	186
Ferritin (µg /L)	66.5	85.6	86.8	4718	437.6	242

Leukocytes;4000-10000 /µl Lymphocyte; 800-5500 /µl C -reactive protein (CRP); 0-0.5 mg/L Sedimentation;0-20 mg/h D -dimer;0-243ng/mL Ferritin; 13-150 ug /L

Table 2. Genome sequence analysis of the patients

	Patient	2. Patient	3. Patient	4. Patient	5. Patient	6. Patient
Age/Gender	30/F	58/F	20/M	61/M	26/F	60/M
CT Value	12.8	12.98	14.66	14.30	11.95	15.75
Number of mutations	18	12	11th	10	17	3
GISEAD access number	EPI_ISL_5403171	EPI_ISL_5403187	EPI_ISL_5403086	EPI_ISL_5403204	EPI_ISL_5403201	EPI_ISL_5403199
Sampling time	07.12.2020	12.09.2020	27.11.2020	12.03.2021	09.12.2020	12.07.2020
Pangolin lineage	B.1.177	B.1.36	B.1.177	B.1.177	B.1	B.1
Pango lineage	B.1 77	B.1.36	B.1.609	B	B	B.1.609
Amino Acid Changes (GISEAD)	Spike Q14H, NR203K, NS8 G8stop, NSP1 S34T, NSP3 S1286I, NSP12 P323L	N S194L, NS3 S177I, NSP4 F390L, NSP12 P323L	Spike D1084Y, N R203K, NSP3 V1795F, NSP12 P323L, NSP15 V66L	N N196T, NSP12 M601I	Spike A570D, Spike D1118H, Spike N501Y, Spike P681H, N D3N, N M1V, NS8 Q27stop, NS8 R52I, NSP2 L550F, NSP3 I1412T	NN196T, NR203, NS3 T151I, NSP12 P323L, NSP12 T739I
Nextrain clade	20A	20A	20A	20A	19A	19A
Changes	C241T, C313T, T365A, C466T, C3037T, G6576T, C6941T, G10870C, C14408T, G20373T, C20451T, G21604T, G27915T, G28881A	C241T, C3037T, C9724A, C14408T, C18877T, C22444T, C25276A, G25922T, C26735T, C27059T, C28854T, G29777T	C241T, C3037T, G8102T, C14408T, G19816T, T19839C, G24812T, G28881A, T29464C	C241T, C3037T, C14408T, C15656T, C25844T, A28860C, G28881A	C2453T, C3037T, C5986T, T6954C, T16548A, C20148T, A23063T, C23271A, C23604A, G24914C, C27972T, G28048T, G28280C	C3037T, G15243T, A28860C
Deletion	-	-	-	-	-	-
Insertion	27864:T, 28881:AC	-	28881:AC	28881:AC	28280:TA	-
pcrPrimerChanges	ChinaCDC_N_F: G28881A	-	ChinaCDC_N_F: G28881A	ChinaCDC_N_F: G28881A		
AA Changes	N:R203K, ORF1a:S34T, ORF1a:S2104I, ORF1b:P314L, ORF8:G8, Q:Q14H	N:S194L, ORF1a:F315L ORF1b:P314, ORF3a:S177I	N:R203K, ORF1a:V2613, ORF1b:P314, ORF1b:V211L, Q:D1084Y	N:N196T, N:R203K, ORF1b:P31, ORF1b:T73I, ORF3a:T15I	N:D3H, ORF1a:L730F, ORF1a:I2230T, ORF8:Q27, ORF8:R52I, Q:N501Y, Q:A570D, Q:P681H, Q:D1118H	N:N196T, ORF1b:M592I
AA deletions	-	-	-	-	-	-
Average Depth (Coverage) Amount	1,331X	1,661X	1,088X	1,494X	12,992X	8,796X
Reference Genome Coverage Ratio (%)	99.86	99.78	99.77	99.78	99.03	99.84

F: Female M: Male NSP: Nonstructural protein AA: amino acid

DISCUSSION

As of 9 September 2023, 770,437,327 confirmed incidents and 6,956,900 deaths have been informed worldwide by WHO.[5] As of March, 2023, there were 17,232,066 incidents and 102,174 deaths announced by the Turkish Ministry of Health.[1] There are full genome sequence analyses of 15,968,508 SARS-CoV-2 viruses in the GISAID's database on Distribution Entire Influenza Information (Global Initiative), 101,592 of which are from Turkey. 30 viruses, including six viruses we uploaded, are from Konya.[6]

Coronavirus disease can be seen at any age,[7] and the mean age of the adult patients included in our paper was 42.5 years (20-61 years).

Clinical findings in coronavirus infection be able to range from asymptomatic to acute respiratory distress syndrome and multi-organ dysfunction.[8] Four of six patients were outpatients with home isolation, and the fifth patient was followed up in the hospital and discharged with recovery. The fourth patient with metastatic lung adenocarcinoma, whose general condition deteriorated while being followed in the ward and died in the intensive care unit, was of B.1.177 lineage by the Pangolin lineage, and mutations were detected in the N, ORF1b and ORF3a regions. The cause of death was associated with metastatic lung cancer, since the SARS-CoV-2 agent of this deceased patient did not have variants of concern ("Variant of Concern";VOC). VOCs are variants with

increased infectiousness of SARS-CoV-2 or that may adversely affect the epidemiology of COVID-19, variants with increased disease properties or a change in the clinical picture, or variants that reduce the effectiveness of communal health measures or raise concerns by reducing the effectiveness of existing diagnostic tests, vaccines or drugs. VOC (WHO, 22.06.2021) variant ALFA (B.1.1.7) was earliest noticed in England, BETA (B.1.351) earliest in the South Africa, GAMMA (P.1) earliest in the Brazil, DELTA (B. 1.617.2) was first noticed in India.[9] None of the variations obtained in our study were found to be VOCs, so no relationship could be established between the variant and clinical findings.

Laboratory tests other than RT-PCR are non-particular in coronavirus infection. The white blood cell calculation is standard or low. There may be lymphopenia and mild thrombocytopenia. C-reactive protein (CRP) and sedimentation (SED) are generally high. But procalcitonin (PCT) levels are generally standard level. A high PCT level may show a bacterial coinfection. Alanine aminotransferase, Aspartate aminotransferase, D-dimer may be high. Ferritin is an acute period reactant, and high serum ferritin level has been associated with organ harm to a larger extent in severe COVID-19 patients.[10,11] In our study, the leukocyte, neutrophil and thrombocyte values of the patients were normal. The CRP, SED, D-Dimer, and ferritin levels of the fourth and fifth patients were high, and the laboratory parameters of the patients were found at different values.

Mutations develop in SARS-CoV-2, although less frequently compared to other RNA viruses.[12] In a paper, 549 and 53 distinctive variations were noticed from 47 SARS-CoV-2 isolates.[13] In the paper prepared by Khailany et al., 156 total and 116 distinctive variations were found in 95 SARS-CoV-2 isolates.[14] In our paper, 71 mutations were detected in six adult patients.

Looking at the SARS-CoV-2 genome, the C>T nucleotide transformation is the most common nucleotide change in the genome.[15] In the study of Karamese et al., it was reported that C>T base change was the most common.[13] In our study, the most common base change was found as C>T. There were 7 C>T base changes in the initial patient, 8 in the second, 3 in the 3rd, 5 in the 4th, 5 in the 5th, and 1 in the 6th patient.

The source of B.1.177 Lineage is the United Kingdom 64%, Spain 10%, Germany 5%, Switzerland 4%, and Italy 4%.[16] Patients 1, 3, and 4 are from lineage B.1.177. This lineage is predominantly European and is thought to have spread as a consequence of the opening of the boundaries in the summertime of 2020. It is most common in the United Kingdom 62%, Spain 12%, Germany 4%, Switzerland 4% and Italy 4%. The earliest was found on 02.02.2020.[17]

B.1.36 Lineage originates from India 29%, Canada 14%, UK 13%, Denmark 8%, Hong Kong 5%.[16] The genome of the second patient is of the B.1.36 lineage, the earliest detected in the world in February 2020 and is most common in India 33%, Canada 31%, UK 8%, Denmark 4%, Hong Kong 3%.[17]

B.1 Lineage appeared in Europe at the beginning of 2020. The B.1 lineage is the recognized dominant worldwide lineage and has been sectioned into more than 70 sublineages. All variants in the B.1 clade share a specific mutation called D614G. This mutation is one of the first to be detected in the US in the early stages of the pandemic, after initially circulating in Europe. There is evidence that variants with the D614G mutation spread faster than viruses without this mutation.[16] The D614G mutation is assumed to be dominant for the reason that it provides more uniform spread of the virus.[18] D614G has been shown to be the most common mutation in the spike glycoprotein.[13] It is thought that this mutation may affect the effectiveness of the vaccine.[19] The presence of mutations in the protein in all strains with the D614G mutation is almost also responsible for the response in replication (ORF1ab P4715L; RdRp P323L), which may affect the virus's rate of replication. This protein is the target of antiviral drugs such as remdesivir and favipiravir, and because it is susceptible to mutations, treatment-resistant strains can emerge rapidly. These variants, which are formed by mutations in the receptor binding region of the spike protein, also facilitate the binding of ACE2 to the receptor on the host cell surface.[20] In the study of Adebali et al., 23 out of 30 genomes have the D614G mutation. The D614G mutation appears to be mutated in 2 synonyms in ORF1ab.[3] In a study we conducted in pediatric patients in Konya, D614G mutation was detected.[21] However, D614G mutation was not detected in this study. The 5th and 6th patients are of the B.1 lineage. The B.1 lineage is a large EU (European) lineage, the starting point of which coarsely corresponds to the outbreak of Northern Italy in the first three months of 2020. It is most common in the US 46%, the UK 9%, Turkey 8%, France 4% and Canada 3%. The earliest was found on 01.01.2020.[17]

In a paper comparing mutation profiles by illness rigorousness, D614G and P323L mutations in SARS-CoV-2 were found to be associated with severe COVID-19 incidents.[22] P323L mutation was detected in NSP12 in patients one, two, three, and six. The disease progressed mildly in these patients.

The most ample amino acid substitutions, P314L (23/30) (ORF1b) and D614G (Spike), were distributed worldwide and were not particularly enriched in Turkey. ORF1Av378I and ORF9S194L were found in two of 30 isolates and demonstrate a high frequency (15 times overall) in Turkey.[3] In the fifth patient, it was observed that proline was converted to histidine at amino acid 681 (P681H) in spike protein. This mutation has been reported to have unique and emergent features with an important exponential increase in global rate of recurrence. The P681H mutation is typical of new-type SARS-CoV-2 variations from the UK and Nigeria.[23] In another study we conducted in pediatric patients, P681H mutation was found in four of six patients.[21]. In our paper, P681H mutation was detected in the fifth patient.

241>C-T, one of the 5'-UTR mutations of the most common SARS-CoV-2 genome worldwide, is also present in all sequences in the study of Sahin et al.[24] In our paper, C241T mutation was noticed in the first, second, third and fourth patients.

According to the available literature, ORF genes have a very important role for the duration of COVID-19.[25] In the paper of Adebali et al., P314L mutation was found in the ORF1b gene area in 23 of 30 samples.[3] In our study, P314L mutation was detected in the ORF1b gene area without D614G mutation in the first and second patients. In the thesis study of Soyak at 21 isolates from our country, Omicron BA.2 subvariants were detected in 12 patients, Omicron BA.1 subvariants in four patients, Omicron BA.5 subvariants in four patients, and Delta variant in one patient. The mutations c.1841A>G (D614G), c.425G>A (G142D), c.9764C>T, NSP4 (T492I), and c.14144C>T (NSP12 P323L) were detected in all isolates analyzed.[26] In our study, mutations were detected in the ORF1a:S34T, ORF1a:S2104I, ORF1b:P314L, ORF8:G8 regions in the first patient, in the ORF1a:F3153L, ORF1b:P314L, ORF3a:S177I regions in the second patient, in the ORF1a:V2613, ORF1b:P314, ORF1b:V211L regions in the third patient, in the ORF1b:P31, ORF1b:T73I, ORF3a:T15I regions in the fourth patient, in the ORF1a:L730F, ORF1a:I2230T, ORF8:Q27, ORF8:R52I regions in the fifth patient, and in the ORF1b:M592I region in the sixth patient.

CONCLUSIONS

In this study, 71 mutations were detected in six adult patients reported from the Konya region. By the Pangolin lineage, three of the patients were B.1.177, two were B.1, one was of B1.36 lineage. By the Pango lineage, two of the patients were B.1.609, one was B.177, one was B.1.36. By the Nexstrain Clade, four of the patients were 20A and two were of 19A lineage. Different mutations were detected in the N regions of the first, second and third patients. In order to investigate the phylogenetic features of SARS-CoV-2 infections in detail, studies should be conducted with more samples from different regions of Turkey. Regular gene sequencing during the pandemic will be beneficial as it will reveal new variants along with known variants. At the same time, we think that genetic sequence analyzes, including our research, can help to understand the dynamics of the virus and to develop vaccines.

ETHICAL DECLARATIONS

Ethics Committee Approval: This academic paper was permitted by the Turkey Health Ministry (Dated 17.06.2020 and numbered 2020-06-12T13_47_55) and the University Ethics Committee (decision no. 2020/2694).

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

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: This study was supported by Necmettin Erbakan University Research Fund

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1320497
J Contemp Med 2023;13(5):914-917

Original Article / Orijinal Araştırma

Clinical Observation in Premature Babies with Feeding Intolerance

Beslenme İntoleransı Olan Erken Doğan Bebeklerde Klinik Gözlem

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Abstract

Aim: Feeding intolerance (FI) is a digestive disorder that presents with gastric residue, abdominal distension, and vomiting, especially in preterm infants, and it often causes a prolongation of the transition to full enteral feeding. Nutrition strategies pose a significant clinical challenge for neonatologists. Attempts to treat FI have used methods such as minimal enteral nutrition and a slow increase in sustenance, probiotic use, the prevention or treatment of necrotizing enterocolitis (NEC) and sepsis, and the use of specially formulated foods, but these methods are only partially effective.

Material and Method: Infants born at less than 32 weeks and 1500 g hospitalized in Konya City Hospital between August 2020 and January 2022 were evaluated retrospectively. Babies with and without FI were divided into two groups, and their demographics and clinical conditions were examined. The treatment modalities of the FI group were evaluated.

Results: Of the 86 patients in the study, 36 were included in the FI group and 50 in the healthy control group. Late neonatal sepsis and duration of parenteral nutrition were found to be statistically significantly higher in the group with FI compared to the control group ($p<0.005$). In eight of the patients, hydrolyzed formula was used, and the transition to total enteral nutrition was achieved in a short period.

Conclusion: The diagnosis of FI is based on nonspecific clinical symptoms. When the underlying etiopathogenesis is clarified, treatment approaches may change. According to our study, it has been shown that regardless of the underlying cause of FI, hydrolyzed formulas may be viable as a alternative dietary option for short-term administration.

Keywords: Premature babies, feeding intolerance, nutrition

Öz

Amaç: Beslenme intoleransı, özellikle preterm bebeklerde görülen gastrik rezidü, abdominal distansiyon ve/veya kusma ile kendini gösteren, sıklıkla tam enteral beslenmeye geçişin uzamasına neden olan sindirim bozukluğudur. Beslenme stratejisi, neonataloglar için önemli bir klinik zorluktur. Minimal enteral beslenme ve beslenmenin yavaş arttırılması, probiyotik kullanımı, NEK ve sepsisten korunma/tedavisi, özel formüllü gıdaların kullanılması gibi yöntemlerle beslenme intoleransı tedavi edilmeye çalışılmaktadır, ancak bu yöntemler tam olarak etkili değildir.

Gereç ve Yöntem: Konya Şehir Hastanesinde Ağustos 2020- Ocak 2022 tarihleri arasında yatırılan 32 hf ve/veya 1500 gr altındaki bebekler retrospektif olarak değerlendirildi. Beslenme intoleransı olan ve olmayan bebekler iki gruba ayrılarak demografik ve klinik durumları incelendi. Beslenme intoleransı olan grubun tedavi şekilleri değerlendirildi.

Bulgular: Çalışmaya alınan seksen altı hastanın, 36 tanesi beslenme intoleransı grubuna 50 tanesi sağlıklı kontrol grubuna dahil edildi. Beslenme intoleransı olan grupta geç neonatal sepsis ve parenteral beslenme süresi kontrol grubuna göre istatistiksel olarak anlamlı derecede daha yüksek saptandı($p<0,005$). Hastalardan 8 tanesinde hidrolize formula kullanılarak kısa sürede tam enteral beslenmeye geçiş sağlandı.

Sonuç: Beslenme intoleransı tanısı, spesifik olmayan klinik belirtilere dayanmaktadır. Altta yatan etiyopatogenez netleştiğinde tedavi yaklaşımları değiştirebilir. Çalışmamız ile, beslenme intoleransının altında yatan neden ne olursa olsun hidrolize formulaların alternatif bir beslenme seçeneği olarak kısa süreliğine kullanılabileceği gösterilmiştir.

Anahtar Kelimeler: Prematüre infant, beslenme intoleransı, nutrisyon

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Received *(Geliş Tarihi)*: 27.06.2023 **Accepted *(Kabul Tarihi)*:** 01.08.2023

INTRODUCTION

The survival rate of preterm infants has increased significantly in recent years due to the development of various medical treatments and life-support technologies. However, quickly and safely achieving total enteral nutrition in preterm infants remains a significant challenge for neonatologists.[1,2] Difficulties with enteral nutrition are due to immature digestion, absorption, and immunological functions. One of these difficulties, feeding intolerance (FI), is a significant problem, especially for babies born at less than 32 weeks of gestational age or fewer than 1,500 g; it occurs in approximately 75% of these cases.[2-4]

FI is a well-known phenomenon in the neonatal intensive care unit (NICU) and is linked to morbidity and mortality in premature infants; however, a universal definition of this concept is lacking. Often, enteral nutrition clinical evidence of intolerance many signs in the literature; the definition is available. The most accepted definition is nutrition decrease, delay, or discontinuation of abdominal gastric residual volume (previously more than 50% of the nutritional amount). It is a digestive disorder with distension and vomiting.[5] Limited gastric acid secretion, restriction in enterokinase, lactase activity, and the deterioration of intestinal flora after birth (cesarean delivery, hospitalization, and antibiotic use) play essential roles, but the etiology is unclear. FI delays the transition to total enteral nutrition and extends the duration of parenteral nutrition in preterm infants, thus increasing the risk of infections, prolonging the length of hospital stays, and increasing economic costs.[6,7] There are some prevention and treatment measures for FI, including the optimization of enteral nutrition, modification of feeding methods, and use of probiotics, but these measures are only partially effective. It is not possible to use a single nutritional protocol or guide for all patients; thus, the feeding strategy for FI is a significant clinical challenge for neonatologists.[6] In this article, we present the characteristics of patients with FI, and we aim to bring to the attention of clinicians our various approaches and experiences regarding nutritional intolerance.

MATERIAL AND METHOD

The study was carried out with the permission of KTO Karatay University Faculty of Medicine Non-Pharmaceutical and Medical Device Research Ethics Committee (Date: 02.03.2023, Decision No: 2023/021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A retrospective cohort study was conducted in Konya City Hospital, Turkey, between August 2020 and December 2022. A total of 86 preterm infants born with a gestational age (GA) of<32 weeks and birthweight (BW) of<1500 g were enrolled. Two groups were formed one with FI and one without FI. The exclusion criteria included significant congenital anomalies, death, and lack of family consent.

Clinical characteristics of the study population, such as BW, GA, gender, mode of delivery, administration of antenatal corticosteroids, preeclampsia/eclampsia, infants of diabetic mothers, chorioamnionitis (clinical or histopathological), respiratory distress syndrome (RDS), intraventricular hemorrhage (grade > 3), early- and late-onset sepsis (EOS and LOS, respectively), hemodynamically significant patent ductus arteriosus (PDA), first feeding time, the use of any diets at first feeding, duration of parenteral nutrition, and diet at discharge were recorded. Data on the causes and treatment modalities of FI were collected.

Statistical analyses were conducted using SPSS version 17.0 (SPSS et al.). The results are presented as numbers (n), frequencies (%), means with respective standard deviation (SD), and medians. Nonparametric tests were used to analyze the continuous variables. The chi-square test was used to compare categorical variables. Logistic regression analysis was performed to determine the independent risk factors for FI. Statistical significance was set at $p<0.05$.

RESULTS

Thirty-six neonates with FI and 50 healthy controls were enrolled. The median BW and GA of the patients with FI were 1130 g (840-14,800 g) and 27 weeks (23-30 weeks), respectively. Patients and controls were similar regarding GA, BW, gender, mode of delivery, ratio of antenatal steroids, RDS, intraventricular hemorrhage (IVH), PDA, and EOS (**Table 1**).

Compared with the control group, patients with FI also had a higher incidence of LOS (30% vs. 72.2%), and the duration of parenteral nutrition (nine vs. 14 days) was significantly higher ($p<0.005$). The two groups had similar nutrition, the first feeding time, and nutrition at discharge. In this study, most preterm infants were expressed human breast milk (HBM). The patient group was discharged with amino acid-based formulas (**Table 1**). Logistic regression analysis revealed that LOS (OR: 6.07, 95% CI: 2.35-15.65, $p<0.001$) was independently associated with the development of FI.

Six patients in the FI group had necrotizing enterocolitis (NEC), and 20 had LOS. Intestinal maturation was accepted as the cause of FI symptoms in 10 patients (**Table 2**). Antibiotics and probiotics were used alone or in combination to treat these patients. Eight patients benefited only from amino acid-based formulas (**Table 3**).

Table 1: Demographic and clinical characteristics

	FI group (n = 36)	Control group (n = 50)	P value
GA*, weeks	27 (23-30)	28 (23-30)	0.325
Birth weight* (g)	1130 (837-1480)	1225 (680-1490)	0.020
Gender (n/%)			
Female	17 (47.3%)	23 (46%)	0.482
Male	19 (52.7%)	27 (54%)	
Delivery type (n/%)			
VD	4 (11.1%)	10 (20%)	0.271
C/S	32 (88.9%)	40 (80%)	
Antenatal steroids (n/%)			
No	11 (30.5%)	13 (26%)	0.566
Single dose	1 (2.8%)	4 (8%)	
Full dose	24 (66.7%)	33 (66%)	
Maternal disease (n/%)			
No	28 (77.8%)	46 (92%)	0.150
Preeclampsia	7 (9.4%)	3 (6%)	
Gestational diabetes	1 (2.8%)	1 (2%)	
PPROM (n/%)			
No	33 (91.7%)	49 (98%)	0.169
Yes	3 (8.3%)	1 (2%)	
RDS (n/%)			
No	12 (33.3%)	24 (48%)	0.174
Yes	24 (66.7%)	26 (52%)	
IVH (n/%)			
No	34 (94.4%)	50 (100%)	0.092
Yes	2 (5.6%)	0 (0%)	
PDA (n/%)			
No	17 (47.2%)	33 (66%)	0.082
Yes	19 (52.8%)	17 (34%)	
EOS (n/%)			
No	35 (97.2%)	45 (90%)	0.195
Yes	1 (2.8%)	5 (10%)	
LOS (n/%)			
No	10 (27.8%)	35 (70%)	<0.005
Yes	26 (72.2%)	15 (30%)	
First feeding time (h)	2.47 ± 1.10	1.98 ± 0.87	0.139
Use of any diets at first feeding			
Fortified HBM	23 (63.9%)	37 (74%)	0.314
Formula for PM	13 (36.1%)	13 (26%)	
Duration of parenteral nutrition (days)	14 (7-42)	9 (5-18)	<0.005
Diet at discharge			
Fortified HBM	16 (44.4%)	40 (80%)	0.005
Formula for PM	11 (30.6%)	10 (20%)	
Hydrolyzed formulas	9 (25.0%)	0 (0%)	

VD: vaginal delivery; C/S: Cesarean section; PPROM: preterm premature rupture of membranes RDS: respiratory distress syndrome; IVH: intraventricular hemorrhage (grade>3), PDA: hemodynamically significant patent ductus arteriosus; EOS: early-onset sepsis; LOS: late-onset sepsis; ROP: retinopathy of prematurity (severe ROP defined as ROP requiring treatment); HBM: human breast milk; PM: premature infant.

Table 2: Causes of FI (n/%)

Disease	n (%)
NEC	6 (16.6%)
LOS	20 (72.2%)
Diğer	10 (11.2%)

NEC: necrotizing enterocolitis; LOS: late onset sepsis.

Table 3: Treatment of FI (n)

Treatment administered	15
Antibiotics	15
Probiotics	6
Antibiotics and probiotics	7
Hydrolyzed formulas	8

DISCUSSION

In this study, we found that the first feeding time and usage of human breast milk (HBM) were similar between the two groups, but that the duration of total parenteral nutrition was more prolonged in patients with FI. FI in preterm infants can be a sign of various problems, ranging from minor, self-limiting illnesses to severe, life-threatening ones.[4,5] Cetinkaya et al. showed that FI was an independent risk factor for LOS development in premature very low BW (VLBW) infants.[8] LOS is a significant complication of prematurity and the leading cause of morbidity and mortality. Early enteral feeding should start as soon as possible to enhance gastrointestinal maturation by stimulating hormone secretion and motility. Delaying the introduction of enteral feeding causes prolonged parenteral nutrition; therefore, parenteral nutrition is associated with complications such as bloodstream infections.[8,9] In our study, we found that the presence of late sepsis increased the risk of FI six times.

It is well known that HBM is the best choice for infants and is associated with a lower incidence of FI, NEC, and LOS.[10,11] Our study found that breastfeeding with HBM exclusively was similar in the two groups. We thought that the development of FI with breastfeeding was due to an intrinsic factor, such as lactose intolerance or differences in genetics and microbiome.

Many studies have found pathologic high-risk factors associated with FI (e.g., low GA, low BW, RDS, enteral feeding delay, premature infant formula feeding, and hemodynamically significant patent ductus arteriosus (hsPDA).[12] In our study, there were no statistical differences in comorbidities and clinical characteristics between the two groups.

One of the underlying causes of FI is NEC pathophysiology. This condition can damage the intestinal lining and lead to the malabsorption of nutrients and a host of other problems. Diagnosing FI and NEC can be challenging, as their symptoms can be similar to those of other conditions; however, doctors can use a combination of blood tests, stool tests, and imaging studies to help make a diagnosis. Once a diagnosis is made, treatment can begin. Treatment for FI often involves avoiding deleterious food or ingredients. In some cases, supplements or alternative foods may be recommended to help replace missing nutrients. The treatment of NEC may involve antibiotics to control infection, surgery to remove damaged tissue, or other interventions, depending on the severity of the condition. NEC is a leading cause of mortality and morbidity in preterm infants and deficient BW infants.[13] Antibiotics and probiotics were used alone or in combination to treat these patients (probiotics and amino acid-based formula [AAF]). Six patients in the FI group had NEC.

HM is associated with less FI and is recommended by the World Health Organization as the first-choice milk for preterm infants. However, when HBM cannot be used in patients with FI, the alternative formulas include preterm formula (PF), partially hydrolyzed formula, extensively hydrolyzed formula, AAF, and others. PF is used frequently in preterm infants.[3,6,14]

In our study, eight babies with resistant FI were fed with AAF and switched to full enteral feeding as early as possible. Hydrolyzed protein formula (HPF) has also been shown to accelerate early feeding advancement in VLBW infants, and Tormo et al. showed that HPF induced higher motilin levels than intact protein formula. Additionally, protein hydrolysis may accelerate gastrointestinal transit via reduced β-casomorphin activity.[15] Mengyuan et al. reported that HFs might improve gastrointestinal tolerance in preterm infants, including reducing the risk of FI and shortening the time required to transition to full enteral feeding. Given the paucity of data on the topic, whether AAF can benefit FI LBW neonates via the exact mechanisms as HFs is still being determined.[16] A study by Raimondi et al. presented, in infants with severe FI, inadequate BW, short-term AAF feeding as a rescue strategy was concluded to be safe and effective. The long-term nutritional adequacy of AAF and HPF in extremely preterm neonates still requires further study.[17]

CONCLUSION

The current definition of FI is based on nonspecific clinical signs. It does not guide clinicians on how to differentiate developmental FI from pathological FI. The clear presentation of an underlying etiopathogenesis may also change treatment approaches. Based on our study, regardless of the underlying cause of FI, AAFs and HFs may be viable alternative nutritional options to be applied for a short time. However, in premature infants with FI, randomized controlled studies are needed to confirm the methodology related to treatment approaches in a robust and large number of patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of KTO Karatay University Faculty of Medicine Non-Pharmaceutical and Medical Device Research Ethics Committee (Date: 02.03.2023, Decision No: 2023/021).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1350196
J Contemp Med 2023;13(5):918-922

Original Article / Orijinal Araştırma

Relationship of Selective IgE Deficiency with Autoimmune Diseases

Selektif IgE Eksikliği ve Otoimmun Hastalık İlişkisi

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Abstract

Aim: Selective IgE deficiency (SIgED) is currently defined as a significant decrease in serum levels of immunglobulin E (IgE) (≤2 kU/L) in a patient whose other immunoglobulin levels are normal. The clinical spectrum of SIgED is unknown still. This study aimed to determine the relationship between SIgED and autoimmune diseases in an allergy and immunology clinic of a university hospital.

Material and Method: A retrospective study of the data obtained from medical records of 40 patients, 27 were female (67.5%), and the mean age was 39 years (range 20–69 years) and IgE levels of ≤2.0 kU/L with normal immunglobulin G (IgG), immunglobulin A (IgA), immunglobulin M (IgM) levels.

Results: A total of 40 patients , 27 females (67.5 %) and 13 males (32.5%), were included in the study. The mean age of the patients was 39±13.06 years (range 20–69). In the present study, 35% of patients had an autoimmune disease (N:14), however 65% of patients did not have any autoimmune disease (N:26). Hashimoto's thyroiditis being the most frequent (N:6) in 15% which is followed by systemic lupus erythematosus (SLE) (N:3) in 7.5%, celiac disease (N: 2) in 5%, chronic spontaneous urticaria (CSU), vitiligo and type 1 diabetes mellitus (DM) (N:1) in 2.5%.

Conclusion: SIgED, should be defined clearly with cut-off values of IgE. Physicians should show more attention to the low IgE values and investigate patients about autoimmune diseases which can be seen together with SIgED. More studies should be conducted to investigate associated diseases with SIgED.

Keywords: Immunoglobulin E, autoimmune disease, selective Immunglobulin E deficiency

Öz

Amaç: Selektif IgE eksikliği (SIgED), günümüzde diğer immünglobulin düzeyleri normal olan bir hastada serum immunglobulin E (IgE) düzeylerinde (≤2 kU/L) anlamlı bir azalma olarak tanımlanmaktadır. SIgED'in klinik spektrumu hala bilinmemektedir. Bu çalışmada bir üniversite hastanesinin alerji ve immünoloji kliniğinde SIgED ile otoimmün hastalıklar arasındaki ilişkinin belirlenmesi amaçlandı.

Gereç ve Yöntem: 27'si kadın (%67,5) yaş ortalaması 39 (dağılım 20-69) ve IgE düzeyi ≤2,0 kU/L iken immunglobulin G (IgG), immunglobulin A (IgA), immunglobulin M (IgM) seviyeleri normal olan 40 hastanın tıbbi kayıtlarından elde edilen veriler retrospektif olarak incelendi.

Bulgular: Çalışmaya 27'si kadın (%67,5) ve 13'ü erkek (%32,5) olmak üzere toplam 40 hasta dahil edildi. Hastaların yaş ortalaması 39±13,06 yıl (dağılım 20-69) idi. Çalışmamızda hastaların %35'inde otoimmün hastalık mevcuttu (N:14), ancak hastaların %65'inde herhangi bir otoimmün hastalık yoktu (N:26). Hashimoto tiroiditi %15 ile en sık görülen (N:6) olup, bunu %7,5 ile sistemik lupus eritematozus (SLE) (N:3), %5 ile çölyak hastalığı (N:2), kronik spontan ürtiker (KSU), vitiligo ve tip 1 diyabetes mellitus (DM) (N:1) %2,5 takip etmektedir.

Sonuç: SIgED, IgE için belirlenecek eşik değerleri ile net bir şekilde tanımlanmalıdır. Klinisyenerin düşük IgE değerlerine daha fazla dikkat etmesi ve hastaları SIgED ile birlikte görülebilen otoimmün hastalıklar açısından araştırmaları gerekmektedir. SIgED ile ilişkili hastalıkların araştırılması için daha fazla çalışma yapılmalıdır.

Anahtar Kelimeler: İmmunglobulin E, otoimmun hastalık, selektif İmmunglobulin E eksikliği

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Received *(Geliş Tarihi)*: 25.08.2023 **Accepted *(Kabul Tarihi)*:** 22.09.2023

INTRODUCTION

Immunoglobulin E (IgE) was discovered in 1966, and we have begun to understand the role of IgE in the development of autoimmunity.[1] Since then, the immune system and the mechanisms leading to autoimmunity continue to be studied. It's known that IgE had important function in the immune system against infections with helminths and elevated serum levels are associated with, parasitic infections, allergic disorders, and specific immunologic disorders but the implications of ultra-low IgE levels are not understood clearly.[2,3] IgE is located bound to the high-affinity receptor (FcεRI) on the surface of basophils and mast cells mostly. When specific IgE/FcεRI and allergen complex occurs, the degranulation of basophils and mast cells begins and different mediators (bronchoconstrictors, vasoactive mediators, interleukins) are released, which create the clinical findings of the allergic reaction (asthma, rhinitis, urticaria, anaphylaxis, angioedema).[4]

According to the recent classification, innate errors of immunity were separated into 10 groups, one of which is "antibody deficiencies" (Group 3).[5,6] immunglobulin M (IgM), immunglobulin G (IgG), immunglobulin A (IgA) have a central role in the humoral immune response. Also, these immunoglobulins play an important role in fighting against viral, bacterial, protozoal, and parasitic infections. They create the defense mechanism so-called acquired immunity mediated by antibodies.[7] In some types of immunodeficiencies, levels of one or more of IgG, IgM, and IgA immunoglobulins are recognized.[5,6] Selective IgE deficiency (SIgED) is defined as normal IgA, IgM and IgG levels in a patient with significantly low serum IgE levels (≤2 kIU/L).[8]

Common variable immunodeficiency (CVID) is the most common combined form and characterized by reduced serum levels of IgG, with a reduction of IgM or IgA, or both. CVID is associated with increased risk of malignancy, autoimmune disorders, granulomatous diseases, recurrent sinopulmonary infections and altered antibody response against various infections.[9,10] Patients who have normal serum IgM and IgA levels but low serum IgG levels are considered to have selective IgG deficiency (SIgGD). The CVID group was more likely to have a higher incidence of granulomas, autoimmune cytopenias, splenomegaly, bronchiectasis, lymphoid neoplasms, and poorer responses to vaccines according to the studies comparing the CVID and SIgGD.[11] IgG subclass deficiency (IgGSD) is a subset of primary immunodeficiencies, that have the triad of low IgG response against pneumococcal vaccines, decreased levels of one or more of the IgG subclasses, and severe or frequent respiratory tract infections.[12,13] Selective IgM (SIgMD) and selective IgA deficiency (SIgAD) are defined in asymptomatic patients as well as people with allergic diseases, recurrent infections, autoimmune processes, and malignant tumors.[14-16]

Serum IgE values between (≤2 kU/L) and up to 100 kU/L are considered normal. There is not a universally accepted minimum level to define IgE deficiency, but an excess of IgE (>100 kU/L) can be established. Researchers used various cut-off points to establish IgE deficiency.[14-17] Most clinicians consider very low or even unmeasurable (≤2 kU/L) IgE values generally "normal" and not pathological. Low levels of IgE is associated with CVID frequently.[18-20] For the diagnosis of CVID, it may be recommended to use routine IgE measurement first, according to the literature.[19,20] The presence of low IgE values is usually associated with some of the other immunoglobulin deficiencies in the classification of primary immunodeficiencies.[5,6] The presence of SIgED alone was not considered in the immundeficiency classification. It has been shown that patients with normal values of other immunoglobulins but a low level of IgE, have generally autoimmune diseases, similar to those patients with CVID, IgGSD or with SIgGD, SIgAD, and SIgMD.[8-11,21-25] SIgED has a relationship with various diseases similar to that seen in other antibody deficiencies, but its clinical spectrum is unknown still. We aimed to determine the association between SIgED and autoimmune diseases in an allergy and immunology clinic of a university hospital.

MATERIAL AND METHOD

Patients who have an IgE concentration ≤2 kU/L with normal IgG, IgM, and IgA concentrations applied to the allergy immunology clinic for any reason between July 2022-2023 was included in the study. A total of 5300 medical records were investigated, of whom 155 patients have IgE concentration ≤2 kU/L, 40 patients have IgE concentration ≤2 kU/L with normal IgG, IgM, and IgA concentrations were included in the study shown in **Figure 1**. Of the 40 patients, 27 were female (67.5%), and the mean age was 39 years (range 20–69 years). Skin prick tests (SPTs) are performed in our clinic with a panel of common allergenic extracts of the aeroallergens in our region in patients with a suspicion of respiratory or food allergy routinely.

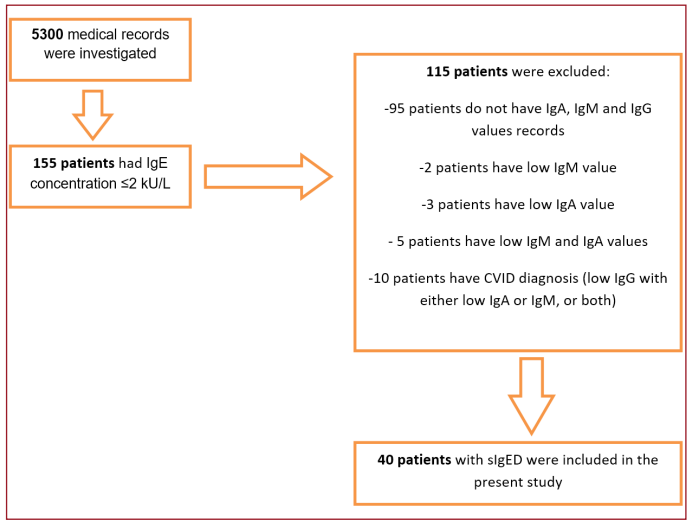

Figure 1. Flow chart of patients analyzed.

Ethical Statement

The study was approved by Manisa Celal Bayar University Clinical Researches Ethics Committee (Date: 15.06.2022, Decision no: 20.478.486/1391). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

The data obtained were evaluated by descriptive statistics (number, mean, percentage distribution, standard deviation, range etc.). Categorical variables were evaluated using Fisher's exact test. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 40 patients were included in the present study. Twenty seven patients were females (67.5%) and 13 patients were males (32.5%). The mean age of the patients partcipating in the study was 39±13.06 years (range 20–69). In the present study, 35% of patients had an autoimmune disease (N:14), however 65% of patients did not have any autoimmune disease (N:26). Investigating the disease spectrum individually, Hashimoto's thyroiditis (N:6) in 15%, systemic lupus erythematosus (SLE) (N:3) in 7.5%, celiac disease (N: 2) in 5%, chronic spontaneous urticaria (CSU) (N:1) in 2.5%, vitiligo (N:1) in 2.5%, type 1 diabetes mellitus (DM) (N:1) in 2.5% were detected (**Table 1**).

Table 1: Autoimmune disease frequency of participants.

Autoimmune Disease	Female (N:27)	Male (N:13)
Hashimato's Thyroiditis	4 (14.8%)	2 (15.4%)
Celiac Disease	1 (3.7%)	1 (7.7%)
SLE	3 (11.1%)	0 (0%)
CSU	0 (0%)	1 (7.7%)
Vitiligo	1 (3.7%)	0 (0%)
Type 1 DM	1 (3.7%)	0 (0%)
Autoimmune disease	17 (63%)	9 (69.2%)

SLE: Systemic lupus erythematosus; CSU: Chronic spontaneous urticaria; DM: Diabetes mellitus.

Seventeen females did not have an autoimmune disease (63%) and 10 females had an autoimmune disease (32.5%). Of the female patients with autoimmune disease, 14.8% had Hashimoto's thyroiditis(N: 4), 11.1% had SLE (N: 3), 3.7% had celiac disease (N: 1), 3.7% had vitiligo (N: 1) and 3.7% had type 1 DM (N: 1). While 9 males did not have an autoimmune disease (69.2%), 4 males had an autoimmune disease (30.8%). Of the male patients with autoimmune disease, 15.4% had Hashimoto's thyroiditis(N: 2), 7.7% had celiac disease (N: 1) and 7.7% had CSU (N: 1).

Of those patients with autoimmune disease, 71.42% were females (N: 10) and 28.58% were males (N: 4). There was no statistically significant difference between gender and having an autoimmune disease (p:0.491). In the present study, 52.5% of the patients had a total IgE of 2.00 (N: 16), 40% had a total IgE of 1 (N: 21), and 7.5% had a total IgE of 0 (N: 3). Mean of serum IgA, IgM, and IgG values of the participants were: IgM 101.87 (range, 18.3–319) mg/dL (normal values (40-230 mg/dL), IgG 1034.20 (range, 552-1830) mg/dL (normal values 700-1600 mg/dL), and IgA 157.45 (range 26.8-352) mg/dL (normal values 70-400 mg/dL). Serum levels of IgG1, IgG2, IgG3, and IgG4 had been assessed in 3, 7, 5 and 5 patients respectively and were normal in all patients, one with low IgG2. SPT results were normal in all patients.

DISCUSSION

An important number of CVID patients had autoimmune diseases (27%).[26] It has been shown that SIgMD,[24,27,28] SIgGD.[12,22] IgGSD (29), and SIgAD.[22,23] are also associated with organ-specific and systemic autoimmune diseases. The clinical manifestations of autoimmune diseases in CVID and other selective immunodeficiencies are various including a plethora of hematologic (thrombocytopenic purpura, cytopenia, Evans syndrome, hemolytic anemia), and non-hematologic diseases (rheumatoid arthritis, autoimmune thyroid diseases, Sjögren´s syndrome, unspecific inflammatory arthritis, SLE, autoimmune hepatitis).[30] In this study Hashimoto's thyroiditis was the most frequent autoimmune disease similar to the literature.[31] Our finding about the relationship between autoimmune diseases and SIgED is similar to the literature that investigated the relationship between deficiencies in other immunoglobulin classes with autoimmune diseases.

The mechanism of protecting against autoimmune reactivity of both IgE and IgA may be by promoting the mucosal exclusion of exogenous antigens. It's known that, SIgAD have a high relationship between autoimmune diseases similar to IgE hypogammaglobulinemia, including rheumatoid arthritis, SLE, Sjogren's syndrome, autoimmune thyroiditis and pernicious anemia. IgA prevents systemic absorption of mucosal antigens and as a result, may protect against autoimmunization. Deficient defense at the mucosal barrier could allow autoimmune responses occurring by the exogenous antigens to be induced by several mechanisms like stimulating autoreactive lymphocytes through molecular mimicry, promoting immune complex formation, superantigen-induced polyclonal activation of lymphocytes, inducing a perturbation of the idiotypic network, and/or by aberrant induction of MHC class II antigens.[21,22] Also, one possible cause may be the lack of protection against the crossing of the mucosal barrier by infectious agents that can trigger autoimmune disease. Another possible explanation for the association between SIgAD and autoimmune disease may be common genetic factors predisposing to both immunoglobulin deficiency and autoimmune phenomenon.

In another study, the association of SIgED with hematological and non-hematological autoimmune diseases was similar to that described in other immunodeficiencies.[31] In the literature, in adults and children with SIgED, isolated and mixed autoimmune diseases were significantly more

common than control populations. Autoimmune diseases reported in patients with SIgED were thyroid diseases, SLE, arthritis, and cytopenias in the literature.[8,21] In conclusion, these findings sustain that autoimmune diseases have relationship with the SIgED.

Additional studies showing an increased association between SIgED with autoimmune diseases compared with healthy controls are needed to demonstrate the relationship between SIgED and autoimmunity.

The limitations of this study was single-centered, the small sample size of patients recruited and its retrospective nature. Also, we used a very low cut-off limit (IgE≤2.0 kU/L) to have specific diagnostic criteria for SIgED. However, patients who have an IgE value close to this level could also have similar associated autoimmune diseases. New studies with different cut-off points for serum IgE level should be conducted.

CONCLUSION

SIgED, should be defined clearly with cut-off values of IgE. Physicians should show more attention to the low IgE values and investigate patients about autoimmune diseases which can be seen together with SIgED.. We wanted to take attention to a spectrum of diseases that may be underestimated in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Manisa Celal Bayar University Clinical Researches Ethics Committee (Date: 15.06.2022, Decision no: 20.478.486/1391).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1350153
J Contemp Med 2023;13(5):923-927

Original Article / Orijinal Araştırma

Evaluation of Neurofibromatosis Type 1 Associated Optic Pathway Gliomas

Nörofibromatozis Tip 1 İlişkili Optik Yol Gliomlarinin Değerlendirilmesi

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Abstract

Aim: Optic pathway gliomas (OPGs) are low-grade gliomas histologically represented by pilocytic astrocytoma (PA) in 90% of cases, can develop from any part of the visual pathways such as optic nerve, chiasm, optic tract, or optic radiations which frequently involve the hypothalamus. OPGs account for 3–5% of childhood central nervous system (CNS) tumors and about 2% of pediatric glial lesions. OPGs are believed to be the most prevalent intracranial tumor in patients with neurofibromatosis type 1 (NF-1) and can occur in 15–20% of NF-1 cases. The aim of this study is to evaluate the clinical features and treatment response in patients diagnosed with optic glioma and NF-1.

Material and Method: All cases diagnosed with OPG and received treatment in the Pediatric Oncology Department, between January 2015 to January 2021 were retrospectively evaluated. Inclusion criteria include children and adolescents with OPG aged between 0 and 18 years. The medical records (gender, age, tumor entity, tumor location) of patients, as well as their treatment history and magnetic resonance imaging (MRI) scans, were examined. The diagnosis of OPG was made clinically and radiologically by the tumor board. The recommendations of the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group were used in the diagnosis and evaluation of treatment response. Patients received intravenous chemotherapy with SIOP LGG 2004 (vincristine- carboplatin) with or without bevacizumab (10 mg/kg, started every 2 weeks), therapy or vinblastine (3 mg/m², weekly).

Results: This study included 27 cases during the study period from January 2015 to January 2021. In this study there were 14 male (51.8 %) and 13 female (48.1 %) patients. The median age was 4.8 (range: 0.5–14.9) years. Biopsy was performed in three patients and the diagnosis was low-grade glioma (pilocytic astrocytoma) for all of them. Chemotherapy was administered to 22 cases in total. Twelve patients received vincristine-carboplatine, 5 patients received vincristine-carboplatin with bevacizumab and 5 patients received vinorelbine. Radiological response was evaluated in all 22 patients at 3 months MRI. No patient had a radiological complete respons, 11 patients (50%) had partial response, 2 patients (9%) presented with a progressive disease, showing an increase in measurements of 35% and 9 patients(40.9%) had stable disease at the 3-month evaluation.

Conclusion: Systemic and visual problems play a significant role to initiate of treatment for pediatric patients with optic gliomas. An essential treatment option for improving symptoms and reducing tumor size is systemic chemotherapy. A crucial therapy option for enhancing vision is bevacizumab for the patients with NF-associated OPG.

Keywords: Pediatric cancers, optic pathway gliomas, bevacizumab

Öz

Amaç: Optik yol gliomaları (OPG'ler), vakaların %90'ında histolojik olarak pilositik astrositom (PA) olan düşük dereceli gliomalardır ve optik sinir, kiazma gibi görme yollarının herhangi bir kısmından hipotalamusa kadar uzanım göstererek gelişebilirler. OPG'ler çocukluk çağı merkezi sinir sistemi (CNS) tümörlerinin %3-5'ini ve pediatrik glial lezyonların yaklaşık %2'sini oluşturur. OPG'lerin, nörofibromatozis tip 1 (NF-1) hastalarında en yaygın intrakranyal tümör olduğu düşünülmektedir ve NF-1 vakalarının %15-20'sinde ortaya çıkabilmektedir. Bu çalışmanın amacı optik gliom ve NF-1 tanısı alan hastaların klinik özelliklerini ve tedavi yanıtını değerlendirmektir.

Gereç ve Yöntem: Ocak 2015 ile Ocak 2021 tarihleri arasında Çocuk Onkoloji Bölümü'nde OPG tanısı alan ve tedavi gören tüm olgular retrospektif olarak değerlendirildi. Dahil edilme kriterleri arasında OPG'li 0 ila 18 yaş arası çocuklar ve ergenler yer almaktadır. Hastaların tıbbi kayıtları (cinsiyet, yaş, tümör varlığı, tümörün yerleşim yeri), tedavi öyküleri ve manyetik rezonans görüntüleme (MRG) tetkikleri incelendi. OPG tanısı tümör konseyi tarafından klinik ve radyolojik olarak konuldu. Tedavi yanıtının tanılanması ve değerlendirilmesinde Pediatrik Nöro-Onkolojide Yanıt Değerlendirmesi (RAPNO) çalışma grubunun önerilerinden yararlanıldı. Hastalar bevacizumab (10 mg/kg, her 2 haftada bir başlanır) ile birlikte veya bevcizumab olmadan SIOP LGG 2004 (vinkristin-karboplatin) ile intravenöz kemoterapi veya vinblastin (haftalık 3 mg/m²) aldı.

Bulgular: Bu çalışmaya Ocak 2015 ile Ocak 2021 arasındaki çalışma döneminde 14'ü erkek (%51,8) ve 13'ü kız (%48,1) toplam 27 vaka dahil edildi. Ortanca yaş 4,8 (aralık: 0,5-14,9) yıldı. Üç hastaya biyopsi yapıldı ve hepsine düşük dereceli glioma (pilositik astrositom) tanısı konuldu. Toplam 22 olguya kemoterapi uygulandı. On iki hastaya vinkristin-karboplatin, 5 hastaya bevacizumab ile birlikte vinkristin-karboplatin ve 5 hastaya vinorelbin verildi. 22 hastanın tamamında 3. aydaki MRG'de radyolojik yanıt değerlendirildi. Hiçbir hastada radyolojik tam yanıt görülmedi, 11 hastada (%50) kısmi yanıt, 2 hastada (%9) ilerleyici, 9 hastada (%40.9) stabil hastalık görüldü.

Sonuç: Optik gliomlu pediatrik hastalarda tedavi seçiminde sistemik ve oküler bulgular önemlidir. Sistemik kemoterapi oküler bulguların iyileştirilmesinde ve tümör boyutunun küçültülmesinde önemli bir seçenektir. Bevacizumab tedavisi tümör boyutunu küçültmese de görsel bulguları iyileştirmektedir.

Anahtar Kelimeler: Pediatrik kanserler, optik yol gliomları, bevacizumab

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Received *(Geliş Tarihi)*: 25.08.2023 **Accepted *(Kabul Tarihi)*:** 23.09.2023

INTRODUCTION

Optic pathway gliomas (OPGs) are low-grade gliomas histologically represented by pilocytic astrocytoma (PA) in 90% of cases, can develop from any part of the visual pathways such as optic nerve, chiasm, optic tract, or optic radiations which frequently involve the hypothalamus.[1] OPGs account for 3–5% of childhood central nervous system (CNS) tumors and about 2% of pediatric glial lesions.[2] OPGs are believed to be the most prevalent intracranial tumor in patients with neurofibromatosis type 1 (NF-1) and can occur in 15–20% of NF-1 cases. Some chromosomal abnormalities, notably deletion of chromosome 17q and neurofibromin (in NF-1 patients), have been regarded as the underlying etiology of this tumor.

The majority of patients with symptomatic optic tract glioma are diagnosed before the age of six years. Children with OPGs are frequently diagnosed after visual deficits are noted; other symptoms at presentation include proptosis or symptoms of the hypothalamic syndrome, correlating with the anatomic tumour location and side. Clinical symptoms differ according to the location of the lesion.[3] Although patients may be asymptomatic, the most commonly described symptom is vision loss, regardless of tumor location. The relationship between tumor size and visual symptoms has not been well established. Tumors located in the anterior part of the optic tract may present with unilateral vision loss, strabismus and/or proptosis. Proptosis is a more common symptom in patients with NF1. A tumor located in the optic chiasm may present with loss of vision, nystagmus, and decreased visual acuity.[1] Hydrocephalus, diencephalic syndrome and multiple endocrine disorders can be detected in lesions in the hypothalamic region.[4]

The visual assessment is crucial since preservation of vision is a critical goal of the management of OPG. Imaging is crucial in the diagnosis and management of OPG together with ocular evaluation. Following a clinical examination and magnetic resonance imaging (MRI), the diagnosis is typically made. A biopsy is not required when a tumor exhibits the typical clinical traits and imaging findings in NF1 patients.

There is no consensus on the best way to handle pediatric OPG; the choice of treatment relies on the patient's age, NF1 status, tumor size, tumor location, and, most importantly, how the tumor affects neurological and visual abilities, leading to functional deficits.

The choice of treatment (wait and see, surgery, radiotherapy, chemotherapy or possibly targeted therapy) is one of the most challenging and controversial aspects of the disease, although current consensus is to treat children with evidence of visual or neurological deterioration.

A variety of different drug regimens have shown efficacy, achieving 5-year progression free survival (PFS) depending on the regimen: weekly vinblastine with a PFS of 53.2%;[5] SIOP LGG 2004 (vincristine- carboplatine) with a PFS of 46%.[6] Among new therapies, bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF).[7] Brain tumors and among-all low grade gliomas have been shown to express high levels of VEGF.[8] The expected mechanisms of action of Bevacizumab are tumor size stabilization/reduction and vision sparing.

The aim of this study is to evaluate the clinical features and treatment response in patients diagnosed with optic gloma and NF-1.

MATERIAL AND METHOD

The study was approved by Gazi University Clinical Researches Ethics Committee (Date: 24.01.2022, Decision no: 49). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

All cases diagnosed with OPG and received treatment in the Pediatric Oncology Department, between January 2015 to January 2021 were retrospectively evaluated. Inclusion criteria include children and adolescents with OPG aged between 0 and 18 years. Patients who had their initial treatment at other centers and were referred to us for further management were excluded from the study.

The medical records (gender, age, tumor entity, tumor location) of patients, as well as their treatment history and MRI scans, were examined. The diagnosis of OPG was made clinically and radiologically by the tumor board. In addition, we removed all identifiers from our data after the analyses were completed to protect patient privacy.

The recommendations of the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group were used in the diagnosis and evaluation of treatment response.

The width, transverse, and length measurements obtained from MRI images were used to evaluate the tumor response criteria. A complete response (CR) was defined as no evidence of disease (enhancing or nonenhancing, measurable or non-measurable) maintained for ≥8 weeks; no new lesions, whereas a partial response (PR) was defined as ≥25% decrease (compared with baseline) in the 2D product of the largest perpendicular diameters (using T2-weighted or FLAIR sequences) maintained for ≥8 weeks. Progressive disease (PD) was defined as ≥25% increase (compared with smallest measurement at any timepoint from trial baseline) in the 2D product of the perpendicular diameters (using T2-weighted or FLAIR sequences), whereas stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. The term "objective response" (OR) was used to describe all patients who had either a PR or a CR. The disease control rate (DCR) was defined as CR + PR + SD, whereas the response rate (RR) was defined as CR + PR.[9]

Clinical evaluation by trained pediatric ophthalmologists was performed at the same time as the radiological evaluation, with assessment of visual acuity, as well as the visual field (VF) whenever feasible.

Biopsy was performed on large masses extending beyond the optic nerve.

In case of tumor progression and visual deterioration, treatment was started.

Patients received intravenous chemotherapy with SIOP LGG 2004 (vincristine- carboplatin) (6) with or without bevacizumab (10 mg/kg, started every 2 weeks), therapy or vinblastine (3 mg/m², weekly).

The criterias of wait and see option are stable mass on MRI and stable vision loss.

Statistics

Calculations were made using the Statistical Package for Social Studies (SPSS, version 18). Descriptive statistical methods were used.

RESULTS

This study included 27 cases during the study period from January 2015 to January 2021. Patients' characteristics are summarized in **Table 1**. In radiological evaluation hamartomas were detected in 11 (44.4%) patients. Epilepsy was identified after further evaluation in a patient.

Biopsy was performed in three patinets and the diagnosis were low grade glioma (pilocytic astrocytoma) for all of them.

Table 1. Patients' characteristics

Median age at diagnosis (range)	4.8 years (0.5–14.9 y)
Female/Male	13/14
Family History	19(70.4%)
Café-au-lait macules	12 (44.4%)
Freckling in the axillary region	8(29.6%)
Neurofibromas	3(11.1%)
Plexiform neurofibromas	1(3.7%)
Lisch nodules	4(14.8%)
Bone abnormalities	1(3.7%)

Five patients were asymptomatic and choice of treatment was wait and see.

Chemotherapy was administered to 22 cases in total. Twelve patients received vincristine-carboplatin, 5 patients received vincristine-carboplatin with bevacizumab and 5 patients received vinorelbine.

The median follow up time was 2.7 (0.8-4.3) years.

Radiological response was evaluated in all 22 patients at 3 months MRI. No patient had a radiological CR, 11 patients (50%) had partial response, 2 patients (9%) presented with a progressive disease, showing an increase in measurements of 35% and 9 patients (40.9%) had stable disease at the 3-month evaluation. Radiological response is summarized in **Table 2**.

Table 2. Objective radiological responses according to RAPNO criteria at 3-month MRI

Radiological Response	3-Month Evaluation
Complete response	0 (0%)
Partial response	11(50%)
Stable disease	9 (40.9%)
Progressive disease	2 (9%)

RAPNO: Response Assessment in Pediatric Neuro-Oncology, MRI: Magnetic Resonance Imaging.

Visual assessment for visual acuity was available for 22 patients. Five patients (18.5%) were not evaluated due to low age and cognitive status. Objective clinical/ophthalmological response to the therapy was the following: steady state in twelve patients (54.5%), significant improvement in six patients (27.2%), and significant worsening in four patients (18.1%).

Radiologic response and visual response were not compatible with each other in all patients, but could not be evaluated because of small the number of the patients.

Five patients received bevacizumab combination therapy and all ofthem had stable disease at the 3-month evaluation. When the ophthalmologic response was evaluated, significant improvement was observed in 3 patients and steady state was observed in 2 patients.

While two patients were being evaluated for malnutrition, they were diagnosed with OPG in MRI. Diencephalic syndrome was observed in these two patients. They were diagnosed at 12 and 18 months of age respectively. Both of them received vincristin, carboplatin with bevacizumab and symptoms were improved with treatment.

There was one patient under the age of 12 months. An optic glioma was detected in the MRI while the 6-month-old girl was being evaluated for febrile seizure. In the patient's three-month follow-up, there was no radiological progression noted.

DISCUSSION

OPGs make up for 3-5% of all pediatric CNS malignancies and are the most common intrinsic optic nerve tumors, but the overall results of any therapeutic approach whether visually or radiologically have not yet been studied well. Children with NF-1 are more likely to develop these tumors, and they do so more frequently in the first ten years of life.[10] OPGs are typically low-grade tumors, but they might behave aggressively, making it difficult to use some therapeutic methods. Age less than one year is thought to be a significant unfavorable factor for mortality in OPG patients.[11] While some studies did not find a significant difference,[12] some studies showed that NF-1 is a good predictive factor. The presence of a diencephalic syndrome at the time of diagnosis, especially when it is linked to leptomeningeal dissemination, is believed to be a significant prognostic factor.[4] In our study the median age was 4.8 (range: 0.5–14.9) years.

Some retrospective evaluations suggest that some children with OPG might not require active intervention.[13] In our study five patients did not receive any chemotherapy, radiotherapy or surgery. We decided for the wait and see approach to treatment, and none of these five patients showed signs of deterioration.

Chemotherapy has never been proven to be totally effective in preventing vision loss. Chemotherapy that is administered systemically may arrest the decline of visual acuity and stabilize vision. Nearly one-third of children who got chemotherapy for NF-associated OPG showed some improvement in their vision. The combination of carboplatin and vincristine regimen and the weekly vinblastine treatment are two of the most often utilized chemotherapy regimens.[5] According to meta analysis which is based on the available data, a favorable radiological outcome was achieved in 72% (95%CI 64–78) of OPG patients who underwent chemotherapy, while a favorable visual outcome was attained in 75% (95%CI 67–81) patients. Overall, chemotherapy is effective at stopping the tumor's progression and vision loss in OPGs.[14] In our study Bevacizumab-based therapies have been used successfully in children with low grade gliomas.[15] The visual threat is still the major reason to use bevacizumab, and it is comforting to see almost all patients achieve stability. After the treatment, a decrease in contrast enhancement and a decrease in the cystic part are observed in the majority of patients.[16] Patients who received bevacizumab in our study either had stable disease or improved clinical and ophthalmological outcomes; none of the patients' diseases worsened.

Gastrointestinal dysfunction, leukopenia and hypertension were the toxic side effects of bevacizumab treatment with the highest incidence in pediatric population. No side effects related to bevacizumab were observed in the study group.

The uncommon symptom complex known as diencephalic syndrome (DS) is connected to malignancies in the hypothalamus and is most frequently observed in children with optic pathway/hypothalamic glioma.[17] Weightloss leading to malnutrition can be seen in DS.[18] In a study consist of 520 patients with low grade gliomas from Toronto, 9 patients with DS were treated with chemotherapy with good treatment response but 7 of them progressed and needed multiple lines of treatment.[19] Two of these 9 patients with DS had NF1 and were treated with chemotherapy.[4] Initial chemotherapy with carboplatin and vincristine was used in NF1-associated OPHG presenting with DS patients.[20] Also, targeted treatment with bevacizumab led to treatment response after progression in some studies.[21] In our study two patients who were being evaluated for malnutrition, were diagnosed with OPG in MRI. Diencephalic syndrome was observed in these two patients. Both of them received vincristin, carboplatin with bevacizumab and symptoms were improved with treatment.

The limitations of the study were that it was a single-center, retrospective study and had a small number of patients.

CONCLUSION

Systemic and visual problems play a significant role for initiating treatment for pediatric patients with optic gliomas. An essential treatment option for improving symptoms and reducing tumor size is systemic chemotherapy. A crucial therapy option for enhancing vision is bevacizumab for the patients with NF-associated OPG.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Gazi University Clinical Researches Ethics Committee (Date: 24.01.2022, Decision no: 49).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1349391
J Contemp Med 2023;13(5):928-931

Original Article / Orijinal Araştırma

Breast Cancer Awareness Among Women Patients of a Private Hospital: A Cross-Sectional Study on Risk Factors, Symptoms, and Attitudes in Turkey

Özel Bir Hastanenin Kadın Hastaları Arasında Meme Kanseri Farkındalığı: Türkiye'de Risk Faktörleri, Semptomlar ve Tutumlar Üzerine Kesitsel Bir Çalışma

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Abstract

Aim: The global prevalence of breast cancer continues to rise, necessitating heightened awareness, early detection, and effective management strategies. This study aimed to assess differences in breast cancer awareness, risk factors, symptoms, and attitudes among economically well-off female patients in Turkey.

Material and Method: A single-center survey was conducted at a private hospital, involving 189 economically well-off patients who presented to the internal medicine outpatient clinic. Descriptive statistics, Chi-square tests, ANOVA, and Kruskal-Wallis tests were used for data analysis.

Results: Participants had a mean age of 50.2 (21-65) years, with the highest awareness of risk factors and symptoms observed in the 31-50 age group. Marital status and education were associated with breast cancer awareness, risk factors, symptoms, and screening methods. Education level correlated with enhanced knowledge of risk factors and symptoms. The prevalence of breast cancer risk awareness was 41.2%, with the most recognized risk factors being smoking and family history. Palpable lump (36.4%) and redness of breast skin (16.9%) were identified as common symptoms. Screening methods included self-breast examination (12.2%), physician examination (13.2%), ultrasonography (19%), magnetic resonance imaging (15.9%), and mammography (23.3%).

Discussion: Breast cancer remains a critical global health concern, necessitating increased awareness and early detection. In Turkey, breast cancer poses a significant health burden. Socioeconomic factors impact awareness and outcomes, with education and marital status influencing awareness levels. The study highlights the need for tailored interventions and accessible screening programs to enhance awareness and early detection.

Conclusion: This study sheds light on breast cancer awareness and attitudes among economically well-off female patients in Turkey. Education, marital status, and age play pivotal roles in shaping awareness levels. Targeted interventions and education are crucial for improving early detection, reducing mortality rates, and effectively addressing breast cancer.

Keywords: Breast cancer, awareness, risk factors, symptoms, screening methods

Öz

Amaç: Meme kanserinin küresel yaygınlığı artmaya devam etmekte ve bu durum yüksek farkındalık, erken teşhis ve etkili yönetim stratejilerini gerektirmektedir. Bu çalışmanın amacı, Türkiye'deki ekonomik olarak iyi durumda olan kadın hastalar arasında meme kanseri farkındalığı, risk faktörleri, semptomlar ve tutumları arasındaki farkları değerlendirmektir.

Gereç ve Yöntem: Özel bir hastanenin iç hastalıkları polikliniğine başvuran 189 hastada anket yapılmıştır. Veri analizi için tanımlayıcı istatistikler, Ki-kare testleri, ANOVA ve Kruskal-Wallis testleri kullanılmıştır.

Bulgular: Katılımcıların yaş ortalaması 50.2 (21-65) yıl olup, en yüksek risk faktörleri ve semptom farkındalığı 31-50 yaş grubunda gözlemlenmiştir. Medeni durum ve eğitim, meme kanseri farkındalığı, risk faktörleri, semptomlar ve tarama yöntemleri ile ilişkilendirilmiştir. Eğitim düzeyi, risk faktörleri ve semptomlar konusundaki gelişmiş bilgi ile uyumludur. Meme kanseri risk farkındalığı yaygınlığı %41.2'dir ve en çok tanınan risk faktörleri sigara içme ve aile öyküsüdür. Elle hissedilebilir kitle (%36.4) ve meme cildinin kızarması (%16.9) yaygın semptomlar olarak belirlenmiştir. Tarama yöntemleri arasında kendi kendine meme muayenesi (%12.2), doktor muayenesi (%13.2), ultrasonografi (%19), manyetik rezonans görüntüleme (%15.9) ve mamografi (%23.3) yer almaktadır.

Tartışma: Meme kanseri, artan farkındalık ve erken teşhis gerektiren önemli bir küresel sağlık sorunudur. Türkiye'de meme kanseri önemli bir sağlık yükü oluşturur. Sosyoekonomik faktörler, farkındalık düzeylerini belirleyip sonuçları etkilerken, eğitim ve medeni durum ise bu farkındalık düzeylerini şekillendiren etkenler arasında yer alır. Çalışma, farkındalığı artırmak ve erken teşhisi sağlamak için özelleştirilmiş müdahalelere ve erişilebilir tarama programlarına ihtiyaç olduğunu vurgular.

Sonuç: Bu çalışma, Türkiye'deki ekonomik olarak iyi durumda olan kadın hastalar arasında meme kanseri farkındalığı ve tutumlarına ışık tutmaktadır. Eğitim, medeni durum ve yaş, farkındalık düzeylerini şekillendirmede önemli roller oynamaktadır. Hedefe yönelik müdahaleler ve eğitim, erken teşhisi artırmak, mortalite oranlarını düşürmek ve meme kanseriyle etkili bir şekilde başa çıkmak için hayati öneme sahiptir.

Anahtar Kelimeler: Meme kanseri, farkındalık, risk faktörleri, semptomlar, tarama yöntemleri

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Received *(Geliş Tarihi)*: 24.08.2023 **Accepted *(Kabul Tarihi)*:** 23.09.2023

INTRODUCTION

According to the latest GLOBOCAN 2020 data obtained from 185 countries by the International Agency for Research on Cancer (IARC), an estimated 19.3 million new cancer cases (excluding non-melanoma skin cancer, which is 18.1 million) and approximately 10.0 million cancer-related deaths (excluding non-melanoma skin cancer, which is 9.9 million) occurred worldwide. Female breast cancer, with an estimated 2.3 million new cases (11.7%), has surpassed lung cancer as the most commonly diagnosed cancer.[1]

In Turkey, 24.175 women were diagnosed with breast cancer in 2020, making it the most common cancer in women. 7.161 women lost their lives due to breast cancer, accounting for 15.1% of deaths in women.[1]

The advanced stage of the disease at the time of diagnosis negatively impacts the mortality rate associated with breast cancer. Economic income, education, family support, and access to healthcare are related to early diagnosis and mortality of breast cancer.[2]

In developed countries, modified lifestyles, delayed marriage age, late first childbirth, working late into the night, and hormone replacement therapy are major risk factors for breast cancer development. In developing countries, the leading causes of high breast cancer incidence and mortality are inadequate awareness or knowledge about the disease, inappropriate screening programs, delayed diagnosis, and inadequate medical facilities.[3]

Awareness of breast cancer symptoms among women is crucial for early diagnosis. In a study conducted in the Czech Republic, it was found that the delay in seeking medical attention despite the development of symptoms was due to patients not being aware of the symptoms of breast cancer and the symptoms not being taken seriously.[4]

The aim of this study is to investigate the differences and attitudes of economically well-off female patients in Turkey regarding breast cancer risk factors, symptoms, and awareness.

MATERIAL AND METHOD

In this single-center survey conducted at a private hospital, a survey measuring breast cancer awareness was conducted on 189 economically well-off patients who presented to the internal medicine outpatient clinic.

This study was approved by the Mediterranean University Faculty of Medicine Ethics Committee with the decision dated 23.08.2023 and numbered 677.

Sample Size Calculation

A sample size calculation was performed to obtain reliable results and ensure accurate representation of the population. The calculation of the sample size is based on the study's objective, the population size, the statistical confidence level, the margin of error, and the population's variability.

A response rate of 80% was estimated, and 200 patients were planned to be invited to participate in the study. Patients who agreed to participate in the survey and provided informed consent were invited to join the study. They were requested to answer the questions honestly.

Statistics

The data were transferred to IBM SPSS version 26 (IBM Inc, Chicago, IL, USA) for evaluation through statistical analyses. Prior to conducting statistical analyses, checks were performed to ensure the absence of data entry errors and whether parameters were within the expected range. Descriptive statistics of mean and standard deviation were presented for continuous variables, while for categorical variables, the number (n) and percentage (%) values were provided. The relationship between categorical variables was examined using the Chi-square test. For independent groups, ANOVA was conducted for variables showing a normal distribution to determine statistically significant differences in means. For variables not showing a normal distribution, the Kruskal-Wallis test was employed. Values of $p < 0.05$ were considered statistically significant.

RESULTS

A total of 189 individuals were included in the study to assess breast cancer awareness. The participants had a mean age of 50.2±12.1 years (ranging from 21 to 65). Among the participants, 153 (81%) were married, and 36 (19%) were single. Demographic data of the participants are summarized in **Table 1**.

Table 1: Demographic characteristics of patients

	n	%
Age Range		
18-30	22	11.6
31-50	43	22.8
51-65	124	65.6
Marital Status		
Married	153	81
Single	36	19
Education Level		
Primary school	21	11.1
High school	87	42.9
University	81	46
Comorbid Disease		
Present	107	56.6
Absent	82	43.4
Chronic Disease		
Diabetes mellitus	51	47.7
Coronary artery disease	28	26.2
Chronic obstructive lung disease	28	26.1
Family history of cancer		
Present	46	24.3
Absent	143	75.7
Smoking history		
Smoker	81	42.9
Non-smoker	108	57.1

The answers to questions about Breast Cancer Risk Factors and Symptoms are presented in **Table 2**.

Table 2: Breast Cancer Risk Factors and Symptoms

	n	%
Breast Cancer Risk Awareness		
Present	78	41.2
Absent	111	59.8
What Are Breast Cancer Risk Factors?		
Early menstruation	10	5.3
Late menopause	13	6.9
Hormone therapy	22	11.6
Nulliparity	27	14.3
Oral contraceptive use	12	6.3
Family history	16	8.5
Alcohol consumption	8	4.2
Smoking	41	21.7
I don't know	40	21.2
What Are Breast Cancer Symptoms?		
Palpable lump	69	36.4
Redness of breast skin	32	16.9
Breast pain	38	20.1
Nipple discharge	30	15.9
I don't know	20	10.7

The answers to questions regarding breast cancer screening methods are displayed in **Table 3**.

Table 3: Breast Cancer Screening Methods

	n	%
Have You Had Breast Examination?		
Yes	76	40.2
No	113	59.8
What arte the Breast Cancer Screening Methods		
Self-breast examination	23	12.2
Physician examination	25	13.2
Ultrasonography	36	19
Magnetic Resonance Imaging (MRI)	30	15.9
Mammography	44	23.3
I don't know	31	16.4

Greater awareness of risk factors was observed among married individuals, and statistically significant relationships were found between marital status and breast cancer risk factors, symptoms, and screening methods ($p < 0.05$). A significant association was observed between education level and breast cancer risk factors, as well as symptoms ($p < 0.05$). The highest awareness of breast cancer risk factors and symptoms was found in the 31-50 age group, and this association was statistically significant ($p < 0.05$).

DISCUSSION

Breast cancer is a significant global health concern, as evidenced by the GLOBOCAN 2020 data from the International Agency for Research on Cancer (IARC). The prevalence of new cases and cancer-related deaths is alarming, emphasizing the need for heightened awareness, early detection, and effective management strategies. In this context, our study aimed to investigate the differences in breast cancer awareness, risk factors, symptoms, and attitudes among economically well-off female patients in Turkey.

The prevalence of breast cancer remains a critical issue worldwide, with the latest GLOBOCAN 2020 data estimating over 2.3 million new cases globally. This alarming figure places breast cancer as the most frequently diagnosed cancer among women, surpassing even lung cancer. These statistics underscore the importance of continuous efforts to raise awareness and implement effective preventive measures.

In Turkey, breast cancer constitutes a significant health burden. The 2020 data revealed that breast cancer was the most common cancer diagnosed among women, with 24.175 cases reported. Furthermore, the mortality rate associated with breast cancer was substantial, causing the deaths of 7.161 women. These figures reflect the urgent need for improved awareness, early detection, and targeted interventions to address the challenges posed by breast cancer in Turkey.

The impact of socioeconomic factors on breast cancer awareness and outcomes is well-documented. Our study focused on economically well-off female patients, allowing for a unique insight into the differences and attitudes within this specific demographic.

Economic challenges can affect people's access to healthcare services and participation in screening programs. Breast cancer screening and treatment services can sometimes be costly. In a globally conducted meta-analysis, especially in developing countries, breast cancer awareness has been found to be low.[5]

In a case-control study conducted in China, it was found that 80% of the participants had very low awareness of breast cancer. The study also revealed that risk factors, particularly family history, were prominent. Additionally, nearly half of the participants were aware that a lump in the breast could be a symptom of breast cancer.[6] In a cross-sectional study conducted in Jordan, the rate of patients seeking healthcare facilities late is 32.2%. The primary reasons for this delayed presentation are patients' insufficient awareness of breast cancer symptoms and negligence.[7] In a cross-sectional study conducted among female university students in Malaysia, it was observed that a majority of the students were not aware of breast cancer risks, and less than 50% practiced self-examination of the breast.[8] A study conducted in India found that breast cancer awareness is associated with education and socioeconomic status.[9] In a study conducted in Iran, it was found that individuals with higher education levels and those with a family history of cancer have higher breast cancer awareness.[10] In a study conducted on perimenopausal patients, breast cancer awareness was not found to be associated with age and socioeconomic status. However, differences were observed based on the place of residence, whether rural or urban.[11] A study conducted among medical faculty students revealed that 55% of the students lacked

sufficient knowledge about breast cancer.[12] In a study conducted on newly diagnosed breast cancer patients, most of the patients indicated that a lump in the breast could be a symptom of breast cancer. Forty-four percent (44%) emphasized the importance of self-examination of the breast for early detection of breast cancer.[13]

The findings revealed noteworthy associations between marital status, education level, and breast cancer awareness. Married individuals exhibited greater awareness of risk factors, aligning with previous research that highlights the role of family support in health awareness.

Education also emerged as a significant factor influencing breast cancer awareness. Patients with higher education levels demonstrated enhanced knowledge of risk factors and symptoms. This finding underscores the importance of education as a key determinant of health literacy, which can empower individuals to engage in proactive health-seeking behaviors.

Our study also illuminated the distribution of breast cancer awareness across different age groups. Notably, the highest awareness of risk factors and symptoms was observed in the 31-50 age range. This finding underscores the critical role of targeted educational campaigns that cater to varying age groups. Tailored interventions can contribute to maximizing awareness and early detection, ultimately improving patient outcomes.

However, our study has some limitations. The sample size, while sufficient for our analysis, may not fully capture the diversity within the economically well-off population. Additionally, self-reported data could introduce response bias, and further qualitative research might provide deeper insights into the attitudes and perceptions of these patients.

CONCLUSION

Breast cancer remains a global health challenge, and our study contributes to the understanding of breast cancer awareness and attitudes among economically well-off female patients in Turkey. The findings underscore the significance of marital status, education, and age in shaping awareness levels. Strategic interventions that focus on education, tailored awareness campaigns, and accessible screening programs are pivotal in improving early detection, reducing mortality rates, and ultimately combating breast cancer on a broader scale.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Mediterranean University Faculty of Medicine Ethics Committee (Date: 23.08.2023, Decision no: 677).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1350938
J Contemp Med 2023;13(5):932-938

Original Article / Orijinal Araştırma

Comparison of Pregnancy Outcomes Among Adolescent Pregnant Women, Young Adult Pregnant Women, and Adult Pregnant Women Over Ten Years in Our Tertiary Care Clinic

Üçüncü Basamak Olan Kliniğimizde On Yıl Boyunca Adolesan Gebeler, Genç Yetişkin Gebeler ve Yetişkin Gebelerin Arasında Gebelik Sonuçlarının Karşılaştırılması

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Abstract

Aim: In this study, we aimed to compare the results of adolescent pregnancies, which we think is a big problem for our country, with young and adult pregnant women.

Material and Method: We included 15705 individuals in our retrospective cohort study. In our study, the adolescent pregnant group was 5235 people, the young adult group was 5235, and the adult group was 5235. We conducted the study with patients who gave birth in our tertiary care center between January 2012 and April 2022. We complied with the Declaration of Helsinki at all stages of the study. In the study, we compared the demographic data of the groups with the maternal and fetal outcomes of pregnancy, delivery, and postpartum. We performed a One-Way Analysis of Variance (ANOVA) to compare group means. We used odds ratio calculation to determine risk ratios between groups. We used SPSS for Windows 24.0 (SPSS Inc., Chicago, IL, USA) for the analyses. We presented the data as mean, standard deviation, and ratio and considered them statistically significant when the p value was less than 0.05.

Results: Our study observed that the risk of having PROM in adolescent pregnant women increased approximately two times compared to adult pregnant women (aOR=01.987, 95%CI=1.197-2454, p=0.001). When we researched the IUGR results, we found that the risk increased approximately two times in adolescent pregnant women (aOR=2.129, 95%CI=1.754-2.947, p<0.0001).

Conclusion: It is understood from the study that some adverse events related to pregnancy increase in adolescent pregnancy. For this reason, although preventing adolescent pregnancies is impossible, the follow-up of these pregnancies should be done more frequently and carefully than routinely.

Keywords: Adolescent, pregnancy, young adult, adult, outcomes

Öz

Amaç: Bu çalışmada ülkemiz için büyük bir sorun olduğunu düşündüğümüz adölesan gebelik sonuçlarını genç ve erişkin gebelerle karşılaştırmayı amaçladık.

Gereç ve Yöntem: Retrospektif kohort çalışmamıza 15705 birey dahil ettik. Çalışmamızda adölesan gebe grubu 5235 kişi, genç yetişkin grubu 5235, yetişkin grubu ise 5235 kişidir. Çalışmayı Ocak 2012 ile Nisan 2022 tarihleri arasında üçüncü basamak olan hastanemizde doğum yapan olgularla yaptık. Çalışmanın her aşamasında Helsinki Deklarasyonuna uyduk. Çalışmada grupların demografik verilerini, gebelik, doğum ve doğum sonrası dönemdeki anne ve fetal sonuçları karşılaştırdık. Grup ortalamalarını karşılaştırmak için Tek Yönlü Varyans Analizi (ANOVA) gerçekleştirdik. Gruplar arasındaki risk oranlarını belirlemek için odds ratio hesaplamasını kullandık. Analizler için Windows 24.0 için SPSS (SPSS Inc., Chicago, IL, ABD) kullandık. Verileri ortalama, standart sapma ve oran olarak sunduk ve P değeri 0,05'ten küçük olduğunda istatistiksel olarak anlamlı kabul ettik.

Sonuçlar: Çalışmamızda ergen gebelerde EMR görülme riskinin erişkin gebelere göre yaklaşık iki kat arttığı görüldü (aOR=01.987, 95%CI=1.197-2454, p=0.001). IUGR sonuçlarını araştırdığımızda ergen gebelerde riskin yaklaşık iki kat arttığını tespit ettik (aOR=2,129, 95%CI=1,754-2,947, p<0,0001).

Sonuç: Çalışmadan, adölesan gebeliklerde gebeliğe bağlı bazı olumsuz olayların arttığı anlaşılmaktadır. Bu nedenle adölesan gebeliklerin önlenmesi mümkün olmasa da bu gebeliklerin takibinin rutinden daha sık ve dikkatli yapılması gerekmektedir.

Anahtar Kelimeler: Hamilelik, genç yetişkin, yetişkin, sonuçlar, adolesan

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Received *(Geliş Tarihi)*: 27.08.2023 **Accepted *(Kabul Tarihi)*:** 22.09.2023

INTRODUCTION

We can define adolescence as a process in which childhood is left behind and the transition to adulthood begins. A very different period begins in adolescence, biologically, psychologically, and socially, starting from childhood. The World Health Organization (WHO) defined the age range of adolescents as 10-19 years.[1] According to WHO reports, approximately 16 million people give birth in adolescence yearly.[2] Unfortunately, preeclampsia, intrauterine growth retardation (IUGR), and preterm birth rates are higher in deliveries under 19 than in all pregnancies.[3-5] The increase in preeclampsia, IUGR, and preterm birth rates we mentioned in adolescents cannot be fully supported in the literature. Some large-scale studies show that these adverse outcomes are not increased in adolescents.[6,7] There needs to be more straightforward information about whether these negative results are due to young maternal age and insufficient biological maturation or other reasons. Our study aims to shed light on this subject, which needs to be clarified in the literature.

MATERIAL AND METHOD

The study was carried out with the permission of İstanbul Kanuni Sultan Süleyman Training and Research Hospita Clinical Researches Ethics Committee (Date: 21.04.2022, Decision No: KAEK/2022.04.109). We complied with the Declaration of Helsinki at all stages of the study.

The character of our study is a retrospective case-control study. Between January 2012 and April 2022, we surveyed a tertiary center, İstanbul Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey. Our clinic is a center that receives intensive applications for obstetrics and gynecology. We included 15705 individuals in our retrospective cohort study. In our study, the adolescent pregnant group was 5235 people, the young adult group was 5235, and the adult group was 5235. In the study, we compared the demographic data of the groups with the maternal and fetal outcomes of pregnancy, delivery, and postpartum.

We collected data about the cases in the study electronically and manually from patient files. In the study, the first group consisted of pregnant women under the age of 19, the second group consisted of pregnant women between the ages of 19-25, and the third case group consisted of pregnant women between the ages of 26-33. Those aged 34 and above who left our clinic without giving birth, those who did not want surgery and postpartum follow-up and left the hospital by refusing treatment, those who were hospitalized for legal reasons, and those who were referred to another hospital were excluded from the study. The parameters evaluated in the study; maternal age, number of pregnancies, number of births, number of miscarriages, maternal body mass index (BMI), tobacco and drug use, number of fetuses in the current pregnancy, mode of delivery, chronic diseases, diseases developing during and after pregnancy (preeclampsia, Gestational Hypertension, Gestational Diabetes mellitus), pregnancy or delivery-related complications, fetal weight, fetal complications at or after birth, intrauterine growth retardation (IUGR), stillbirth, preterm birth, APGAR scores, and umbilical cord blood PH values. We calculated the gestational age determinations according to the last menstrual dates of the cases. We verified with the first-trimester head rump length (CRL). While premature births occur before 37 weeks, deliveries after 41 weeks constitute delayed births. When diagnosing preeclampsia and gestational hypertension (GHT), blood pressure was measured twice, at least 4 hours apart, and other markers were taken into account in cases with systolic blood pressure of 140 mmHg and above and/or 90 mmHg and above.[8] When diagnosing the cases with GDM, a two-stage glucose test (50g and 100g) was applied in 24-28 weeks.

Statistical Analysis

We performed a One-Way Analysis of Variance (ANOVA) to compare group means. We used the odds ratio calculation to determine the risk ratios for pregnancy complications between groups. We used the mean and standard deviation of the results for comparisons. We used SPSS for Windows 24.0 (SPSS Inc., Chicago, IL, USA) for the analyses. We presented the data as mean, standard deviation, and ratio and considered it statistically significant when the P value was less than 0.05.

RESULTS

Demographic information among the cohorts in our study is shown in **Table 1**. The mean ages of the groups were 17.13±1.01, 22.43±1.49, and 30.27±1.54 years, respectively, and there was a statistically significant difference (p=0001). When the gravida ratios were examined, they were 1.12±0.42, 2.23±1.22, and 2.92±1.27, respectively, and all values were statistically significantly different from each other (p=0001). The mean parity values were 0.13±0.27, 0.97±0.32, and 1.43±0.95, respectively, and all values were statistically significantly different from each other (p=0001). The mean pregnancies resulting in miscarriage of the groups were 0.06±0.01, 0.12±0.05, and 0.21±0.07, respectively, and all values were statistically significantly different from each other (p=0001). The nulliparity rates in all groups were 4346 (83.02%), 1529 (29.21%), and 788 (15.05%), and all values were statistically significantly different from each other (p=0001). Smoking rates among the groups were 580 (11.08%), 528 (10.09%), and 537 (10.26%), respectively. Smoking rates of the adolescent pregnant group were statistically significantly different from the other two groups (p=0.009).

Cesarean section rates and indications among the groups are shown in **Table 2**. Cesarean section rates were 1257 (24.01%), 2276 (43.48%), and 2472 (47.22%), respectively. Each of these ratios was statistically significantly different (p<0.0001). Severe preeclampsia rates were 51 (4.06%), 70 (3.08%), and 80 (3.24%), respectively, and were statistically significantly different to the detriment of the first group (p=0.003). Fetal distress rates were 3644 (28.96%), 162 (7.12%), and 117 (4.74%), respectively. These rates were statistically significantly different from each other (p=0.023). The previous cesarean rates were 219 (17.42%), 1226 (53.87%), and 1536 (62.14%), respectively. These rates were

Table 1. Demographic characteristics.

	Group1 (adolescent) N: 5235	Group 2 (19-25 years old) N: 5235	Group 3 ((26-33 years old) N: 5235	P value
Age (year)	17.13±1.01[a,b]	22.43±1.49[c]	30,27±1.54	<0.0001*
Gravide	1.12±0.42[a,b]	2.23±1.22[c]	2.92±1.27	<0.0001*
Parite	0.13±0.27[a,b]	0.97±0.32[c]	1.43±0.95	<0.0001*
Abortion	0.06±0.01[a,b]	0.12±0.05[c]	0.21±0.07	<0.0001*
Nulliparity	4346 (83.02%)[a,b]	1529 (29.21%)[c]	788 (15.05%)	<0.0001*
Maternal weight (kg)	63.56±13.45	64.12±17.23	63.12±12.78	0.678
Smoking	580 (11.08%)[a,b]	528 (10.09%)	537 (10.26%)	0.009*
Drug	6 (0.11%)	8 (0.15%)	7 (0.13%)	0.876
Chronic disease	11 (0.21%)	14 (0.27%)	13 (0.25%)	0,679

One-Way Analysis of Variance (ANOVA), p<0.05 statistically significant, a the difference between group 1 and group 2, b the difference between group 1 and group 3, c the difference between group 2 and group 3

Table 2. Cesarian ratio and indications.

	Group1 (adolescent pregnancy) N: 5235	Group 2 (19-25 years old) N: 5235	Group 3 ((26-33 years old) N: 5235	P value
Vaginal delivery	3978 (75.99%)[a,b]	2959 (56.52%)[c]	2763 (52.78%)	<0.0001*
Cesarean section	1257 (24.01%)[a,b]	2276 (43.48%)[c]	2472 (47.22%)	
Indications of CS n (%)	1257 (100%)[a,b]	2276 (100%)[c]	2472 (100%)	<0.0001*
Severe preeclampsia	51 (4.06%)[a,b]	70 (3.08%)	80 (3.24%)	0.003*
Labor arrest	120 (9.55%)[a,b]	163 (7.16%)[c]	80 (3.24%)	0.001*
CPD (cephalo-pelvic discordance)	152 (12.09%)[a,b]	79 (3.47%)[c]	33 (1.33%)	0.005*
Fetal distress	364 (28.96%)[a,b]	162 (7.12%)[c]	117 (4.74%)	0.023*
Previous C/S	219 (17.42%)[a,b]	1226 (53.87%)[c]	1536 (62.14%)	0.0001*
Malpresentation	128 (10.18%)[a,b]	53 (2.33%)	55 (2.22%)	<0.0001*
Macrosomia	22 (1.75%)[a,b]	66 (2.90%)	70 (2.83%)	0.022*
Eclampsia	2 (0.16%)[a,b]	27 (1.19%)	32 (1.29%)	<0.0001*
Multiple gestations	103 (8.19%)[a,b]	340 (14.94%)	363 (14.68%)	<0.0001*
Placenta previa	14 (1.11%)[a,b]	34 (1.49%)	39 (1.58%)	0.001*
Placental abruption	26 (2.07 %)[a,b]	29 (1.27 %)	36 (1.46 %)	0.039*
Cord prolapse	14 (1.11%)	22 (0.97%)	27(1.09%)	0.223
Denial of vagynal delivery	42 (3.34%)[a,b]	5 (0.22%)	4 (0.16%)	0.0001*

One-Way Analysis of Variance (ANOVA), p<0.05 statistically significant, a the difference between group 1 and group 2, b the difference between group 1 and group 3, c the difference between group 2 and group 3

statistically significantly different from each other (p=0.0001).

Complication rates of the groups during pregnancy, delivery, and postpartum are shown in **Table 3**. Fetal complication rates were 52 (1.32%), 38 (0.73%), and 41 (0.78%), respectively, and were statistically significantly different in favor of the second and third groups (p=0.034). Maternal complication rates were 162 (3.09%), 241 (4.60%), and 279 (5.33%), respectively, and all values were statistically significantly different from each other (p=0.001).

Maternal results during and after pregnancy are shown in **Table 4**. GDM rates were 112 (2.14%), 157 (3.00%), and 164 (3.13%) in the order of the groups, and these rates were statistically significant in favor of the adolescent pregnant group (p=0.016). Preeclampsia rates were 174 (3.32%), 286 (5.46%), and 276 (5.37%), respectively, and these rates were statistically significant in favor of the first group (p=0.027). Eclampsia rates were 17 (0.32%), 32 (0.61%), and 34 (0.65%), respectively, and these rates were statistically significant in favor of the first group (p=0.009). The HELLP rates were 8 (0.15%), 25 (0.48%), and 21 (0.40%), respectively, and these rates were statistically significant in favor of the first group (p=0.034). The PROM rates were 162 (3.09%), 88 (1.68%), and 90 (1.72%), respectively, and these rates were statistically significant (p=0.021) to the detriment of the first group. Multiple gestations rates were 152 (2.90%), 416 (7.95%), and 407 (7.77%), respectively, and these rates were statistically significant to the detriment of the first group (p=0.005).

Fetal outcomes during and after pregnancy are seen in **Table 5**. The mean fetal weight values were 3027.39±673 g, 3225.39±479 g, and 3309.39±781 g, respectively, and there was a statistically significant difference between all mean values (p=0.44). The mean fetal delivery weeks were 37.37±2.76, 37.79±2.44, and 37.77±2.06 weeks, respectively, and there was a statistically significant difference in favor of the first and third groups (p=0.017). IUGR rates were 198 (3.78%), 84 (1.60%), and 88 (1.68%), respectively, and there was a statistically significant difference to the detriment of the first group (p=0.017). Premature birth rates were 601 (11.48%), 372 (7.11%), and 366 (6.99%), respectively, and there was a statistically significant difference to the detriment of the first group (p=0.0001). APGAR scores for the first-minute mean values were 7.69±2.11, 7.81±1.87, and 7.88±2.05, respectively, and there was a statistically significant difference to the detriment of the first group (p=0.007). APGAR scores for the fifth minute mean values were 8.12±1.78, 8.63±2.11, and

Table 3. Fetal and maternal complications at or after delivery.

	Group1 (adolescent pregnancy) N: 5235	Group 2 (19-25 years old) N: 5235	Group 3 (26-33 years old) N: 5235	P value
Fetal complications at or after birth (%) None	5166 (98.68%)[a,b]	5197 (99.27%)	5194 (99.22%)	0.034*
Meconium aspiration syndrome	42 (0.80%)[a,b]	21 (0.40%)	25 (0.48%)	0.002*
Asfixy	12 (0.23%)[a,b]	7 (0.13%)	6 (0.11%)	0.005*
Brachial plexus injury	4 (0.08%)[a,b]	2 (0.04%)	2 (0.04%)	0.023*
Long Bone fracture	0 (0.00%)[a,b]	1(0.02%)[c]	0 (0.00%)	0.044*
Fetal death	11 (0.21%)[a,b]	7 (0.13%)	8 (0.15%)	0.001*
Total	52 (1.32%)[a,b]	38 (0.73%)	41(0.78%)	0.044*
Maternal complications at or after birth None	5073 (96.91%)[a,b]	5020 (95.40%)[c]	4956 (94.67%)	0.022*
Sphincter injury	21 (0.40%)[a,b]	11 (0.21%)[c]	7 (0.13%)	0.033*
Blood transfusions for peri/postpartum hemorrhage	103 (1.97%)	99 (1.89%)	107 (2.04%)	0.459
Bladder injury	5 (0.10%)[a,b]	17 (0.32%)[c]	25 (0.48%)	0.027*
İleus	6 (0.11%)[a,b]	15 (0.29%)	19 (0.36%)	0.001*
Wound infections	22 (0.42%)[a,b]	69 (1.32%)[c]	88 (1.68%)	0.001*
Pulmonary emboly	1 (0.02%)[a,b]	6 (0.11%)	7 (0.13%)	0.037*
Deep vein thrombosis	1 (0.02%)[a,b]	11 (0.21%)	10 (0.19%)	0.047*
Hematoma	3 (0.06%)[a,b]	7 (0.13%)	9 (0.17%)	0.002*
Relaparatomy for hemorrhage	0 (0.00%)[a,b]	6 (0.11%)	7 (0.13%)	0.0001*
Total	162 (3.09%)[a,b]	241 (4.60%)[c]	279 (5.33%)	0.001*

One-Way Analysis of Variance (ANOVA), p<0.05 statistically significant, a the difference between group 1 and group 2, b the difference between group 1 and group 3, c the difference between group 2 and group 3

Table 4. Maternal Outcomes during pregnancy and after delivery

	Group1 (adolescent pregnancy) N: 5235	Group 2 (19-25 years old) N: 5235	Group 3 (26-33 years old) N: 5235	P value
GDM	112 (2.14%)[a,b]	157(3.00%)	164 (3.13%)	0.016*
Gestational HT	15 (0.29%)	16 (0.31%)	17 (0.32%)	0.213
Preeclampsia	174 (3.32%)[a,b]	286 (5.46%)	276 (5.37%)	0.027*
Eclampsia	17 (0.32%)[a,b]	32 (0.61%)	34 (0.65%)	0.009*
HELLP	8 (0.15%)[a,b]	25 (0.48%)	21 (0.40%)	0.034*
PROM	162 (3.09%)[a,b]	88 (1.68%)	90 (1.72%)	0.021*
Multiple gestations	152(2.90%)[a,b]	416 (7.95%)	407 (7.77%)	0.005*

One-Way Analysis of Variance (ANOVA), p<0.05 statistically significant, a the difference between group 1 and group 2, b the difference between group 1 and group 3, c the difference between group 2 and group

Table 5. Fetal outcomes during and after delivery

	Group1 (adolescent pregnancy) N: 5235	Group 2 (19-25 years old) N: 5235	Group 3 ((26-33 years old) N: 5235	P value
Fetal weight (gram)	3027.39±673[a,b]	3225.39±479[c]	3309.39±781	0.044*
Gestational age of birth (weeks)	37.37±2.76[a,b]	37.79±2.44	37.77±2.06	0.017*
Growth retardation (IUGR)	198 (3.78%)[a,b]	84 (1.60%)	88 (1.68%)	0.0001*
Stillbirth	71 (1.36%)	79 (1.51%)	82 (1.57%)	0.131
Premature birth	601 (11.48%)[a,b]	372 (7.11%)	366 (6.99%)	0.0001*
Postmature birth	151 (2.88%)	134 (2.56%)	127 (2.43%)	0.067
APGAR scores the first minute	7.69±2.11[a,b]	7.81±1.87	7.88±2.05	0.007*
APGAR scores the fifth minute	8.12±1.78[a,b]	8.63±2.11	8.66±2.11	0.001*
APGAR scores the tenth minute	9.29±2.28	9.32±2.32	9.34±2.36	0.323
Umbilical cord blood PH values	7.42±0.45	7.44±0.54	7.43±0.48	0.212

One-Way Analysis of Variance (ANOVA), p<0.05 statistically significant, a the difference between group 1 and group 2, b the difference between group 1 and group 3, c the difference between group 2 and group 3

8.66±2.11, respectively, and there was a statistically significant difference to the detriment of the first group (p=0.001).

We see the crude and adjusted odds ratios of fetal and maternal results among the cohorts in **Table 6**. Our study observed that the risk of having PROM in adolescent pregnant women increased approximately two times compared to adult pregnant women (aOR=01.987, 95%CI=1.197-2454, p=0.001). When we look at the IUGR results, we found that the risk increased approximately two times in adolescent pregnant women (aOR=2.129, 95%CI=1.754-2.947, p<0.0001). As it can be understood from here, it is seen in Table VI that the risk of fetal weight, gestational age, preterm birth, APGAR first

Table 6. Crude and adjusted odds ratios of obstetric outcomes in adolescent pregnancies

	Crude OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
PROM[a]	2.112 (1.459-2.891)	<0.001	1.987 (1.197-2.454)	0.001
Fetal weights[b]	1.342 (1.232-1.456)	0.003	1.134 (1.104-1.232)	0.021
Gestational birth weeks	1.253 (1.123-1.456)	0.002	1.122 (1.021-1.219)	0.003
IUGR[b]	2.545 (1.965-3.465)	<0.000	2.129 (1.754-2947)	<0.0001
Preterm births[a]	1.532 (1.167-1.743)	<0.0001	1.265 (1.003-1.549)	0.001
APGAR first minute[c]	1.321 (1.274-1.421)	0.036	1.112 (1.109-1.302)	0.047
APGAR fifth minute[c]	1.119 (1.187-1.239)	0.022	1.097 (1.053-1157)	0.039

OR: Odds ratio; CI: Confidence Interval; IUGR: Intrauterine growth restriction; PROM: premature rupture of membranes; GDM: Gestational Diabetes Mellitus.
a Adjusted for smoking, age category (adolescent), IUGR, multiple gestation, and nulliparity.
b Adjusted for age category, macrosomia, IUGR, multiple gestation, and smoking.
c Adjusted for age category, multiple gestation, nulliparity, preeclampsia, IUGR, and preterm birth.

minute, and APGAR fifth minute values increase in adolescent pregnancy.

DISCUSSION

In our study, premature rupture of membranes, intrauterine growth retardation, and preterm delivery were higher in our adolescent pregnant cohort than in adult pregnant cohorts. Gestational age, first and fifth-minute APGAR values were lower in the adolescent cohort compared to the other groups. Fetal weight increased with increasing age in the groups. On the other hand, pregnant women younger than 19 years had lower rates of preeclampsia, gestational diabetes, HELLP, placenta previa, and multiple gestations.

Pregnancy under the age of 19 is a significant public health problem in all countries of the world. It has not been clarified whether pregnancies under 19 are associated with adverse obstetric outcomes such as preterm birth, pregnancy hypertensive diseases, gestational diabetes, low birth weight, multiple pregnancies, placental location anomalies, and intrauterine growth retardation. However, it is thought that among pregnant women under 19 and adults, these problems may be due to various factors such as different races, sociocultural and socioeconomic status, behavioral factors, biological immaturity, and inability to access health services.[9-11]

When we review the literature, while premature rupture of membranes does not differ between adolescents and adults in some studies, in parallel with our study, the risk of PROM doubles in adolescents in some studies.[12,13] The increase in PROMs in the adolescent pregnant group may be that these pregnant women are biologically immature—the immature uterus and cervix cause premature water flow and premature birth in pregnant adolescents.[14] Stevens-Simon et al. have shown immaturity-related shortening of the cervix length and increased cervical funneling in adolescents with decreasing age (15). Accordingly, an increase in the rate of PROM is likely in adolescent pregnant women. In our study, fetal weight was lower in the adolescent group compared to both adult groups. In the literature, regardless of whether adolescent pregnant women are in underdeveloped, developing, or developed countries, their babies' weight is lower than that of adult pregnant women.[16-22] Gestational age was also lower in the adolescent pregnant group compared to the adult cohorts. It is understood that this situation is associated with preterm birth and IUGR. Parallel to this situation, in our study, preterm birth and IUGR were also higher in the adolescent group than in the adult group. In this context, low gestational age, preterm birth, and IUGR rates parallel with some studies in the literature.[19-21,23,24] Demirci et al.[25] reported that the risk of IUGR is lower in pregnant women under the age of 19, while other studies show that the risk of IUGR is increased in young pregnancies.[21,26] In order to eliminate this contradiction, long-term, multi-center, forward-looking, multi-participant studies covering all segments of society are needed. We have associated obstetric problems such as increased preterm births, decreased fetal birth age, and decreased fetal birth weight with underdeveloped pelvic bones and muscles and immature cervix and uterus in adolescents.[14,15] In a study involving many centers (including African, South Asian, and Latin American countries), the risk of preterm labor is more than double under the age of 15.[11] In our study, in parallel with the literature, the risk of preterm birth in adolescent pregnant women increased with decreasing age of adolescents, and the risk of preterm labor in adolescents was 1.5 times compared to adults (Table VI). The first and fifth APGAR values between the groups were low to the detriment of adolescent pregnant women. Similar to our study, in the literature, there were studies with low first and fifth APGAR values to the detriment of the adolescent group. However, there were also studies where no significant difference could be found between the groups.[4,20,21,24,26] However, since obstetric problems such as PROM, low birth weight, low gestational age, and IUGR will impair fetal well-being, it is reasonable to have low APGAR values in the adolescent pregnant group.

Preeclampsia is a condition that negatively affects both the mother and the fetus. In the literature, some studies have shown an increased risk of preeclampsia in young pregnancies,[24,27] while others have reported a reduced risk of preeclampsia.[7,28] Leppälahti et al. found an increased preeclampsia and preterm delivery risk in the 13-15 age group.[29] In our cohort, the risk of preeclampsia was lower in the adolescent group and higher in the adult group. Among the adult groups, preeclampsia

was higher in the 25-33 age range than in the 19-24 age range. We could not find any information in the literature to explain or support this situation. However, we associated this situation with referring perinatological patients from many regions to our center, which accepts patients by reference. So, this rate may not reflect the average population. In order to eliminate this contradictory situation, long-term multi-center, prospective, multi-participant studies covering all parts of society are needed. Gestational DM is a condition that can have severe maternal and fetal consequences during pregnancy. In our study, low rates of GDM were found in the adolescent group, in line with the literature.[4,6,21,24] In our study, HELLP syndrome was found to be lower in the adolescent pregnant group, parallel to the study of Gomez et al.[22] Although the reason for this is not fully explained, we associated it with the high prevalence of hypertensive diseases of pregnancy in adult pregnant groups. In our study of placenta previa, we found low rates in the adolescent group, and there are conflicting results in the literature. In some studies, while it was low in the adolescent group, no difference was found in some groups.[13,21] We attributed this to the increase in placental location anomalies due to the high cesarean section rates and abortion in the adult group. Multiple pregnancies are also a condition that causes adverse maternal and fetal outcomes. In this context, the rate of multiple pregnancies in the adolescent pregnant group in our study was lower than in the adult group. This situation showed parallelism with other studies in the literature.[13,22] We think the low rate of multiple pregnancies in the adolescent pregnant group is due to assisted reproductive techniques in adult groups and the immature cervix and uterus of the adolescent pregnant group.

When the birth patterns of the cohorts were compared, we found statistically significant differences for each cohort. C/S ratios were relatively low in adolescents. At the same time, C/S ratios were lower in the young adult group compared to the adult pregnant group. When the literature was examined for this purpose, many studies also showed decreased C/S ratios with decreasing age.[4,6,7,18,20,25] argue that the reason for this may be related to parity. As the parity increases, the increase in C/S indications, mainly due to previous C/S, draws attention. The results were close to the literature when we looked individually at the cesarean section indications.[13,23] While fetal distress is the leading cause of cesarean section in the adolescent study group, this situation is due to previous cesarean sections in adult study groups. We attributed the increase in C/S ratios due to fetal distress in pregnant adolescents to the increase in standard vaginal birth rates. Of course, standard vaginal delivery does not cause fetal distress, but the frequency of procedures such as augmentation, induction, and forceps/vacuum increases in the delivery of adolescent pregnant women, increasing the fetal distress rate. The reason for all this is that adolescents are immature, including the uterus, pelvic muscles, and bones.[14,15]

An increase in anal sphincter damage, one of the maternal complications, draws attention in the adolescent pregnant group. We attributed this to the increased need for augmentation, induction, and forceps/vacuum during the active period of labor due to immature pelvic muscles and bones and uterine immaturity. In the literature, sphincter injury was not different from the adult groups.[13] Our study found that fetal complications such as meconium aspiration syndrome, fetal asphyxia, brachial plexus injury, and fetal death rates increased in the adolescent group. The literature shows that tertiary complications and the need for intensive care, including neonatal resuscitation and fetal deaths, increase adolescent pregnancies.[4,19,20] We did not encounter any information in the literature on brachial plexus increase. However, we attributed this to the poor development of the pelvis, especially the bony pelvis.

CONCLUSION

Pregnancy is inherently unpredictable. We found an increase in IUGR, PROM, low birth weight, preterm birth, fetal asphyxia, meconium aspiration syndrome, brachial plexus injury, and fetal death, especially in adolescent pregnant women. What we need to understand here is that the detection and follow-up of adolescent pregnancies are crucial in order to minimize these situations, many of which are unpredictable. Adolescent pregnancies should be followed more carefully and more frequently than the follow-up of an adult healthy pregnant woman, and very experienced obstetricians should be involved in labor. Only such intensive visits and approaches will reduce such dire consequences. Of course, it is necessary to give importance to sociological studies and contraception to reduce adolescent pregnancies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Kanuni Sultan Suleyman Training and Research Hospita Clinical Researches Ethics Committee (Date: 21.04.2022, Decision No: KAEK/2022.04.109).

Informed Consent: Written informed consent taken from the patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1351577
J Contemp Med 2023;13(5):939-948

Original Article / Orijinal Araştırma

Evaluation of Response to Stereotactic Radiosurgery and Survival Outcomes in Patients with Brain Metastases from Gastrointestinal Cancers

Gastrointestinal Kanserlerden Gelişen Beyin Metastazı Olan Hastalarda Stereotaktik Radyocerrahiye Yanıtın ve Sağkalım Sonuçlarının Değerlendirilmesi

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Abstract

Aim: Gastrointestinal cancers rarely metastasize to the brain and constitute 4-8% of all brain metastases (BM). Survival is generally poor for BM from gastrointestinal cancers and stereotactic radiosurgery (SRS) is frequently used in its management. Since the data are still insufficient due to their rare presentation, we aim to analyze the clinical results of patients who underwent SRS for BM due to gastrointestinal cancers.

Material and Method: We retrospectively reviewed patients with BM from gastrointestinal cancers who received robotic SRS with CyberKnife at our institute from October 2013 to December 2022. Clinical characteristics and treatment outcomes were recorded. Study endpoints were local control rates, distant brain control rates, and overall survival (OS).

Results: A total of 61 BM were detected in 42 patients. The median clinical follow-up time was 7 (0.5-36) months. Nine lesions progressed in the irradiated area, 14 new lesions were observed outside the irradiated area. The local control rate was 85.1% and the distant brain control rate was 77%. The median OS was 8 months; 12-month and 24-month OS were 31.6% and 10.5%, respectively. Patients with high performance status had better OS (p=0.016). The prognostic scoring scales recursive partitioning analysis (RPA) and graded prognostic assessment scores for gastrointestinal cancers (GI-GPA) were both associated with OS, in univariate analysis (p=0.049, p=0.002). Multivariate analysis found a significant association between GI-GPA classes and OS (p=0.011).

Conclusion: We obtained comparable results in terms of local control, distant brain control and OS in this challenging patient population. The use of GI-GPA prognostic scoring scales in routine practice will guide the selection of the most appropriate patient for SRS.

Keywords: Brain metastases, gastrointestinal cancer, prognosis, stereotactic radiosurgery

Öz

Amaç: Gastrointestinal kanserler nadiren beyne metastaz yapar ve tüm beyin metastazlarının (BM) %4-8'ini oluşturur. Gastrointestinal kanserlerden gelişen BM için prognoz genellikle kötüdür ve tedavisinde stereotaktik radyocerrahi (SRS) sıklıkla kullanılır. Nadir prezentasyonları nedeniyle veriler hala yetersiz olduğundan, gastrointestinal kanserlerden gelişen BM için SRS uygulanan hastaların klinik sonuçlarını analiz etmeyi amaçladık.

Gereç ve Yöntem: Ekim 2013'ten Aralık 2022'ye kadar enstitümüzde CyberKnife ile robotik SRS alan gastrointestinal kanserlerden gelişen BM'li hastaları retrospektif olarak incelendi. Klinik özellikler ve tedavi sonuçları kaydedildi. Çalışma sonlanım noktaları, yerel kontrol oranları, uzak beyin kontrol oranları ve genel sağkalım (OS) idi.

Bulgular: 42 hastada toplam 61 BM tespit edildi. Ortalama klinik takip süresi 7 (0,5-36) aydı. Işınlanan sahada 9 lezyonda progresyon izlenirken, ışınlanan alan dışında 14 yeni lezyon gözlendi. Lokal kontrol oranı %85,1, uzak beyin kontrol oranı ise %77 olarak saptandı. Medyan OS 8 aydı; 12 aylık ve 24 aylık OS sırasıyla %31,6 ve %10,5 idi. Performans durumu yüksek olan hastaların OS'si daha iyiydi (p=0,016). Tek değişkenli analizde, prognostik skorlama ölçeklerinden recursive partitioning analysis (RPA) ve gastrointestinal kansrler için graded prognostic assessment (GI-GPA) her ikisi de OS ile ilişkiliydi (p=0,049, p=0,002). Çok değişkenli analizde, GI-GPA sınıfları ile OS arasında anlamlı bir ilişki bulundu (p=0,011).

Sonuç: Bu zorlu hasta popülasyonunda lokal kontrol, uzak beyin kontrolü ve OS açısından karşılaştırılabilir sonuçlar elde ettik. GI-GPA prognostik skorlama ölçeklerinin rutin uygulamada kullanılması, SRS için en uygun hastanın seçimine yol gösterecektir.

Anahtar Kelimeler: Beyin metastazı, gastrointestinal kanser, prognoz, stereotaktik radyocerrahi

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Received *(Geliş Tarihi)*: 28.08.2023 **Accepted *(Kabul Tarihi)*:** 26.09.2023

INTRODUCTION

Gastrointestinal cancers rarely metastasize to the brain and constitute 4-8% of all brain metastases (BM).[1] Esophageal and gastric cancers cause BM at a lower rate than colorectal cancers.[2] Especially in colorectal cancers, the increase in the follow-up period due to the prolongation of survival is associated with the development of metastatic disease. At the same time, the more widespread use of imaging methods allows for more frequent detection of BM.

Survival is quite poor when BM develops in gastrointestinal cancers, and a median survival of about 6 months has been reported in many studies.[2,3] Although there are no optimal treatment recommendations with a high level of evidence for BM associated with gastrointestinal cancers, treatment options such as surgery, whole brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS) are applied.[3,4] The choice of treatment is made by considering several factors, such as the condition of the disease, the response to previous treatments, the presence of extracranial metastases, the number and location of BM, and the performance status.[1,5] Surgical treatment cannot be applied frequently due to extensive extracranial disease, advanced age, or decreased performance status. In this situation, radiotherapy remains the most common treatment method. WBRT is a radiotherapy technique that has traditionally been used for BM for many years, and today it is more commonly preferred in patients with widespread disease, leptomeningeal involvement, and low performance scores. Over the years, technological developments have enabled the development of modern radiotherapy techniques, and in this context, WBRT has largely left its place to SRS techniques with the accumulating evidence.[6,7]

SRS has advantages such as having fewer neurological side effects, shortening the treatment time, and increasing patient compliance compared to WBRT. In addition, it does not require invasive procedures compared to surgery. The most important oncological contribution of SRS is that it increases local tumor control.[6,7] Studies evaluating the outcome of SRS include reviews involving lung and breast cancer patients with an increased incidence of BM.[6,7] Since the incidence of BM due to gastrointestinal cancers is much lower, SRS results in this group of patients are still not sufficient and are often based on retrospective data.[2-4,8] In a retrospective series in which different treatment modalities were evaluated, it was reported that survival times increased from 4 months to 11.1 months with SRS compared to WBRT in patients with gastrointestinal cancer.[4] This survival contribution following SRS is quite significant, as the expected median survival times after BM development are approximately 6 months.[2-4,8] Since the data are still insufficient due to the rarity of BM due to gastrointestinal cancers, we aim to analyze the clinical results of patients who underwent SRS in our clinic since 2013. The purpose of this retrospective study was to determine local and distant intracranial control rates and survival rates and to determine prognostic factors associated with clinical outcomes in patients who underwent SRS with a diagnosis of BM due to gastrointestinal cancers.

MATERIAL AND METHOD

Patient Characteristics

The study was approved by The University of Health Sciences, Samsun Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (Date: 2023, Decision No: 15/4). Because the study was designed retrospectively, no written informed consent form was obtained from patients. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.[9]

We retrospectively reviewed patients with BM from gastrointestinal cancers who received robotic SRS with the CyberKnife device at the Radiation Oncology Clinic of Samsun Training and Research Hospital from October 2013 to December 2022.

Patients with histopathologically confirmed gastrointestinal cancer (esophagus, gastric, liver, biliary tract, pancreas, small bowel, colon, rectum, and anal canal) as the primary and with BM according to imaging studies were included. In addition, patients with BM whose primary tumor location was unknown but histopathologically demonstrated to have spread from a gastrointestinal primary after surgery for BM were also included in the study. Patients who underwent WBRT alone or surgery alone were not included in the study.

The analysis was extracted utilizing the medical records system. Clinical data, including patient age, gender, Karnofsky performance status (KPS), date of initial diagnosis, stage of initial diagnosis, location of initial diagnosis, date of BM diagnosis, location of BM, size and volume of BM, number of BM, recursive partitioning analysis (RPA) scores,[10] graded prognostic assessment (GI-GPA) scores for gastrointestinal cancers,[11] KRAS status, HER-2 status, presence of extracranial metastases, whether the primary disease is under control, and treatment data, including chemotherapy, surgery, and radiotherapy were collected. The biologically effective dose (BED) calculated using $a/\beta = 10$ (BED10) and $a/\beta = 3$ (BED3) for tumor effects and normal tissue effects.

Treatment Planning and Delivery

SRS treatment planning and delivery was done on the CyberKnife® (Accuray, Sunnyvale, USA) Robotic SRS system. For immobilization, a custom-made thermoplastic mask was fitted. Thin-slice computed tomography images and contrast-enhanced magnetic resonance imaging (MRI) were acquired in the supine position. Image fusion was performed for accurate tumor delineation. The gross target

volume (GTV) was defined as the contrast-enhancing lesion, the planning target volume (PTV) was defined as 0-1 mm and 2 mm isotropic expansion from GTV for SRS and cavity SRS. The software Multiplan v4.5 (MultiPlan, Inc., New York, USA) was used for treatment planning. BM with a large target volume and located close to the brainstem or optic chiasm were treated with fractionated treatments; otherwise, single fractions were used.

Follow up

The clinical assessment was evaluated by neurological examination and imaging. The first clinical evaluation after treatment was made at the visit two weeks later. Follow-up MRI studies were usually first obtained within 1 to 2 months after SRS, then performed at 2-month intervals. The Response Evaluation Criteria in Solid Tumors (RECIST) [12] was used for response assessment. Stable disease, partial or complete response according to MRI findings was accepted as local control. An increase in the size of the radiographically enhanced lesion in the irradiated area was accepted as local progression, and new enhancement outside the irradiated area was considered distant brain failure.

Endpoints and Statistical Analysis

Local and distant brain control rates were the primary endpoints of the study, and overall survival (OS) was the secondary endpoint. OS was set from the day of BM diagnosis to the date of death or loss to follow-up. The radiographic follow-up duration was defined as the time from the date of SRS to the last date of imaging follow-up, and the clinical follow-up duration was defined as the time from the date of SRS to the last date of follow-up.

Baseline patient and tumor variables (age, gender, size, volume of BM, treatment parameters, dose, etc.) were analyzed for descriptive characteristics (mean, median, percentage, etc.). The Fisher exact test, or the chi-square test, was applied to analyze intergroup differences. The independent t-test was used when the datasets were normally distributed; otherwise, datasets were compared by the Kruskal-Wallis test. Kaplan-Meier estimates were used for the calculation of local control rates, distant brain control rates, and OS. The log-rank test was used to evaluate the associations of local control rates, distant brain control rates, and OS with various clinical factors. The Cox proportional-hazards model was used for univariate and multivariate analyses. A p value of less than 0.05 was considered to indicate a statistically significant difference. SPSS v25 (SPSS Inc., Chicago, USA) statistical program was used.

RESULTS

Table 1 provides the clinical and treatment characteristics of the study cohort. A total of 61 BM developed from gastrointestinal cancer were identified in 42 patients, including 3 esophageal cancers, 9 gastric cancers, 1 biliary cancer, 15 colon cancers, and 14 rectal cancers. The median patient age at diagnosis of BM was 63 (41-77) years. In 40 (95.2%) of the patients, adenocarcinoma constituted the majority of the tumor histology. Fourteen patients were analyzed for mutations in KRAS (10 wild-type, 4 mutated), and seven patients were analyzed for HER-2 receptor status (2 positive, 5 negative). Eighteen (42.8%) of the patients were stage 4 at the time of initial diagnosis, and four (9.5%) of them were diagnosed with BM. Five (11.9%) patients underwent open neurosurgical resection before SRS. Prior to SRS, WBRT was given to 20 patients (47.6%), with a median dose of 30 Gy (20-37.5). For radiosurgery, a median of 20 Gy (15-24) was applied to 38 BM in 1 fraction, and a median of 24 Gy (16-30) was applied to 23 BM in a median of 3 (2-5) fractions. Regarding patient and treatment characteristics by the location of primary diagnosis, there was no difference between upper gastrointestinal and lower gastrointestinal malignancies (**Table 1**).

The median clinical follow-up time was 7 (0.5-36) months. MRI could not be performed because 14 patients died in the first 3 months after SRS, and only physical examination records of these patients were available. Apart from these, the median radiographic follow-up period was 5 months (1-23) in 27 patients who were followed up with MRI after SRS. In the irradiated area, nine (14.8%) lesions progressed in a median of 7 months (4-20). Outside the irradiated area, 14 (23%) new lesions were observed at a median of 3 months (2-11). SRS (2nd series SRS in 6 patients, 3rd series SRS in 3 patients, and 4th series SRS in 1 patient) was applied to the new lesions detected during the follow-up period. Salvage WBRT was applied to 3 patients with multiple BM in a median of 10 months (9-15), and 2 of these patients received 3rd series SRS before WBRT.

The local control rate was 85.1% at the last follow-up, the 6-month, 12-month, and 24-month, local control rates were 94.9%, 71.6%, and 61.4%, respectively. There was no difference in the local control ratio in terms of patient, tumor, and treatment characteristics (**Table 2**). The distant brain control rate was 77% at the last follow-up; the 6-month, 12-month, and 24-month distant brain control rates were 78.6%, 48.9%, and 48.9%, respectively. There was no difference in the distant brain control ratio in terms of patient, tumor, and treatment characteristics, except for the location of the primary tumor (**Table 2**). According to the location of the primary tumor, the 12-month local control rate for upper and lower gastrointestinal cancers was 63.8% and 85.7%, respectively, but there was no statistically significant difference (**Figure 1a**). In contrast, the 12-month distant brain control rate was 93.8% and 27.6% for upper and lower gastrointestinal cancers, with a statistically significant difference (p=0.018, HR: 1.50, 95%: CI 8.05-13.54) (**Figure 1b**). Multivariate analysis found no association with primary tumor location for distant brain control (p=0.059, HR: 7.16, 95% CI: 0.92-55.49).

Table 1. Clinical and treatment characteristics of patients with brain metastases from upper and lower gastrointestinal cancers

Characteristic	Upper GI (n, %) (mean+/-SD)	Lower GI (n, %) (mean+/-SD)	p
Age			
<60	5 (38.5)	8 (27.6)	0.495
≥60	8 (61.5)	21 (72.4)	
Gender			
Female	4 (30.8)	13 (44.8)	0.391
Male	9 (69.2)	16 (55.2)	
KPS			
90-100	8 (61.5)	9 (31)	0.097
70-80	2 (15.4)	8 (27.6)	
60	3 (23.1)	12 (41.4)	
RPA			
I	5 (38.5)	3 (10.3)	0.057
II	5 (38.5)	14 (48.3)	
III	3 (23.1)	12 (41.4)	
GI-GPA			
0-1.0	1 (7.7)	7 (24.1)	
1.5-2.0	6 (46.2)	13 (44.8)	0.080
2.5-3.0	2 (15.4)	7 (24.1)	
3.5-4.0	4 (30.8)	2 (6.9)	
Stage of primary diagnosis			
Stage 2-3	7 (53.8)	17 (58.6)	0.773
Stage 4	6 (46.2)	12 (41.4)	
Controlled primary			
Yes	6 (46.2)	18 (62.1)	0.335
No	7 (53.8)	11 (37.9)	
Extracranial metastases			
Yes	9 (69.2)	22 (75.9)	0.713
No	4 (30.8)	7 (24.1)	
Number of brain metastases			
1	6 (46.2)	15 (51.7)	0.739
≥2	7 (53.8)	14 (48.3)	
Size of brain metastases (cm)			
<2 cm	5 (38.5)	11 (37.9)	0.618
≥2 cm	8 (61.5)	18 (62.9)	
Volume of brain metastases (cc)			
<10 cc	11 (84.6)	20 (69)	0.453
≥10 cc	2 (15.4)	9 (31)	
Surgery for brain metastases			
Yes	2 (15.4)	3 (10.3)	0.637
No	11 (84.6)	26 (89.7)	
WBRT			
Yes	5 (38.5)	15 (51.7)	0.426
No	8 (61.5)	14 (48.3)	
SRS			
1 fx	6 (46.2)	15 (51.7)	0.739
2-5 fx	7 (53.8)	14 (48.3)	
SRS Dmax (cGy)	2405+/-443	2518+/-464	0.517
Coverage (%)			
<98.5	5 (38.5)	14 (48.3)	0.524
≥98.5	8 (61.5)	15 (51.7)	
HI	1.18+/-0.06	1.18+/-0.045	0.990
CI	1.38+/-0.26	1.29+/-0.18	0.190
nCI	1.40+/-0.26	1.32+/-0.19	0.265
BED10			
<40	5 (38.5)	5 (17.2)	0.238
≥40	8 (61.5)	24 (82.8)	
BED3			
<90	6 (46.2)	9 (31)	0.488
≥90	7 (53.8)	20 (69)	
Chemotherapy			
Yes	13 (100)	28 (96.6)	0.690
No	0 (0)	1 (3.4)	
Targeted agent therapy			
Yes	2 (15.4)	17 (58.6)	0.091
No	11 (84.6)	12 (41.4)	

BED: Biologically effective dose, CI: Conformity index, GI: Gastrointestinal, GPA: Graded prognostic assessment, HI: Homogeneity index, KPS: Karnofsky performance score, nCI: New conformity index, RPA: Recursive partitioning analysis, SRS: Stereotactic radiosurgery, WBRT: Whole brain radiotherapy

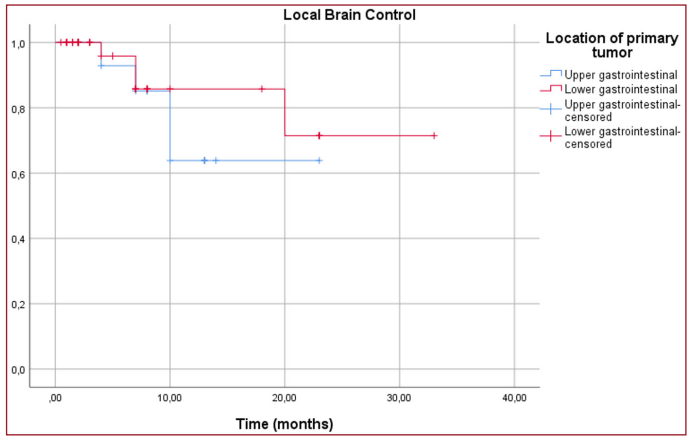

Figure 1a. Kaplan-Meier graph of local control rate according to the location of the primary tumor.

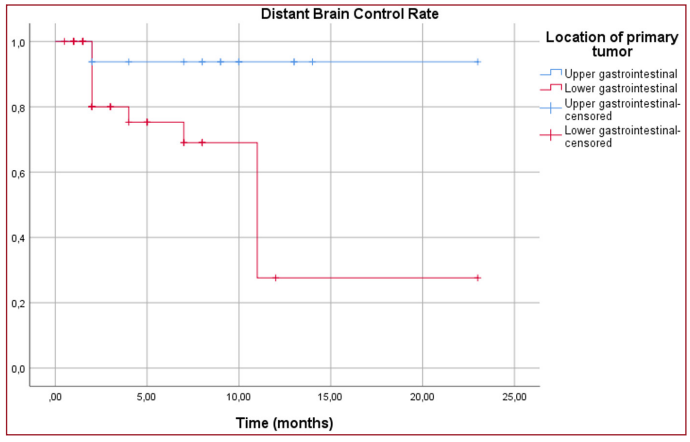

Figure 1b. Kaplan-Meier graph of distant brain control rate according to the location of the primary tumor.

Of the 42 patients included in the study, only four were alive at the last follow-up. The median OS was 8 months (HR: 2.51, 95% CI: 3.07-12.92), and the 6-month, 12-month, and 24-month OS were 57%, 31.6%, and 10.5%, respectively (**Figure 2a**). According to the location of the primary tumor, the 12-month OS for upper and lower gastrointestinal cancers was 50% and 20.9%, respectively, but there was no statistically significant difference (p=0.567, **Table 3**) (**Figure 2b**). Patients with high performance status had better OS than patients with low performance status (p=0.016, **Table 3**) (**Figure 2c**). The prognostic scoring scales RPA and GI-GPA were both associated with OS (p=0.049, p=0.002, **Table 3**) (**Figures 2d**, **2e**). The median OS was longer in patients with a controlled primary tumor and those undergoing surgery for BM, but it was not statistically significant (p=0.296, p=0.814, **Table 3**). Since all but one patient received chemotherapy at some point in their treatment period, its effect on OS could not be evaluated statistically. In terms of those receiving targeted therapy, the OS contribution could not be shown statistically (p=0.604, **Table 3**). Multivariate analysis found a significant association between GI-GPA classes (except GPA 0 to 1.0 vs. 1.5 to 2.0) and OS (p=0.011, HR: 0.10, 95% CI: 0.01-0.58).

Table 2. Univariate analysis for factors influencing Local control and Distant brain control

Characteristic	Local control rate HR (CI 95%)	p	Distant brain control rate HR (CI 95%)	p
Age <60 vs ≥60	0.72 (0.19-2.73)	0.635	0.70 (0.23-2.09)	0.525
Gender Female vs male	1.20 (0.31-4.53)	0.788	0.81 (0.27-2.37)	0.706
KPS 90-100 vs 70-80 vs 60	0.80 (0.45-3.15)	0.530	0.95 (0.33-4.12)	0.381
Primary disease Upper GI vs lower GI	0.46 (0.10-2.07)	0.314	1.50 (8.05-13.54)	0.018
RPA I vs II vs III	2.21 (0.74-6.60)	0.152	1.74 (0.74-4.07)	0.198
GI-GPA 0-1.0 vs 1.5-2.0 vs 2.5-3.0 vs 3.5-4.0	0.68 (0.25-2.55)	0.711	1.30 (0.56-2.96)	0.534
Stage of primary diagnosis Stage 2-3 vs stage 4	1.74 (0.46-6.54)	0.407	2.08 (0.72-6.05)	0.175
Controlled primary Yes vs no	0.16 (0.02-1.34)	0.093	1.69 (0.59-4.84)	0.327
Extracranial metastases Yes vs no	0.96 (0.23-3.99)	0.963	0.64 (0.17-2.33)	0.505
KRAS status + vs -	1.39 (0.57-3.33)	0.462	0.64 (0.32-1.28)	0.215
Her 2 status + vs -	1.14 (0.32-3.77)	0.874	0.69 (0.27-1.24)	0.435
Number of brain metastases 1 vs ≥2	0.87 (0.21-3.49)	0.846	1.55 (0.47-5.07)	0.461
Size of brain metastases (cm) <2 cm vs ≥2 cm	0.84 (0.22-3.18)	0.803	0.85 (0.29-2.45)	0.764
Volume of brain metastases (cc) <10 cc vs ≥10 cc	0.83 (0.17-4.04)	0.821	1.49 (0.49-4.48)	0.473
Surgery for brain metastases Yes vs no	0.57 (0.07-4.69)	0.605	23.47 (0.00-66.77)	0.437
WBRT Yes vs no	4.07 (0.83-19.94)	0.083	1.64 (0.56-4.79)	0.362
SRS 1 fx vs 2-5 fx	0.87 (0.23-3.28)	0.848	1.58 (0.54-4.59)	0.396
Coverage (%) <98.5 vs ≥98.5	0.85 (0.22-3.19)	0.815	0.75 (0.49-4.48)	0.602
BED10 <40 vs ≥40	1.20 (0.14-9.84)	0.862	28.82 (0.05-156.84)	0.296
BED3 <90 vs ≥90	0.74 (0.18-2.97)	0.674	1.00 (0.31-3.21)	0.999
Targeted agent therapy Yes vs no	1.12 (0.24-5.08)	0.879	0.75 (0.24-2.32)	0.620

BED: Biologically effective dose, CI: Confidence interval, CI: Conformity index, GI: Gastrointestinal, GPA: Graded prognostic assessment, HI: Homogeneity index, HR: Hazard Ratio; KPS: Karnofsky performance score, nCI: New conformity index, RPA: Recursive partitioning analysis, SRS: Stereotactic radiosurgery, WBRT: Whole brain radiotherapy

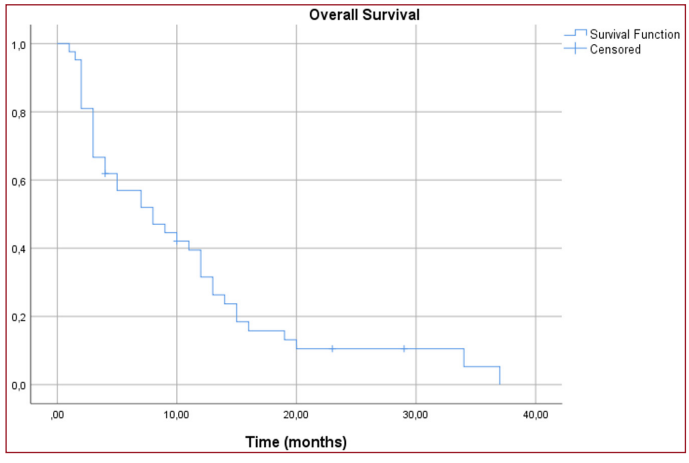

Figure 2a. Kaplan-Meier graph of OS.

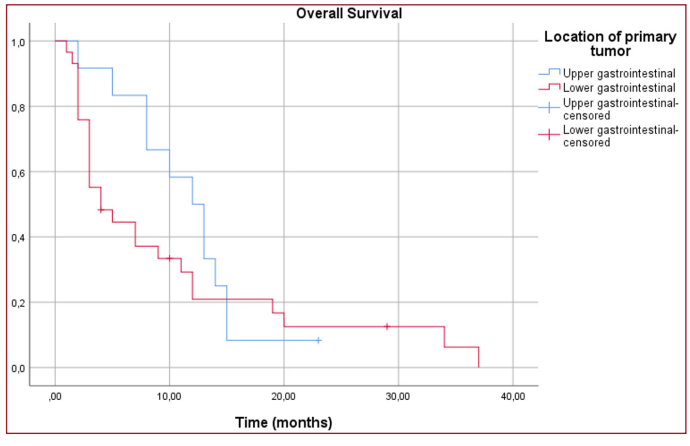

Figure 2b. Kaplan-Meier graph of OS according to the location of the primary tumor.

Table 3. Univariate analysis for factors influencing OS

Characteristic	6-m	12-m	24-m	Median OS	HR (CI 95%)	p
Age						
<60	61.5	46.2	0	12	3.59 (4.95-19.04)	0.369
≥60	47.6	24.7	12.4	7	2.04 (2.980-11.01)	
Gender						
Female	64.7	40.3	13.4	9	3.97 (1.21-16.78)	0.353
Male	51.4	25.7	8.2	8	2.35 (3.39-12.60)	
KPS						
90-100	81.9	56.7	18.9	13	2.95 (7.20-18.79)	0.016
70-80	30	20	0	4	1.05 (1.93-6.06)	
60	40	8.9	0	3	0.47 (2.07-3.93)	
RPA						
I	75	50	0	12	1.88 (8.30-15.69)	0.049
II	51.3	34.2	17.1	10	4.10 (1.94-18.05)	
III	40	8.2	0	3	0.47 (2.07-3.93)	
GI-GPA						
0-1.0	37.5	0	0	3	0.68 (1.65-4.34)	
1.5-2.0	36.8	18.4	0	5	1.07 (2.89-7.10)	0.002
2.5-3.0	64.8	38.9	38.9	13	2.67 (7.76-18.23)	
3.5-4.0	83.3	66.7	16.7	15	3.67 (7.79-22.20)	
Primary disease						
Upper GI	83.3	50	0	12	1.73 (8.60-15.39)	0.567
Lower GI	44.6	20.9	12.5	4	1.74 (0.57-7.42)	
Stage of primary diagnosis						
2-3	62.2	29.6	0	9	1.75 (5.56-12.43)	0.823
4	38.9	33.3	11	5	1.05 (2.93-7.06)	
Controlled primary						
Yes	57.8	34.2	14.7	10	3.01 (4.09-15.90)	0.296
No	44.4	27.8	0	5	3.18 (0.00-11.23)	
Extracranial metastases						
Yes	47.8	37	7.4	7	3.31 (0.50-13.49)	0.922
No	63.6	18.2	0	8	1.65 (4.76-11.23)	
Number of brain metastases						
1	41.9	36.7	10.5	5	2.74 (0.00-10.38)	0.983
≥2	66.7	26.8	5.4	9	2.28 (4.51-13.48)	
Size of brain metastases						
<2 cm	50	37.5	6.3	9	7.0 (0.00-22.72)	0.997
≥2 cm	57.2	36.3	9.1	7	1.82 (3.42-10.58)	
Volume of brain metastases (cc)						
<10 cc	48.4	28.2	5.3	7	1.94 (3.18-10.81)	0.341
≥10 cc	61.4	40.9	10.2	12	3.81 (4.53-19.46)	
Surgery for brain metastases						
Yes	60	40	0	12	4.38 (3.41-20.58)	0.814
No	53.8	30.5	12.2	7	2.43 (2.22-11.78)	
WBRT						
Yes	55	30	15	8	2.23 (3.61-12.38)	0.422
No	49.2	33.8	0	7	2.92 (1.26-12.73)	
SRS						
1 fx	42.9	28.6	0	4	1.90 (0.26-3.73)	0.183
2-5 fx	61	34.3	17.1	9	2.12 (4.83-13.16)	
BED10						
<40	40	20	0	5	3.16 (0.00-11.19)	0.157
≥40	59.2	35.4	14.2	8	3.21 (1.70-14.29)	
BED3						
<90	53.3	20	0	8	1.89 (4.28-11.71)	0.444
≥90	59.3	38.8	12.9	10	3.80 (2.54-17.45)	
Targeted agent therapy						
Yes	52.6	24.6	0	7	2.86 (1.37-12.62)	0.604
No	69.2	26	17.3	10	3.30 (3.52-16.47)	

BED: Biologically effective dose, CI: Confidence interval, GI: Gastrointestinal, GPA: Graded prognostic assessment, HR: Hazard Ratio; OS: Overall survival, RPA: Recursive partitioning analysis, SRS: Stereotactic radiosurgery, WBRT: Whole brain radiotherapy

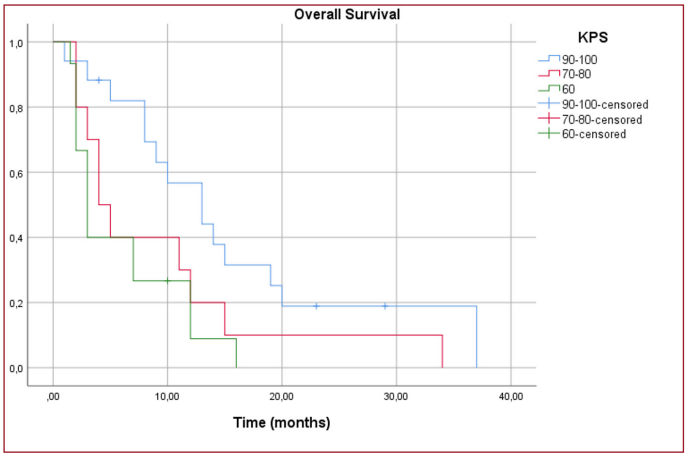

Figure 2c. Kaplan-Meier graph of OS according to KPS.

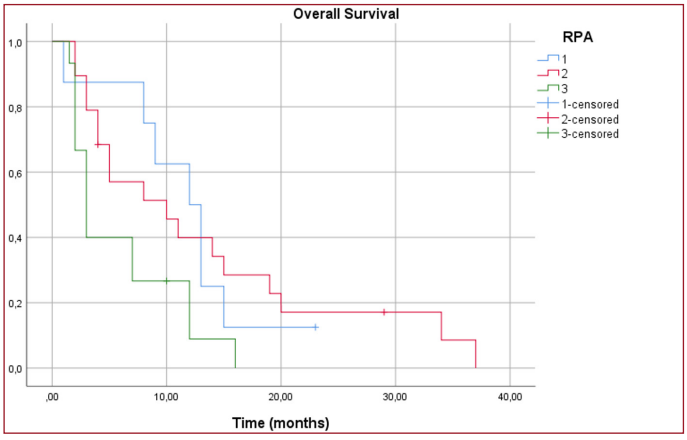

Figure 2d. Kaplan-Meier graph of OS according to RPA.

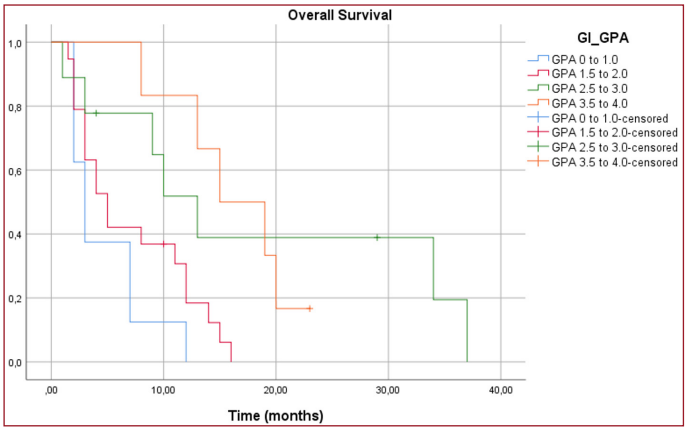

Figure 2e. Kaplan-Meier graph of OS according to GI-GPA.

DISCUSSION

In a cohort of patients with BM from gastrointestinal cancers treated with SRS, we retrospectively evaluated the clinical outcomes of SRS. We identified two main findings: First, comparable results were obtained in terms of the local control rate and the distant brain control rate. Second, the performance status and prognostic scoring scales RPA and GI-GPA were associated with OS.

The outcomes of SRS are typically based on the findings of retrospective series due to the rarity of BM in gastrointestinal malignancies.[2-4,13-15] Tumor control is a crucial component of SRS for the treatment of BM. To our knowledge, local tumor control rates of 64% to 94% have been reported to be achieved with SRS for gastrointestinal BM. In a study in which 40 patients underwent SRS in 118 BM from gastrointestinal cancer, a local control rate of 91% was reported in 25 patients with radiological follow-up.[13] Another study showed a local control rate of 94.1% after SRS in 261 BM from 86 patients.[2] In the series of Paudel et al.[14], which included 53 patients and 148 BM, the 6-month and 12-month local control rates were determined as 74.33% and 57.21%, respectively. Despite the limited number of patients and BM treated in these series, excellent outcomes in terms of local control rates were found. In contrast, series with lower local control rates are also seen. For instance, in the series that included 21 patients with 28 BM, the local control rate was 64.3%, and the 6-month local control rate was 47% in patients with radiographic follow-up.[15] In accordance with previous research that also demonstrated encouraging local control rates, we observed that the local control rate in our study was 85.1%, and the 12-month local control rate was 71.6%.

According to previous investigations, there are some criteria that are assumed to predict local control.[2,15-17] The treatment dose is one of the parameters that has been demonstrated to increase local control. Triffletti et al.[2] reported that a margin dose ≥20 Gy had a significant effect on local control in their series of Gamma Knife SRS. In the study of Shangvi et al.[15], treatment dose was defined as a factor affecting the development of distant brain metastasis without influencing local control. However, the Italian study, which examined 262 BM from 185 colorectal patients and was published in 2020, failed to identify any factors affecting local control.[16] Preliminary results of a multicenter study involving 263 patients with 543 BM showed improved local brain control with a high performance score, a lower patient age, and a small tumor diameter.[17] In this series, although the treatment dose was effective for local control in univariate analysis, it lost its importance in multivariate analysis. As can be observed, factors determined to be predictive of local control in one cohort may be inconsequential in another. The rarity of BM associated with gastrointestinal cancers renders studies inconclusive and yields inconsistent findings. In our study, a factor related to local control, such as the Italian multicenter study, could not be determined.

Although local control rates in BM with SRS are quite good, distant brain control remains a challenging issue. In a series of 53 patients with a median follow-up of 6 months, it was reported that distant BM developed in almost half of the patients (26 patients) at the final follow-up.[14] In another series of 33 patients with a median radiographic follow-up of 3.9 months, the rate of distant brain control

was reported as 46.4% at the last control.[15] In the Italian multicenter study, distant BM developed in 71 (38.4%) patients in a median of 3 months (1-82), and the 6-month, 12-month, and 24-month distant brain control rates were 66.4%, 55.3%, and 47.5%, respectively.[16] In our study, distant brain control was 77% at the last follow-up, with a median 5-month radiographic follow-up. The 6-month, 12-month, and 24-month distant brain control rates were 78.6%, 48.9%, and 48.9%, respectively. As such, it appears that we have comparable results in terms of distant brain control.

Increasing number of BM and advanced patient age have been identified as factors that reduce distant brain control.[18] Half of the patients included in our study had single BM; there was no difference in distant brain control compared to patients with multiple BMs. On the other hand, advanced patient age was not found to be a factor affecting distant brain control in our study. In the study evaluating BM from 802 gastrointestinal cancers, no difference was found in terms of upper and lower gastric cancers after SRS.[19] In our study, it was determined that distant brain control was better in upper gastrointestinal localized patients, but this difference did not persist in the multivariate analysis.

Survival is generally dismal for BM from gastrointestinal cancers, with several studies reporting a median survival of approximately 6 months.[2-4,8,13,16,19,20] The median survival was 5 months in the series of Hagesava et al.[20], which included 39 patients, and 6.7 months in the series of Da Silva et al.[13], which included a similar number of patients. Page et al.[8] reported a median survival of 7.1 months in 62 patients. Two multicenter studies with larger numbers of patients did not yield different results in terms of OS. One of them, the Italian study, reported median, 6-month and 12-month OS rates of 7 months, 52.7%, and 33%.[16] In the other, the median survival was 5.7 months, and the 6-month and 12-month OS rates were 46.3% and 21.9%, respectively.[19] In our study, the median OS, 6-month OS, and 12-month OS were 8 months, 57%, and 31.6%, respectively. The survival results in our study were consistent with previous studies.

In our study, we categorized the patients as having upper and lower gastrointestinal cancer to evaluate whether the primary tumor location had an effect on the results. Although the median survival times we found for upper and lower gastrointestinal tumors were different, they were not statistically significant. To our knowledge, studies often included either studies examining all gastrointestinal cancers together or colorectal cancers, as they were more common than other gastrointestinal cancers. We found two retrospective series in which SRS was applied only for the diagnosis of gastric cancer. The number of patients in both series was quite small, with median OS after SRS of 17 months in 11 patients and 10 months in 15 patients.[21,22] In another study, a median OS of 16 months was reported in 21 patients with esophageal cancer.[23] In larger series involving 93 and 116 colorectal cancer patients, the median OS was found to be 7 and 10.3 months, respectively.[24,25] In the study of Yamomota et al.[19], which has the highest number of patients on this subject, it is thought that those with lower gastrointestinal cancer had a longer survival than those with upper gastrointestinal cancer (5.9 months vs. 4.8 months), but this finding was not statistically significant. In our study, we found that upper and lower gastrointestinal cancers were similar in terms of patient and treatment parameters; we did not detect a statistically significant difference between the two groups.

When previous research was analyzed, it was discovered that performance status is one of the most important determinants of survival.[2,19,23,24] This finding was corroborated by both small-patient studies and multicenter studies. In addition, controlled primary cancer and the absence of extracerebral metastases were variables found in previous studies that were significantly associated with OS.[8,19,24] Also, several studies have shown improved survival with single BM and resection for BM.[2,19,24] In our study, only performance status was found to be a factor influencing OS in univariate analysis, but this effect did not exist in multivariate analysis.

In fact, the performance score was the sole essential prognostic baseline component of the GI-GPA. Patient age, the number of BM, and the presence or absence of extracranial metastases are the parameters used in the algorithm to calculate GI-GPA along with KPS.[11] It is not unexpected that the aforementioned studies show that these parameters are prognostic for survival, even when evaluated separately. However, it is clearly known that not all parameters have a prognostic effect in terms of survival in every study.[2,15,24] Since it is more difficult to predict the prognosis with a single parameter, more accurate and reliable information can be obtained with GI-GPA.

The requirement to establish a prognosis led to the development of prognostic risk scoring. Historically, RPA has been defined and long used for BM.[10] For instance, Park et al.[22] showed that RPA II class was associated with prolonged survival. But new prognostic classifications have become necessary in the era of SRS, as there are aggregations among RPA classes, especially in RPA II. The GPA developed in this context was further modified, and disease-specific subclassifications were created.[11] In this regard, a retrospective cohort study of 802 patients was designed for GI-GPA validation.[19] Median survival times for the GI-GPA subgroups (1, 2, 3, and 4) were reported as 3.5 vs. 6.1 vs. 7.7 vs. 11 months, respectively. However, there was no significant difference in survival between subgroups 2 and 3. In our study, survival rates of 3 vs. 5 vs. 13 vs. 15 months were determined for the GI-

GPA subgroups, respectively. In our cohort, the survival difference between subgroups 1 and 2 was not significant (p=0.186). Although the number of our patients was quite low compared to the validation study, GI-GPA efficiency could still be demonstrated. We consider that GI-GPA retains its predictive effect on survival regardless of the size of the cohort.

Finally, we noted KRAS status and HER-2 status while recording patient characteristics. There were not many patients whose data, including receptor status, we could access. We could not detect a significant difference with the available data. However, in the cohort in which the results of SRS in colorectal cancers were published recently, it was reported that the survival of those with KRAS mutations worsened, and this issue was highlighted.[25]

There were several limitations to the current series. First of all, the retrospective design with the small sample size from a single institution was subject to biases. Secondly, given the sparsity of the cases, there was significant heterogeneity in the patient population. Our series may not have been able to provide frequencies to generalize since the number of patients was small and it included all gastrointestinal cancers. Lastly, the fact that KRAS status and HER-2 status were unknown in all patients is another limitation of our study.

CONCLUSION

In conclusion, BM from gastrointestinal cancer is infrequent and has a poor prognosis. In this challenging patient population, our SRS treatment outcomes in terms of local control, distant brain control, and survival are comparable to those of previous research. In routine practice, using GI-GPA prognostic scoring scales as well as the patient's performance status will be a guide to selecting the most suitable patient for SRS.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by The University of Health Sciences, Samsun Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (Date: 2023, Decision No: 15/4).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1347031
J Contemp Med 2023;13(5):949-953

Original Article / Orijinal Araştırma

Knowledge Level About HPV Infection and Cervical Cancer Screening Tests

HPV Enfeksiyonu ve Rahim Ağzı Kanseri Tarama Testleri Hakkında Bilgi Düzeyi

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Abstract

Aim: Understanding HPV and cervical cancer is vital for prevention, early diagnosis, and treatment. Nurses play a crucial role in implementing screening and are also at risk. This study examines nurses' knowledge and practices regarding HPV and cervical cancer screening in a tertiary center.

Material and Method: It is a prospective survey study conducted with nurses. A total of 191 nurses participated in the three-part and 53-item survey that evaluated demographic data, HPV knowledge levels and cervical cancer screening awareness.

Results: A total of 2895 nurses work at the hospital. The rate of participation in the research was 6.6% with 191 participants. The average age of the participants is 27.1. Majority of the participants are female (n: 171, 89.5%), only 20 (10.5%) are male. While 81.9% of the respondents had knowledge about sexually transmitted diseases, only 13.5% had gone to regular gynecological examinations. Despite 98.4% of the participants who had knowledge about cervical cancer and screening practices, only 11% (n:19) had undergone cervical cancer screening and 94.2% (n:180) had not received HPV vaccine. The most mis-answered question about HPV was whether current vaccines protect against both genital warts and cervical cancer.

Conclusion: In conclusion, nurses' knowledge level and screening practices about HPV and cervical cancer need to be improved. It is also important to increase awareness of the HPV vaccine and encourage more people to receive it. This effort could positively impact health outcomes related to cervical cancer and HPV.

Keywords: HPV, knowledge level, cervical cancer

Öz

Amaç: HPV ve rahim ağzı kanserini anlamak, önleme, erken teşhis ve tedavi için hayati öneme sahiptir. Hemşireler, taramanın uygulanmasında çok önemli bir rol oynar ve aynı zamanda risk altındadır. Bu çalışmada, üçüncü basamak bir merkezde hemşirelerin HPV ve rahim ağzı kanseri taramasına ilişkin bilgi ve uygulamalarını incelemeyi amaçladık.

Gereç ve Yöntem: Çalışma hemşirelerin HPV ve serviks kanseri ile ilgili bilgi düzeylerini ölçmek için gerçekleştirilen prospektif bir anket çalışmasıdır. Değerlendirme demografik verileri, HPV bilgi düzeylerini ve servikal kanser taraması farkındalığını değerlendiren, üç bölümden ve 53 sorudan oluşan bir anket ile yapılmıştır. Toplam 191 hemşire çalışmaya katılmıştır.

Bulgular: Hastanede toplam 2895 hemşire çalışıyordu. Araştırmaya katılım oranı 191 katılımcı ile %6,6 idi. Katılımcıların yaş ortalaması 27,1 idi. Katılımcıların çoğunluğu kadındı (n: 171, %89,5), sadece 20'si (%10,5) erkekti. Katılımcıların %81,9'u cinsel yolla bulaşan hastalıklar hakkında bilgi sahibiyken, sadece %13,5'i düzenli jinekolojik muayeneye gitmişti. Katılımcıların %98,4'ü rahim ağzı kanseri ve tarama uygulamaları hakkında bilgi sahibi olmasına rağmen, sadece %11'i (n:19) rahim ağzı kanseri taraması yaptırmış ve %94,2'si (n:180) HPV aşısı yaptırmamıştı. HPV ile ilgili en yanlış cevaplanan soru, mevcut aşıların hem genital siğillere hem de rahim ağzı kanserine karşı koruma sağlayıp sağlamadığıydı.

Sonuç: Sonuç olarak, hemşirelerin HPV bilgi düzeylerinin ve rahim ağzı kanseri ile ilgili tarama uygulamalarının geliştirilmesi gerekmektedir. HPV aşısı farkındalığını artırmak ve daha fazla insanı aşı olmaya teşvik etmek de önemlidir. Bu çaba, rahim ağzı kanseri ve HPV ile ilgili sağlık sonuçlarını olumlu yönde etkileyebilir.

Anahtar Kelimeler: HPV, bilgi düzeyi, serviks kanseri

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Received *(Geliş Tarihi)*: 21.08.2023 **Accepted *(Kabul Tarihi)*:** 20.09.2023

INTRODUCTION

Human papillomavirus (HPV) is considered the most common sexually transmitted agent worldwide.[1] While the 16 and 18 genotypes of HPV are the types most associated with cervical cancer, the 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 genotypes are also high-risk genotypes that can cause cancer.[2] In the cervical cancer control process, HPV prevention and early detection of HPV-induced changes play a crucial role in reducing morbidity and mortality.[3] Studies have shown that approximately 79 million individuals worldwide are infected with HPV, approximately 14 million people in the United States of America (USA) are diagnosed with HPV positivity each year, and approximately 99.7% of cervical cancers in the USA are of HPV origin.[4]

In the female population, HPV infection peaks between the ages of 20 and 24 (44.8%) and gradually declines between the ages of 25 and 29 (19.6–27.5%).[5,6]

While the immune system typically clears the virus within two years in infected individuals, persistent HPV infection is known to cause cervical cancer and genital warts in some individuals.[7,8]

Studies on HPV show that the prevalence is much higher in women under the age of 25 compared to other age groups.[9] It is known that the risk of cervicovaginal HPV infection in women is directly related to the number of male sex partners. In addition, as with other sexually transmitted infections, it is known that having sex with a new partner poses a higher risk of transmission of HPV than having sex with the same partner for a long time.[10]

Cervical cancer, which is an essential problem for women's health, is a significant health problem to what extent the HPV test, pap smear test, and primary prevention HPV vaccine, which is used to detect cervical cancer early, is known and applied by the society.[11,12] Having knowledge about HPV and cervical cancer is extremely important in prevention, early diagnosis, and treatment. The knowledge, attitudes, and approaches of health professionals, especially nurses, are fundamental in the implementation and development of screening tests in the community. In addition, nurses are in the risk group in terms of HPV infection and related complications. Nurses have the responsibility and awareness to protect and improve the health of themselves and the patients they care for. This study, it was aimed to examine the knowledge and behaviors of nurses working in the tertiary center about HPV and cervical cancer screening tests.

MATERIAL AND METHOD

The study was carried out with the permission of Basaksehir Cam and Sakura State Hospital Clinical Researches Ethics Committee (Date: 14.04.2021, Decision No: 33). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This prospective survey-based study was conducted on hospital nurses between July 1, 2022 and July 1, 2023. A self-administered online questionnaire was developed using the Google Documents program.

Before starting the survey, the participants were informed that the survey was for research purposes and their participation would be anonymous. Those who accepted were directed to the questionnaire by the program. 191 nurses actively working in the hospital, who did not work in the gynecological oncology clinic before or currently, participated in the survey. Nurses working in the gynecological oncology clinic were excluded from the study. The questionnaire consisted of 3 parts and included 53 main questions in total. The survey took 10 minutes to complete. In the first part, there were demographic data consisting of 10 questions. The second part included the HPV knowledge scale and included 33 questions. In the last part, there was a 10-question test measuring awareness about cervical cancer screening tests. Participants did not have to answer all questions to complete the survey.

The data obtained from the completed questionnaires were recorded in the Google Documents database and analyzed through this database. Categorical data were defined using frequencies (percentages). The Cronbach's alpha coefficient of the questionnaire was 0.96 with an acceptable internal consistency.

RESULTS

A total of 2895 nurses has work in the hospital, 191 participants agreed to participate in the study with the 6.6% response rate. The median age was 27,1 (min:18, max:44). One hundred and seventy-one (n:171, %89.5) of the participants were women, whereas only 20 (%10.5) of the participants were male. Most of them were single (n:131, %68.9) and only 29 (%15.2) participants had child. While majority of participants had been working shorter than 5 years (n:151, %79.1), 5 (%2.6)of them had been working more than 20 years. The demographic characteristics of the respondents are shown in **Table 1**.

Knowledge of the Cervical Cancer Screening

When the participants had asked if they had a family member with gynecological cancer history, 25 of them answered positive and among of them endometrial cancer is the most common type. Whereas 188 (%81.9) respondents have information about sexually transmitted diseases, only 23 (%13.5) of them went to regular gynecological examination. Participants were also asked to knowledge of cervical cancer and their screening practice.

Although %98.4 of the respondents know cervical cancer, only %11 of them (n:19) had undergone cervical cancer screening and %94.2 of them (n:180) had no HPV vaccination. When asked the reason for not having smear testing, the leading answer was “having no complaint” (n:74, %53.6), followed by “having no sexual intercourse” (n:60, %43.5) and “fear of gynecological examination” (n:16, %11.6). (**Table 2**)

Table 1. Demographic characteristics of the participants

Age (mean)	27,1 (min:18, max:44)
Gender	
Female	171 (90%)
Male	20 (10%)
Educational Status	
High School	8 (4%))
University	162 (85%)
Degree	21 (11%)
Years of Work	
<5 years	151 (79%)
5-10 years	23 (12%)
10-20 years	12 (6%)
>20 years	5 (3%)
Smoker	
Yes	73 (38%)
No	118 (62%)
Alcohol	
Yes	46 (24%)
No	145 (76%)
Marital status	
Married	60 (31%)
Single	131 (69%)
Having child	
Yes	29 (15%)
No	162 (85%)
Please mark the region where you spent the longest part of your life	
Marmara	73 (38%)
Central Anatolia	22 (12%)
Black Sea	20 (10%)
Mediterranean	27 (14%)
Aegean	21 (11%)
Eastern Anatolia	13 (7%)
Southeast Anatolia	16 (8%)

Table 2. Knowledge of the Cervical Cancer Screening

Do you know anything about sexually transmitted diseases?	
Yes	188 (98%)
No	3 (2%)
Do you regularly go for gynecological examinations?	
Yes, every year	23 (13%)
I only go when I have complaints	140 (82%)
I don't go for gynecological examinations even if I have complaints	8 (5%)
Have you ever heard of cervical cancer before?	
Yes	188 (98%)
No	3 (2%)
Have you undergone a Pap Smear or HPV test as part of the cervical cancer screening program? (If you are male, please skip this question.)	
I have had both of them done	13 (8%)
I haven't had them done	138 (80%)
I have had a smear test done	19 (11%)
I have had an HPV test done	2 (1%)
If your answer to the previous question was no, what is the reason for that?	
I have never had sexual intercourse	63 (41%)
I'm afraid of getting a bad result	4 (3%)
I have no complaints	72 (47%)
I'm afraid of vaginal examinations	13 (9%)

Table 2. Knowledge of the Cervical Cancer Screening

Have you received the HPV vaccine so far?	
Yes	11 (6%)
No	180 (94%)
It can only be performed by gynecologists in hospitals.	
Yes	81 (42%)
No	88 (46%)
I don't know	22 (12%)
It is a paid service.	
Yes	32 (17%)
No	142 (74%)
I don't know	17 (9%)
It has no benefit in early cancer detection.	
Yes	17 (9%)
No	167 (87%)
I don't know	7 (4%)
It is a painful procedure.	
Yes	23 (12%)
No	139 (73%)
I don't know	29 (15%)
After the test is done, sexual intercourse is prohibited for 1 week.	
Yes	36 (19%)
No	75 (39%)
I don't know	80 (42%)
It is not advisable to undergo these tests during pregnancy.	
Yes	60 (31%)
No	61 (32%)
I don't know	70 (37%)
Getting screened once is sufficient for a lifetime protection against cancer.	
Yes	9 (5%)
No	166 (87%)
I don't know	16 (8%)
HPV infection only affects women and causes diseases.	
Yes	23(12%)
No	135(71%)
I don't know	33(17%)
HPV testing can also be performed in male patients.	
Yes	106(55%)
No	34(18%)
I don't know	51(27%)
Smear and HPV tests should be done annually.	
Yes	95 (50%)
No	66 (35%)
I don't know	30 (16%)
Cancer screening tests should be repeated every 3-5 years.	
Yes	161 (84%)
No	10 (5%)
I don't know	20 (10%)
HPV enfeksiyonu ileri yaş kadınlarda saptanmamaktadır	
Yes	11 (6%)
No	147 (77%)
I don't know	33 (17%)
Screening tests are recommended for women between the ages of 30 and 65.	
Yes	120 (63%)
No	51 (27%)
I don't know	20 (10%)

Table 2. Knowledge of the Cervical Cancer Screening	
Since HPV is not observed in women under 30, this age group is screened only with a smear test.	
Yes	54 (28%)
No	79 (41%)
I don't know	58 (30%)
Since HPV is commonly seen in women under 30, it is not recommended to perform HPV testing in this age group.	
Yes	27 (14%)
No	122 (64%)
I don't know	42 (22%)
When HPV test is negative and abnormalities are detected in the smear, no further investigation is needed.	
Yes	11 (6%)
No	139 (73%)
I don't know	41 (21%)
When HPV test is positive, regardless of the smear result, further investigation is required.	
Yes	129 (68%)
No	15 (8%)
I don't know	47 (25%)
Women who have had their uterus removed can be excluded from cervical cancer screening programs, regardless of their HPV infection history.	
Yes	38 (20%)
No	95 (50%)
I don't know	58 (30%)
Even in women who have had their uterus removed, cervical cancer screening should be conducted using HPV and smear tests.	
Yes	99 (52%)
No	33 (17%)
I don't know	59 (31%)
HPV infection can be transmitted from women to men.	
Yes	79 (41%)
No	62 (32%)
I don't know	50 (26%)
HPV infection can be transmitted from men to women.	
Yes	102 (53%)
No	37 (19%)
I don't know	52 (27%)
It is possible to determine from which partner the HPV infection was acquired.	
Yes	56 (29%)
No	62 (32%)
I don't know	73 (38%)
Once HPV infection is contracted, it persists for a lifetime.	
Yes	73 (38%)
No	62 (32%)
I don't know	56 (29%)
HPV infection often causes temporary infections.	
Yes	65 (34%)
No	60 (31%)
I don't know	66 (35%)
Removing the uterus protects against diseases related to HPV infection.	
Yes	31 (16%)
No	101 (53%)
I don't know	59 (31%)

Knowledge of the HPV

In our cohort, median calculated knowledge of HPV score was 18.1. According to subtitles of questionnaire, the first section about of the general knowledge of HPV mean score was 10.3, the second section about knowledge of HPV screening tests mean score was 2.8, the third section of knowledge of HPV vaccination mean score was 4, and the last section of national HPV vaccination programme mean score was 1. The examples of the most wrong and correct questions in the 4 separate sections of the test are given in **Table 3**.

Table 3 Knowledge of the HPV		
	Mostly True	**Mostly False**
General Knowledge of HPV		
	Having many sexual partners increases the risk of getting HPV	HPV usually doesn't need any treatment
	T n:175 (92%) F n: 16 (8%)	T n: 10 (5%) F n:181 (95%)
Knowledge of HPV Screening Test		
	If a woman tests positive for HPV she will definitely get cervical cancer	If an HPV test shows that a woman does not have HPV, her risk of cervical cancer is low
	T n:126 (66%) F n: 65 (34%)	T n:67 (35%) F n: 124 (65%)
Knowledge of HPV vaccination		
	Girls who have had an HPV vaccine do not need a Pap test when they are older	The HPV vaccines are most effective if given to people who have never had sex
	T n: 141 (74%) F n: 50 (26%)	T n: 73 (38%) F n: 118 (62%)
HPV vaccination schedule information		
	HPV vaccine is recommended for all females ages 11-26 years	Both HPV vaccines that are available (Gardasil&Cervarix) protect against both genital warts and cervical cancer
	T n: 111 (58%) F n: 80 (42%)	T n: 3 (2%) F n: 188 (98%)

DISCUSSION

HPV is a common sexually transmitted infection worldwide and is particularly common among young women.[13] The importance of HPV in the prevention and early diagnosis of cervical cancer is always emphasized in studies.[5,14] It is noted that certain HPV genotypes increase the risk of cervical cancer.[15] According to the results of our study, it is seen that nurses generally have good knowledge about HPV and cervical cancer screening tests. However, despite this information, the number of people who do not have cervical cancer screening tests or who are not vaccinated against HPV seems to be quite high.

There are many studies examining the most common reasons for women not having cervical cancer screening tests, and these reasons may differ by country, culture, and health system.[16,17] However, in general, the reasons frequently encountered in the literature include ignorance

or lack of awareness, fear of gynecological examination, absence of symptoms, difficulties in accessing health services, inability to find opportunities due to time and work problems, factors such as social norms, cultural beliefs and family pressure, cost, and finally It can be counted as lack of communication with health professionals or poor quality of health services.[18,19] In our study, it is stated that the most common reason for those who do not have cervical cancer screening tests is "not having any complaints". In addition, fear of gynecological examination stands out as an obstacle.

In a study by Satilmisoglu et al. in 2018 that included nurses, although 88% of the participants knew how to screen for cervical cancer, 68% did not have regular cervical cancer screening. According to the same study data, although cervical cancer was heard by 98% of the participants, cervical cancer screening was not performed by 80% of the participants.[20] Levels of knowledge about HPV and cervical cancer varied among participants. In particular, there are misunderstandings and incomplete information about the HPV vaccine. According to the results of the study, the majority of the participants do not go to regular gynecological examinations. In addition, the rate of participation in cervical cancer screening is low. And unfortunately, most of the participants did not have the HPV vaccine.

CONCLUSION

This study helps us to understand the knowledge level and behaviors of nurses about HPV and cervical cancer screening tests. There is a need to raise awareness of nurses about HPV and cervical cancer more, as they play an important role in the implementation of screening tests in the society and they are the occupational group that stays in contact with the patient for longer periods of time. Thus, it will contribute to a further reduction in the incidence of cervical cancer in the community.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Basaksehir Cam and Sakura State Hospital Clinical Researches Ethics Committee (Date: 14.04.2021, Decision No: 33).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1352503
J Contemp Med 2023;13(5):954-958

Original Article / Orijinal Araştırma

Liver Protection of Hydroxytyrosol Mediated by Spexin and TRPM2

Spexin ve TRPM2'nin Aracılık Ettiği Hidroksitirozolün Karaciğer Koruması

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Abstract

Aim: In the study, the role of Spexin (SPX) and Transient Receptor Potential (TRP) Melastatin-Like Subfamily Member 2 (TRPM2) in the protective effect of Hydroxytyrosol (HT) in rats given Corn Syrup was evaluated.

Material and Method: The rats were divided into 4 groups (6 rats in each) (Control, HT, Corn Syrup, Corn Syrup +HT). Rats were given 30% Corn Syrup with drinking water for 6 weeks. Four ml/kg/day liquid containing HT was applied by oral gavage alone and together with Corn Syrup for 6 weeks. Molecular parameters SPX and TRPM2 were examined histopathologically in liver tissue.

Results: The SPX levels decreased and the TRPM2 levels increased more in the Corn Syrup-given Group than in the Control Group. SPX levels increased and TRPM2 levels decreased after HT treatment. In the HT Group only, no differences were detected when compared to the control Group.

Conclusion: SPX and TRPM2 may mediate the protective effect of HT on the liver in rats given corn syrup.

Keywords: Corn Syrup, Hydroxytyrosol, Spexin, TRPM2

Öz

Amaç: Araştırmada Mısır Şurubu verilen sıçanlarda Hidroksitirozol (HT)'ün koruyucu etkisinde Spexin (SPX) ve geçici reseptör potansiyeli (TRP) melastatin benzeri alt aile üyesi 2 (TRPM2)'nin rolü değerlendirildi.

Gereç ve Yöntem: Sıçanlar 4 gruba (her grupta 6 sıçan) ayrıldı (Kontrol, HT, Mısır Şurubu, Mısır Şurubu +HT). Sıçanlara 6 hafta süreyle %30'luk Mısır Şurubu içme suyuyla birlikte verildi. HT içeren 4 ml/kg/gün sıvı, tek başına ve Mısır Şurubu ile birlikte 6 hafta süreyle oral gavajla uygulandı. Karaciğer dokusunda SPX ve TRPM2 moleküler parametreleri histopatolojik olarak incelendi.

Bulgular: Mısır Şurubu verilen grupta SPX seviyeleri azaldı ve TRPM2 seviyeleri kontrol grubuna göre daha fazla arttı. HT tedavisinden sonra SPX seviyeleri arttı, TRPM2 seviyeleri ise azaldı. Yalnızca HT grubunda kontrol grubuyla karşılaştırıldığında herhangi bir farklılık tespit edilmedi.

Sonuç: SPX ve TRPM2, mısır şurubu verilen sıçanlarda HT'nin karaciğer üzerindeki koruyucu etkisine aracılık edebilir.

Anahtar Kelimeler: Mısır Şurubu, Hidroksitirosol, Spexin, TRPM2

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Received *(Geliş Tarihi)*: 30.08.2023 **Accepted *(Kabul Tarihi)*:** 26.09.2023

INTRODUCTION

Glucose and fructose are closely related to simple sugars, but fructose is associated more with metabolic diseases. The main source of fructose was fruit until the 1960s, but then High Fructose Corn Syrup (HFCS) became a dominant component of the Western Diet.[1] Consumption of fructose as sugar and High Fructose Corn Syrup has increased significantly in recent years. This trend is associated with increasing metabolic diseases. The biochemical pathways of fructose metabolism were described in the early 1990s and fructose metabolism and its pathophysiological effects on the body at the organismal level have only recently been investigated.[2]

Hydroxytyrosol (HT) in olive oil is a polyphenol that has antioxidant characteristics that support the healthy characteristics of olive oil along with other components such as polyphenols and flavonoids.[3] HT includes cardio-protective, anti-inflammatory, anti-cancer, and antimicrobial effects,[3] which are the characteristics of olives as a healthy food. It was shown previously that HT prevents damage caused by Reactive Oxygen Species (ROS)[4] in endothelial cells and reduces endothelial damage and atherogenic injuries.[5] Previous studies reported that HT exerts its protective effects through the following mechanisms; (i) by preventing Low-Density Lipoprotein (LDL) oxidation, (ii) by inhibiting platelet aggregation, (iii) by mitigating mitochondrial abnormalities and preventing the metabolic syndrome (MetS) induced by a high fructose diet,[6] and (iv) by producing anti-inflammatory effects in conjunction with decreased Cyclooxygenase 1 (COX1) and COX2 enzyme activity.[7]

Spexin (SPX) is a 14 amino acid-long peptide hormone expressed extensively in central and peripheral tissues and secreted into the circulation as a response to metabolic stress. Studies show that SPX acts as a multifunctional peptide in metabolic processes. Endogenous SPX is sensitive to metabolic changes. It was reported that circulating SPX levels were reduced in chronic diseases. This suggests that SPX is a potential drug target for the development of novel pharmacological strategies.[8]

Transient Receptor Potential (TRP) Melastatin-Like Subfamily Member 2 (TRPM2) is a Ca^{2+} permeable cation channel with extremely low Ca^{2+} selectivity,[9,10] and is highly present in different cells.[11,12] TRPM2 is involved in different cellular and physiological processes, including cytokine production, cell death, oxidative stress, and fibrosis. Also, TRPM2 is an important factor in cell death caused by oxidative stress over the activation of caspase cleavage.[13,14] However, more studies are required to clarify its functional roles.

Although the protective effects of HT on metabolic diseases are known, data on how these effects happen are insufficient. In the present study, it was investigated whether SPX and TRPM2 had any roles in the protective effect of HT on liver damage in rats as a result of consuming Corn Syrup with drinking water (30% for six weeks).

MATERIAL AND METHOD

Animals and experimental design

The study was approved byAdıyaman University Animal Experiments Ethics Committee (Date: 06.10.2022, Decision No: 2022/051-2). The experiments were carried out per the "Guide for the Care and Use of Laboratory Animals". Twenty-four male, 200-250 g Sprague-Dawley rats (8-10 weeks) provided by Adıyaman University Experimental Research Center given ad libitum standard water and feed were used in the study in 4 groups (n: 6); Group I (Control), Group II (HT), Group III (Corn Syrup), and Group IV (Corn Syrup+HT). No applications were made to the Control Group. HT was supplied in liquid form from Kale Natural Herbal Products Company in Turkey. From this liquid containing HT, 4 ml/kg/day was administered orally for 6 weeks to rats in Groups II and IV. Rats in Groups III and IV were given 30% Corn Syrup with drinking water for 6 weeks.[15] At the end of 6 weeks, the rats were anesthetized with IP Ketamine (75 mg/kg)+Xylazine (10 mg/kg), and blood samples were taken from the hearts of all groups (Blood was drawn from the hearts of the rats to terminate the study). The liver tissues were fixed in a 10% formaldehyde solution for histological evaluations.

Immunohistochemical examination

Liver tissues of animals were passed through histological follow-up series and embedded in paraffin blocks. Immunohistochemical staining was applied with 5-µm sections as described by Kocaman and Artas.[16] Immunohistochemistry (IHC) was applied on 3-µm histological tissue microarray slides with Spexin primary antibodies (A04088-1, Booster Biological Technology, Pleasanton, CA, USA) and rabbit polyclonal anti-TRPM2 antibodies (Ab-11168), Abcem, Cambridge, UK) and were photographed with Zeiss Axio Scope A1 microscope (Carl Zeiss Microscopy GmB H 07745 Jena, Germany) and a histoscore was established for SPX and TRPM2.

In the microscopic evaluation of the staining density; the negative staining areas were given “0”, areas with < 25 % staining were given “0.1”, areas with 26-50% staining were given “0.4”, areas with 51-75% staining were given “0.6”, and areas with near-homogeneous staining (76-100%) were given “0.9”. The final histoscore was calculated with the following formula. Histoscore = Distribution × Intensity.[16]

Statistical analysis

The SPSS 22 (IBM Corporation, USA) was used for the analysis. The One-Way ANOVA Test was used and post-hoc multiple comparisons were made with Tukey HSD. The data are given as Mean ± SD. $P<0.05$ was taken as statistically significant.

RESULTS

Immunohistochemical Findings

With the immunohistochemical staining of SPX and TRPM2 immunoreactivity in liver tissue under the light microscope, the following results were achieved.

SPX immunoreactivity was lower in the Corn Syrup Group when compared to the Control and HT Groups ($p<0.001$). SPX immunoreactivity was elevated in the Corn Syrup+HT Group than in the Corn Syrup Group ($p<0.001$) (**Table 1**). SPX immunoreactivity histoscores for the four groups are given in **Figure 1**.

Table 1: Immunohistochemical findings for SPX in the liver tissues

Groups	Control	HT	Corn Syrup	Corn Syrup+HT
SPX	1.05±0.16	1.1±0.15	0.08±0.03[ab]	0.55±0.08 [abc]

Error bars show SD; a. $p<0.05$ compared to control; b. $p<0.05$ compared to HT; c. $p<0.05$ compared to Corn Syrup.

TRPM2 immunoreactivity was elevated in the Corn Syrup Group when compared to the Control and HT Groups ($p<0.001$). TRPM2 immunoreactivity was lower in the Corn Syrup+HT Group than in the Corn Syrup Group ($p<0.001$) (**Table 2**). TRPM2 immunoreactivity histoscores for the four groups are given in **Figure 2**.

Table 2: Immunohistochemical findings for TRPM2 in the liver tissues

Groups	Control	HT	Corn Syrup	Corn Syrup+HT
TRPM2	0.06±0.02	0.08±0.03	1.2±0,33 [ab]	0.5±0.08[abc]

Error bars show SD; a. $p<0.05$ compared to control; b. $p<0.05$ compared to HT; c. $p<0.05$ compared to Corn Syrup.

DISCUSSION

The role of SPX and TRPM2 molecules in the protective effect of HT on the pathological changes in the liver because of Corn Syrup consumption in rats was evaluated histopathologically in the present study. It was shown in the study for the first time that SPX and TRPM2 may mediate the protective effects of HT, whose metabolic protective effect is known, against liver damage because of Corn Syrup.

SPX is commonly found in endocrine and epithelial tissue[17] and is considered to be involved in metabolic disorders. SPX was lower in patients with MetS in a clinical study. Also, an inverse relationship was detected between SPX and glucose, lipid, and blood pressure in MetS.[18] SPX treatment decreased fatty acid uptake into hepatocytes.[19] However, Subcutaneous (SC) injection of SPX was shown to reduce appetite and reduce caloric intake by approximately 32% in rats.[20] Also, Behrooz et al.[21] reported an inverse relationship between SPX levels and dietary fat intake in obese children. SPX has potential regulatory roles in metabolic status. SPX treatment reduced hepatic lipid storage, Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT) in Diet-Induced Obese (DIO) mice. Also, the uptake of Long-Chain Fatty Acids (LCFAs) in hepatocytes was reduced by SPX.[19] Similarly, another study conducted with DIO mice showed that SPX reduced lipid accumulation and glycogen levels.[18] Also, hepatic glucose production was reduced due to SPX in DIO rats, and CRISPR/Cas9-mediated silencing of SPX in Human Liver Cancer Cells (HepG2) triggered gluconeogenesis.[22] Similarly, plasma SPX levels were found to be lower in Non-Alcoholic Fatty Liver Disease (NAFLD) patients when compared to controls,[23] which indicates the potential therapeutic value of SPX in the treatment of hepatic steatosis/NAFLD.[8] It was found in the present study that the SPX levels decreased in the liver tissue in the Corn Syrup Group when compared to the Control Group, and the SPX level increased after HT treatment, which suggests that SPX may also contribute to this characteristic of HT, which is known to have protective effects on the liver. Because HT consumption, which is one of the main components of olive oil and has significant antioxidant, anti-inflammatory, and antimicrobial characteristics, is associated with the improvement of MetS and related disorders,[24] it has been recently found to

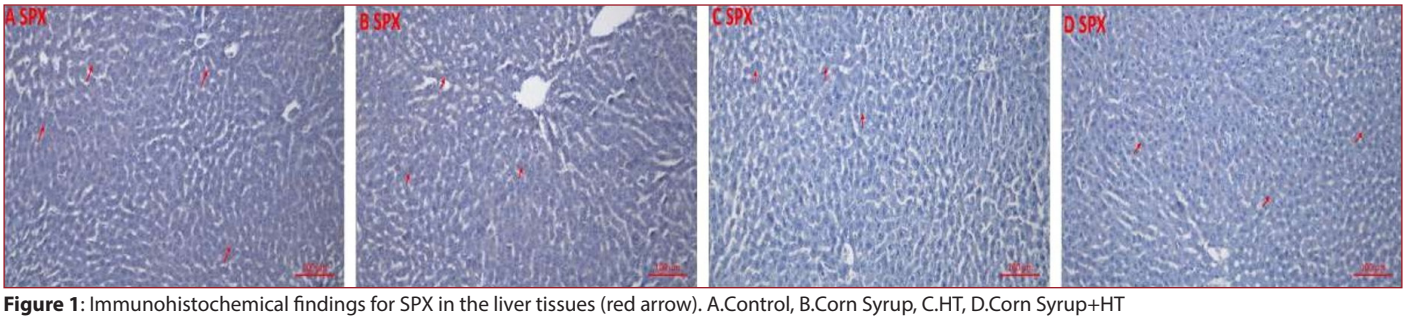

Figure 1: Immunohistochemical findings for SPX in the liver tissues (red arrow). A.Control, B.Corn Syrup, C.HT, D.Corn Syrup+HT

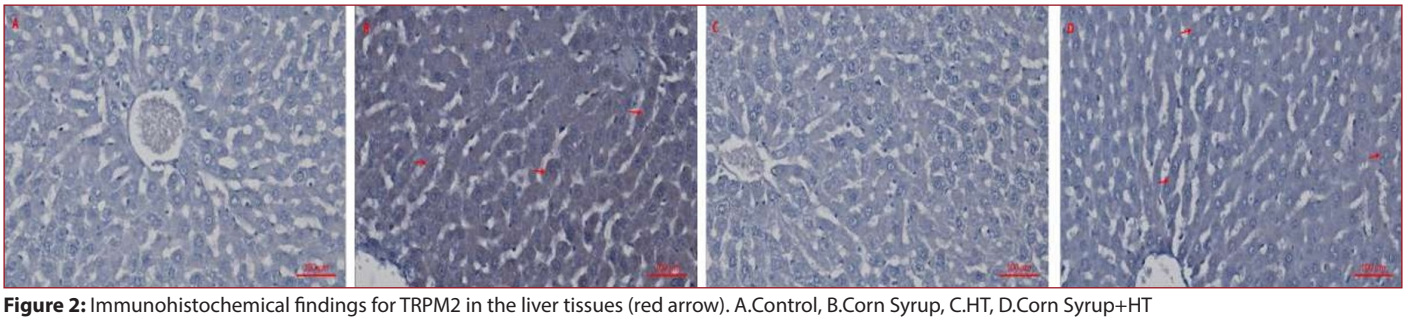

Figure 2: Immunohistochemical findings for TRPM2 in the liver tissues (red arrow). A.Control, B.Corn Syrup, C.HT, D.Corn Syrup+HT

improve Insulin Resistance and obesity by modulating the gut microbiota.[25] HT-rich olive leaf extracts were shown to have hypolipidemic and hepatoprotective effects on high-fat diet-induced lipid metabolism disorder and liver injury in rats after improving the antioxidative defense system and blocking protein expression in inflammation and liver damage and against metabolic disorders induced by high-fructose diet.[28] In another study, dietary supplementation with 5 mg of HT attenuated the deleterious metabolic effects that were produced by a high fructose diet in mice. HT's protective effects in the liver are considered to be associated with (i) the restoration of the activity of A-5 and A-6 desaturase enzymes by preventing depletion of n-3 LCPUFAs, (ii) reduced oxidative stress, (iii) the down-regulation of lipogenic factor SREBP-1c, and (iv) preservation of n-3 LCPUFA levels in extrahepatic tissues.[29] SPX is likely to play roles in these mechanisms of action, which belong to the protective characteristics of HT. However, more studies are needed to understand this mechanism.

TRPM2 activity is indispensable for many physiological processes, including insulin secretion in pancreatic β-cells, monocyte chemokine production, and heat sensation of hypothalamic neurons.[30] Because of its Ca^{2+} permeability, TRPM2 is also involved in many pathophysiological processes that cause cell death because of the production of Reactive Oxygen Species (ROS).[31] For this reason, TRPM2 has become an attractive pharmacological target. In a previous study, evaluation of acetaminophen-induced liver injury due to blood liver enzyme concentration and liver histology exhibited less severe liver injury in TRPM2 knockout mice compared to WT mice.[32] TRPM2 channels are an integral part of the acetaminophen-induced hepatocellular death mechanism. For this reason, TRPM2-mediated cell death is an important mechanism in NAFLD-induced liver injury.[33] In our study, it was found that the TRPM2 levels increased in the Corn Syrup given Group when compared to the Control Group, and the TRPM2 level decreased after HT treatment, which suggests that TRPM2 may be involved in the mechanism of action of HT's protective characteristics, which has anti-inflammatory and antioxidant characteristics. TRPM2, which is proinflammatory, provides the basis for discoveries regarding this pathology in terms of liver damage.

The most important limitation of the study was that methods such as PCR and Western Blot Analysis could not be used because of financial reasons. Further studies involving larger numbers of animals to explain the association of HT with SPX and TRPM2 will support the molecular mechanisms of the study. Also, the protective effects of HT on the liver must be supported by clinical findings.

CONCLUSION

It is considered that some novel molecules such as SPX and TRPM2 may contribute to the protective effects of HT against the harmful effects of Corn Syrup on the liver.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved byAdıyaman University Animal Experiments Ethics Committee (Date: 06.10.2022, Decision No: 2022/051-2).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1341380
J Contemp Med 2023;13(5):959-965

Original Article / Orijinal Araştırma

Evaluation of Endoscopy Timing in Patients with Acute Upper Gastrointestinal Bleeding in Emergency Department

Acil Servise Başvuran Akut Üst Gastrointestinal Kanamalı Hastalarda Endoskopi Zamanının Değerlendirilmesi

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Abstract

Aim: Endoscopy is recommended in acute upper gastrointestinal bleeding (AUGIB) to detect the bleeding source and stop the bleeding. The optimal timing of endoscopy in AUGIB is controversial. We aimed to investigate the time of endoscopy and the factors affecting it.

Material and Method: Retrospective, single-center study. The patients were divided into four groups: endoscopy after discharge, 0-12 hours endoscopy, 12-24 hours endoscopy and 24 hours later. Age, sex, vital signs, laboratory findings were recorded. Glasgow-Blatchford Score (GBS) and Charlson comorbidity index (CCI) were calculated. The obtained data were compared between these four groups. All-cause mortality for 30 days was recorded.

Results: A total of 318 patients were included. In the comparison of endoscopy times, the parameters found to be statistically significant between the four groups are Hb, BUN, and INR levels, GBS and CCI. As a result of CHAID analysis, the most crucial variable affecting the timing of endoscopy was found to be the Hb value of the patients ($\chi 2=66.528$; adjusted p=0.000). Mortality occurred in 10.69% of the patients. The timing of endoscopy did not affect mortality. In binary logistic regression analysis, low systolic BP (0.967 times increase), high CCI (86,402 times increase) were found to affect mortality.

Conclusion: The factors affecting the timing of endoscopy are the signs of bleeding. A thorough follow-up of vital signs in patients presenting to the emergency department with acute gastrointestinal bleeding, particularly an evaluation of systolic blood pressure and detailed questioning of additional comorbid conditions, is critical to reduce mortality.

Keywords: endoscopy timing, emergency, upper gastrointestinal bleeding, acute gastrointestinal bleeding

Öz

Amaç: Endoskopi akut üst gastrointestinal kanamada (AUGIB) kanama kaynağını tespit etmek ve kanamayı durdurmak için önerilir. Endoskopinin AUGIB'de optimal zamanlaması tartışmalıdır. Çalışmamızda endoskopi zamanını ve etkileyen faktörleri araştırmayı amaçladık.

Gereç ve Yöntem: Çalışma retrospektif, tek merkezlidir. Hastalar taburculuk sonrası endoskopi, 0-12 saat endoskopi, 12-24 saat endoskopi ve 24 saat sonra endoskopi olmak üzere 4 gruba ayrıldı. Yaş, cinsiyet, vital bulgular, laboratuvar bulguları kaydedildi. Glasgow-Blatchford Skoru (GBS) ve Charlson komorbidite indeksi (CCI) hesaplandı. Elde edilen veriler bu dört grup arasında karşılaştırıldı. 30 gün boyunca tüm nedenlere bağlı ölümler kaydedildi.

Bulgular: Toplam 318 hasta dahil edildi. Endoskopi sürelerinin karşılaştırılmasında dört grup arasında istatistiksel olarak anlamlı bulunan parametreler Hb, BUN ve INR seviyeleri, GBS ve CCI'dır. CHAID analizi sonucunda endoskopi zamanını etkileyen en önemli değişkenin hastaların Hb değeri olduğu bulundu ($\chi 2=66,528$; düzeltilmiş p=0,000). Mortalite hastaların %10.69'unda meydana geldi. Endoskopinin zamanlaması mortaliteyi etkilemedi. Binary lojistik regresyon analizinde düşük sistolik KB (0,967 kat artış), yüksek CCI (86.402 kat artış) mortaliteyi etkilediği bulundu.

Sonuç: Endoskopinin zamanlamasını etkileyen faktörler kanama belirtileridir. Akut gastrointestinal kanama ile acil servise başvuran hastalarda hayati bulguların tam olarak izlenmesi, özellikle sistolik kan basıncının değerlendirilmesi ve ek komorbid durumların ayrıntılı olarak sorgulanması, mortaliteyi azaltmak için kritik öneme sahiptir.

Anahtar Kelimeler: endoskopi zamanlaması, acil durum, üst gastrointestinal kanama; akut gastrointestinal kanama.

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Received *(Geliş Tarihi)*: 11.08.2023 **Accepted *(Kabul Tarihi)*:** 05.09.2023

INTRODUCTION

Gastrointestinal bleeding (GIB) is the most common gastrointestinal disease in the United States and requires hospitalization. There are more than half a million admissions regarding the number of patients. Approximately 80% of these patients have upper gastrointestinal bleeding (UGIB). UGIB refers to bleeding caused by the proximal part of the esophagus, stomach, or treitz ligament.[1] In acute UGIB (AUGIB), endoscopy is recommended to detect the bleeding source and stop the bleeding.[2] However, the optimal timing of endoscopy in AUGIB is controversial.[3-5] Current guidelines agree that early endoscopy (within 24 hours of admission) for AUGIB leads to better outcomes in terms of mortality and hospital stay.[2]

On the other hand, the definition of "too early" endoscopy is still controversial, and although the European Society for Gastrointestinal Endoscopy (ESGE) defines it as <12 hours, some authors suggest alternative timing in their study (e.g., <2 hr, < 6 hr).[6-8] Very early endoscopy is recommended for patients with a high risk of bleeding characterized by a Glasgow-Blatchford Score (GBS) ≥ 12, suspected acute variceal bleeding, significant comorbidity, and contraindications for reversal of anticoagulation. However, there is no consensus on this issue yet.[9,10]

The GBS is the recommended score to be used in the guidelines for identifying risky patients and deciding on the endoscopy time.[2] GBS has the highest accuracy in predicting the need for immediate intervention and mortality.[10,11] Guidelines suggest that patients with GBS ≤1 can be treated as outpatients.[2,10,12]

It is still suggested that endoscopic hemostasis may have an advantage over medical therapy alone in reducing rebleeding. However, it does not appear to provide any benefit in terms of transfusion requirement or mortality.[13,14] Due to these conflicting data, we aimed to investigate the time of endoscopy and the factors affecting it and to determine the parameters affecting mortality in patients who presented to the emergency department with AUGIB.

MATERIAL AND METHOD

This study was conducted as a retrospective, and carried out with the permission of İzmir Katip Celebi University Clinical Research Ethics Committee (Date: 22/05/2022, Decision No: 0234). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. According to the ICD-10 (K92.9, K29.0, K25, K28.0) code, the patients admitted to our emergency department between January 1, 2021, and March 31, 2022, who were diagnosed with AUGIB were retrospectively scanned.

Inclusion Criteria: Patients over 18 years who were not pregnant were included in the study.

Exclusion Criteria: Patients with variceal bleeding, trauma patients, and patients whose files did not have sufficient data were excluded from the study.

Primary Outcomes

Age, sex, vital signs (systolic blood pressure, pulse), laboratory findings such as hemoglobin (Hb), blood urea nitrogen (BUN), creatinine, international normalized ratio (INR), and platelet (PLT) levels of the patients were recorded. Whether the patient had syncope in the admission complaint, liver disease diagnosed by a gastroenterologist from comorbid diseases, or heart failure diagnosed by a cardiologist were added to the data. For diagnosis liver disease, patients with cirrhosis or bilirubin >2 x normal and AST/ALT/AP >3x normal were considered to have 'liver disease'.[15] Following the 2021 ESC Acute Heart Failure Guidelines, patients who had a volume excess, respiratory distress, exercise dyspnea, paroxysmal nocturnal dyspnea or orthopnea were considered heart failure patients.[16] The patients use of anticoagulant/antiaggregant drugs (acetylsalicylic acid, clopidogrel, warfarin, ticagrelor, apixaban, and rivaroxaban) was recorded. Rectal examination findings were grouped as normal stool, empty rectum, melena, and hematochezia. The GBS was calculated from the data obtained (Hb, BUN, systolic BP, sex, heart rate, melena present, recent syncope, hepatic disease history, and cardiac failure present). According to the GBS, the patients were divided into groups 0-1, 2-12, and ≥12.[10] The patients comorbid diseases were divided into ≤5 and 6≥ according to the Charlson comorbidity index (CCI).[17] The treatments administered were recorded (medical therapy, sclerotherapy, sclerotherapy+hemoclips, band ligation, hemoclips). All-cause mortality for 30 days was recorded. Factors affecting mortality were investigated.The time from admission to the emergency department until endoscopy was calculated, and the patients were divided into four groups: endoscopy after discharge, 0-12 hours endoscopy, 12-24 hours endoscopy and 24 hours later. The obtained data were compared between these four groups.

Statistical Method

Statistical analysis were evaluated in the IBM SPSS Statics Version 20 package program. Descriptive statistics and frequency and percentage distribution, mean, standard deviation and minimum and maximum values for continuous variables were calculated. The conformity of continuous variables to a normal distribution was evaluated with Kolmogorov-Smirnova and Shapiro-Wilk ($p<0.05$) tests, and then it was decided to use parametric or nonparametric tests. While chi-square test statistics were used to compare categorical variables between groups, Mann-Whitney U statistical analyses were used for comparisons between two groups, and Kruskal-Wallis statistical analyses were used for comparisons of more than two groups since continuous data consisted of values that did not conform to a normal distribution.

The data obtained in the study to determine the variables that may affect the mortality status of the patients admitted to the emergency department were evaluated with a binary logistic regression model. The factors affecting the endoscopy time were evaluated with CHAID analysis.

RESULTS

A total of 318 patients who met the study criteria were included. The general characteristics of the patients were as follows: The mean age of the patients was 67.01±16.96 years, 54.09% of the patients were males. A total of 52.2% of the patients were not using anticoagulant and/or antiaggregant drugs. Melena was detected on rectal examination in 66.04% of the patients. The GBS of 51.57% of the patients was 12 and above, and the CCI of 67.92% was in the range of 0-5. A total of 27.67% of the patients received endoscopy within 0-12 hours, 37.11% received endoscopy within 13-24 hours, 29.56% received endoscopy after 24 hours, and 5.66% underwent elective endoscopy after discharge.

In the comparison of endoscopy times, the parameters found to be statistically significant between the four groups are as follows. The Hb level of the patients who underwent endoscopy between 0-12 hours was found to be 7.5±2.08 mg/dl (p<0.00). The BUN level of the patients who underwent endoscopy after discharge was 26.89±14.14 mg/dl (p<0.01), and the INR level of the patients who underwent endoscopy between 13-24 hours was 1.83±3.57 (p<0.03). The rectal examination finding of 84.1% of the patients who underwent endoscopy at 0-12 hours was melena. Rectal examination was normal in 36.17% of those who had endoscopy after 25 hours. 33.3% of the patients who underwent endoscopy after discharge did not use anticoagulant/antiaggregant drugs. There was a statistically significant difference between the timing of endoscopy in terms of anticoagulant/antiaggregant drug use (p<0.00). The GBS of 72.34% of those who underwent endoscopy after 25 hours was between 2-12, and 70.5% of those who underwent endoscopy between 0-12 hours had a GBS ≥12. According to the presence of comorbid disease; The CCI of 78.72% of those who underwent EGD at 24 hours and later was found to be between 0-5, and the CCI of 40.68% of those who underwent EGD at 12-24 hours was between 6-37 (p<0.03) (**Table 1**).

The factors affecting the endoscopy time were analyzed by CHAID analysis. The Hb value of the patients was found to be the most crucial variable (χ2=66,528; adjusted p=0.000). Patients with an Hb level below 6.6 mg/dl who underwent endoscopy between 0-12 and 13-24 hours constituted 80.8% of the total. Endoscopy was performed in 45.8% of patients with Hb levels between 6.6 mg/dl and 9.0 mg/dl between 13-24 hours. Endoscopy was performed in 37.5% of patients with Hb levels between 9.0 mg/dl and 10.9 mg/dl over 25 hours (**Figure 1**).

Mortality occurred in 10.69% of the patients. In the comparison of deceased and living patients; The mortality rate of patients with systolic blood pressure between 101.12±25.01 mmHg, liver disease, undergoing endoscopic procedure (sclerotherapy, hemoclips, band), GBS score ≥12, and CCI 6-37 was higher than surviving patients (**Table 2**). Binary logistic regression analysis was performed for these parameters. The Nagelkerke R2 value of 0.510 was found to be 51.0% effective in explaining the response variable (mortality) of the model. The sensitivity of the model was 97.2%, the selectivity was 29.4%, and the accuracy rate was 89.9%. The probability of survival of patients with low systolic BP values is 0.967 times lower than that of patients with high systolic BP values. The probability of survival of patients with a high CCI value was 86,402 times lower than that of patients with a low CCI value. Depending on the type of treatment, the patient's survival probability increases by 2,938 times. Based on the GBS, patient survival probability varied by 0.107. The higher the GBS, the higher the death rate (**Table 3**).

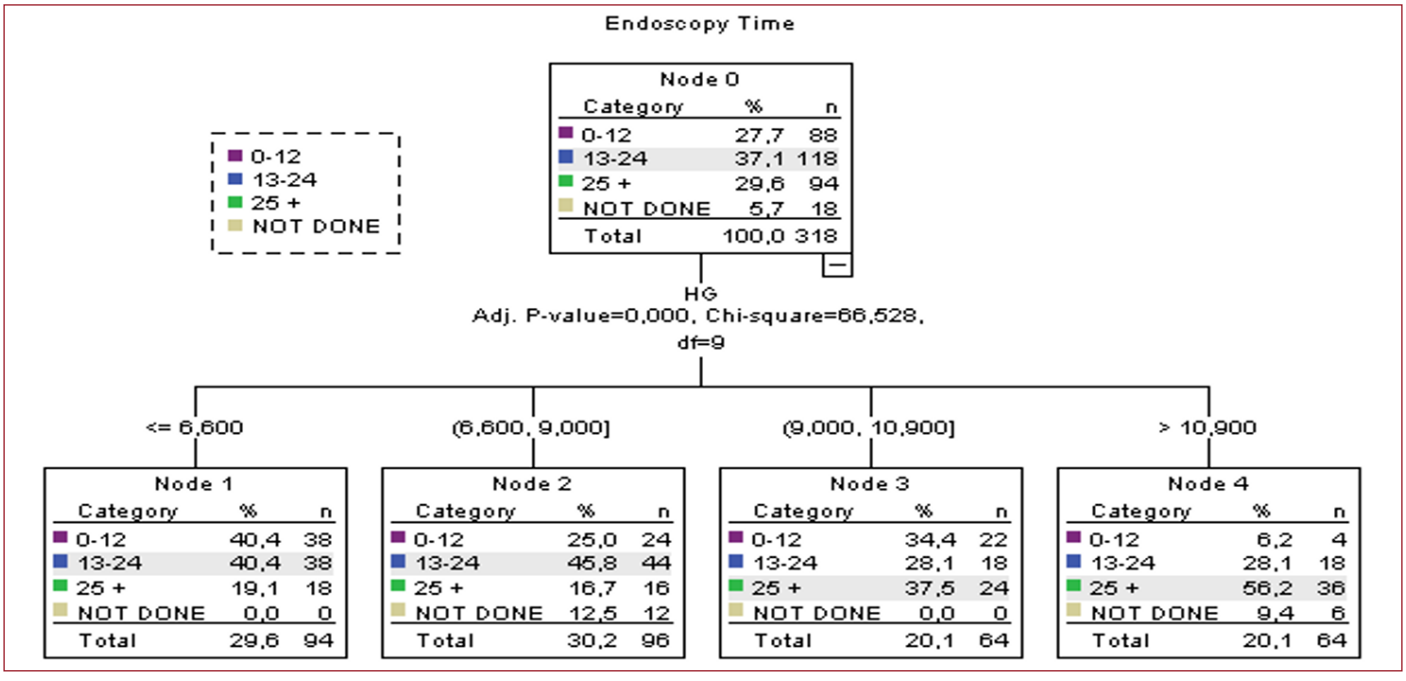

Figure 1. CHAID analysis for factors affecting endoscopy timing

Table 1. Comparison of patients' general characteristics and study parameters between endoscopy timing groups

Variables	All patients N=318	After discharge n=18	0- 12 hours n=88	13-24 hours n=118	25 hours and above n=94	p
	mean±std (min-max)	mean±std (min-max)	mean±std (min-max)	mean±std (min-max)	mean±std (min-max)	
Age/year	67.02±16.91 (18-95)	68.22±12.95 (51-93)	65.52±19.14 (18-95)	70.95±13.03 (21 -93)	63.26±18.75 (29-93)	0.05
Pulse/min	91.88±17.28 (12-143)	93.11±12.74 (79-121)	93.02±16.22 (61-135)	94.1±17.77 (60 -143)	87.79±17.88 (60-128)	0.13
Systolic blood pressure/mmHg	118.56±24.21 (57-190)	120.78±33.91 (80-190)	116.61±24.31 (57-190)	118.15±25.47 (75 -186)	120.47±20.26 (75-186)	0.59
Hemoglobin-gr/dl	8.49±2.75 (3-16.4)	9.34±1.77 (7.1-12.1)	7.5±2.08 (3-11.7)	8.14±2.76 (3.9 -15)	9.68±2.98 (3.0-16.4)	0.00
BUN-mg/dL	39.13±25.82 (5-151)	26.89±14.14 (12-53)	40.68±25.95 (5-151)	42.68±27.4 (6 -120)	35.57±24.51 (7-151)	0.01
INR	1.64±2.42 (0.87-28)	1.66±1.18 (0.91-4.7)	1.74±1.58 (0.9-8.29)	1.83±3.57 (0.89 -28)	1.3±1.09 (0.87-28)	0.03
PLT-mcL	251.91±104.89 (24-589)	258.89±122.27 (63-505)	256.32±104.51 (31-589)	258.97±106.42 (24 -547)	237.57±100 (24-589)	0.29
Creatinine-mg/dL	1.3±0.96 (0.5-6.92)	1.92±2.2 (0.52-6.92)	1.23±0.69 (0.5-4.63)	1.39±1.09 (0.63 -6.7)	1.12±0.39 (0.59-4.63)	0.49
	Count (%)	Count (%)	Count (%)	Count (%)	Count (%)	
Gender						
Male	172 (54.09)	10 (55.56)	44 (50)	68 (57.63)	50 (53.19)	0.75
Female	146 (45.91)	8 (44.44)	44 (50)	50 (42.37)	44 (46.81)	
Rectal Examination						
Melena	210 (66.04)	6 (33.33)	74 (84.1)	80 (67.8)	50 (53.19)	0.00
Normal stool	78 (24.53)	6 (33.33)	12 (13.6)	26 (22.03)	34 (36.17)	
Empty rectum	28 (8.81)	6 (33.33)	2 (2.3)	10 (8.47)	10 (10.64)	
Hematochezia	2 (0.63)	0 (0)	0 (0)	2 (1.69)	0 (0)	
Treatment						
Medical therapy	282 (88.68)	18 (100)	74 (84.1)	106 (89.83)	84 (89.36)	0.08
Sclerotherapy	8 (2.52)	0 (0)	0 (0)	4 (3.39)	4 (4.26)	
Sclerotherapy-Hemoclips	12 (3.77)	0 (0)	6 (6.8)	4 (3.39)	2 (2.13)	
Band ligation	4 (1.26)	0 (0)	4 (4.5)	0 (0)	0 (0)	
Hemoclips	12 (3.77)	0 (0)	4 (4.5)	4 (3.39)	4 (4.26)	
Anticoagulant Drug Use						
ASA	42 (13.21)	6 (33.33)	10 (11.4)	16 (13.56)	10 (10.64)	0.00
ASA + ticagrelor	8 (2.52)	0 (0)	0 (0)	6 (5.08)	2 (2.13)	
ASA + warfarin	4 (1.26)	0 (0)	2 (2.3)	2 (1.69)	0 (0)	
ASA + clopidogrel	14 (4.4)	0 (0)	0 (0)	10 (8.47)	4 (4.26)	
ASA + rivaroxaban	2 (0.63)	0 (0)	2 (2.3)	0 (0)	0 (0)	
warfarin	34 (10.69)	4 (22.22)	12 (13.6)	12 (10.17)	6 (6.38)	
apixaban	8 (2.52)	2 (11.11)	0 (0)	4 (3.39)	2 (2.13)	
clopidpgrel	26 (8.18)	0 (0)	6 (6.8)	10 (8.47)	10 (10.64)	
rivaroxaban	14 (4.4)	0 (0)	2 (2.3)	10 (8.47)	2 (2.13)	
No	166 (52.2)	6 (33.33)	54 (61.4)	48 (40.68)	58 (61.7)	
Mortality						
Alive	284 (89.31)	16 (88.89)	76 (86.4)	102 (86.44)	90 (95.74)	0.12
Ex	34 (10.69)	2 (11.11)	12 (13.6)	16 (13.56)	4 (4.26)	
GBScore						
2-12	154 (48.43)	10 (55.56)	26 (29.5)	50 (42.37)	68 (72.34)	0.00
≥12	164 (51.57)	8 (44.44)	62 (70.5)	68 (57.63)	26 (27.66)	
CCI						
0-5	216 (67.92)	12 (66.67)	60 (68.2)	70 (59.32)	74 (78.72)	0.03
6-10	102 (32.08)	6 (33.33)	28 (31.8)	48 (40.68)	20 (21.28)	

BUN: Blood Urea Nitrogen, INR: Internationel Normalized Ratio, PLT: Platelet, ASA: Acetylsalicylic acid, GBS: Glasgow-blatchford score, CCI: Charlson Comorbidity Index

Table 3. Evaluation of Risk Factors Associated with Mortality in Binary Logistic Regression Model

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1a	Systolic Blood Pressure	-.033	.012	8.243	1	.004	.967	.946	.989
	CCI	4.459	.953	21.878	1	.000	86.402	13.337	559.734
	Hepatic Disease	.903	.574	2.475	1	.116	2.467	.801	7.600
	Applied Treatment	1.078	.355	9.214	1	.002	2.938	1.465	5.893
	GBS Score	-2.236	1.131	3.910	1	.048	.107	.012	.980
	Constant	-3.198	2.886	1.228	1	.268	.041		

a. Variable(s) entered on step 1: Systolic, Comorbit, Hepatic, Treatment, GBS, Blood Transfusion. GBS: Glasgow-blatchford score, CCI: Charlson Comorbidity Index

Table 2. Comparison of the parameters considered in the study between deceased and living patients

Variables	Alive n=284 mean±std (min-max)	Ex n=34 mean±std (min-max)	p
Age/year	66.7±16.99 (18-95)	69.71±16.27 (25-90)	0.27
Pulse/min	91.84±17.44 (12-143)	92.24±16.16 (64-121)	0.98
Systolic blood pressure/mmHg	120.65±23.3 (80-190)	101.12±25.01 (57-158)	0.00
Hemoglobin gr/dl	8.57±2.77 (3-16.4)	7.82±2.51 (3.1-13)	0.22
BUN mg/dL	38.78±25.93 (5-151)	42.06±25.06 (6-87)	0.27
INR	1.69±2.56 (0.87-28)	1.25±0.33 (1-2.26)	0.38
PLT-mcL	255.49±100.06 (26-589)	222±137.07 (24-538)	0.08
Creatinine-mg/dL	1.31±0.99 (0.58-6.92)	1.22±0.59 (0.5-2.47)	0.92
	Count (%)	Count (%)	
Gender			
Male	156 (54.93)	16 (47.06)	0.38
Female	128 (45.07)	18 (52.94)	
Rectal Examination			
Melena	190 (66.9)	20 (58.82)	
Normal stool	66 (23.24)	12 (35.29)	0.44
Empty rectum	26 (9.15)	2 (5.88)	
Hematochezia	2 (0.7)	0 (0)	
Syncope			
No	246 (86.62)	32 (94.12)	0.21
Yes	38 (13.38)	2 (5.88)	
Hepatic Disease			
No	264 (92.96)	24 (70.59)	0.00
Yes	20 (7.04)	10 (29.41)	
Cardiac Failure			
No	228 (80.28)	24 (70.59)	0.19
Yes	56 (19.72)	10 (29.41)	
Applied Treatment			
Medical therapy	256 (90.14)	26 (76.47)	
Sclerotherapy	6 (2.11)	2 (5.88)	
Sclerotherapy-Hemoclips	10 (3.52)	2 (5.88)	0.04
Band ligation	2 (0.7)	2 (5.88)	
Hemoclips	10 (3.52)	2 (5.88)	
Anticoagulant Drug Use			
ASA	40 (14.08)	2 (5.88)	
ASA + ticagrelor	8 (2.82)	0 (0)	
ASA + warfarin	4 (1.41)	0 (0)	
ASA + clopidogrel	12 (4.23)	2 (5.88)	
ASA + rivaroxaban	2 (0.7)	0 (0)	0.26
warfarin	32 (11.27)	2 (5.88)	
apixaban	8 (2.82)	0 (0)	
clopidpgrel	24 (8.45)	2 (5.88)	
rivaroxaban	10 (3.52)	4 (11.76)	
No	144 (50.7)	22 (64.71)	
GBS Score			
0-1	0 (0)	0 (0)	
2-12	146 (51.41)	8 (23.53)	0.02
≥13	138 (48.59)	26 (76.47)	
CCI			
0-5	214 (75.35)	2 (5.88)	0.00
6-10	70 (24.65)	32 (94.12)	
Endoscopy Time			
After discharge	16 (5.63)	2 (5.88)	
0-12 hours	76 (26.76)	12 (35.29)	0.18
13-24 hours	102 (35.92)	16 (47.06)	
≥25 hours	90 (31.69)	4 (11.76)	

BUN: Blood Urea Nitrogen, INR: Internationel Normalized Ratio, PLT: Platelet, ASA: Acetylsalicylic acid, GBS: Glasgow-blatchford score, CCI: Charlson Comorbidity Index

DISCUSSION

The 2021 ESGE recommends endoscopy within 24 hours of hospital admission for AUGIB patients to identify the bleeding source and provide endoscopic treatments.[2] Few clinical data exist on the optimal 24-hour endoscopy timing.[7,12,18] BUN, Hb, GBS score, melena, anticoagulant use, and CCI values were statistically significant in four patient groups based on EGD timing. Our results showed that low CCI patients had endoscopy late and high CCI patients within 12-24 hours. A CCI is calculated by evaluating 19 factors. The scoring process weighs diseases.[18] Thus, a high CCI indicates worse comorbidities. In our study, UGIB increased the comorbidity burden in high CCI patients. Thus, early endoscopy is appropriate for high CCI patients.

The GBS, which was statistically significant between patient groups, is the best risk assessment score for identifying low-risk patients who can avoid hospitalization and should be treated outpatiently. The American College of Gastroenterology (ACG) and the UK National Institute for Health and Care Excellence (NICE) recommend outpatient evaluation of GBS = 0 patients.[19] The 2015 ESGE guidelines and 2018 Asia-Pacific consensus group guidelines recommend using GBS ≤ 1 to identify low-risk patients, reflecting recent evidence and publications.[18,19] No endoscopy timing is recommended based on GB score. A randomized controlled study by Wong et al. found that emergency endoscopy was not beneficial for high-risk patients with GBS ≥12, either within 6 hours or 24 hours of admission.[20] In our study, 70.5% of patients with endoscopy at 0-12 hours had GBS≥12. In patients with high GBS, early EGD may be due to changes in the parameters that make up this score, not the calculated GBS score. Melena, low Hb, and high BUN indicate active bleeding when the statistically significant GBS parameters are evaluated separately. Thus, early endoscopy was likely performed on the patients. Sasaki et al. found that endoscopic intervention is needed at 22.4 BUN.[21] Lin et al. classified patients by nasogastric tube aspirations.[22] Patients with blood aspirates had endoscopy within 12 hours. Early endoscopy helps actively bleeding patients. Our study found melena on rectal examination in 85% of endoscopy patients at 0-12 hours. We think bleeding findings in UGIB patients help decide on early endoscopy. Hb level was the most effective factor on endoscopy time, according to CHAID analysis. Endoscopy was performed within 24 hours in 80.8% of Hb-low patients. Low Hb levels in bleeding patients indicate acute blood loss and should be treated with endoscopy immediately. Thus, the bleeding focus can be found and hemostasis achieved. Cooper et al. recommended early endoscopy for endoscopic hemostasis patients because it reduced rebleeding and surgery.[24]

However, patients without active bleeding should not undergo early endoscopy. Schacher et al. found that emergency department endoscopy within 3 hours did not improve patient outcomes.[25] In their study, Lau et al. compared urgent (<6 hours) and early (<24 hours) endoscopy patients.[7] The two groups had similar mortality and rebleeding rates. He reported

that more urgent endoscopy patients received endoscopic hemostatic treatment than early endoscopy patients. because urgent endoscopy found more ulcers that were actively bleeding and had major stigmas. Because early endoscopy patients received medical treatment, the number of ulcers with possibly bleeding stigmas decreased. Stabilization with medical treatment was advised over early endoscopy.[7] Our study found similar treatment modalities to Schacher et al. and Lau et al.[7,25] Our survivors received medical treatment 90.14% of the time. The regression analysis showed that the treatment method increased survival by 2.908 times. We found that endoscopic patients had higher mortality. Early endoscopic treatment also involves medically controlled bleeding foci, which may not be necessary for low-risk patients. Using graphs, Laursen et al. examined the relationship between endoscopy timing and mortality.[8] The distribution charts showed lower mortality in patients who had endoscopy between 6-24 hours. Lee et al. and Schacher et al. found no significant mortality difference between early (≤3 hours) and late endoscopy (≥48 hours) groups.[12,25] Lau et al. and Guo et al. found no mortality difference between early and urgent endoscopy (<6 hours) patients.[7,23] These studies also show that endoscopy within 3-6 hours of admission does not improve clinical outcomes. Our findings match these studies. The timing of endoscopy does not affect patient mortality.

Systolic BP affects mortality. Systolic BP values of deceased patients were 101±12.25.01/mmgHg, while surviving patients had 120±65.23.3/mmHg. Low-BP patients are 0.967-fold less likely to survive than high-BP patients. A drop in systolic BP indicates class 3 hemorrhagic shock with a 40% volume loss.[26] Systolic hypotension in UGIB patients causes hemorrhagic shock and death from rapid blood loss. A decrease in blood oxygen-carrying capacity causes hypoxia and ischemia in all organs and tissues as blood loss increases. GBS parameters include systolic BP. GBS also affected mortality in our study. The 2000 GBS risk assessment tool predicts hospital-based treatment like blood transfusion, endoscopic treatment, or surgery.[10] Guidelines recommend assessing GBS≥12 patients as high-risk.[2,10] In accordance with recommendations, 76.47% of deceased patients had GBS≥12. According to regression analysis, patient survival probabilities ranged from 0.107. The mortality rate increased with score.

The most influential mortality factor was CCIndex. Our regression analysis showed that patients with a CCI of 6-37 were 86,402 times more likely to die than those with a CCI of 0-5. CCI, which we used to assess comorbid diseases, increases with age, severity, and number of diseases.[17] Siddique et al. found that GIB patients with comorbital disease are at risk for complications, hospitalization, and death.[27] In a similar study by Siebenhüner et al., 61% of patients took additional antithrombotic drugs.[28] UGIB risk factors include nongastrointestinal comorbidities, according to Crooks et al.[29] Comorbid diseases may be the leading cause of patient death. A high CCI indicates a higher death risk and more severe comorbidities.[29] Carlson et al. found that the higher the CCI for any disease state, including UGIB, the higher the mortality.[17] Insufficient compensating mechanisms against bleeding owing to concomitant disorders in UGIB patients with high CCI may potentially lead to high mortality.

CONCLUSION

In conclusion, we can say that the factors affecting the timing of endoscopy in patients admitted to the emergency department due to UGIB are the signs of bleeding. We found that patients with low Hb, high BUN values, GBS≥12, and melena on rectal examination underwent endoscopy early in 0-12 hours. However, we found that the timing of endoscopy did not affect mortality. The main factors affecting mortality are systolic BP, CCI, treatment modality, and GBS. Specifically, CCI was found to be the most important determinant of mortality. A thorough follow-up of vital signs in patients presenting to the emergency department with UGIB, particularly an evaluation of systolic blood pressure and detailed questioning of additional comorbid conditions, is critical to reduce mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İzmir Katip Celebi University Clinical Research Ethics Committee (Date: 22/05/2022, Decision No: 0234).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1319280
J Contemp Med 2023;13(5):966-974

Original Article / Orijinal Araştırma

Threat of mpox (Monkeypox) Outbreak after the COVID-19 Pandemic: Are Healthcare Professionals Ready for New Psychological Wars?

COVID-19 Salgını Sonrası mpox (Maymun Çiçeği) Salgını Tehdidi: Sağlık Çalışanları Yeni Psikolojik Savaşlara Hazır Mı?

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Abstract

Aims: In this study, it was aimed to evaluate the psychological status of healthcare professionals regarding the COVID-19 pandemic, and to examine their perspectives and knowledge levels regarding the mpox epidemic.

Material and Method: Having a cross-sectional design, the present study was carried out by using questions addressing sociodemographic characteristics of healthcare professionals, their experiences with the COVID-19 pandemic, and their knowledge and anxiety levels regarding mpox.

Results: 202 healthcare professionals were involved in the present study. Of the participants, 55% were female and the mean age was 35.0±7.7 years. The majority (63.4%) of the participants were midwives/nurses/medical assistants. Of the participants, 68.8% were infected by COVID-19 during the pandemic. Considering the questions addressing their level of knowledge about mpox, 44.1% of participants stated that they had never heard of this disease before. Participants were found to have mainly moderate levels of depression and anxiety and low level of stress, whereas the ratios of very severe depression and anxiety were 5.0% and 7.4%, respectively.

Conclusion: It was determined that almost half of the participants had no full knowledge of the disease before the increase in mpox cases. It was found that the participants varying levels of depression, anxiety, and stress about a new pandemic. We think that it is important to provide healthcare professionals with psychosocial support, make effort in order to determine and eliminate the sources of psychological negativities.

Keywords: Anxiety, COVID-19, depression, monkeypox, mpox

Öz

Amaç: Bu çalışmada, sağlık çalışanlarının COVID-19 pandemisine ilişkin psikolojik durumlarının değerlendirilmesi, mpox salgınına bakış açılarının ve bilgi düzeylerinin incelenmesi amaçlandı.

Gereç ve Yöntem Kesitsel bir tasarıma sahip olan bu çalışma, sağlık çalışanlarının sosyodemografik özellikleri, COVID-19 pandemisi ile ilgili deneyimleri ve mpox'a ilişkin bilgi ve kaygı düzeylerini ele alan sorular kullanılarak gerçekleştirildi.

Bulgular: Çalışmaya 202 sağlık çalışanı dahil edildi. Araştırma kapsamına alınanların %55'i kadındı ve yaş ortalaması 35.0±7.7 yıldı. Katılımcıların büyük çoğunluğu (%63.4) ebe/hemşire/sağlık memuruydu. Katılımcıların %68.8'i pandemi sırasında COVID-19 ile enfekte oldu. Mpox ile ilgili bilgi düzeylerine yönelik yöneltilen sorularda katılımcıların %44.1'i (n=89) bu hastalığı daha önce hiç duymadıklarını ifade etti. Katılımcıların ağırlıklı olarak orta düzeyde depresyon ve anksiyete ile düşük düzeyde strese sahip olduğu, çok şiddetli depresyon ve anksiyete oranlarının ise sırasıyla %5.0 ve %7.4 olduğu bulundu.

Sonuç: Çalışmada katılımcıların neredeyse yarısının mpox vakalarındaki artıştan önce hastalık hakkında tam bilgiye sahip olmadığı belirlendi. Katılımcıların yeni bir pandemiye karşı farklı düzeylerde depresyon, kaygı ve stres yaşadıkları tespit edildi. Psikolojik olumsuzlukların kaynaklarının belirlenip ortadan kaldırılması için sağlık çalışanlarına psikososyal destek verilmesinin, çaba gösterilmesinin önemli olduğunu düşünüyoruz.

Anahtar Kelimeler: Anksiyete, COVID-19, depresyon, maymun çiçeği, mpox

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Received *(Geliş Tarihi)*: 23.06.2023 **Accepted *(Kabul Tarihi)*:** 17.07.2023

INTRODUCTION

On 11 March 2020, coronavirus disease-2019 (COVID-19) was announced as a global pandemic by the World Health Organization (WHO).[1] The disease spread out to more than 220 countries worldwide. At the global scale, the number of cases reached 767 million and deaths to 6.9 million.[2] Developing due to SARS-CoV-2, COVID-19 is carried between humans through droplets. Healthcare professionals are at risk because of their contact with patients and social transmission.[3] It was reported that this increase in the risk to catch the virus for healthcare professionals during the pandemic increased the anxiety of becoming ill and might cause burnout for both these professionals and their families/friends.[4]

The new outbreak caused by the monkeypox virus (MPXV) while the world is still struggling with the COVID-19 pandemic increased the anxiety of healthcare officials that this disease might be a new threat.[5,6] Caused by MPXV, mpox (formerly known as monkeypox disease) is a zoonotic infection and is widely seen in Central and Western Africa. The first mpox case in humans was reported in Democratic Kongo Republic in the year 1970.[7,8] Contagion of MPXV to humans occurs via direct contact with an infected human or animal or through materials contaminated with the virus.[9]

Although MPXV has been in circulation for years where it is endemic, mpox studies have been ignored and the studies on this subject have not been funded sufficiently.[10] In May 2022, multiple mpox cases were detected in several non-endemic countries.[11] On 23 July 2022, WHO declared the mpox as a "Global Emergency".[12] As of the date 6 June 2023, 87,929 mpox cases and 146 deaths were reported from 111 countries worldwide. It is seen that the number of cases has decreased on a global scale since August 2022, and on May 10 2023, WHO declared mpox is no longer a global emergency.[13]

The increasing number of human mpox cases indicates the importance of protection from the disease, early diagnosis, and epidemic management. Besides that, in a report prepared by the WHO, it was reported that one of the difficulties in preventing the outbreak of mpox was the lack of information about mpox, especially among healthcare professionals.[7,14] In this study, it was aimed to evaluate the psychological status of healthcare professionals regarding the COVID-19 pandemic, and to examine their perspectives and knowledge levels regarding the mpox epidemic.

MATERIAL AND METHOD

Ethical Approval and Permissions

The study was carried out with the permission of Harran University Clinical Researches Ethics Committee (Date: 08.08.2022, Decision No: HRÜ/22.15.20). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Subjects

The universe of this study consists of all the healthcare professionals working in different branches and at different positions in administration and service departments of Batman Training and Research Hospital. The data were collected between August 2022 and November 2022. Without using a sampling method, all the volunteer healthcare professionals were involved in this study. The present study was completed with 202 participants. The healthcare professionals (55 professionals), who were not volunteer in participating in the study, were excluded (Participation ratio: 78.6%).

Data Collection Tools

The study data were collected using a survey that consists of 4 sections. The first section of the survey consists of 9 items addressing the sociodemographic characteristics and comorbidity, whereas the second section consists of 7 items examining their professional and personal experiences during the COVID-19 pandemic. While the third section consists of 19 items investigating their level of knowledge and anxiety about mpox, the fourth section consists of the "Depression, Anxiety, and Stress Scale-2021 (DASS-21)" developed in order to determine the depression, anxiety, and stress disorder levels of participants. Developed by Lovibond P. F. and Lovibond S. H., the Depression Anxiety Stress Scale (DASS) consists of 42 items.[15] It was revised into its 21-item short form (DASS-21) by Sarıçam H.[16] The scale includes 3 subdimensions, each of which consists of 7 items, addressing depression, anxiety, and stress. The scale is rated between 0 (never) and 3 (always) in order to determine the depression, anxiety, and stress levels in the last week. Cronbach's Alpha internal consistency coefficient of the scale was found to be 0.87 for depression, 0.85 for anxiety, and 0.81 for stress. In this study, the DASS-21 scale's internal consistency Cronbach alpha coefficient was found to be 0.85 for depression, 0.80 for anxiety, and 0.77 for stress and considered to be at a sufficient level.

Statistical Methods

The data obtained were analyzed using IBM SPSS Statistics v.22.0 (IBM Corp.; Armonk, NY, USA) package software. During the statistical analyses, mean ± standard deviation and minimum-maximum values were used for continuous variables, whereas numbers and percentages were used for nominal variables. Continuous variables' fitness to normal distribution was tested using the Shapiro-Wilk test, normal distribution diagrams, and skewness and kurtosis coefficients. The significance of differences for continuous variables was examined using independent samples t-test and F-test (One-way ANOVA). The level and direction of relationships between two numerical variables were analyzed using Pearson's correlation analysis. For all the analyses, statistical significance was set at $p<0.05$.

RESULTS

In total, 202 healthcare professionals were involved. Of the participants, 55.0% (n=111) were women and the mean age was found to be 35.0±7.7 (min-max=22-57) years. The portion of married participants was 67.3% (n=136) and the mean number of children was 2.4±1.3 (min-max=1-5). The highest portion of participants (63.4%, n=128) consisted of midwives /nurses/medical assistants, while the mean duration of employment was 11.8±7.6 (min-max=1-37) years. It was determined that 77.7% (n=157) of the participants have worked in departments, where COVID-19-related services were offered, during the pandemic (**Table 1**).

Table 1. Participant's sociodemographic characteristics and their experiences with the COVID-19 pandemic

Characteristics	n (%)
Gender	
Female	111 (55.0)
Male	91 (45.0)
Age [Mean ±SD (Min-Max)]	35.0±7.7 (22-57)
Marital status	
Non-married	66 (32.7)
Married	136 (67.3)
Number of children [Mean ±SD (Min-Max)]	2.4±1.3 (1-5)
Position	
Specialist physician/Physician	32 (15.8)
Midwife/Nurse/Medical assistant	128 (63.4)
Other supporting medical personnel	26 (12.9)
Administration and service personnel	16 (7.9)
Professional employment time [Mean ±SD (Min-Max)]	11.8±7.6 (1-37)
Active workplace during the pandemic	
Pandemic-related units	157 (77.7)
Units that are not related with the pandemic	45 (22.3)
Chronic physical disorder	
No	174 (86.1)
Yes	28 (13.9)
Chronic mental disorder	
No	197 (97.5)
Yes	5 (2.5)
Diagnosed with COVID-19	
No	63 (31.2)
Yes	139 (68.8)
Family member diagnosed with COVID-19	
No	30 (14.9)
Yes	172 (85.1)
Loss of a family member due to COVID-19	
No	183 (90.6)
Yes	19 (9.4)
COVID-19 diagnosis in social circle	
No	5 (2.5)
Yes	197 (95.5)
Death by COVID-19 in social circle	
No	50 (24.8)
Yes	152 (75.2)
Colleague diagnosed with COVID-19	
No	3 (1.5)
Yes	199 (98.5)
Loss of a colleague due to COVID-19	
No	144 (71.3)
Yes	58 (28.7)
Vaccination against COVID-19	
No	23 (11.4)
Yes	179 (88.6)
Number of COVID-19 vaccine doses [Mean ±SD (Min-Max)]	2.8±1.4 (0-6)
Side effects after COVID-19 vaccine	
No	150 (74.3)
Yes	52 (25.7)

The COVID-19 infection ratio among the participants during the pandemic was 68.8% (n=139), whereas the same ratio was found to be 85.1% (n=172), 95.5% (n=197), and 98.5% (n=199) for their family members (spouse, parents, children, etc.), social circle (relatives, friends, etc.), and colleagues, respectively. The ratios of COVID-19-related death were found to be 9.4%, 75.2%, and 28.7% for family members, social circle, and colleagues, respectively. The ratio of participants, who moved from the place they have been actively living before the pandemic during the pandemic period, was 26.2% (n=53). The ratio of participants that have been vaccinated for COVID-19 was 88.6% (n=179) (**Table 1**).

In questions addressing the level of knowledge about mpox, 44.1% (n=89) stated that they had never heard about this disease before. Of the participants, 46% (n=93) had accurate information about the cause of the disease, 54% (n=109) had accurate information about the infection pathway, and 35.6% (n=72) had accurate information about the places, where the disease is endemic to. While 24.3% (n=49) were informed about the smallpox vaccine, the response of 48.0% (n=97) of the participants to the question if the smallpox vaccine is protective against mpox was "yes" (**Table 2**).

Table 2. Participant's knowledge and attitudes about mpox

Characteristics	n (%)
Having knowledge about mpox before the announcement of WHO*	
No	89 (44.1)
Yes	113 (55.9)
Having knowledge about the cause of mpox	
No information	104 (51.5)
Wrong information	5 (2.5)
Accurate information	93 (46.0)
Having knowledge about the mode of transmission of mpox	
No information	53 (26.2)
Wrong information	40 (19.8)
Accurate information	109 (54.0)
Having knowledge about risky contact time for mpox	
No knowledge	174 (86.1)
Accurate knowledge	28 (13.9)
Having knowledge about regions, where mpox is endemic	
No knowledge	66 (32.7)
Wrong information	64 (31.7)
Accurate information	72 (35.6)
Having knowledge about protection measurements against mpox	
No information	100 (49.5)
Accurate information	102 (50.5)
Having knowledge about diagnosis methods for mpox	
No information	9 (4.5)
Wrong information	93 (46.0)
Accurate information	100 (49.5)
Having knowledge about treatment methods for mpox	
No	128 (63.4)
Yes	74 (36.6)
Having knowledge about the Mpox vaccine	
Wrong information	153 (75.7)
Accurate information	49 (24.3)
Having knowledge about the protectiveness of the smallpox vaccine	
No	105 (52.0)
Yes	97 (48.0)

*WHO: World Health Organization

DAS-21, a standard measurement tool, was used to determine the psychological state of healthcare workers trying to meet the increasing healthcare needs with the COVID-19 pandemic, in case of a possible new pandemic [16]. The mean total score of the scale was found to be 12.68±11.16 (min-max=0-46), whereas the mean scores in depression, anxiety, and stress subdimensions were 4.55±4.15 (min-max=0-19), 3.34±3.48 (min-max=0-14), and 4.79±4.07 (min-max=0-16), respectively. Besides that, the portions of participants in the regions, which were classified between mild to extremely severe by the developer, for depression, anxiety, and stress were 46.6%, 40.1%, and 22.7% (**Table 3**). It was determined that the participants generally had moderate level of depression and anxiety and mild level of stress, whereas the portions of participants having extremely severe depression and anxiety were 5.0% and 7.4%, respectively.

The distribution of participants' mean scores by their sociodemographic characteristics, their experiences with COVID-19 pandemic, and knowledge about mpox are presented in **Table 4**. The participants, who had a chronic psychological disorder, in the total scale and in all subdimensions were found to be statistically significantly higher mean scores ($p<0.05$). The COVID-19 vaccine caused a significant change in the mean scores ($p<0.05$). Those not having knowledge about the diagnosis and treatment of mpox were found to have significantly higher mean scores in the total scale and in all subdimensions ($p<0.05$).

Table 3. Correlation analysis and categorical distribution of the participant's scores in the DASS-21 scale and its subdimensions

Variables	$\bar{x}$ ±SD (Min-Max)	1	2	3
1 Depression	4.55±4.15 (0-19)	1	0.834 (<0.001)	0.886 (<0.001)
2 Anxiety	3.34±3.48 (0-14)		1	0.871 (<0.001)
3 Stress	4.79±4.07 (0-16)			1
Total score	12.68±11.16 (0-46)	0.955 (<0.001)	0.940 (<0.001)	0.966 (<0.001)

Pearson's correlation analysis, r(p)

Category	Depression, n (%)	Anxiety, n (%)	Stress, n (%)
Normal	108 (53.4)	121 (59.9)	156 (77.3)
Mild	35 (17.3)	25 (12.4)	18 (8.9)
Moderate	39 (19.3)	26 (12.9)	14 (6.9)
Severe	10 (5.0)	15 (7.4)	14 (6.9)
Extremely severe	10 (5.0)	15 (7.4)	-

Table 4. Distribution of various characteristics of participants by the mean scores in DASS-21 total scale and subdimensions

Characteristics	DASS-21 Mean±SD	DASS-21D Mean±SD	DASS-21A Mean±SD	DASS-21S Mean±SD
Gender				
Male	10.43±10.54	4.03±4.02	2.48±3.29	3.91±3.80
Female	14.52±11.37	4.98±4.21	4.04±3.49	5.50±4.15
t	-2.630	-1.624	-3.223	-2.813
p	0.009	0.106	0.001	0.005
Age groups				
20-29 years	15.42±11.50	5.53±4.30	4.18±3.53	5.70±4.32
30-39 years	11.69±11.17	4.23±4.09	2.98±3.56	4.49±4.08
40 years and older	11.28±10.46	4.02±3.96	2.98±3.21	4.28±3.67
F	2.632	2.453	2.558	2.219
P	0.074	0.089	0.080	0.111
Marital status				
Non-married	15.95±12.36	6.18±4.67	4.09±3.79	5.68±4.54
Married	11.09±10.21	3.76±3.63	2.97±3.27	4.35±3.76
t	2.960	4.027	2.162	2.196
p	0.003	<0.001	0.032	0.029
Having child				
No	15.90±11.44	5.94±4.15	4.17±3.54	5.79±4.42
Yes	10.65±10.53	3.69±3.92	2.81±3.36	4.15±3.71
t	3.330	3.881	2.727	2.839
p	0.001	<0.001	0.007	0.005
Active workplace during the pandemic				
Pandemic-related units	13.42±11.43	4.84±4.11	3.52±3.64	5.06±4.17
Units that are not related to the pandemic	10.09±9.88	3.56±4.15	2.69±2.81	3.84±3.57
t	1.774	1.842	1.418	1.771
p	0.078	0.067	0.158	0.078
Chronic physical disorder				
No	12.01±10.89	4.36±4.03	3.12±4.43	4.53±3.92
Yes	16.82±12.14	5.75±4.69	4.68±3.52	6.39±4.63
t	-2.134	-1.649	-2.217	-2.272
p	0.034	0.101	0.028	0.024
Chronic mental disorder				
No	12.18±10.66	4.38±4.01	3.17±3.29	4.63±3.91
Yes	32.40±13.95	11.40±3.84	10.00±4.63	11.00±5.78
t	-4.157	-3.862	-4.535	-3.554
p	<0.001	<0.001	<0.001	<0.001
Infection diagnosis				
No	10.17±10.10	3.81±11.47	2.70±3.27	3.67±3.64
Yes	13.81±11.47	4.89±4.31	3.63±3.54	5.29±4.16
t	-2.165	-1.726	-1.761	-2.673
p	0.032	0.086	0.080	0.008

Table 4. Distribution of various characteristics of participants by the mean scores in DASS-21 total scale and subdimensions

Characteristics	DASS-21 Mean±SD	DASS-21D Mean±SD	DASS-21A Mean±SD	DASS-21S Mean±SD
Infection diagnosis in the family				
No	11.07±11.45	4.33±4.07	2.93±3.68	3.80±4.11
Yes	12.96±11.12	4.59±4.17	3.41±3.45	4.96±4.05
t	-0.856	-0.316	-0.686	-1.443
p	0.393	0.753	0.493	0.151
Loss of a family member due to the infection				
No	12.63±11.43	4.55±4.27	3.30±3.50	4.79±4.17
Yes	13.11±8.42	4.58±2.73	3.74±3.33	4.79±2.91
t	-0.175	-0.038	-0.525	-0.004
p	0.861	0.970	0.600	0.997
Infection diagnosis in the social circle				
No	8.60±12.64	2.80±4.08	2.80±4.38	3.00±4.24
Yes	12.78±11.14	4.60±4.15	3.35±3.47	4.83±4.06
t	-0.826	-0.957	-0.348	-0.994
p	0.410	0.340	0.728	0.321
Death caused by infection in the social circle				
No	12.38±11.77	4.42±4.34	3.28±3.78	4.68±4.20
Yes	12.78±11.00	4.60±4.09	3.36±3.39	4.83±4.04
t	-0.217	-0.263	-0.132	-0.214
p	0.828	0.792	0.895	0.831
Infection diagnosis among colleagues				
No	18.33±18.03	6.00±6.24	5.67±6.65	6.67±5.85
Yes	12.59±11.08	4.53±4.13	3.30±3.43	4.76±4.05
t	0.883	0.607	1.168	0.805
p	0.378	0.545	0.244	0.422
Loss of a colleague due to infection				
No	11.47±10.16	4.14±3.83	3.02±3.14	4.31±3.64
Yes	13.17±11.54	4.72±4.27	3.47±3.61	4.98±4.22
t	-0.979	-0.905	-0.826	-1.057
p	0.329	0.367	0.410	0.292
Vaccinated for Covid-19				
No	7.04±7.74	2.00±2.33	2.00±2.46	3.04±3.25
Yes	13.40±11.34	4.88±4.22	3.51±3.56	5.01±4.11
t	-3.485	-4.968	-2.603	-2.641
p	0.001	<0.001	0.013	0.013
Having knowledge about mpox before WHO's announcement				
No	11.74±10.94	4.27±4.14	2.98±3.44	4.49±3.86
Yes	13.42±11.33	4.78±4.15	3.62±3.50	5.02±4.23
t	-1.058	-0.865	-1.302	-0.907
p	0.291	0.388	0.194	0.366
Having knowledge about the cause of mpox				
No information	13.18±11.31	4.74±4.19	3.46±3.62	4.98±3.98
Wrong information	12.40±9.81	4.20±3.56	4.20±3.56	4.00±2.91
Accurate information	12.13±11.15	4.37±4.15	3.15±3.34	4.61±4.23
F	0.218	0.217	0.351	0.294
P	0.804	0.805	0.705	0.745
Having knowledge about mpox's mode of transmission				
No information	13.83±11.40	5.04±4.19	3.62±3.78	5.17±4.05
Wrong information	12.48±11.44	4.43±4.20	3.25±3.49	4.80±4.21
Accurate information	12.19±11.01	4.37±4.12	3.23±3.35	4.60±4.05
F	0.389	0.488	0.241	0.352
P	0.678	0.615	0.786	0.704
Having knowledge about the regions mpox is endemic to				
No information	14.55±12.90	4.95±4.74	3.95±3.95	5.64±4.72
Wrong information	11.86±9.87	4.55±3.82	2.88±3.09	4.44±3.60
Accurate information	11.69±10.45	4.19±3.85	3.18±3.31	4.32±3.73
F	1.379	0.575	1.683	2.172
p	0.254	0.563	0.189	0.117
Having knowledge about protective measurements against mpox				
No information	13.52±11.56	4.88±4.33	3.56±3.52	5.08±4.23
Accurate information	11.85±10.75	4.24±3.95	3.12±3.45	4.50±3.90
t	1.061	1.104	0.902	1.012
p	0.290	0.271	0.368	0.313
Having knowledge about diagnosis methods for mpox				
No information (1)	22.44±14.80	7.67±5.09	6.33±5.12	8.44±5.50
Wrong information (2)	14.00±11.48	5.03±4.32	3.77±3.52	5.19±4.15
Accurate information (3)	10.57±9.90	3.83±3.72	2.66±3.09	4.08±3.64
F	6.177	4.850	6.256	5.875
P	0.002	0.009	0.002	0.003
Post hoc test (Tukey HSD)	(1-3)	(1-3)	(1-3)	(1-2), (1-3)
Having knowledge about the protectiveness of the smallpox vaccine				
No	14.46±12.03	5.16±4.61	3.93±3.72	5.36±4.20
Yes	10.75	3.90±3.49	2.69±3.09	4.16±3.84
t	2.401	2.208	2.586	2.105
p	0.017	0.028	0.010	0.037

t: Independent sample t-test, F: One-Way ANOVA

Some potential and psychiatric variables for the participants after the introduction of mpox into WHO's agenda and the news about the increases in case numbers and the changes in total scale and subdimensions are presented in **Table 5**. The anxiety of transmitting the infection to the family-social circle caused a significant increase in the mean total score and in the mean scores of all subdimensions ($p<0.05$). Considering the period after learning about the increase in the number of cases, statistically significant increases were found in the mean scores in the anxiety subdimension for participants reporting a loss of appetite, in total scale, depression, and anxiety subscales for those reporting sleep problems, and in total scale and all subdimensions for those reporting stomach problems ($p<0.05$).

Table 5. Distribution of participant's opinions about mpox by DASS-21 total scale and subdimensions

Characteristics	DASS-21 Mean±SD	DASS-21D Mean±SD	DASS-21A Mean±SD	DASS-21S Mean±SD
Anxiety of being infected				
Never/Very rarely	10.23±10.65	3.72±3.96	2.49±3.24	4.02±3.95
Sometimes	12.46±11.54	4.49±4.16	3.35±3.43	4.62±4.38
Mostly	14.87±10.88	5.30±4.20	4.00±3.62	5.58±3.72
F	2.327	3.024	2.452	2.807
P	0.100	0.051	0.089	0.063
Anxiety of not being able to be treated				
Never/Very rarely	10.55±9.89	3.84±3.75	2.56±2.95	4.15±4.76
Sometimes	13.18±11.15	4.65±4.02	3.65±3.59	4.88±4.11
Mostly	14.77±12.39	5.35±4.67	3.93±3.83	5.49±4.33
F	2.437	2.985	1.775	2.190
p	0.090	0.053	0.172	0.115
Anxiety of having contact with a foreign national				
Never/Very rarely (1)	7.78±9.31	2.81±3.45	1.88±2.77	3.09±3.55
Sometimes (2)	14.91±11.06	5.37±4.23	4.02±3.48	5.52±3.98
Mostly (3)	14.53±11.42	5.20±4.21	3.88±3.63	5.45±4.13
F	8.438	7.690	7.610	7.570
P	<0.001	<0.001	<0.001	<0.001
Post hoc test (Tukey HSD)	(1-2), (1-3)	(1-2), (1-3)	(1-2), (1-3)	(1-2), (1-3)
Thinking that personal hygiene principles would not be enough				
Never/Very rarely	15.05±11.06	5.31±4.09	4.07±3.43	5.67±4.06
Sometimes	12.58±11.17	4.69±3.99	3.23±3.68	4.67±4.20
Mostly	11.83±11.17	4.21±4.23	3.11±3.41	4.51±4.00
F	1.273	1.097	1.202	1.266
P	0.282	0.336	0.303	0.284
Anxiety of transmitting the infection to family/social circle				
Never/Very rarely (1)	8.47±9.32	3.25±3.79	2.08±2.70	3.15±3.39
Sometimes (2)	13.62±11.58	4.76±4.07	3.76±3.68	5.10±4.27
Mostly (3)	14.58±11.33	5.21±4.27	3.80±3.61	5.57±4.05
F	5.464	3.895	4.890	6.372
p	0.005	0.022	0.008	0.002
Post hoc test (Tukey HSD)	(1-2), (1-3)	(1-3)	(1-2), (1-3)	(1-2), (1-3)
Loss of appetite after learning about the increase in the number of cases				
Never/Very rarely (1)	12.02±10.95	4.37±4.10	3.05±3.31	4.60±4.07
Sometimes (2)	17.59±11.27	6.00±4.25	5.27±3.80	6.32±3.67
Mostly (3)	13.67±14.29	4.50±4.72	4.50±5.08	4.67±5.00
F	2.488	1.508	4.459	1.760
p	0.086	0.224	0.013	0.175
Post hoc test (Tukey HSD)			(1-2)	
Sleep problems after learning about the increase in the number of cases				
Never/Very rarely (1)	11.89±10.84	4.31±4.06	3.03±3.30	4.56±4.02
Sometimes (2)	18.69±10.26	6.44±3.65	5.44±3.28	6.81±3.71
Mostly (3)	20.33±16.69	7.00±6.29	7.00±5.65	6.33±5.20
F	4.313	3.075	7.368	2.751
p	0.015	0.048	<0.001	0.066
Post hoc test (Tukey HSD)	(1-2)	(1-2)	(1-2), (1-3)	
Stomach problems after learning about the increase in the number of cases				
Never/Very rarely (1)	11.24±10.38	4.12±3.93	2.76±3.05	4.35±3.95
Sometimes (2)	21.36±11.80	7.32±4.50	6.55±3.87	7.50±3.78
Mostly (3)	18.10±13.37	5.90±4.67	6.00±4.69	6.20±4.39
F	10.087	6.706	16.824	6.827
p	<0.001	0.002	<0.001	0.001
Post hoc test (Tukey HSD)	(1-2)	(1-2)	(1-2), (1-3)	(1-2)

t: Independent sample t-test, F: One-Way ANOVA

DISCUSSION

It is known that healthcare professionals had remarkable stress during previous pandemics. It was reported that healthcare professionals were emotionally affected during the recent SARS pandemic.[17,18] Various studies showed that healthcare professionals were at risk of psychiatric disorders due to various reasons during the COVID-19 pandemic.[19-22] In a previous meta-analysis carried out by Mahmud et al.[23] the prevalence of depression, anxiety, stress, and sleeplessness among healthcare professionals was reported to be 37.1%, 41.4%, 44.9%, and 43.8%. In a meta-analysis by Li et al.[24] on 65 studies carried out on 97,333 healthcare professionals from 21 countries, the pooled prevalence of depression was found to be 21.7% and that of anxiety to be 22.1%. Of 202 healthcare professionals involved in the present study, it was determined that 77.7% have worked in departments offering services related to COVID-19, 68.8% were infected by COVID-19 during the pandemic, and infection and COVID-19-related death ratios of family members, social circle, and colleagues were reported to be (85.1%-9.4%), (95.5%-75.2%), and (98.5%-28.7%), respectively. In this study, the DASS-21 scale was used in determining the psychological conditions of healthcare professionals considering the possibility of a new pandemic. Accordingly, the ratios of participants found to have depression, anxiety, and stress were 46.6%, 40.1%, and 22.7%. The ratios of extremely severe depression and anxiety were calculated to be 5% and 7.4%. Among the participants, women had higher anxiety and stress levels in comparison to men (p=0.001-p=0.005). The participants, who worked in departments offering services related to COVID-19 during the pandemic, were found to have higher depression, anxiety, and stress levels but the difference was not statistically significant. In comparison to participants, who have not been diagnosed with COVID-19, the participants diagnosed with COVID-19 were found to have statistically significantly higher mean scores in the total scale (p=0.032) and in the stress subdimension (p=0.008). When compared to those not vaccinated for COVID-19, the participants vaccinated for COVID-19 had lower mean scores in the total scale (p<0.001). The participants having a chronic psychological disorder were found to have higher mean scores in the total scale and in all subdimensions (p<0.05). The participants having chronic physical disorders were determined to have higher mean scores in anxiety and stress subdimensions (p=0.034, p=0.028, p=0.024). In a study carried out on the psychosocial effects of COVID-19 on healthcare professionals in Italy, various factors such as female gender, working as a nurse, working in a hospital, and having contact with COVID-19 patients were found to be predictor determinants.[25] In a study carried out in China, it was observed that healthcare professionals working at the front line during the pandemic had more anxiety, sleeplessness, and general psychological disorders.[26] In the present study, the factors such as female gender, COVID-19 history, COVID-19 vaccination, and chronic psychologic and physical disorders were found to be the factors related with depression, anxiety, and stress.

In order to prevent disease transmission, healthcare professionals, especially physicians, should rapidly identify new cases, report them, and have knowledge about the clinical symptoms of mpox.[7] In some of previous studies, it was reported that healthcare professionals did not have sufficient information about mpox. In a survey study carried out on physicians, pharmacists, nurses, medical technicians, and dentists in Jordan, only 4 of 11 questions about mpox were answered accurately at a higher level than 70% and the knowledge level of physicians about mpox was found to be higher than other groups. In the same study, 33.3% of the participants stated that the smallpox vaccine might be protective against mpox and 58.7% stated that homosexuality was an important factor in the spread of the disease.[27] In another study carried out in Italy, 27% of the participants stated that they knew mpox before, whereas 58.6% thought that the smallpox vaccine was effective against mpox.[28] In a study carried out in Indonesia, it was reported that practicing physicians had a very low level of knowledge about mpox and only 10% of them had a sufficient level of knowledge.[7] In the present study, 44.1% of participants stated that they had never heard about mpox before the announcements of WHO, while 46% of participants had accurate information about the cause of the disease, 54% had accurate information about the infection pathway, and 35.6% had accurate information about the regions, where the disease is endemic. Moreover, 24.3% of the participants were aware of the smallpox vaccine, while the ratio of those thinking that the smallpox vaccine was protective against mpox was 48%. The data indicating the clinical efficiency of the smallpox vaccine against mpox (85%) were reported in surveillance studies on pandemics in Central Africa in the 1980s and in following years and these data were supported by animal studies.[29] The data obtained here showed that the healthcare professionals' knowledge of mpox before the pandemic was at very low level and this finding is consistent with the literature.

The declaration of a possible mpox outbreak by WHO during the COVID-19 pandemic created an uncertain anxiety state disorder. In a society-based study carried out in Saudi Arabia, it was shown that the participants infected by COVID-19 before had more anxiety about mpox.[30] In the present study, examining the somatic and psychiatric changes in participants in relation to declarations made by WHO and international media organs about the increase in mpox cases, it was found that anxiety of transmitting the disease to family members or social circle and anxiety of contacting with foreign nationals caused a significant increase in mean depression, anxiety, and stress scores, whereas there were significant increases in mean anxiety score among the participants reporting a loss of appetite, in mean depression and anxiety scores among those reporting sleeplessness, and mean depression, anxiety, and stress scores of those reporting stomach problems. Accordingly, it can be stated that an idea of a potential pandemic might have negative psychological and physiological effects on healthcare

professionals. Moreover, it was determined in the present study, regarding the subdimensions about information on mpox (having prior information about the disease, factors, mode of transmission, incubation period, endemic regions, etc.), there was no difference between the participants having information and those having no information. It might indicate that psychological and physiological effects occurred independently. In order to eliminate the negative effects of the idea of a potential pandemic after the COVID-19 pandemic, it might be useful to provide healthcare professionals with psychosocial support at specific intervals, make effort to eliminate the factors that might cause anxiety, stress, and depression, and use suitable motivation instruments. In in the past, it is important to keep the motivation of healthcare professionals, who will be at the front line in potential pandemics in the future, at maximum level.

The present study has also limitations. The main limitations are that the present study was carried out in a single hospital and that participants had limited capacity to present the universe. Moreover, since the predictable numbers couldn't be reached, no assessment could be made about profession-specific knowledge, experience, awareness, and psychology. Besides that, although it is a standard measurement instrument, there might be qualitative errors due to self-reported data since depression, anxiety, and stress conditions of healthcare professionals cannot be confirmed using a clinical assessment. Determining the potential changes in the medical labor force in order to meet the acute medical needs of a society in cases such as a pandemic. For this reason, it is thought that the results achieved here would be useful for policymakers.

CONCLUSION

The COVID-19 pandemic created many negative results among healthcare professionals, from both physiological and psychological aspects. Various factors such as increasing workload during the pandemic, high potential of catching the disease, and anxiety of transmitting the infection to family members and social circle might cause negative effects on healthcare professionals. The increase in mpox cases between May and August of 2022 raise the question if healthcare professionals are physically and mentally ready for a new pandemic. It was determined that, after the increase in the number of mpox cases, almost half of the participants had no complete information about the disease at any dimension (diagnosis, transmission, treatment, protection, etc.). In the present study carried out aiming to determine the psychological condition in case of a new pandemic, it was determined that depression, anxiety, and stress levels of the participants were high. Many somatic and psychiatric changes were observed among healthcare professionals, such as anxiety of transmitting the infection to family members or social circle, contacting with foreign nationals, loss of appetite, sleep problems, and dyspeptic complaints. It is thought that providing healthcare professionals, who are at the front line in pandemics, with psychosocial support, make effort to determine and eliminate other factors causing negative psychological effects, and use suitable motivational instruments..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Harran University Clinical Researches Ethics Committee (Date: 08.08.2022, Decision No: HRÜ/22.15.20).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1345525
J Contemp Med 2023;13(5):975-981

Original Article / Orijinal Araştırma

Outcomes of Low and Middle Income Children with Relapsed Acute Lymphoblastic Leukemia: Single-Center Experience

Nüks Eden Akut Lenfoblastik Lösemili Düşük ve Orta Gelirli Çocukların Sonuçları: Tek Merkez Deneyimi

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Abstract

Aim: Despite numerous advances in treating acute lymphoblastic leukemia (ALL) in children, relapse continues to be the leading cause of mortality. This study aimed to analyze patient characteristics and outcomes of children with relapsed ALL.

Material and Method: We retrospectively analyzed the records of patients aged 1–18 years old diagnosed with relapsed ALL between January 2004 and December 2018.

Results: 452 ALL patients were followed up in the study period and 55 patients relapsed. The relapse rate was 12.1%. Thirty-four (61.8%) of the relapsed patients were male. The median age was 7 years (1–17 years). Forty-six patients (83.6%) had precursor B-cell ALL and nine patients (16.3%) had T-cell ALL. The site of relapse was the bone marrow in 41 patients (74.5%), and extramedullary (central nervous system, testis, or soft tissue) in 11 patients (20%). The mean duration from the initial diagnosis to relapse was 32 months (min-max: 4 -108 months, SD±21.2) and 20 months (min-max: 7-38 months, SD± 11.1) in patients with B- cell ALL and T- cell ALL, respectively. The median follow-up time was 39.8 months (min-max: 3–198 months, SD±44.5) from the initial diagnosis. Thirty-seven patients (67.3%) died. The 5-year overall survival rate was 41.6%. Recurrent relapse and progressive disease were the most common causes of death. The mortality rate was significantly associated with immunophenotype, treatment response on days 8, 15, and 33 of initial diagnosis, the risk group at initial diagnosis, the site of relapse, and hematopoietic stem cell transplantation ($p<0.05$). Immunophenotype and the site of relapse were the independent variables associated with mortality.

Conclusion: Relapse affects a significant portion of patients with ALL. Survival rates are still poor in patients with relapsed ALL. Also, our findings that T-cell immunophenotype and the site of relapse (isolated bone marrow relapse) were independent risk factors for mortality suggest that more specialized treatment options are needed for patients with T-ALL and bone marrow relapse.

Keywords: Relapse, acute lymphoblastic leukemia, children

Öz

Amaç: Çocuklarda akut lenfoblastik löseminin (ALL) tedavisindeki sayısız ilerlemeye rağmen, nüks mortalitenin önde gelen nedeni olmaya devam etmektedir. Bu çalışma ile, nüks eden ALL' li çocuk hastaların özelliklerinin analiz edilmesi amaçlanmıştır.

Gereç ve Yöntem: Ocak 2004 ile Aralık 2018 tarihleri arasında nüks ALL tanısı alan 1-18 yaş arası hastaların kayıtlarını retrospektif olarak inceledik.

Bulgular: Çalışma döneminde 452 ALL hastası izlendi ve 55 hasta nüks ettiği görüldü. Nüks oranı %12.1 idi. Bu hastaların 34'ü (%61,8) erkekti. Medyan yaş 7 yıl (min-maks:1-17 yaş) idi. Kırk altı hastada (%83,6) öncül B-hücreli ALL ve dokuz hastada (%16,3) T-hücreli ALL vardı. Kırk bir hastada (%74,5) nüks yeri kemik iliği, 11 hastada (%20) ekstramedüller (merkezi sinir sistemi, testis veya yumuşak doku) idi. İlk tanıdan nükse kadar geçen ortalama süre B hücreli ALL'li hastalarda 32 ay (min-maks: 4 -108 ay, SD±21,2) ve T-hücre ALL' de 20 ay (min-maks: 7-38 ay, SD± 11,1) idi. Tanıdan itibaren ortanca takip süresi 39,8 aydı (min-maks: 3–198 ay, SD±44,5). Otuz yedi hasta (%67,3) öldü. 5 yıllık genel sağkalım oranı %41.6 idi. Tekrarlayan nüks ve ilerleyici hastalık en yaygın ölüm nedenleriydi. Mortalite oranı, immünofenotip, ilk tanının 8., 15. ve 33. günlerinde tedaviye yanıt, ilk tanı anındaki risk grubu, nüks bölgesi ve hematopoietik kök hücre nakli ile anlamlı şekilde ilişkiliydi ($p<0.05$). İmmünofenotip ve nüks bölgesi, mortalite ile ilişkili bağımsız değişkenlerdi.

Sonuç: Nüks, ALL hastalarının önemli bir bölümünü etkiler. Tekrarlayan ALL'li hastalarda hayatta kalma oranları hala düşüktür. Ayrıca, T-hücre immünofenotipi ve nüks bölgesi (izole kemik iliği nüksü) mortalite için bağımsız risk faktörleri olduğuna dair bulgularımız, T-ALL ve kemik iliği nüksü olan hastalar için daha özel tedavi seçeneklerine ihtiyaç olduğunu düşündürmektedir.

Anahtar Kelimeler: Nüks, akut lenfoblastik lösemi, çocuk

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Received *(Geliş Tarihi)*: 18.08.2023 **Accepted *(Kabul Tarihi)*:** 16.09.2023

INTRODUCTION

Recent advances in chemotherapy and hematopoietic stem cell transplantation (HSCT) protocols and supportive care have improved the survival rate of children with acute lymphoblastic leukemia to over 80–90% (ALL).[1,2] Despite this progress, relapse remains the main limiting issue for treatment success.[3] Relapse can occur due to the proliferation of drug-resistant clonal cells that could not be eliminated and/or another group of clonal cells with new genetic modifications.[4] Although the recurrence rate has been reduced to 15–25% with risk-based regimens, survival rates of relapsed ALL are still low.[1-7]

This study aimed to analyze the data on patient characteristics and outcomes in children with relapsed ALL.

MATERIAL AND METHOD

Ethical Consideration

The study was carried out with the permission of Ankara Pediatrics Hematology Oncology Training and Research Hospita Ethics Committee (Date: 30.07.2019, Decision No: 2019228). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The data of patients aged 1–18 years who were followed up with the diagnosis of relapsed ALL at the pediatric hematology department of the University of Health Sciences Ankara Pediatric Hematology-Oncology Training and Research Hospital between January 2004 and December 2018 were analyzed retrospectively. Our hospital mostly serves children of lower or middle income families from all over Turkey. Patients with mature B-cell ALL, secondary ALL, and infant leukemia were excluded from the study. The demographic and clinical characteristics, treatment regimens, risk category at diagnosis, and treatment outcomes of the relapsed ALL patients were recorded.

Patients were divided into the standard risk group (SRG), intermediate risk group (IRG), and high risk group (HRG) according to their clinical, laboratory and genetic characteristics at the time of diagnosis in the BFM protocol.

Relapse was defined as the presence of a confirmed greater than 5% leukemic cell infiltration in the bone marrow or any other site in a patient who had previously achieved complete remission.[8] Isolated bone marrow relapse was defined as the presence of >25% lymphoblasts in the bone marrow with no leukemic involvement at any extramedullary site. Isolated extramedullary relapse was defined as extramedullary leukemic involvement with <5% blasts in the bone marrow.[8]

Patients were grouped into very early, early, and late relapse according to the first complete remission duration. Relapses occurring less than 18 months after initial diagnosis were defined as very early relapse; those occurring more than 18 months after initial diagnosis but less than six months after the completion of initial treatment were described as early relapse. Relapses appearing six months or later after the completion of initial treatment were defined as late relapses.[8]

Cytogenetic analysis, fluorescent in situ hybridization (FISH), and polymerase chain reaction (PCR) results of the patients were recorded. Genetic alterations at initial diagnosis were categorized as unfavorable (hypodiploidy (chromosomes ≤44), t (4;11) [MLL/AF4], t(9;22) BCR/ABL) and favorable (hyperdiploidy: chromosome number >50), t(12;21)).

REZ BFM 2002 (2003–2018) and ALL-IC REL 2016 (2018–present) protocols were given as first-line relapse therapy. The FLAG-IDA (fludarabine, cytarabine, idarubicine, G-CSF) treatment protocol was used as second-line therapy. Third-line salvage therapies were given to patients who did not go into remission or developed recurrent relapses. Patients with hematopoietic stem cell transplantation (HSCT) indication were transplanted.

Statistical Analysis

Continuous variables were tested for normality of distribution using the Kolmogorov–Smirnov test. Descriptive statistics are presented as mean ± standard deviation or frequency and percentage. Univariate comparisons of normally distributed variables were performed using an independent t-test and one-way ANOVA. Duncan's multiple comparison tests were then used to determine which groups differed. Categorical variables were analyzed with the chi-square test. In multivariate analysis, potential factors determined in previous studies were used to evaluate independent variables predicting survival using Cox regression analysis with the backward selection method. Model fit and proportional hazard assumptions were tested using residual (Schoenfeld and Martingale) analyses. Survival rates were calculated using Kaplan–Meier survival analysis. A univariate log-rank test was used to examine the effects of variables on survival. Bonferroni correction was used in comparisons of survival time between more than two groups. P values less than 0.05 were considered statistically significant in all analyses. IBM SPSS Statistics version 21.0 for Windows (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

RESULTS

Patient Characteristics

In the study period, 452 patients were diagnosed with ALL, and 55 of the patients (12.1%) relapsed. During the study period, patients were treated with the modified St Jude Total XIII (2004-2008; total number of patients: 82 and 17 patients relapsed), TR-ALL BFM 2000 (the modified BFM 95 protocol) (2009–2012; total number of patients: 136, relapsed patients: 9), and the ALL-IC BFM 2009 protocol (2013–2018; total number of patients: 234, relapsed patients: 27). There were 6 patients who relapsed after hematopoietic stem cell transplantation (HSCT).

Relapse rates of the modified St Jude Total XIII protocol (before 2008) and BFM protocols (after 2008) were 20.7% and 11.6%, respectively. The median age of the patients at relapse was 7 years (range; 1–17 years) and 34 patients (61.8%) were boys. Forty-six patients (83.6%) had B-cell ALL (B-ALL) and nine patients (16.3%) had T-cell ALL (T-ALL). The demographic and clinical characteristics of the patients are shown in **Table 1**. Twenty-nine B cell ALL patients (63%) had isolated bone marrow (BM) relapse, two (4.3%) had isolated central nervous system (CNS) relapse, three patients (6.5%) had isolated testis relapse, and one patient had localized soft tissue relapse (2%). The relapse site was isolated BM in 5 patients (55.5%), combined BM and CNS in 2 patients (22.2%), and isolated CNS in 2 patients (22.2%) with T cell ALL. No statistically significant difference was found between relapse sites according to the blastic cell type (p: 0.731).

Table 1. Patient Characteristics

	Patient (n)	%
Leukemia type		
B-ALL	46	83.6
T-ALL	9	16.4
Gender		
Male	34	61.8
Female	21	38.2
Age at diagnosis (years)		
Mean ± SD	7.8 ± 4.2	
Median (range)	7 (1-17)	
>1 to<6	19	34.5
≥6 to<18	36	65.5
Initial WBC count		
< 50x10^9/L	28	50.9
≥ 50x10^9/L	27	49.1
Initial risk group (patients receiving only the BFM protocol n:38)		
IRG	26	68.5
HRG	12	31.5
Time of Relapse		
Very early relapse	20	36.3
Early relapse	20	36.3
Late relapse	15	27.2
Relapse Site		
Isolated BM	34	61.8
Extramedullary	10	18.1
Combined	11	20.1
Genetic Abnormalities		
Favorable*	16	29
Unfavorable**	10	18.1
Karyotype Analysis		
Metaphase could not be obtained	11	20
Normal	35	63.6
Abnormal	9	16.4

*ETV6-RUNX1 or hyperdiploidy (>50chromosomes), **Hypodiploidy (<44chromosomes), MLL rearrangements, BCR-ABL1, B –ALL (precursor B cell acute lymphoblastic leukemia), T ALL (T cell acute lymphoblastic leukemia), IRG (intermediate risk group), HRG (high-risk group), BM (Bone marrow), WBC (white blood cell)

The duration between diagnosis and relapse was 28.7 months, (min-max: 2–184, SD: 21.7). 30.7±3.28 months (min-max: 4–184) in B-ALL and 18.6 ± 4.48 months (min-max: 2–38) in T-ALL patients. Relapse time in T-ALL was shorter than in B-ALL, but the difference was not statistically significant (p:0.122).

Twenty patients (36.4%) had a very early relapse, 20 patients (36.4%) had early relapse, and 15 patients (27.3) had late relapse. 15 patients (32.6%) had very early relapse, 16 patients (34.8%) had early relapse, and 15 patients (32.6) had late relapse in the B-ALL group. 5 patients (56%) had very early relapse and 4 patients (44%) had early relapse in the T-ALL group.

Karyotype analysis was normal in 35 patients (63.6%) and could not be determined in 11 patients (20%) (metaphase could not be obtained) at the initial diagnosis. By using polymerase chain reaction and/or fluorescent in situ hybridization methods, favorable genetic changes were detected in 16 patients (29%) and unfavorable genetic changes were detected in 10 patients (18.1%).

The duration of time to relapse was not associated with age, sex, or relapse site (p>0.05). When patients who received only the BFM protocol were evaluated, the mean time to recurrence was shorter in HRG patients at the time of diagnosis (p:0,023). Factors associated with time to relapse are shown in **Table 2**.

Tablo 2. Variables significantly associated with time to relapse

Variables	Time to Relapse	P Value
Diagnosis		
B –ALL	30.75±3.28	0.04
T –ALL	18.60±4.49	
Gender		
Male	26.70±2.59	0.371
Female	32.09±6.35	
Age		
1-6	32.47±5.59	0.357
≥6	26.80±3.31	
Initial Risk Group (Patients receiving only the BFM protocol n:38)		
IRG	28.32±3.44	0.023
HRG	18.01±4.10	
Genetic analysis		
Favorable*	30.15±6.81	0.972
Unfavorable**	29.21±3.58	
Cytogenetic analysis		
Metaphase could not be obtained	19.93±7.73	0.290
Normal	29.58±3.71	
Abnormal	34.74±4.69	
Relapse Site		
Isolated BM	26.51±3.40	
Combined	31.27±10.19	0.606
Isolated extramedullary	33.43±4.37	
WBC counts		
<50x 10^9/L	33.56±5.26	0.388
≥50x 10^9/L	22.88±2.63	
Day 8 (PGR) (Patients receiving only the BFM protocol n:38)		
Yes	24.53±2.60	0.002
No	12.72±5.12	
Day15 MRD (Patients receiving only the BFM protocol n:38)		
Negative	29.66±2.58	0.000
Positive	14.27±3.03	
Day 33 Remission (Patients receiving only the BFM protocol n:38)		
Yes	29.13±3.58	0.008
No	9.53±3.39	

*ETV6-RUNX1 and Hyperdiploid(>50chromosomes)
**Cytogenetic of poor prognosis; Hypodiploid(<44chromosomes), MLL rearrangements, BCR-ABL1 B –ALL(precursor B cellacutelymphoblasticleukemia), T ALL (T cellacutelymphoblasticleukemia),SRG (Standard risk group),IRG (intermediate risk group), HRG (high risk group), BM (Bone Marrow), PGR (prednisolonegoodresponse), MRD (Minimal ResidualDisease).

REZ BFM 2002 (2003–2018) and ALL-IC REL 2016 (2018–present) protocols were given as the first-line relapse therapy. The FLAG-IDA (fludarabine, cytarabine, idarubicine, G-CSF) treatment protocol was used as second-line therapy. Third-line salvage therapy was given to patients who did not go into remission or developed recurrent relapses. Details of relapse treatments are shown in **Figure 1**. HSCT was performed on 22 patients after relapse. Relapsed patients who had recurrent relapse (minimum-maximum:1-4) or resistant disease (n=10) received different salvage regimens such as clofarabine-based regimens (clofarabine, etoposide, cyclophosphamide or clofarabine, cyclophosphamide, etoposide, bortezomib), nelarabine for T-cell ALL or bortezomib-based regimens (bortezomib, vinorelbine, topotecan, thiotepa, dexamethasone). The third line treatment details are shown in **Figure 2**.

Thirty-seven (67.3%) patients died. The most common causes of death were progressive disease (30 patients, 81%) and infection (7 patients, 19%). The 5-year overall survival rate was 41.6%. The 1-, 3-, and 5-year overall survival (OS) rates of the relapsed patients with B-ALL were 86%, 68%, and 48%, respectively. The 1-, 3- and 5-year OS rates of the relapsed T-ALL patients were 64.5%, 27%, and 18%, respectively. A Log-rank test was performed to identify differences in survival according to diagnostic variables. There was a statistically significant difference in survival between B -ALL and T- ALL patients (X2=20.324, P <0.001). Kaplan Meier survival analyses are shown in **Figure 3**. The 5-year OS rates of the patients with very early, early, and late relapse were 22%, 46%, and 58%, respectively. The 5-year OS rates of the B-ALL patients with very early, early, and late relapse were 26.6%, 40.2%, and 72.4%, respectively. The 3-year OS rates of the T-ALL patients with very early and early relapse were 14.8% and 32%, respectively.

All patients who received salvage therapies died due to progressive disease or infection.

The mortality rate was significantly associated with immunophenotype, the risk group at initial diagnosis, the site of relapse, and post-relapse HSCT (p<0.05). Sex, age at diagnosis, and genetic profiles were not associated with mortality (p>0.05). The mean post-relapse survival was longer in the group with HSCT than in the group without HSCT (97.55 months and 45.50 months, respectively (X2=4.168, p=0.041).

After univariate survival analyses of variables associated with mortality were performed by log-rank test, those found to be significant were further examined by Cox regression analysis with the backward selection method (-2 Log Probability=228.176). Cox regression analysis is summarized in **Table 3**. T-ALL immunophenotype and isolated bone marrow relapse were determined as the independent variables affecting mortality.

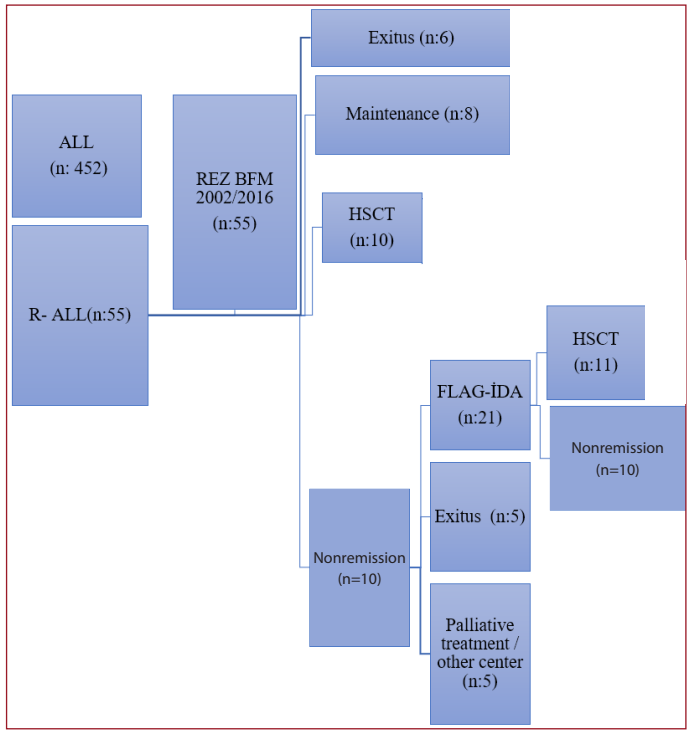

Figure 1. Details of treatments

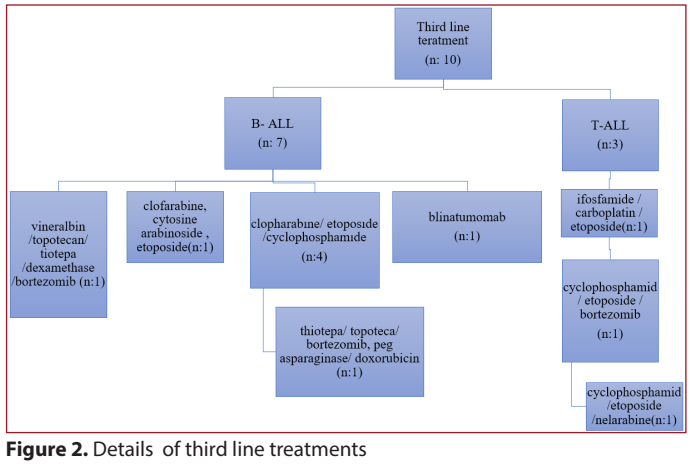

Figure 2. Details of third line treatments

Table 3: Coefficients of the best model obtained by Cox regression analysis

Variables	B	Wald	Sig.	Exp(B)	95.0% CI for Exp (B)	
					Lower	Upper
Immunophenotype (T cell ALL)	1.898	16.768	0.000	6.671	2.690	16.544
Relapse Sitea (Isolated BM)		4.459	0.108			
Relaps Site (Combined)	1.156	4.445	0.035	3.176	1.085	9.298
Relaps Site (Isolated extramedullary)	0.949	2.223	0.136	2.582	0.742	8.986

a Reference category, BM (Bone Marrow)

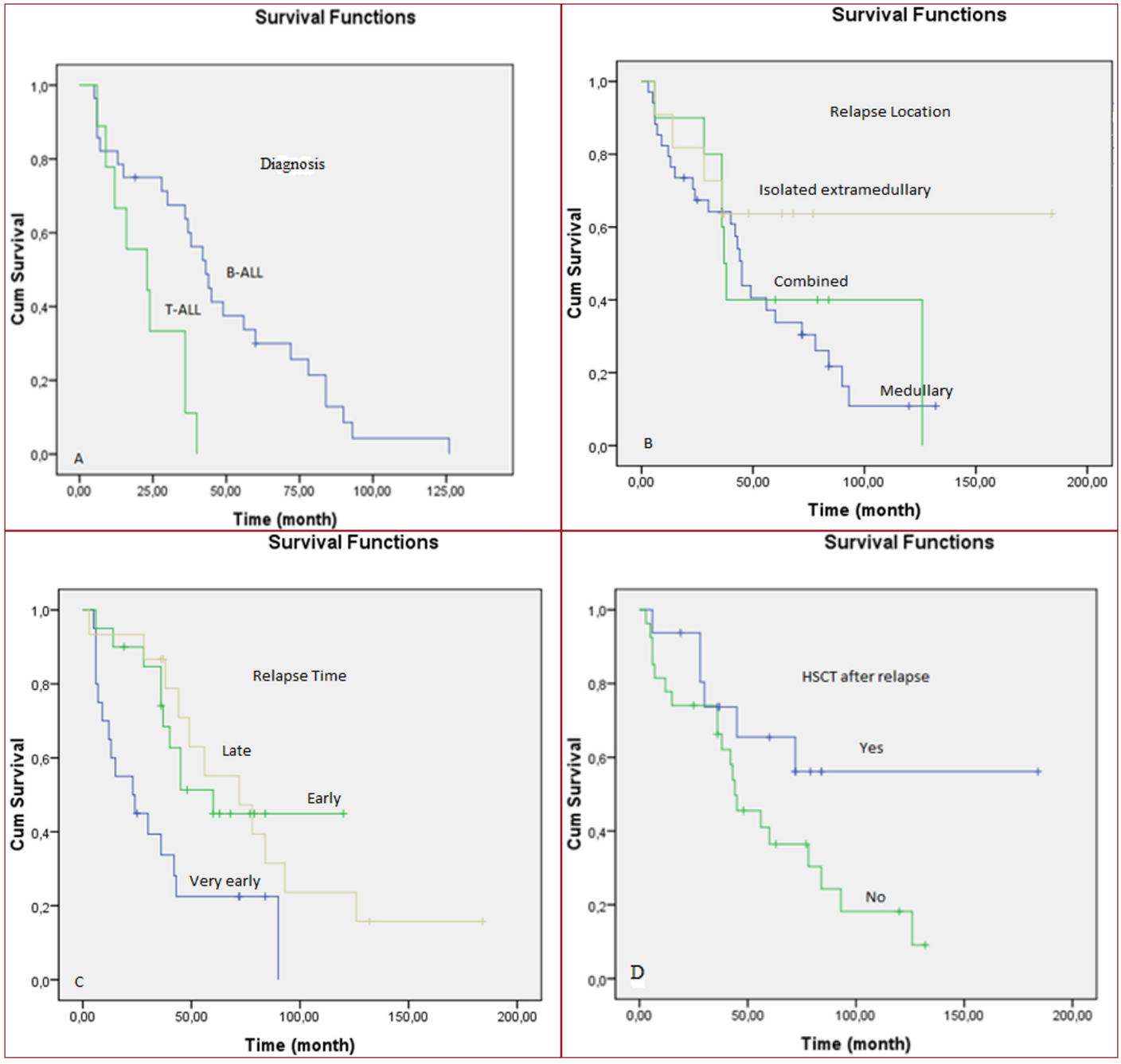

Figure 3. A; Overall survival according to diagnosis. B; Overall survival according to site of relaps.. C; Overall survival according to time of time of relaps. D; Overall survival according to HSCT treatment.

DISCUSSION

Relapse affects 15–25% of pediatric ALL patients and continues to be an important determinant of treatment success.[1-5] Relapse rates of the pediatric ALL have been reported as 15-35% in different studies. In the present study, the relapse rate was 12.1% compared to the aforementioned studies. Immunophenotype, the site of relapse, duration time of the first complete remission, the risk group at diagnosis, genetic abnormalities, and response to relapse treatment influence the prognosis in relapsed ALL patients.[12,13] Although the second remission rates vary between 71 and 93% in those patients, the short duration of the second remission causes long-term survival rates to decrease to 35.5–40%.[14,15] In our study, the 5-year OS rate was 41.6% in general and the T-ALL group showed a substantially lower survival rate compared to B-ALL; 18% and 48%, respectively. B cell ALL and T cell ALL patients have several differences in terms of clinical features, genetic characteristics, and sensitivity to chemotherapeutics. Patients with T-cell ALL are often older than patients with B-cell ALL. Furthermore, patients with B-cell ALL may have favorable genetic subtypes (e.g., ETV6–RUNX1 and hyperdiploidy) and

appropriate targeted therapies may be administered in some patients.[16] T-cell immunophenotype was a poor prognostic factor associated with a high initial white blood cell count.[17] In our study, the T-cell immunophenotype was independently associated with a high mortality rate. Therefore, the development and widespread use of T-ALL-specific treatment regimens are important for improving the outcomes of these patients.[18]

Bone marrow is the most common site of relapse in pediatric ALL patients.[1] Patients with isolated bone marrow relapse have been reported to have poorer survival outcomes than patients with extramedullary relapse.[7,12,17] Similarly, isolated bone marrow relapse was also most prevalent in our study, and patients with isolated bone marrow relapse had lower survival rates than those with CNS, testicular, and combined bone marrow relapse. Additionally, isolated bone marrow relapse was identified as an independent variable associated with mortality in our study.

In particular, unfavorable genetic risk factors have an important place in determining the risk grouping of the patient.[18] Conventional chromosomal analysis could not be performed in approximately 20% of patients due to failure to obtain metaphases. The fact that these patients had a shorter time to relapse than other patients suggests that genetic changes associated with poor prognosis may not have been detected. Most of the patients (66%) diagnosed with relapsed B-ALL were in the IRG at the time of diagnosis. We also suggest that in some patients genetic changes that play a key role in the risk assessment could not be detected. Therefore, new genetic methods such as next generation sequencing could be used to predict prognosis.

Philadelphia chromosome (Ph)-like ALL can be an example of a genetic change that we could not analyse during the study period. Philadelphia-like ALL is characterized by a gene expression profile similar to BCR-ABL1 positive, but the BCR-ABL1 oncogene is not detected.[19] The rate of Ph-like ALL among all ALL cases has been reported to be 12% in children and 21% in adolescents.[20] Detecting genetic changes that affect prognosis is of great importance in determining the appropriate risk group.[21] The impact of Ph-like ALL on outcomes could not be evaluated in our study. Comprehensive genomic studies will also enable molecular targeted therapies to be found, such as tyrosine kinase inhibitors.[22]

The duration of time to relapse has been described as the most important determinant of mortality.[7] Survival rates are particularly lower in patients with early bone marrow relapse.[14] Nguyen et al. reported 5-year OS rates after isolated bone marrow relapse as 11.5%, 18.4%, and 43.5% in patients with early, intermediate, and late relapse, respectively.[7] In our study, 5-year OS rates (very early, early, and late relapse were 22%, 46%, and 58%, respectively) were higher compared to that study. These results may indicate that time to relapse is still an important indicator of survival, as demonstrated in previous studies.

The ultimate treatment goal in relapsed ALL is to provide complete remission and to perform HSCT.[23] Studies comparing the outcomes of conventional chemotherapy and HSCT after complete remission in relapsed patients have yielded different results.[24,25] In particular, the utility of HSCT in late bone marrow relapse remains unclear.[26] In our study, relapsed patients who underwent HSCT had a better survival rate.

Until recently, treatment options were limited to intensive cytotoxic chemotherapy and allogeneic hematopoietic stem cell transplantation, whereas in recent years, therapeutic immunotherapeutic drugs for children with relapsing ALL have been investigated to a greater extent.[22] It has been reported that the use of blinatumomab, inotuzumab ozogamicin, and CAR-T cell treatments in relapsed patients improves survival rates.[22] We used these treatments in a small number of patients in the years that covered our study.

CONCLUSION

Relapse affects a significant portion of patients with ALL. Survival rates are still poor in patients with relapsed ALL. It is estimated that the risk groups of patients may change by comprehensive analysis of genetic risk factors at the time of diagnosis. Also, our findings that T-cell immunophenotype and the site of relapse were independent risk factors for mortality suggest that more specialized treatment options are needed for patients with T-ALL and bone marrow relapse.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Pediatrics Hematology Oncology Training and Research Hospita Ethics Committee (Date: 30.07.2019, Decision No: 2019228).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1345365
J Contemp Med 2023;13(5):982-986

Original Article / Orijinal Araştırma

"What if I Die Before Him?" Concerns of Caregivers in Palliative Care

"Ya Ondan Önce Ölürsem?" Palyatif Bakımda Bakımverenlerin Endişeleri

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Abstract

Aim: Caregivers are family members who provide unpaid assistance to their ill spouses. In Turkey, family caregiving, engagement, and support are needed when patients are hospitalized. This study aims to better understand the feelings of caregivers behind their behaviors in a terrier palliative care setting.

Material and Method: This research is a cross-sectional qualitative study designed with phenomenology. Five family caregivers who volunteered to participate were interviewed face-to-face. Inclusion criteria were adult informal caregivers who currently provided care to the patient at home and in the hospital.

Results: The family caregivers consist of five spouses with a mean age of 44.8±4.80 years. Each caregiver is a female and the spouse of the patient. Of the patients diagnosis was Alzheimer's disease, dementia, gastric cancer, and stroke, respectively. The caregiving time was approximately 2.79±1.62 years. Four themes and eleven subthemes were indicated: Concerns about themselves: Overestimating their health care problems, Anxiety about staying strong; Consequences of the patient: Remembering the patient like a "hero"; Acceptance of the situation Fear of "finding him death" Challenges about caregiving Sacrificing from life Excessive responsibility Embarrassment from diaper care Lack of orientation for caregiving at first Coping strategies Devine providence Religious beliefs.

Conclusion: The findings of the study indicate that family caregivers have concerns about themselves and the consequences of their roles. Even if they try to cope with spirituality, healthcare providers can support them by recognizing their essential roles.

Keywords: Palliative care, family caregivers, concerns, spirituality

Öz

Giriş: Bakımverenler, hastalarına ücretsiz yardım sağlayan aile üyeleridir. Türkiye'de hastalar hastaneye yatırıldığında aile bakımı, katılım ve desteğe ihtiyaç duyulmaktadır. Bu çalışma, palyatif bakım ortamında bakımverenlerin davranışlarının ardındaki duygularını daha iyi anlamayı amaçlamaktadır.

Gereç ve Yöntem: Bu araştırma fenomenoloji ile tasarlanmış kesitsel nitel bir çalışmadır. Katılmak için gönüllü olan beş yüz yüze görüşme yapıldı. Dahil etme kriterleri, hastaya evde ve hastanede bakım sağlayan yetişkin refakatçiler olarak belirlendi.

Bulgular: Bakımverenlerin yaş ortalaması 44,8±4,80 yıl olan beş kadından oluşmaktadır. Hastaların tanısı sırasıyla Alzheimer hastalığı, demans, mide kanseri ve inme idi. Bakım süresi yaklaşık 2,79±1,62 yıldı. Dört tema ve on bir alt tema belirtildi: Kendileriyle ilgili endişeler: Sağlık sorunlarını abartmak, Güçlü kalma kaygısı; Hastaya bağlı sonuçlar: Hastayı kahraman gibi hatırlamak; Durumun kabulü "Onu ölü bulma" korkusu; Bakıcılıkla ilgili zorluklar Hayattan fedakarlık, Aşırı sorumluluk, Bebek bezi bakımından utanç, bakım vermeye başladığında oryantasyon eksikliği Başa çıkma stratejileri Dini inançlar.

Sonuç: Çalışmanın sonucunda, bakımverenlerin kendileri ve rollerindeki sonuçlar hakkında endişeleri olduğunu göstermektedir. Maneviyatla başa çıkmaya çalışsalar bile, sağlık hizmeti sağlayıcıları temel rollerini kabul ederek onlara destek olabilirler.

Anahtar Kelimeler: Palyatif bakım, bakımverenler, endişeler, spirtualizm

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Received *(Geliş Tarihi)*: 17.08.2023 **Accepted *(Kabul Tarihi)*:** 30.09.2023

INTRODUCTION

The International Association for Hospice and Palliative Care developed a new way of understanding palliative care in a consensus-based manner and caregivers added not only patients but also caregiver quality of health to the description.[1]

Family caregivers in palliative care are defined as 'individuals who may be friends, relatives, or partners actively engaged in providing care for a patient confronting a severe, life-threatening illness'.[2] However, caring often presents itself as an exhausting and emotionally taxing burden, creating a situation where caregivers can struggle to distinguish between their personal needs and their responsibilities in providing care.[3] In the public health systems recently, there has been a reduction in the number of hospital beds, accompanied by a rise in outpatient care. This change has highlighted the growing importance of family caregivers within this system.[2] In addition, the literature emphasizes the importance of addressing the requirements of family caregivers engaged in palliative care. This importance is particularly evident in terms of providing them with information and directing them to resources for respite, financial assistance, education, and psychosocial support.[4]

Healthcare planning is often apart from the unmet needs of family caregivers, and in most cases support for caregivers is suboptimal. For people who need palliative care, family caregivers are likely to provide a high level of care for the rest of the patient's life. This can cause uncertainty in time and process, which can result in enormous stress and an impact on the caregiver's health.[5]

In the literature, there are many studies about the burden of caregivers, depression and anxiety disorders, and financial problems.[6,7] Also, there are studies about caregivers' financial problems.[8,9] The expectations, confidence, pain management challenges, and problems of family caregivers were tried in various studies.[5,10-12]

To deliver patient- and family-centred care within palliative care services, it is crucial to thoroughly evaluate the needs and anticipations of family caregivers.[13] This study aims to better understand the feelings of caregivers behind their behaviors.

METHOD

Study Design

In terms of exploring the unmet needs of family caregivers and to better understand their caregiving experiences, the phenomenological design was chosen. The selection of this study approach was justified due to the unique and innovative nature of the research. It was considered the most suitable method to address the research question, which was designed to understand the needs and perspectives of family caregivers in depth.[14]

Recruitment of Participants

To share specific knowledge about a phenomenon, researchers use purposeful sampling to select individuals to participate in a study.[15] For this reason, family caregivers were selected from whom patients were hospitalized in a palliative care unit. The inclusion criteria were informal adult caregivers (18 years or over), who currently provided a combination of unpaid physical and emotional care to the patient at home in addition to the hospital.

Conduct of the Study

The interviews were carried out by a single researcher after the approval of the clinical ethics committee (01.09.2019 – 01.12.2019); in a semi-structured individual format, ensuring privacy, and lasting approximately between 30 minutes and 1 hour. The researcher used clarification, reflection, and requests for examples of interview techniques as a matter of phenomenological method.[15] At the beginning of the interviews, participants were asked to provide their consent for voice recording. Following the initiation of the audio recording upon obtaining verbal consent, the participants were asked to share their experiences with their patients. Following this initial phase, the interviews continued using a semi-structured format, with the following questions: 1. What obstacles do you come across in the process of caring for the patient? 2. How emotionally respond to your current situation? 3. What strategies do you employ to manage and overcome these challenges? To gain a deeper understanding of informal caregiver feelings and unmet needs in palliative caregiving, six semi-structured interviews were conducted. Of these interviews, five were selected based on the richness of our research objectives and according to the interpretative phenomenological analysis methodology guidelines.[16]

Data Analysis

The data interpretation process involved the use of content analysis techniques. During the analysis phase, the collected data were initially transcribed from interviews and then encoded using abbreviations formed by the initials of the respective caregivers of the participant's family, identified as K1, K2, K3, etc. Subsequently, the transcribed data was meticulously examined line by line, leading to the identification of emerging themes and categories. This study has been analyzed following the phenomenological procedures proposed by Moustakas.[14] First, we read the transcripts for general understanding and listed each statement about the experience. This resulted in a list of 108 important statements directly related to the experience. Then, by limiting the important overlapping expressions, we found the invariant components. Next, we create units of meaning from immutable structures, which is the process of creating meaning from important expressions of participants. Our goal in these first analysis steps was not to distort the original meaning but to distinguish the meaning by thinking over verbatim phrases. Then, we clustered and created themes from units of meaning.

Ethical considerations

The study protocol conformed to ethical guidelines of the 1975 Declaration of Helsinki, approved by the Erzincan Binali Yıldırım University Faculty of Medicine Clinical Ethic Committee date 30/05/2019 and number 06.

RESULTS

Socio-demographic status of the participants: The family caregivers consist of five spouses with a mean age of 44.8±4.80 years, the youngest being 38 and the oldest 50 years. Each caregiver is a female and daughter or granddaughter of the patient. Of the patients enrolled in the study, their diagnosis was Alzheimer's disease, dementia, gastric cancer, and stroke, respectively. Their mean age was 63.00±5.10 years. The caregiving time was approximately 2.79±1.62 years. All patients had a performance status of 3 or 4 according to the WHO performance stage. This includes patients who spend most of their waking hours in bed (more than 50%) or are entirely bedridden and have limited or no ability to self-care. Regarding the socio-demographic profile, the educational level of caregivers was primary to secondary school and the socioeconomic level was low to middle in a rural setting (**Table 1**).

The themes and subthemes of the study: Four themes and eleven subthemes were indicated by the phenomenological method (**Table 2**).

Table 2. Presentation of themes and sub themes

Themes	Sub-themes
Concerns about themselves	Overestimating their health care problems
	Anxiety about staying strong
Consequences of the patient	Remembering the patient like a "hero"
	Acceptance of "patient won't get well"
	Fear of "finding him death"
Challenges about caregiving	Sacrificing from life
	Excessive responsibility
	Embarrassment from diaper care
	Lack of orientation for caregiving at first
Coping strategies	Devine providence
	Religious beliefs

Concerns About Themselves

At the beginning of the intervention, all caregivers started claiming their health status. At first sight, they seemed to focus on their health care problems to take some attention from the surrounding as all the attention is on the patient. As the conversation progresses, it is understood that their healthcare problems started right after giving the care. An additional question was added to the intervention: 'Do you think that the reason for your health care problems is caregiving? All of them denied it, they were careful while choosing the words to not blame the patient or the patient's bedriven situation. The problem is: 'They want to be healthy; they want to stay strong to continue caring.'

"*I also have lupus. I assure you, I'm following the prescribed medications, just like my grandmother. When I see her and compare it to my situation, it is a blessing* '**K1**

"*…I underwent hernia surgery. I mean, they did not waste any time – as soon as I got there, they rushed me to the operating room. However, now they continue to advise me on self-care, but what choice do I have? I need to take care of myself...*" **K2**

Consequences of the Patient

All caregivers have obstacles concerning the consequences of the patient. Some of them worry about 'finding him dead', while others are upset that their patient will not get well. On the other hand, all caregivers needed to talk about their patient's life before the illness and they all agreed that she was a stunning person.

"*The children are quite anxious; the girls and my son watch her closely all the time, wondering if she is getting worse or not. We've developed this habit over time.*"**K3**

"*I am very sorry. Our patient is deteriorating before our eyes.*" **K1**

'*Also, why is my father like this?' We value him very much...*' **K5**

Challenges About Caregiving

All caregivers struggled with some issues, especially at the beginning of their patient's disease, due to the lack of orientation of caregivers. Some others claimed about diaper change problems and find it embarrassing. The others talked about the sacrificed life they had, late marriages, less social life, etc.

Table 1. Sociodemographic properties of participants

Code	Patient age Gender	Patient Diagnosis	Caregivers' age Gender	Spouse	Duration of caregiving	Caregivers diagnosis	Education level of caregivers	Economic status of caregivers
K1	63 Female	Alzheimer	38 Female	Granddaughter	2 years	Systemic Lupus Erythematosus	Primary school	Low income
K2	55 Female	Dementia, hypertension	46 Female	Daughter	5 years	Breast Cancer	Secondary school	Middle income
K3	67 Male	Gastric cancer	48 Female	Daughter	1.75 years	Hypertension	Primary school	Low income
K4	68 Female	Stroke	50 Female	Daughter	1.2 years	Endometrium Cancer	Secondary school	Middle income
K5	62 Male	Stroke	42 Female	Daughter	4 years	Lumbal Hernı	Primary school	Middle income

"My brother and I look after her like a baby, I kiss and hold her as well. We cannot predict how the patient would react if something were to happen to us. ' **K4**

'*We initially had problems taking the drugs, but after they took us to the list of bedridden patients, we had no problem with the healthcare system.*' **K3**

I change diapers two times a day, it was difficult at first, but now I am used to it. **K2**

Coping Strategies

They remain strong, and the underlying reason for it was both religious beliefs. They never feel guilty or blame the patient. Instead, they think it is a gift from God to show their religious beliefs.

'*Whatever God decrees will come true. I believe in divine fate, but I hope everything turns out well for our mother. It is not an easy situation.* ' **K4**

DISCUSSION

This study revealed an essential understanding of the concerns, feelings, and coupling strategies of family caregivers among the burden of palliative care. The study sample was similar to the literature where most of the family caregivers are daughters of patients who are married women of middle age and unemployed, where their economic status is low to middle.[17,18]

Palliative caregivers face the task of not only preparing for caregiving responsibilities but also anticipating the dying of the patient.[2] Although caregivers were often confident about how to care for physical needs, they had difficulties understanding the dying process.[12] In this study, it is stated that even family members have the anxiety of finding the death of the patient, and it became a habit to control it. Habit means a kind of acceptance that the patient won't suffer. Also, in a study where the core components of the well-being of caregivers were investigated, acceptance was mentioned, which means the capacity to allow things to happen naturally.[19]

Family caregivers (FCs) care for bedriven patients and they are at risk of physical and psychological issues that can result in healthcare problems.[20] On the other hand, FCs also had to struggle with their own physical and psychological health status.[21] In this study, the dominant topic was the caregiver's concerns for themselves. They try to give the best care to themselves as well as to the patient as possible because they have the anxiety of leaving the patient without care. Regarding anxiety, in another study conducted by an outpatient oncology clinic, FCs documented higher rates of anxiety and depression than individuals with cancer.[10] As their loved one's health deteriorates, caregivers discover it increasingly challenging to step away and have a break. Despite the genuine need for respite, caregivers paradoxically feel compelled to maximize their time with their loved one, recognizing its finite nature.[22] That's the underlying reason they worry about leaving them without care.

The entire process transforms a spousal or parent-child dynamic into that of a caregiver and care recipient, where caregivers suspend their own lives to care for their loved ones.[22] That means sacrificing your social and private life spontaneously (**Table 2**) that cannot even go out freely, feeling dependent and bound strongly.

Spirituality was the most common strategy and naturally preferred couping strategy.[20,23] Similar to this study, even though FCs have various concerns and challenges, they feel strong and blessed with spirituality. Although in the literature, the specific findings of spirituality in palliative care are underestimated.[23,24]

CONCLUSION

The findings of the study indicate that family caregivers have concerns about themselves and the consequences of their roles. Even if they try to cope with spirituality, healthcare providers can support them by recognizing their essential roles; understanding their experiences and needs. These strategies aim to assist caregivers in managing their own lives and in effectively caring for the patient without burden.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Erzincan Binali Yıldırım University Clinical Researches Ethics Committee (Date: 30/05/2019, Decision No: 06/04).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Note: This study was a poster presentation in 87th EGPRN meeting.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1317474
J Contemp Med 2023;13(5):987-993

Original Article / Orijinal Araştırma

Evaluation of Scientific Publications on Osteoblastoma Published between 2000 and 2022

Osteoblastom ile İlgili 2000 ile 2022 Yılları Arasında Yayımlanan Bilimsel Yayınların Değerlendirilmesi

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Abstract

Aim: The aim of this bibliometric study was to review the scientific outputs published between 2000 and 2022 on osteoblastoma, a benign aggressive bone tumor.

Material and Method: Scientific research articles on osteoblastoma published between 2000 and 2022 were targeted and data were obtained from the Web of Science database. The data obtained were analyzed and visualized using bibliometric programs.

Results: A total of 679 articles about osteoblastoma published between 2000-2022 met our inclusion criteria. Most of the articles on osteoblastoma (n=48) were published in 2020. There was no noteworthy peak in the trend of the number of publications between 2000 and 2022. These articles cited 10366 times in total and 15.27 times per article. At least 62 various countries and regions took part in osteoblastoma publishing research over the past 22 years. The United States (192) was the largest contributor to osteoblastoma publications followed by China (60), India (51), Italy (50), and Turkey (46). The United States was the country that published the most publications in all years between 2000 and 2022. Especially China's publications increased in 2022. The United States was also the country with the highest level of publication collaboration (such as citation and co-authorship) among countries.

Conclusion: The number of published articles is well below the expected level. Although the number of scientific publications from China has increased in recent years, the United States still ranks first.

Keywords: Publication, osteoblastoma, bibliometric

Öz

Amaç: Bu bibliyometrik çalışmanın amacı, iyi huylu agresif bir kemik tümörü olan osteoblastom hakkında 2000 ile 2022 yılları arasında yayınlanan bilimsel çıktıları gözden geçirmektir.

Gereç ve Yöntem: Osteoblastoma ile ilgili 2000-2022 yılları arasında yayınlanan bilimsel araştırma makaleleri hedeflendi ve veriler Web of Science veri tabanından elde edildi. Elde edilen veriler bibliyometrik programlar kullanılarak analiz edilmiş ve görselleştirilmiştir.

Bulgular: Osteoblastom ile ilgili 2000-2022 yılları arasında yayınlanan toplam 679 makale dahil edilme kriterlerimizi karşıladı. Osteoblastom ile ilgili makalelerin çoğu (n=48) 2020 yılında yayınlanmıştır. 2000 ile 2022 yılları arasındaki yayın sayısı trendinde kayda değer bir zirve olmamıştır. Bu makaleler toplamda 10366 kez ve makale başına 15,27 kez atıf almıştır. En az 62 farklı ülke ve bölge, son 22 yılda osteoblastoma yayın araştırmalarına katıldı. Amerika Birleşik Devletleri (192) osteoblastoma yayınlarına en büyük katkıyı yapan ülke oldu ve bunu Çin (60), Hindistan (51), İtalya (50) ve Türkiye (46) izledi. 2000 ile 2022 yılları arasındaki tüm yıllarda en çok yayın yapan ülke Amerika oldu. 2022'de özellikle Çin'in yayınları arttı. Amerika Birleşik Devletleri aynı zamanda yayın işbirliğinin (atıf ve ortak yazarlık gibi) en yüksek olduğu ülke oldu.

Sonuç: Yayınlanan makale sayısı beklenen düzeyin oldukça altındadır. Son yıllarda Çin'den yapılan bilimsel yayınların sayısı artsa da Amerika Birleşik Devletleri hala ilk sırada yer alıyor.

Anahtar Kelimeler: Osteoblastom, bibliyometrik, çalışma

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Received *(Geliş Tarihi)*: 20.06.2023 **Accepted *(Kabul Tarihi)*:** 17.07.2023

INTRODUCTION

Osteoblastoma is a rare, benign but aggressive and bone-forming neoplasm that makes up 10% of all osseous spinal neoplasms, 1% of all primary bone tumors, and 1% to 5% of all benign bone tumors.[1,2]

Due to its histopathologic resemblance to osteoid osteoma, it was previously known as large osteoid osteoma. However, the general consensus is that they are distinct pathologic entities with different clinical presentations, despite the fact that some writers believe the entities to be different manifestations of the same pathogenic process.[1] It frequently occurs in the second decade of life and more frequently in males.[3]

The most usual location for osteoblastoma to develop is in the axial skeleton, and the pain is typically not worse at night and is less likely to be relieved by non-steroidal anti-inflammatory drugs.[4] About 30 to 40 % of osteoblastoma develops in the posterior parts of the spine and the sacrum.[1] The diagnosis is made in light of the symptoms, imaging, and histological examination.[5] En bloc resection and intralesional curettage, which are primarily surgical techniques, are used in its treatment. In order to avoid recurrence, the procedure should be carefully planned and the tumor should be completely removed.[3] Although surgical excision remains the gold standard of care, less invasive radiological procedures like thermoablation and, more recently, high intensity focused ultrasound, are becoming more significant in recent years.[5]

Bibliometric analysis is a methodology for analyzing works of literature using statistical and mathematical methods to gain a comprehensive grasp of an resarch area. Additionally, it is a tool for exploring the organization and patterns of a subject through visualization and statistics for a quantitative evaluation of the effects of the research literature on certain research fields, nations or regions, research collaborations, journals, institutions, and authors over a specific time frame.[6,7]

In recent years, bibliometric analysis has gained interest in the field of medicine,[8-11] and orthopedics research area.[12,15]

However, no recent bibliometric studies have been conducted on osteoblastoma and no emphasis has been placed on estimating research hotspots. The purpose of this study is to forecast the state of the osteoblastoma field in academia and to suggest future research directions.

MATERIAL AND METHOD

As it is not a human or animal study there is no need for ethical approval.

Data Collection

With the help of the following retrieval techniques, we completed a thorough collection of all articles from the Thomson Reuters Web of Science database between 2000 and 2022: osteoblastoma AND human. [Topic (Abstract, keywords, title); limited to article; time span: 2000-2022].

The Web of Science database was chosen for this study, because it is the most authorized and commonly used electronic database for bibliometric studies. No language restrictions were applied for the entire literature review.

In order to prevent errors due to the Web of Science database updates, downloads completed in one day on April 13, 2023.

Two authors separately collected all the data, yielding an agreement rate of 0.99, which is a good level of agreement.[16]

The data obtained as a result of the search were converted into txt and plain text formats and imported into VOSviewer (version 1.6.19)[17] and the Online Analysis Platform of Literature Metrology (https://bibliometric.com/app) applications for make further analysis.

Statistical and Bibliometric Methods

First, we evaluated and compiled data on a wide range of variables (such as countries/regions, institutions/affiliations, journals, the Hirsch index, and the impact factor (IF) of the Journal Citation Reports (JCR) version (2021) for all extracted articles.

Additionally, through the online bibliometric platforms, the annual publishing volumes and trends of various countries/regions were discovered. The Vosviewer application and BIBLIOMETRC.COM platform were used for visualizations.

We analyzed the 25 most cited papers and their number of citations, the journals they were published in and the year of publication.

With the help of the Vosviewer application, keywords' co-occurrence analysis was carried out to forecast new areas of study and trends. Depending on the purpose of our analysis, we selected several nodes whose size corresponds to the number of publications or the number of citations. We also tabulated the most frequent keywords (more than 10 occurrences) and total link strengths.

RESULTS

A total of 679 articles about osteoblastoma published between 2000-2022 met our inclusion criteria. Most of the articles on osteoblastoma (n=48) were published in 2020. There was no noteworthy peak in the trend of the number of publications between 2000 and 2022 (**Figure 1**). These articles cited 10366 times in total and 15.27 times per article. The mean of the Hirsch index was 48.

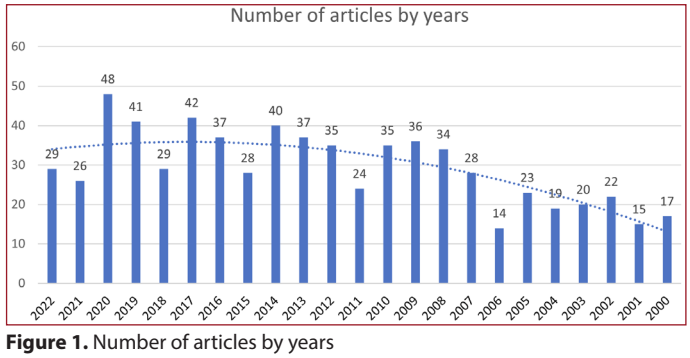

Figure 1. Number of articles by years

At least 62 various countries and regions took part in osteoblastoma publishing research over the past 22 years. The United States (192) was the largest contributor to osteoblastoma publications followed by China (60), India (51), Italy (50), and Turkey (46). The countries with the highest number of publications on osteoblastoma between 2020-2022 and the number of publications are summarized in **Figure 2**. According to this graph, the United States was the country that published the most publications in all years between 2000 and 2022. Especially China's publications increased in 2022. The United States was also the country with the highest level of publication collaboration (such as citation and co-authorship) among countries. The graph also implies that there are no academic interactions taking place between countries that have notable publications and countries with minimal numbers.

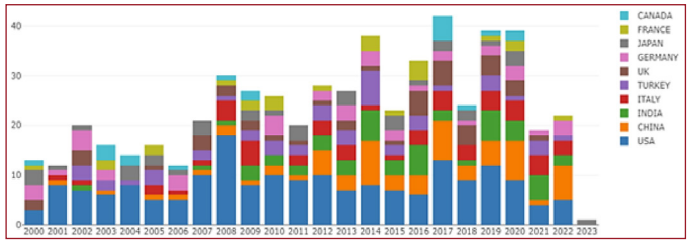

Figure 2 . Number of articles of the mostly publishing countries according to years

In terms of institutions (924 in total), European, Chinese, and the United States universities in the top 10 had published the highest number of articles on osteoblastoma. In addition, Leiden University (the Netherlands) and Harvard University (the United States) had the highest number of citations, with 132 and 130, respectively. However, publications originating from Klinikum Neustadt had the highest number of citations per publication (72) (**Table 1**).

These 679 publications were published in 330 different journals, and the top 10 most popular journals published a total of 90 publications. Most of the articles on osteoblastoma were published in Skeletal Radiology. Articles published in this journal received 112 citations. The articles which published in The Journal of Surgical Oncology journal had highest avarage citation number (avarage citation: 26) (**Table 2**).

Table 1. The top 10 organisations contributing to publications on osteoblastoma

Organisation name (Country)	Total number of articles	Total citations	Average citations
Leiden University (the Netherlands)	24	132	5.50
Harvard University (the United States)	17	130	7.65
Peking University (China)	17	95	5.59
São Paulo University (Brazil)	12	88	7.33
Childrens Hospital	8	72	9
The University of Münster (Germany)	2	72	36
Klinik Neustadt (Germany)	1	72	72
The Children's Hospital of Philadelphia(the United States)	17	69	4.06
Massachusetts General Hospital (the United States)	13	66	5.08
Heidelberg University (Germany)	3	63	21

As seen in **Figure 3**, the number of citations has shown an accelerating trend over the years.

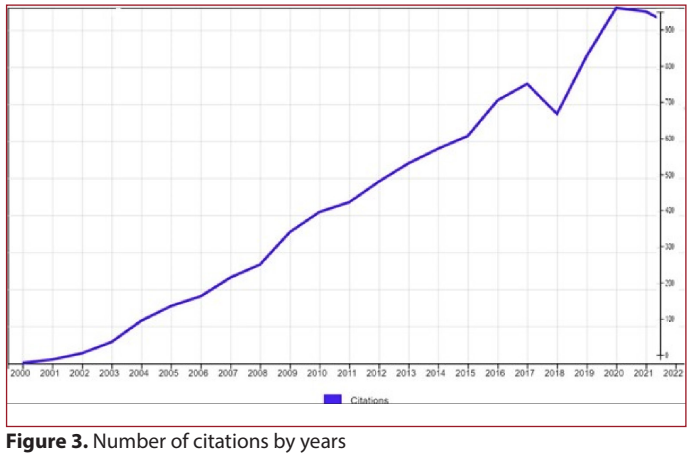

Figure 3. Number of citations by years

The top 25 articles in the field of osteoblastoma with the most citations were presented in **Table 3**. Most of these were animal and clinical studies, including descriptive studies. Clinical studies were radiological studies and diagnostic-treatment studies.

Table 2. The top 10 most popular journals published about osteoblastoma

Journal name	Total number of articles	Total citations	Avarage citations	Journal impact factor ™ 2021	Journal impact factor five year
Skeletal Radiology	26	112	4.31	2.128	2.073
Spine	14	105	7.50	3.269	3.753
Clinical Orthopaedics and Related Research	10	102	10.20	4.837	5.885
European Spine Journal	13	73	5.62	2.721	3.362
Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics	5	66	13.20	1.457	1.815
Radiology	5	62	12.40	29.146	17.483
Archives of Pathology & Laboratory Medicine	5	57	11.40	5.686	5.913
The Journal of Surgical Oncology	2	52	26.00	2.885	3.445
European Journal of Radiology	7	42	6	4.531	4.218
Neurosurgery Clinics of North America	3	32	10.67	3.348	3.471

Table 3. Most cited 25 articles about osteoblastoma

Title	Authors	Source Title	Publication Year	Total Citations	Average per Year
Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1-34) for 2 years and relevance to human safety	Vahle, JL; Sato, M; Long, GG; Young, JK; Francis, PC; Engelhardt, JA; Westmore, MS; Ma, YFL; Nold, JB	Toxicologic Pathology	2002	475	21.59
Osteoid osteoma: Percutaneous treatment with radiofrequency energy	Rosenthal, DI; Hornicek, FJ; Torriani, M; Gebhardt, MC; Mankin, HJ	Radiology	2003	363	17.29
Osteosarcoma - Anatomic and histologic variants	Klein, MJ; Siegal, GP	American Journal of Clinical Pathology	2006	309	17.17
Bone neoplasms in F344 rats given teriparatide [rhPTH(1-34)] are dependent on duration of treatment and dose	Vahle, JL; Long, GG; Sandusky, G; Westmore, M; Ma, YL; Sato, M	Toxicologic Pathology	2004	253	12.65
USP6 and CDH11 oncogenes identify the neoplastic cell in primary aneurysmal bone cysts and are absent in so-called secondary aneurysmal bone cysts	Oliveira, AM; Perez-Atayde, AR; Inwards, CY; Medeiros, F; Derr, V; Hsi, BL; Gebhardt, MC; Rosenberg, AE; Fletcher, JA	American Journal Of Pathology	2004	252	12.6
Radiologic Diagnosis of Osteoid Osteoma: From Simple to Challenging Findings	Chai, Jee Won; Hong, Sung Hwan; Choi, Ja-Young; Koh, Young Hwan; Lee, Joon Woo; Choi, Jung-Ah; Kang, Heung Sik	Radiographics	2010	139	9.93
A YKL-40-Neutralizing Antibody Blocks Tumor Angiogenesis and Progression: A Potential Therapeutic Agent in Cancers	Faibish, Michael; Francescone, Ralph; Bentley, Brooke; Yan, Wei; Shao, Rong	Molecular Cancer Therapeutics	2011	126	9.69
Inactive Wnt/beta-catenin pathway in conventional high-grade osteosarcoma	Cai, Yongping; Mohseny, Alexander B.; Karperien, Marcel; Hogendoorn, Pancras C. W.; Zhou, Gengyin; Cleton-Jansen, Anne-Marie	Journal of Pathology	2010	123	8.79
The diagnostic accuracy of MR imaging in osteoid osteoma	Davies, M; Cassar-Pullicino, VN; Davies, AM; McCall, IW; Tyrrell, PNM	Skeletal Radiology	2002	121	5.5
Spinal tumors	Van Goethem, JWM; van den Hauwe, L; Ozsarlak, O; De Schepper, AMA; Parizel, PM	European Journal of Radiology	2004	118	5.9
Fusions at the craniovertebral junction	Ahmed, Raheel; Traynelis, Vincent C.; Menezes, Arnold H.	Childs Nervous System	2008	106	6.63
Defining a noncarcinogenic dose of recombinant human parathyroid hormone 1-84 in a 2-year study in Fischer 344 rats	Jolette, Jacquelin; Wilker, Clynn E.; Smith, Susan Y.; Doyle, Nancy; Hardisty, Jerry F.; Metcalfe, Anna J.; Marriott, Thomas B.; Fox, John; Wells, David S.	Toxicologic Pathology	2006	102	5.67
Surgical approaches: postoperative care and complications transoral-transpalatopharyngeal approach to the craniocervical junction	Menezes, Arnold H.	Childs Nervous System	2008	101	6.31
Imaging of osteoid osteoma with dynamic gadolinium-enhanced MR imaging	Liu, PT; Chivers, FS; Roberts, CC; Schultz, CJ; Beauchamp, CP	Radiology	2003	99	4.71
Osteosarcoma of the jaws: A 30-year retrospective review	Bennett, JH; Thomas, G; Evans, AW; Speight, PM	Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontology	2000	99	4.13
Osteoid osteoma and osteoblastoma of the spine: Experiences with 22 patients	Ozaki, T; Liljenqvist, U; Hillmann, A; Halm, H; Lindner, N; Gosheger, G; Winkelmann, W	Clinical Orthopaedics and Related Research	2002	96	4.36
Activation of AMPK protects against hydrogen peroxide-induced osteoblast apoptosis through autophagy induction and NADPH maintenance: New implications for osteonecrosis treatment?	She, Chang; Zhu, Lun-qing; Zhen, Yun-fang; Wang, Xiao-dong; Dong, Qi-rong	Cellular Signalling	2014	92	9.2
COX-1 and COX-2 expression in osteoid osteomas	Mungo, DV; Zhang, XP; O'Keefe, RJ; Rosier, RN; Puzas, JE; Schwarz, EM	Journal of Orthopaedic Research	2002	81	3.68
Thermal Ablation of Spinal Osteoid Osteomas Close to Neural Elements: Technical Considerations	Rybak, Leon D.; Gangi, Afshin; Buy, Xavier; Vieira, Renata La Rocca; Wittig, James	American Journal of Roentgenology	2010	75	5.36

Table 3. Most cited 25 articles about osteoblastoma

Title	Authors	Source Title	Publication Year	Total Citations	Average per Year
Recurrent rearrangements of FOS and FOSB define osteoblastoma	Fittall, Matthew W.; Mifsud, William; Pillay, Nischalan; Ye, Hongtao; Strobl, Anna-Christina; Verfaillie, Annelien; Demeulemeester, Jonas; Zhang, Lei; Berisha, Fitim; Tarabichi, Maxime; Young, Matthew D.; Miranda, Elena; Tarpey, Patrick S.; Tirabosco, Roberto; Amary, Fernanda; Grigoriadis, Agamemnon E.; Stratton, Michael R.; Van Loo, Peter; Antonescu, Cristina R.; Campbell, Peter J.; Flanagan, Adrienne M.; Behjati, Sam	Nature Communications	2018	74	12.33
CT-guided radiofrequency ablation of osteoid osteoma and osteoblastoma: Clinical success and long-term follow up in 77 patients	Rehnitz, Christoph; Sprengel, Simon David; Lehner, Burkhard; Ludwig, Karl; Omlor, Georg; Merle, Christian; Kauczor, Hans-Ulrich; Ewerbeck, Volker; Weber, Marc-Andre	European Journal of Radiology	2012	74	6.17
Primary vertebral osteosarcoma: Imaging findings	Ilaslan, H; Sundaram, M; Unni, KK; Shives, TC	Radiology	2004	73	3.65
Osteoblastoma: A 30-year study of 99 cases	Berry, Micah; Mankin, Henry; Gebhardt, Mark; Rosenberg, Andrew; Hornicek, Francis	Journal of Surgical Oncology	2008	72	4.5
Benign bone tumors and tumor-like lesions: value of cross-sectional imaging	Woertler, K	European Radiology	2003	71	3.38
Interstitial laser photocoagulation for the treatment of osteoid osteoma - Results of a prospective study	Witt, JD; Hall-Craggs, MA; Ripley, P; Cobb, JP; Bown, SG	Journal of Bone and Joint Surgery-British Volume	2000	68	2.83

Keyword Analysis

Bibliometrics theory states that keywords reveal hotspots and trends in a research topic.[18] Due to the fact that keywords represent an article's or author's focus, they also provide a typical summary of research trends for the journal.[19] The network map is grouped based on the study of term co-occurrence, which depicts the fundamental knowledge structure of associated research disciplines. In order to group terms from literature, we utilize the VOSviewer program. A unit is made up of circles and labels, and units of various colors make up various clusters. The clusters of different colors are the distinct research trajectories, respectively. The final analysis included keywords that the authors of the publication listed and that appeared more than five times in the Web of Science core collection database. Only 1187 of the 78 keywords actually met the criteria. Also **Table 4** summarizes the keywords with more than 10 occurrences (**Figure 4**).

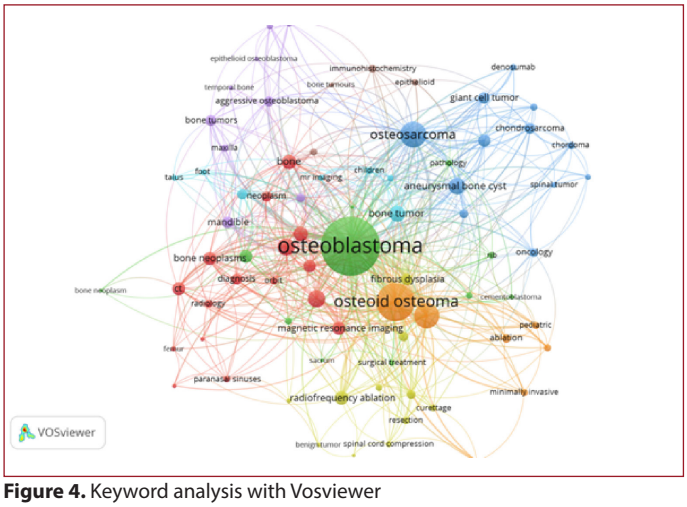

Figure 4. Keyword analysis with Vosviewer

Table 4. Keywords with more than 10 occurrences

Keyword	Number of occurrences	Total link strength
Aggressive osteoblastoma	18	26
Aneurysmal bone cyst	27	56
Benign bone tumor	11	20
Bone	19	46
Bone neoplasms	14	38
Bone tumor	27	53
Bone tumors	14	29
Cervical spine	18	24
Child	12	30
Children	12	17
Computed tomography	19	59
CT	13	38
Diagnosis	12	28
Fibrous dysplasia	10	33
Giant cell tumor	11	34
Magnetic resonance imaging	20	40
Mandible	18	31
MRI	18	38
Oncology	10	20
Osteoblastoma	260	415
Osteoid osteoma	120	207
Osteoma	28	62
Osteosarcoma	55	112
Radiofrequency ablation	20	44
Spine	45	109
Surgery	16	37
Tumor	18	46

DISCUSSION

This study included 679 research articles from Web of Science database on osteoblastoma and it is the first bibliometric analysis of osteoblastoma research.

The coverage, focus, and tools offered by various literature databases (such as PubMed, Scopus, and Web of Science) vary from one another. While Scopus and Web of Science are multidisciplinary, PubMed primarily focuses on life sciences and biomedical disciplines. Both Web of Science and Scopus offers search analysis tools that allow for representative data.[20] We selected the Web of Science database as detailed citation reports can be reached from this database.

Our statistical and quantitative analysis revealed that the number of publications in the field of osteoblastoma research not increased much between 2000 and 2022. Of the 679 articles, the United States contributed most of the research articles, demonstrating the strong collaboration and highest centrality with other countries. The other largest contributors to osteoblastoma publications were China (60), India (51), Italy (50), and Turkey (46) with lesser cooperation and relatively low centrality.

In terms of institutions, (924 in total), European, Chinese, and United States universities in the top 10 had published the highest number of articles on osteoblastoma. Leiden University (the Netherlands) and Harvard University (the United States) had the highest number of citations, with 132 and 130, respectively. However, publications originating from Klinikum Neustadt (Germany) had the highest number of citations per publication.

The journals that publish the most on osteoblastoma are those in the fields of radiology, orthopedics, oncology and neurosurgery. Most of the articles on osteoblastoma have been published in Skeletal Radiology, Spine and Clinical Orthopedics and Related Research. The Journal of Surgical Oncology, published in the field of oncology surgery, received the highest number of average citations, while the journal Skeletal Radiology, published in the field of radiology, received the highest number of citations.

Examining the most cited articles among those published on a topic can guide researchers on this topic.[14,21-23] In this study, we analyzed the 25 most cited articles on osteoblastoma published between 2000 and 2022. An animal experimental study on osteoblastoma published by Vahle et al.[26] was the most cited article with 475 citations. Also, most of the most cited papers were experimental, clinical and radiological studies.

The main themes, concepts, ideas, or arguments of a text are summarized in the keywords, which offer high-level summaries of the subject matter. It is essential to the processing of documents, including indexing, categorization, clustering, and summarization. For instance, describing the context of a statement could be as simple as stating the word that comes before or after the phrase of interest.[24,25] We used the VOSviewer program to group the most important keywords in our study. As a result, we summarized the keywords with more than 10 occurrences in **Table 4**. These keywords may provide perspective to those who will conduct research on osteoblastoma.

Limitations

It is important to note some of this study's limitations. The sole database used in this study was the Web of Science database because it has been considered to be the most significant source of information for bibliometric analysis. As a result, some studies might have been skipped. As a result, depending on the database chosen, the outcomes of bibliometric analyses may differ. The bibliometric community should keep working to create techniques and metrics that take into account scientific output not taken into account in global databases (Web of Science, Scopus, etc.) such as domain-specific and country citation indices.

Additionally, the analysis employed only articles and publications in the English language, which could have influenced the results in a biased way. Furthermore, it was unable to definitively determine the author's affiliation. Also, some authors may have names that are identical and that may cause bias. When utilizing Web of Science JSON files, only the first authors are taken into consideration with Vosviewer application.

CONCLUSION

Osteoblastoma is a rare benign tumor of the bone. Treatment experience is limited. Diagnosis and management of this lesion includes multimodal radiological imaging and careful histological and surgical evaluations to determine the best treatment protocol. Surgical resection in patients with osteoblastoma may provide satisfactory clinical and radiographic results and further studies in this area are worth recommending.

The number of published articles is well below the expected level. Although the number of scientific publications from China has increased in recent years, the United States still ranks first. The United States is also the leader in international collaborations. Looking at the citation graph, there is an upward trend in the number of citations for osteoblastoma. Those who will publish on this topic can benefit from our keyword analysis.

ETHICAL DECLARATIONS

Ethics Committee Approval: As it is not a human or animal study there is no need for ethical approval.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1335202
J Contemp Med 2023;13(5):994-998

Original Article / Orijinal Araştırma

Evaluation of Vitamin B12, Folic Acid, Ferritin and Vitamin D Levels in Obsessive Compulsive Disorder

Obsesif Kompulsif Bozuklukta B12 Vitamini, Folik Asit, Ferritin ve D Vitamini Düzeylerinin Değerlendirilmesi

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Abstract

Aim: Obsessive compulsive disorder (OCD) is a heterogeneous disorder characterized by obsessions and compulsions. Despite the studies, etiopathogenesis is not fully understood. Pharmacological and psychosocial interventions in OCD may be insufficient due to limited knowledge of etiopathogenesis. Therefore, it is important to find inexpensive and easily determined biochemical parameters related to etiopathogenesis. In this study, the relationship between OCD and vitamin B12 (VitB12), folic acid (FA), vitamin D (VitD) and ferritin was investigated.

Material and Method: 50 patients with OCD (12 female, 38 male) and 50 healthy controls (HC) (13 female, 37 male) were included in this retrospective study. Serum VitB12, FA, ferritin and 25-OH VitD levels of both groups were compared.

Results: VitB12 (p <0.001), FA (p =0.004) and 25-(OH)VitD (p =0.001) serum levels were significantly lower in the OCD group than in the HC group. There was no significant difference between the two groups in terms of ferritin values.

Conclusion: Our study shows that serum VitB12, FA and VitD deficiency can contribute to etiopathogenesis in OCD patients. This study may lead to research to find new pathways related to etiopathogenesis. For this, prospective studies, including the post-treatment phase, are needed.

Keywords: Obsession, vitamin B12, folic acid, ferritin and vitamin D

Öz

Amaç: Obsesif kompulsif bozukluk (OKB), obsesyon ve kompulsiyonlarla karakterize heterojen bir bozukluktur. Yapılan çalışmalara rağmen etyopatogenezi tam olarak anlaşılamamıştır. OKB'de farmakolojik ve psikososyal müdahaleler, sınırlı etyopatogenez bilgisi nedeniyle yetersiz olabilir. Bu nedenle etiyopatogenez ile ilgili ucuz ve kolay saptanabilen biyokimyasal parametrelerin bulunması önemlidir. Bu çalışmada OKB ile B12 vitamini (VitB12), folik asit (FA), D vitamini (VitD) ve ferritin ilişkisi araştırıldı.

Gereç ve Yöntem: Bu retrospektif çalışmaya 50 OKB hastası (12 kadın, 38 erkek) ve 50 sağlıklı kontrol (SK) (13 kadın, 37 erkek) dahil edildi. Her iki grubun serum VitB12, FA, ferritin ve 25-OH VitD düzeyleri karşılaştırıldı.

Bulgular: VitB12 (p <0.001), FA (p =0.004) ve VitD (p =0.001) serum düzeyleri OKB grubunda HC grubuna göre anlamlı olarak düşüktü. Ferritin değerleri açısından iki grup arasında anlamlı fark yoktu.

Sonuç: Çalışmamız OKB hastalarında serum VitB12, FA ve VitD eksikliğinin etyopatogenez ile ilişkili olabileceğini göstermektedir. Bu çalışma, etiyopatogenez ile ilgili yeni araştırmalara öncülük edebilir. Bunun için tedavi sonrası dönemi de içeren prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Obsesyon, B12 vitamini, folik asit, ferritin ve D vitamini

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Received *(Geliş Tarihi)*: 31.07.2023 **Accepted *(Kabul Tarihi)*:** 16.08.2023

INTRODUCTION

Obsessive compulsive disorder (OCD) is a highly heterogeneous disorder characterized by obsessions and compulsions. Obsessions are unwanted and disturbing thoughts and images. Compulsions, on the other hand, are repetitive thoughts and behaviors done to eliminate or relax these disturbing thoughts.[1] OCD reduces the quality of life. It is one of the major causes of disability. It causes the loss of many social and occupational functions.[2,3] Its prevalence is around 1.6-2.3%.[4] In some epidemiological studies, the lifetime prevalence of OCD has been reported to be between 1.3-3%.[5,6] Despite the studies, it is a disorder whose etiopathogenesis is not fully understood.[7] Neurochemical, immunological and genetic factors are thought to play a role in the etiopathogenesis of OCD.[8] Due to limited information on etiopathogenesis, pharmacological and psychosocial interventions may be insufficient in OCD.[9] Therefore, it is important to find inexpensive and easily detectable biochemical parameters related to etiopathogenesis. On the other hand, it is known that levels of VitB12, FA, VitD and ferritin affect brain functions.[10-13] These vitamins and ferritin protein are necessary for various biochemical functions in our body. S-adenosylmethionine synthesis is decreased in vitamin B12 and FA deficiency. S-adenosylmethionine (SAM) deficiency is associated with many psychiatric diseases.[14] In addition, homocysteine levels increase in VitB12 and FA deficiency.[15,16] Increasing homocysteine may cause mitochondrial damage and oxidative stress, leading to various psychiatric disorders.[17] Homocysteine acts as an agonist for N-methyl-D-aspartate receptors. With the stimulation of these receptors, the intracellular secondary messenger Ca ion increases. It is thought that increasing Ca ion induces cell damage and prepares the ground for various psychiatric disorders.[18] In addition, high homocysteine may cause neurotoxicity in brain tissue by changing GABAergic and glutamatergic levels.[19] Homocysteine cannot be reconverted to methionine and SAM due to FA and VitB12 deficiency. SAM synthesis is also decreased with the increase of neurotoxic homocysteine. SAM deficiency causes hypomethylation. Hypomethylation can lead to disruption in the synthesis of neurotransmitters necessary for the structural integrity of the brain.[20] In addition, it is thought that VitB12 and FA may be effective in the treatment of OCD due to their relationship with neurotransmitters.

VitD was previously known to act only on calcium and phosphorus metabolism. With increasing technology, VitD is known to affect nearly 2000 gene regions on DNA today. For this reason, many studies are being conducted on VitD. These researches range from the antioxidant properties of VitD, its relationship with cardiovascular diseases, to cancer, and even to the fact that it is the most effective Vitamin against COVID-19. For all these reasons, VitD may be associated with psychiatric disorders.[21-24]

Iron is essential for life but too much iron is toxic. For this reason an iron storage protein is needed to regulate tissue and body iron homeostasis. Ferritin is one of the iron-storing proteins. In recent studies, it has been revealed that ferritin is not only an intracellular iron storage protein, but also has an important role in protecting brain cells against oxidative stress damage by binding excess iron.[25] The relationship between OCD and oxidative stress has been proven in many studies.[26] Therefore, there may be a relationship between OCD and ferritin. There are few studies investigating the relationship between OCD and serum VitB12, FA, VitD and ferritin. The results of these studies are different from each other.

Based on the aforementioned literature, our main aim in this study is to compare serum levels of VitB12, FA, VitD and ferritin between individuals with OCD and healthy control group and to investigate the relationship of these biochemical parameters with OCD.

MATERIAL AND METHOD

The study was carried out with the permission of Karamanoglu Mehmetbey University Clinical Researches Ethics Committee (Date: 01.06.2023, Decision No: 5-17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this retrospective study, the patient group was selected from the patients who applied to the Training and Research Hospital Psychiatry Clinic between January 1, 2017 and January 1, 2022. This study included a total of 50 treatment-naive patients who were diagnosed with OCD (study group). The patients with OCD were diagnosed by a psychiatrist, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria.

The control group was composed of people who donated to the hospital blood bank according to age and gender. The age range of the OCD and healty control (HC) groups was between 18 and 65 years. The control group consisted of a total of 50 healthy individuals (male 37, female 13). None of the control groups were using any medication or vitamin supplements. After obtaining the necessary permissions, a retrospective file search was performed in the hospital archive.

The levels of serum VitB12, FA, ferritin, and 25(OH)VitD were measured using commercially available kits based on routine methods on Maglumi X3/X8 System (Snipe Diagnostic, Shenzhen, P.R. China).

Statistical Analysis

The data were analyzed using the IBM SPSS 16.0 packet data software, with 95% confidence limits (p=0.05). In the statistical evaluation of biochemical tests, The Mann-Whitney U test was used. Data were given as mean values ± standard deviation (SD), as well as confidence interval values.

RESULTS

When the patient and control groups were compared in terms of age and gender, no statistically significant difference was found (data were not shown). The patient group consisted of 38 men and 12 women. In the patient group, in addition to the diagnosis of OCD, 3 patients had major depressive disorder and 2 patients had anxiety disorder. The age range of the patient group was 18-48. OCD onset age was 21±6.5 years. The duration of the disease was 16±3.2 months. The age range of the control group was 18-47 years (**Table 1**). Serum levels of VitB12 (p<0.001), FA (p=0.004) and VitD (p=0.001) were found to be lower in the OCD group than in the healthy control group. There was no significant difference between OCD and HC in terms of ferritin values (p=0.164), (**Table 2**). In the OCD group, VitB12 was below the normal limit in 12 patients, FA in 2 patients, and VitD in 32 patients (**Table 3**). Although it was higher in the control group than in the OCD group, VitD was below normal values in 14 patients (**Table 3**). In terms of ferritin, both groups were within the normal range, there was no deficiency or excess.

Table 1: Comparison of demographic values in obsessive compulsive disorder and healthy control groups.

Parameters	OCD (n= 50)	HC (n= 50)
	mean±SD / CI	mean±SD / CI
Age (years)	27.7±8.1 / 25.4-30.2	27.7±5.9 / 26.1-29.4
Gender (M/F)	37 / 13	38 / 12
BMI (kg/m2)	28.7	27.2
Age of onset	21±6.5	-
Duration (month)	16±3.2	-

OCD: obsessive compulsive disorder, HC: healthy control groups, BMI: Body Mass Index

Table 2: Comparison of vitamin B12, folic acid, Vitamin D and ferritin levels in obsessive compulsive disorder and healthy control groups.

Parameters	OCD (n= 50) mean±SD / CI	HC (n= 50) mean±SD / CI	p values
Vitamin B12 (pg/ml)	285±81.5 / 262-308	398±120 / 364-432	<0.001
Folic acid (ng/ml)	7.98±3.22 / 7.06-8.89	9.50±3.31 / 8.55-10.4	=0.004
Ferritin (ng/ml)	27.5±26.8 / 19.9-35,1	34.3±26.7 /26.7-41.9	0.164
Vitamin D (ng/ml)	10.4±4.57 / 9.11-11.7	13.6±4.79 / 12.3-15.0	=0.001

Note: CI: Lower and upper values at 95% confidence interval forthe mean. Mann-Whitney test. OCD: obsessive compulsive disorder, HC: healthy control groups, SD: standard deviation, CI:confidence interval

Table 3: Vitamin B12, folic acid, Vitamin D deficiency in obsessive compulsive disorder and healthy control group

Parameters	OCD (n= 50)	HC (n= 50)
Vitamin B12 (<210 pg/ml)	12	0
Folic acid (<3.1 ng/ml)	2	0
Vitamin D (<10 ng/ml)	32	14

OCD: obsessive compulsive disorder, HC: healthy control groups,

DISCUSSION

In this retrospective study, VitB12, FA, ferritin, and VitD levels were evaluated in the OCD group compared to the HC group. The low levels of VitB12 in the OCD group in our study are consistent with the literature. In the two most recent meta-analyses, the level of VitB12 was found to be somewhat lower than the healthy control groups of OCD.[27,28] In our study, the FA level was found to be significantly low in OCD studies.

In terms of FA, there are different results in the literature. While some specific OCD groups had higher FA levels than the healthy control group,[29] no difference was found between a study OCD and HC groups.[30] Consistent with our study, several studies have reported lower FA levels in the OCD group.[31] In the studies in the literature, the small number of patients in the groups and the fact that FA was affected by nutrition may have led to conflicting results.[32] In a study in the literature, it was reported that the addition of FA to the treatment-resistant OCD treatment was not beneficial.[33] This situation can be clarified with prospective studies with larger participation.

In our study, VitD levels were found to be significantly lower in the OCD group compared to the HC group. There are few studies in the literature investigating the relationship between OCD and VitD levels. Most of the studies were conducted in children and adolescent groups. In some studies, no significant difference was found in serum VitD in OCD patients compared to the HC group.[23,34] In a few studies, the VitD level was found to be significantly lower in the group with OCD, consistent with our study.[35-37] This difference between study results may be due to the fact that Vit D metabolism is affected by many factors.The relationship between OCD and serotonin, norepinephrine and dopamine has been demonstrated in various studies.[38-40] The active form of VitD, 1,25 dihydroxy vitamin D3, has a regulatory role for tryptophan hydroxylase and triosine hydroxylase enzymes. These two enzymes act as rate limiters in the synthesis of serotonin, dopamine norepinephrine and epinephrine. VitD can also act as an antioxidant by inhibiting inducible nitric oxide synthase.[41] VitD deficiency may play a role in OCD by both causing impaired neuroprotection and affecting serotonin and catecholamine synthesis. In some studies, it has been reported that VitD supplementation is beneficial for resistant OCD patients.[42] Larger, prospective studies are needed to support our findings and determine the efficacy of VitD supplementation in patients with OCD.

In our study, no significant difference was found between the OCD and HC groups in terms of serum ferritin levels. In a study involving all psychiatric patients treated at the hospital, a non-significant lower ferritin level was found in the group with OCD compared to other psychiatric diseases such as depression, bipolar, and schizophrenia.[43] In another study conducted in children with Tourette's syndrome, which is known to be associated with OCD, ferritin levels were found to be low. In this study, it was reported that patients' tics decreased with iron supplementation.[44] This study suggests that there may be a relationship between ferritin and OCD. Large prospective studies are needed to determine whether there is a relationship between OCD and ferritin. Considering the limited number of studies in the literature, our study can contribute to the literature at this point.

Limitations

Our study had some limitations. Our sample was small. It is a separate limitation that remission and subclinical OCD cases were not included in the study and the severity of OCD was not taken into account. In addition, the fact that the subtypes and severity of the disease were not evaluated was a limitation.

CONCLUSION

The low levels of serum VitB12, FA and VitD in OCD patients compared to the HC group in our study may lead to new studies to find pathways related to etiopathogenesis. Although there is sufficient evidence that deficiencies of these vitamins play a role in the etiopathogenesis of other psychiatric disorders, there is still no consensus on their relationship with OCD. It is possible that the deficiencies of these vitamins play a role in the etiopathogenesis of OCD through very different mechanisms. It may also guide studies encouraging the use of these vitamins in patients with treatment-resistant OCD. For this, prospective studies, including the post-treatment phase, are needed..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karamanoglu Mehmetbey University Clinical Researches Ethics Committee (Date: 01.06.2023, Decision No: 5-17).

Informed Consent: All participants in the study provided informed consent and written permission to publish their data.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1350836
J Contemp Med 2023;13(5):999-1007

Original Article / Orijinal Araştırma

An Investigation into the Assessment of Nutritional Status, Quality of Life, and Adherence to the Mediterranean Diet among Women Affected by Breast Cancer

Meme Kanseri Tanısı Almış Kadınlarda Beslenme Durumu, Yaşam Kalitesi ve Akdeniz Diyetine Bağlılığın Değerlendirilmesine İlişkin Bir Araştırma

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Abstract

Aim: The aim of this study is to assess the quality of life and adherence to the Mediterranean diet (MD) among female breast cancer patients.

Material and Method: The study included a cohort of 120 women who received a breast cancer diagnosis within the last year. Anthropometric measurements were conducted, and body composition analysis was carried out to determine body fat percentage. The Mediterranean Diet Adherence Scale (MEDAS) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) were employed for data collection.

Results: A total of 120 breast cancer patients, with an average age of 49.8±10.56 years, were enrolled in the study. Among these participants, 42.5% were categorized as having a normal weight. The mean waist circumference and waist/hip ratio were 94.6±12.20 cm and 0.87±0.10, respectively. Body fat percentages were determined to be 36.8±8.61%. The average total energy intake was 1944.9±385.24 kcal, with the percentage of total fat intake from energy averaging at 35.6±4.81%. Patients had a mean body mass index (BMI) of 29.0±5.80 kg/m^2, with 40.8% of them classified as obese. The mean MEDAS score was 7.3±2.65, and the EORTC QLQ-C30 score averaged at 69.7±11.94. There is a negative correlation was found between BMI, waist circumference and MEDAS score; A positive correlation was found between MEDAS scores and EORTC scores.

Conclusion: Breast cancer patients with high compliance with the Mediterranean diet have a higher quality of physical, emotional and social life. Therefore, evaluation of modifiable risk factors in breast cancer patients is essential for the prognosis of the disease.

Keywords: Mediterranean diet, breast cancer, quality of life, diet

Öz

Amaç: Bu araştımanın amacı meme kanseri tanısı almış kadınlarda yaşam kalitesi ve Akdeniz diyetine uyumun araştırılmasıdır.

Gereç ve Yöntem: Bir yıl içerisinde tanı almış 120 meme kanserli kadın araştırmaya katılmıştır. Bazı antropometrik ölçümler alınmıştır. Ayrıca Akdeniz Diyeti Kalite İndeksi (MEDAS) ve Avrupa Kanser Tedavi ve Organizasyon Komitesi Yaşam Kalitesi Ölçeği (EORTC QLQ-C30) kullanılmıştır.

Bulgular: Ortalama yaşları 49,8±10,56 yıl olan 120 meme kanserli katılımcının %42,5'i normal ağırlıktadır. Katılımcıların bel çevreleri ve bel/kalça oranları sırasıyla ortalama 94,6±12,20 cm, 0,87±0,10'dir. Vücut yağ yüzdeleri %36,8±8,61 olarak saptanmıştır. Toplam enerji alımları 1944,9±385,24 kkal ve toplam alınan yağın enerjiden gelen yüzdesi ortalama %35,6±4,81 olarak saptanmıştır. Hastaların beden kütle indeksi (BKİ) değerleri 29,0±5,80 kg/m² olup; %40,8'i obezdir. Ortalama MEDAS skoru 7,3±2,65; EORTC QLQ-C30 skoru ise 69,7±11,94'dur. Hastalarda BKİ, bel çevresi ile MEDAS skoru arasında negatif; MEDAS skorları ile EORTC skorları arasında pozitif korelasyon saptanmıştır.

Sonuç: Akdeniz diyeti uyumu yüksek olan meme kanseri hastalarının, fiziksel, duygusal ve sosyal yaşam kalitesi daha yüksektir. Bu nedenle meme kanserli hastalarda değiştirilebilir risk faktörlerinin değerlendirilmesi hastalığın prognozu açısından elzemdir.

Anahtar Kelimeler: Akdeniz diyeti, meme kanseri, yaşam kalitesi, diyet

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Received *(Geliş Tarihi)*: 27.08.2023 **Accepted *(Kabul Tarihi)*:** 23.09.2023

INTRODUCTION

Breast cancer stands as the predominant form of cancer in women and ranks as the second most prevalent cancer globally.[1] Reports indicate a growing awareness of the need for women who have survived breast cancer to prioritize the adoption of healthy lifestyle choices. This is not only critical for improving their quality of life before and after treatment but also for mitigating potential health complications associated with the treatment itself.[2] With rates of overweight and obesity reaching epidemic proportions, a significant proportion of newly diagnosed breast cancer patients embark on treatment already at risk of a poorer prognosis. Moreover, it's noteworthy that weight gain is a commonly observed adverse outcome during chemotherapy within the context of breast cancer treatment.[3,4] Weight gain during breast cancer treatment has been linked to an elevated risk of cancer recurrence, under-treatment, and increased mortality. These risks tend to escalate with greater weight gain.[5] Various factors contribute to weight gain during the course of breast cancer treatment, including the administration of adjuvant medications, reduced physical activity, the presence of depression, and inadequate nutritional intake.[6-8] Prioritizing the modification of diet and lifestyle factors to mitigate treatment-induced weight gain is of paramount importance for this patient population.[9] The Mediterranean diet (MD) has demonstrated associations with weight maintenance, enhanced quality of life, and the prevention of cancer recurrence in individuals diagnosed with breast cancer.[10] The protective effects of Mediterranean diet against breast cancer stem from its richness in fiber, antioxidants, flavonoids, vitamins, carotenoids, and olive oil. Additionally, the MD may influence breast cancer risk by reducing endogenous estrogens, elevating sex hormone binding globulin levels, neutralizing free radicals, preventing DNA damage, and reducing oxidative stress.[11] Available evidence suggests that adherence to the MD may positively impact the overall prognosis and longevity of women diagnosed with breast cancer.[12] Obesity significantly inceases the risk of developing breast cancer. The MD has the potential to mitigate obesity, thus reducing the risk of breast cancer by promoting weight management. Furthermore, the MD bears substantial implications in the context of breast cancer by playing a pivotal role in preventing disease progression, enhancing overall quality of life, and extending lifespan. This study aims to investigate dietary and lifestyle factors among individuals recently diagnosed with breast cancer.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara Medipol University Faculty of Health Sciences Ethics Committee (Date: 09/12/2020, Decision No: 51). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study encompassed female individuals aged 18 to 65 who sought medical care at a privately-owned oncology clinic and had received a breast cancer diagnosis within the previous year. The sample size for this research was determined using the G*Power 3.1 program, with an effect size of 0.5, a Type I error (α) level of 0.05, and a test power of 0.80 (α= 0.05, 1-β= 0.90), resulting in a minimum required sample size of 102. A total of 120 women diagnosed with breast cancer voluntarily participated in the study. The data collection period spanned from November 2020 to April 2021.

Exclusion criteria included individuals with a prior history of cancer treated with chemotherapy, those diagnosed with triple-negative breast cancer and tested negative for estrogen receptors (ER-), progesterone receptors (PR-), and human epidermal growth factor receptor 2 (HER-), as well as pregnant and breastfeeding individuals. Additionally, women with cognitive, visual, or hearing impairments that hindered effective communication were excluded from the study.

Participants were provided with comprehensive information regarding the study's content and objectives. Moreover, each participant who expressed their willingness to participate in the study read and signed an informed consent form. The researcher conducted face-to-face interviews to administer the questionnaire to the subjects.

The questionnaire comprises five distinct sections:

1. Demographic characteristics, disease information, dietary habits
2. Anthropometric measurements and body composition analysis
3. 24-hour food consumption record
4. Mediterranean Diet Adherence Scale (MEDAS)
5. European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 -Version 3.0)

Anthropometric Measurements and Body Composition Analysis

During a fasting state, body weight was measured with participants wearing light clothing and barefoot, and body composition was assessed using the segmental bioelectrical impedance analysis method. All measurements were conducted using a TANITA BC 601 bioelectrical impedance analyzer (BIA). Height measurements were also obtained by the researcher.[13] Body Mass Index (BMI) was calculated using the formula weight (kg) / height^2 (m^2) and categorized according to the World Health Organization (WHO) guidelines. Specifically, BMI was classified as follows: <18.50 kg/m^2 as underweight, 18.50-24.99 kg/m^2 as normal, 25.00-29.99 kg/m^2 as overweight, and ≥30.00 kg/m^2 as obese.[14]

The waist and the hip circumference of the participants was measured by the researcher. Waist circumference of individuals is classified according to WHO. Accordingly, a waist circumference of ≥80 cm in women was evaluated in the risk group in terms of metabolic complications. The waist-to-hip

ratio was determined by dividing the waist circumference measurement by the hip circumference measurement. A ratio of ≥0.80 in women, as per WHO guidelines, is considered a high risk factor for chronic diseases. The waist-to-hip ratio was determined by dividing the waist circumference measurement by the hip circumference measurement. A ratio of ≥0.80 in women, as per WHO guidelines, is considered a high risk factor for chronic diseases.[13]

24-hour Food Consumption Record

The dietary intake of patients over a 24-hour period was recorded and evaluated using the Computer-Aided Nutrition Program known as BEBIS 7.2.[15]

Mediterranean Diet Adherence Screener (MEDAS)

The Mediterranean Diet Adherence Screener (MEDAS) comprises 14 questions. This scale assesses factors such as the types of fats used in meals (e.g., margarine, butter, olive oil), daily olive oil consumption, fruit and vegetable portions, red meat consumption, weekly wine consumption, legumes, fish and seafood, nuts, cake consumption, tomato sauce with olive oil, and white meat vs. red meat consumption rates. Each question is assigned specific criteria based on consumption amounts, with 1 or 0 points allocated accordingly. The total score for all 14 questions is calculated, with a score of 7 or higher indicating acceptable adherence to the Mediterranean diet and a score of 9 or higher indicating strong adherence.[16]

European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30)

The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30) is widely recognized as one of the most reliable instruments for assessing the quality of life in cancer patients.[17] The EORTC QLQ-30 Quality of Life Scale, developed by Aaronson et al. [17] comprises 30 questions organized into three sections: global health status, functional score, and symptom score. The functional score section, consisting of 15 questions, assesses various aspects of functioning, including physical, role, emotional, cognitive, and social function. The symptom score section, composed of 13 questions, addresses symptoms such as fatigue, nausea and vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties. This section serves to elucidate prominent factors affecting the patient's quality of life. The last two questions in the scale pertain to general health function and overall assessment of the patient's quality of life. Responses to the first 28 questions employ a four-point Likert scale, with options ranging from "1- Not at all" to "4- A lot." In the 29th and 30th questions, patients are asked to rate their general health and general quality of life on a scale from "1- Very poor" to "7- Excellent." The cumulative scores derived from the entire scale are used to gauge the patient's quality of life through specific calculations. A higher score corresponds to a higher quality of life.

Statistical Analysis

The data obtained were statistically analyzed using the SPSS 24.0 software package in a computerized environment. Descriptive statistical measures, including the mean, standard deviation, minimum and maximum values, as well as percentiles, were employed for data summarization. Parametric tests were selected based on the fulfillment of their respective assumptions. Specifically, the Independent Sample t-test was utilized to assess mean differences between two independent groups. Analysis of variance (ANOVA) was applied when comparing more than two independent groups, with the Tukey post hoc test employed for identifying specific group differences when homogeneity of variances was met. Alternatively, the Tamhane's T2 test was used when homogeneity was not satisfied. In the evaluation of categorical data, the Chi-square test and Fisher's Exact test (with post hoc Benferroni corrected Z test when necessary) were conducted to determine both the direction and significance of relationships between variables. Pearson correlation coefficient was used to examine the relationship between two quantitative data sets. The predetermined level of statistical significance was set at 0.05.

RESULTS

The sociodemographic characteristics and disease-related profiles of the participants, along with anthropometric measurements and body composition analyses, are provided in **Table 1**. **Table 2** presents a comparative analysis of anthropometric measurements between premenopausal and postmenopausal women.

Table 1. Characteristics of participants (n=120)

Variables	n (%) or mean±SD (min-max)	
Age (year)	49.8±10.56 (21-65)	
Menopause		
Premenopause	60	50.0
Postmenopause	60	50.0
Menarche age	13.4±1.30 (11-16)	
Having children		
Yes	89	74.2
No	31	25.8
Age at first birth (year)	22.6±10.65 (17-35)	
Lactation duration (month)	11.6±8.77 (0-30)	
Smoking status		
Yes	7	5.8
No	88	73.4
Quit	25	20.8
Metastasis history		
Yes	45	37.5
No	75	62.5
Metastasis		
Bone	19	15.8
Brain	8	6.7
Lung	6	5.0
Liver	12	10.0
Cancer Stage		
1.Stage	37	30.8
2.Stage	45	37.5
3.Stage	21	17.5
4.Stage	17	14.2

Table 2. Comparison of anthropometric measurements of pre-menopausal and post-menopausal women

Variables	n (%) or mean±SD (min-max)						
	Premenapause (n=60)		Postmenapause (n=60)		Total		p
Body weight (kg)	74.8±13.23 (48.5-112.8)		74.7±16.29 (43.8-138.4)		74.8±14.77 (43.8-138.4)		t*=0.050 p=0.960
Height (cm)	158.7±4.49 (150.0-169.0)		162.5±6.25 (149.0-180.0)		160.6±5.75 (149- 180)		t*=-3.894 p=0.000
Body mass index (kg/m²)	29.8±5.26 (19.2-46.9)		28.3±6.26 (17.2-49.6)		29.0±5.80 (17.2- 49.6)		t*=1.393 p=0.166
BMI classification							
Underweight	2	3.3	3	5.0	5	4.2	
Normal	24	40.0	27	45.0	51	42.5	t*=3.696
Overweight	5	8.3	10	16.7	15	12.5	0.296
Obese	29	48.4	20	33.3	49	40.8	
Waist circumference (cm)	98.7±15.46 (68.0-136.0)		90.4±15.98 (63.0-147.0)		94.6±12.20 (63.0- 147.0)		t*=2.909 p=0.004
Waist circumference							
<80 cm	6	10.0	15	25	21	17.5	t*=4.675
≥80 cm	54	90.0	45	75	99	83.5	0.031
Hip circumference (cm)	106.6±10.87 (86.0-137.0)		108.2±12.56 (83.0-138.0)		107.4±11.71 (83.0- 138.0)		t*=-0.747 p=0.456
Waist-to-hip ratio	0.9±0.11 (0.7-1.2)		0.8±0.08 (0.7-1.1)		0.87±0.10 (0.71- 1.20)		t*=5.189 p=0.000
Waist-to-height ratio	0.6±0.10 (0.4-0.8)		0.6±0.11 (0.4-0.9)		0.6±0.10 (0.38- 0.89)		t*=3.119 p=0.002
Body fat (%)	38.4±7.48 (20.1-56.2)		35.2±9.40 (17.5-51.9)		36.8±8.61 (17.5- 56.2)		t*=2.102 p=0.038
Body fat (kg)	30.9±10.85 (11.0-56.1)		28.5±13.73 (8.5-71.8)		29.7±12.37 (8.5- 71.8)		t*=1.047 p=0.297
Body fat classification							
Low	2	3.3	3	5.0	5	4.2	t**=2.400
Moderate	14	23.3	21	35.0	35	29.2	p=0.301
High	44	73.4	36	60.0	80	66.6	
Body muscle mass (%)	57.0±6.42 (41.6-72.0)		60.3±7.87 (38.3-76.4)		58.7±7.34 (38.3- 76.4)		t**=-2.528 p=0.013
Body muscle mass (kg)	42.2±5.66 (26.6-54.1)		44.4±6.44 (38.3-76.4)		43.3±6.13 (22.0- 63.3)		t*=-2.013 p=0.046
Weight changes in the last 6 months							
Increased	38	63.3	35.0	58.3	73	60.8	t*=1.750
Decreased	19	31.7	18.0	30.0	37	30.8	p=0.417
Don't know	3	5.0	7.0	11.7	10	8.4	
Weight gain in the last 6 months (kg)	6.4±2.72 (2.0-14.0)		7.1±5.30 (2.0-20.0)		6.8±2.28 (2-20)		t*=-0.545 p=0.590
Weight loss in the last 6 months (kg)	6.4±3.57 (1.0-13.0)		4.0±1.38 (1.5-6.1)		5.4±1.73 (1-13)		t*=2.460 p=0.022

*Student t test

The study revealed that the participants had a daily energy intake of 1944.9±385.24 kcal, with 35.6±4.81% of their energy derived from fat, and an average daily carbohydrate consumption of 238.4±48.61 g per day (**Table 3**).

Table 3. Daily energy and macro nutrient intakes of participants

Energy and macronutrients	mean±SD (min-max)
Total Energy (kkal)	1944.9±385.24 (923-3147)
Carbohydrate (g)	238.4±48.61 (116-368)
Carbohydrate (%)	49.1±5.21 (32-62)
Protein (g)	76.5±23.86 (30-256)
Protein (%)	15.4±1.98 (10-27)
Fat (g)	80.3±33.64 (31-378)
Fat (%)	35.6±4.81 (22-47)
Average daily protein intake per kg	1.0±0.35 (0.46-4.11)
Fiber (g)	16.7±5.43 (11-36)

In **Table 4**, which presents a comparison of breast cancer stage among participants along with various variables, a significant association was observed between cancer stage and BMI (p<0.05).

The **Table 5** displays the MEDAS and EORTC QLQ scores, as well as its subscale scores, for the participants. The total score for MEDAS was 7.3±2.65, while the total score for the EORTC QLQ scale was 69.7±11.94.

MEDAS scores were observed to be higher in individuals who were underweight, possessed a waist circumference of 80 cm or less, exhibited a waist/hip ratio of 0.85 or below, maintained a waist/height ratio of 0.5 or below, and consumed less than 25% of their daily energy intake from fats. Those with higher MEDAS scores tended to report a higher quality of life. However, these differences were not found to be statistically significant (**Table 6**).

Table 4. Comparison of breast cancer stage with some variables (n,%)

Variables	1. Stage		2. Stage		3. Stage		4. Stage		Test*/p
	n	%	n	%	n	%	n	%	
Body mass index									
Underweight	1	2.7	3	6.7	-	-	1	5.9	
Normal	19	51.4	18	40.0	8	38.1	6	35.3	X²=30.390
Overweight	5	13.5	2	4.4	4	19.1	4	23.5	p=0.011
Obese	12	32.4	22	48.9	9	42.8	6	35.3	
Waist circumference (cm)									
< 80	6	16.2	10	22.2	4	19.0	1	5.90	X²=2.361
≥ 80	31	83.8	35	77.8	17	81.0	16	94.1	p=0.501
Waist-to-hip ratio									
< 0.85	21	56.8	22	48.9	11	52.4	7	41.2	X²=1.124
≥ 0.85	16	43.2	23	51.1	10	47.6	10	58.8	p=0.743
Waist-to-height ratio									
<0.50	9	24.3	11	24.4	4	19.0	2	11.8	X²=1.426
≥ 0.50	28	75.7	34	75.6	17	81.0	15	88.2	p=0.700
Daily fat intake (E%)									
< 25	2	5.4	-	-	1	4.80	-	-	X²=3.312
≥ 25	35	94.6	45	100.0	20	95.2	17	100.0	p=0.346

* Chi square test

Table 5. MEDAS and EORTC QLQ scores of the participants (n=120)

Scales	mean	SD	min	max
MEDAS	7.3	2.65	2	13
EORTC QLQ-C30	69.7	11.94	34.00	100.00
Functional Scales				
Physical functioning	79.4	18.74	26.67	100.00
Role functioning	79.0	21.77	33.30	100.00
Cognitive functioning	79.6	21.33	33.30	100.00
Social functioning	79.0	22.61	33.30	100.00
Emotional functioning	75.6	24.17	25.00	100.00
Global Health Status/QoL	78.7	21.42	16.67	100.00
Symptom Scales				
Pain	24.4	21.70	0.00	100.00
Nausea-vomiting	27.5	24.60	0.00	100.00
Fatigue	44.9	38.56	0.00	100.00
Constipation	42.6	36.54	0.00	100.00
Dyspnoea	23.6	20.32	0.00	100.00
Insomnia	47.9	31.62	0.00	100.00
Diarrhoea	33.3	34.17	0.00	100.00
Loss of appetite	26.6	31.57	0.00	100.00
Financial difficulties	28.0	33.74	0.00	100.00

QoL: Quality of life

It has been found that there is a strong positive correlation between body weight and BMI, WC, WHR, body fat (%), W/H, and energy intake ($p < 0.0001$). These findings indicate a close interrelation among metabolic factors such as body weight, BMI, WC, WHR, body fat (%), W/H, and energy intake ($p < 0.05$). A negative correlation was observed between the MEDAS score and body weight, BMI, WC, WHR, body fat (%), and W/H. While a weak negative correlation was found between fat intake (E%) and EORTC-QLQ, a weak positive correlation was found between fat intake (E%) and MEDAS. Furthermore, a weak negative correlation was found between MEDAS and EORTC-QLQ. This suggests that individuals with higher fat consumption may have a higher likelihood of experiencing cancer-related fatigue. A positive correlation was found between EORTC-QLQ and WC, WHR (**Table 7**).

Table 6. Comparison of MEDAS and EORTC total scores based on participants' anthropometric measurements and the overall fat content of their diets

Variables	EORTC		MEDAS	
	mean± SD	Test /p	mean± SD	Test /p
Changes in body weight (kg) (n=44)				
≤ +5	72.52±9.83	F*=0.004	7.3±9.60	F*=1.120
+6-10	72.39±1.,03	p=0.996	7.6±2.45	p=0.336
≥ +11	72.82±9.64		9.0±2.94	
Body mass index				
Underweight	71.01±10.31		9.2±3.76	
Normal	68.63±12.89	F*=1.062	7.2±2.66	F*=1.483
Overweight	66.88±9.47	p=0.155	6.5±2.06	p=0.142
Obese	72.95±10.04		6.9±2.52	
Waist circumference (cm)				
< 80	65.11±11.66	t**=-1.848	7.8±2.64	t**=0.958
≥ 80	70.58±11.81	p=0.067	7.2±2.65	p=0.340
Waist-to-hip ratio				
< 0.85	67.93±11.11	t**=-1.579	7.5±2.64	t**=1.189
≥ 0.85	71.43±12.58	p=0.117	6.9±2.65	p=0.237
Waist-to-height ratio				
< 0.50	68.31±14.05	t**=-0.638	8.1±2.62	t**=1.882
≥ 0.50	70.06±11.40	p=0.525	7.0±2.62	p=0.062
MEDAS Score				
< 7	68.40±12.48	t**=-1.339	-	-
≥ 7	71.36±11.11	p=0.183		
Daily fat intake (E%)				
< %25	67.15±16.10	t**=-0.374	7.3±2.51	t**=0.049
≥ %25	69.77±11.90	p=0.709	7.3±2.66	p=0.961
Metastasis				
Yes	70.75±11.64	t**=-0.727	6.73±2.64	t**=-1.693
No	69.09±12.15	p=0.705	7.57±2.62	p=0.093
Cancer stage				
1.stage	69.35±10.80		7.22±2.89	
2.stage	71.58±12.08	F*=1.129	7.38±2.55	F*=0.344
3.stage	70.05±13.03	p=0.340	7.52±2.35	p=0.794
4.stage	65.35±12.47		6.71±2.84	

*One Way Anova test, **Independent Sample t test

Table 7. Correlations between some variables in participants

Variables		Body weight	BMI	WC	WHR	Body fat (%)	W/H	Energy intake	Fat intake (E%)	MEDAS	EORTC--QLQ
Body weight	r		0.936**	0.786**	0.337**	0.767**	0.713**	0.634**	0.147	-0.157	0.088
	p		0.000	0.000	0.000	0.000	0.000	0.000	0.110	0.087	0.346
BMI	r	0.936**		0.873**	0.488**	0.831**	0.841**	0.528**	0.148	-0.102	0.115
	p	0.000		0.000	0.000	0.000	0.000	0.000	0.107	0.269	0.216
WC	r	0.786**	0.873**		0.753**	0.749**	0.950**	0.422**	0.176	-0.107	0.197*
	p	0.000	0.000		0.000	0.000	0.000	0.000	0.055	0.245	0.033
WHR	r	0.337**	0.488**	0.753**		0.383**	0.726**	0.133	0.204*	-0.078	0.229*
	p	0.000	0.000	0.000		0.000	0.000	0.149	0.025	0.399	0.013
Body fat (%)	r	0.767**	0.831**	0.749**	0.383**		0.720**	0.381**	0.054	-0.092	0.049
	p	0.000	0.000	0.000	0.000		0.000	0.000	0.554	0.316	0.599
W/H	r	0.713**	0.841**	0.950**	0.726**	0.720**		0.305**	0.144	-0.086	0.220*
	p	0.000	0.000	0.000	0.000	0.000		0.001	0.116	0.351	0.017
Energy intake	r	0.634**	0.528**	0.422**	0.133	0.381**	0.305**		0.136	0.011	0.017
	p	0.000	0.000	0.000	0.149	0.000	0.001		0.138	0.908	0.854
Fat intake (E%)	r	0.147	0.148	0.176	0.204*	0.054	0.144	0.136		0.021	-0.007
	p	0.110	0.107	0.055	0.025	0.554	0.116	0.138		0.820	0.939
MEDAS	r	-0.157	-0.102	-0.107	-0.078	-0.092	-0.086	0.011	0.021		0.210*
	p	0.087	0.269	0.245	0.399	0.316	0.351	0.908	0.820		0.022
EORTC-QLQ	r	0.088	0.115	0.197*	0.229*	0.049	0.220*	0.017	-0.007	0.210*	
	p	0.346	0.216	0.033	0.013	0.599	0.017	0.854	0.939	0.022	

Pearson correlation. *p<0.05. **p<0.005, WC: Waist circumference, WHR: Wait-to-hip ratio, W/H: Waist to height ratio, MEDAS: Mediterranean Diet Adherence Screener, EORTC-QLQ: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire

DISCUSSION

Physiological alterations are evident in individuals with breast cancer and the treatments they receive. While therapeutic modalities such as chemotherapy and radiation have shown effectiveness in managing the disease, they are associated with various adverse consequences, including cardiovascular, metabolic, and nutritional complications. These treatment-related complications have been observed to adversely affect various aspects of patients' well-being, including their aerobic capacity, fatigue levels, and muscle strength. These adverse effects have been found to contribute to the development of depressive symptoms, ultimately diminishing the overall quality of life experienced by individuals undergoing treatment[18] The importance of adopting a healthy lifestyle, characterized by consistent engagement in physical activity and adherence to proper nutrition, is emphasized as a means to mitigate the psychological and physiological side effects of medical treatment.[19] This study aimed to assess the correlation between anthropometric measurements, nutritional status, adherence to the Mediterranean Diet (MD), and the quality of life among women diagnosed with breast cancer.

It has been observed that women undergoing breast cancer treatment may experience weight gain. In women aged 40 or younger diagnosed with breast cancer, there is a phenomenon of ovarian function suppression, attributed to factors such as extensive chemotherapy, premature ovarian failure, or adjuvant endocrine therapy. The onset of menopause, characterized by treatment-induced amenorrhea, has been associated with an increased susceptibility to weight gain.[20] Maintaining an optimal body weight in women diagnosed with breast cancer has been shown to reduce the risk of disease recurrence, improve long-term survival rates, and lower the susceptibility to chronic diseases.[21,22] The findings of our investigation revealed that 60.8% of women experienced a change in body weight over the last six months (**Table 2**). Among these individuals, 45.5% reported a weight gain of 5 kg or less, while 51.8% reported a weight loss of 5 kg or less (not shown in the table). Considering these values, it was determined that the average weight gain in the last 6 months was 6.8±2.28 kg, and the average body weight loss in the last 6 months was 5.4±1.73 kg (**Table 2**). Based on these results, it was observed that the trends of weight gain and loss among women diagnosed with breast cancer were similar.

Obesity is known to contribute to increased inflammation in adipose tissue, creating an environment conducive to the initiation and progression of breast cancer. There exists a correlation between obesity and the incidence of postmenopausal breast cancer, as well as an elevated risk of breast cancer recurrence and mortality. A systematic meta-analysis of 82 studies, encompassing 213,075 breast cancer survivors and 23,182 breast cancer-related deaths, revealed a correlation between BMI and breast cancer survival.[23] Both low BMI (<18.5 kg/m^2) and high BMI (>27.0 kg/m^2) negatively affect the prognosis of breast cancer treatment. Specifically, chemotherapy-induced symptoms such as nausea, malaise, and fatigue can reduce treatment adherence, weaken immunity, lead to emotional distress, negatively impact quality of life, and result in increased appetite.[24] Our survey findings showed that 4.2% of women were categorized as "underweight" based on their BMI. The low number of underweight individuals may be attributed to the fact that 68.3% of our patients were in stages 1 or 2 of cancer (**Table 4**). Waist circumference measurement serves as an indicator of visceral adiposity, and as visceral adiposity increases, several metabolic and hormonal alterations occur, including the development of insulin resistance, reductions in sex hormone-binding globulin concentrations, and elevations in androgen levels and aromatization.[25] The international literature, predominantly based on data from developed societies, underscores that the risk of breast cancer is higher in women with abdominal adiposity compared to women with fat accumulation in the hips and lower extremities.[26] A study conducted by Lee et al.[27] aimed to assess the association between waist circumference and breast cancer. They found that the average waist circumference during the premenopausal period was 72.9±8.3 cm, while it was 79.9±8.4 cm during the postmenopausal period. Additionally, they observed that 19.6% of premenopausal women and 50.3% of postmenopausal women in the sample had a waist circumference over 80 cm. The study also revealed a statistically significant correlation between breast cancer and waist circumference. Our investigation yielded a mean waist circumference of 94.6±12.20 cm for the participants, with 82.5% of women having a waist circumference over 80 cm. In this study, waist circumference was found to be higher in premenopausal women than in postmenopausal women. (**Table 2**). Based on these findings, it is apparent that the average waist circumference of women is higher than reported in the literature, and this difference may be influenced by factors such as average age, BMI, and physical activity level. Consequently, these results suggest that excess waist circumference or waist-hip ratio is more strongly associated with postmenopausal breast cancer risk.[28] Studies investigating the relationship between waist-hip ratio and breast cancer risk have indicated that the risk of breast cancer increases with an elevated waist-hip ratio.[29] It is widely believed that individuals with a waist-hip ratio exceeding 0.85 are more susceptible to developing breast cancer. Our investigation revealed that the waist-hip ratio of participants was determined to be 0.87±0.10. Based on these findings, it was evident that the participants had a high waist-hip ratio, indicating an increased vulnerability to breast cancer when compared to existing literature. Recent research has indicated that women with a normal BMI but excessive body fat may be at an increased risk of breast cancer.[30,31] Excess body fat is closely associated with

adipocyte hypertrophy, and insulin resistance is a known consequence of excessive body fat.[32] In our study, the percentage of body fat in women diagnosed with breast cancer was 36.8±8.61%, while fat mass was 29.7±12.37%. According to the classification of fat mass, 66.6% of female participants had a "high" fat mass (**Table 2**). This finding aligns with existing literature, providing evidence that women diagnosed with breast cancer have a notable proportion of adipose tissue and overall body mass.

The Women's Health Initiative Randomized Controlled Dietary Modification study, a significant randomized controlled study conducted in the United States, investigated the impact of daily fat consumption quantity and fat type on the occurrence of breast cancer. This study included a total of 48,835 postmenopausal women. The results indicated that a low-fat diet potentially decreases the risk of developing breast cancer by approximately 9% when women who consume a low-fat diet (20% of total energy from fat) are followed for 8 years.[33] Secondary analyses suggested a potentially more significant decrease in risk among female participants who initially followed a high-fat diet as part of their regular eating habits. The study findings revealed that 97.5% of female participants had a daily fat consumption rate exceeding 25%, with an average daily total fat intake of 80.3±33.64 g. Based on these results, it is evident that the daily fat intake of the women participating in the study was high.[33] There is a suggestion that the specific type of fat ingested in one's dietary intake could potentially influence the likelihood of experiencing menopause. A meta-analysis found that postmenopausal women who consumed diets high in total fat and polyunsaturated fats had a higher risk of developing breast cancer, while dietary fat had protective effects in premenopausal women.[34] Our study findings revealed that a majority of the participants, specifically 53.3%, reported daily consumption of butter (not shown in the table). While the quantity of saturated fat consumed is indeed significant, it is crucial to note that excessive consumption of such lipids, which inherently contain saturated fat, can potentially raise concerns.

The World Health Organization defines quality of life as people's perceptions of their place in the culture and value system relative to their goals, expectations, standards, and concerns.[35] Quality of life is determined by the individual's functional health status, pain level, self-perception, and quality of interaction with their environment. A systematic review by Lis et al.[36] reported a strong association between nutritional status and quality of life in the cancer population. When evaluating the scale dimensions according to the EORTC QLQ-C30 Quality of Life Scale, which we used in our study to measure quality of life, the results were as follows: physical function (79.4±18.74), role function (79.0±21.77), mental function (79.6±21.33), social function (79.0±22.61), and emotional function (75.6±24.17). It was determined that the participants obtained the highest and lowest scores in the mental function and emotional function sub-dimensions, respectively (**Table 5**). It can be suggested that the participants exhibit a quality of life that exceeds the mean, enabling them to lead lives of high quality despite the presence of breast cancer. In a study by Montagnese et al.[37] which evaluated the effect of lifestyle changes for 12 months after treatment on the quality of life in women diagnosed with breast cancer, physical functionality, role function, and social functionality improved. However, certain indicators related to the quality of life showed a reduction. When the mean scores of quality of life symptoms were evaluated in our study, it was determined that dyspnea (23.6±20.32) had the lowest score, while the highest difficulty was experienced in sleeping (47.9±31.62). Based on this result, it can be concluded that dyspnea is one of the significant symptoms that negatively affect the quality of life in breast cancer patients in our sample.

Numerous studies and meta-analyses have explored the relationship between anthropometric measurements and breast cancer occurrence.[38-40] Positive associations have been reported between body mass index (BMI), waist-to-hip ratio, and the risk of developing breast cancer in previous research. One study involving breast cancer patients found that adherence to the Mediterranean Diet (MD) was associated with improved patient prognosis.[41] According to the literature, patients with high adherence to the MD had a 15-year overall survival rate of 63.1%, whereas patients with low compliance had a rate of 53.6%. Another study applied the MD to 100 individuals with breast cancer for 6 months, resulting in observed reductions in BMI and waist circumference.[41] According to epidemiological studies, a diet rich in fat, alcohol consumption, a sedentary lifestyle, and obesity play a significant role in breast cancer.[1] James and et al. have argued that BMI alone is not a sufficient measure for evaluating body fat composition and have advocated the use of waist-to-hip ratio (WHR) for assessing central obesity. Based on this, 16 studies were conducted to investigate the association between BMI and body fat (%) with breast cancer risk. These studies have shown a stronger relationship between WHR increase and breast cancer.[42] In our study, a strong positive correlation was found between BMI, WC, WHR, body fat (%), W/H, and energy intake. It was observed that calorie balance and fat ratio are more important than a specific diet for breast cancer. Studies conducted have similarly demonstrated that an increased fat intake in individuals with breast cancer is associated with a decreased quality of life.[43,44] In a study patients with higher MEDAS scores were found to have lower quality of life compared to those with lower MEDAS scores. Research also indicates that as waist circumference and waist-to-hip ratio increase in breast cancer patients, their quality-of-life decreases.[37] In our study, a positive correlation was observed between EORTC-QLQ and WC, WHR, which may be attributed to the participants being newly diagnosed and in the early stages of breast cancer (**Table 7**).

CONLUSION

This study aimed to highlight the impact of nutrition on breast cancer risk, drawing on a large body of basic molecular and cellular research on the disease. Weight gain during and after breast cancer treatment is associated with increased mortality, increased rates of obesity, cardiovascular disease, and diabetes. In our study, the quality of life scores of individuals diagnosed with breast cancer were found to be close to the average. The fact that MEDAS scores are close to the average shows that many patients tend to pay more attention to their eating habits after diagnosis. The energy and the nutrients consumed by the participants were within the normal range, and 50% or more of the participants were found to be overweight or obese. This cross-sectional study showed us that there is a negative relationship between the Mediterranean Diet and the increase in patients' values such as body weight, BMI and waist circumference, which are modifiable risk factors. It has also been found that as patients' diet quality increases, their quality of life also increases.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Medipol University Faculty of Health Sciences Ethics Committee (Date: 09/12/2020, Decision No: 51).

Informed Consent: Written informed consent taken from the patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Note: This article is extracted from first author's master thesis entitled “Meme Kanserli Kadınlarda Beslenme Durumu ve Yaşam Kalitesinin Saptanması”, supervised by Asst. Prof. Sine Yılmaz (Master’s Thesis, Ankara Medipol University, Ankara, Türkiye, 2022).

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1355300
J Contemp Med 2023;13(5):1008-1012

Original Article / Orijinal Araştırma

Tracheostomy Practices in Pediatric Intensive Care Unit, Single Center Experience

Çocuk Yoğun Bakım Ünitesinde Trakeostomi Uygulamaları, Tek Merkez Deneyimi

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Abstract

Aim: Tracheostomy is one of the most frequently performed surgical procedures in the pediatric intensive care unit (PICU). While it used to be an emergency treatment method in patients with laryngeal obstruction, it is now mostly used in patients with prolonged mechanical ventilation under elective conditions. In this study, we aimed to evaluate patients who underwent tracheostomy in our PICU, indications, and complications.

Material and Method: This retrospective study was conducted from February 2018 through April 2022. Data was collected from the patient's records and analyzed.

Results: Forty-three patients were included in the study. The median age of the patients was 5±4.99 (0-17 years) and 30 patients (69.8%) were male. During the four-year study period, the tracheostomy rate was 2.4% and the decannulation rate was 7%. The most common indication for tracheostomy was prolonged mechanical ventilation (88.3%). The median time of mechanical ventilation before tracheostomy was 68.33±27.22 (range 0-240) days. No surgical complications were observed during the PICU follow-up. All patients were discharged from PICU with a home-type mechanical ventilator. The median number of outpatient controls after discharge was 7.28±1.89 (range 3-10), and the median number of annual cannula replacements was 3.62±0.76 (range 1-5). 14 patients died after discharge from the PICU. The median time of death was 30±13.97 (range 11-56) months after discharge from the PICU. When the surviving and deceased patients were compared according to age, mechanical ventilation time, and length of stay in the PICU, no significant difference was found (p=0.291, p=0.115, and p=0.291, respectively).

Conclusion: In our study, long mechanical ventilation time was the most common indication for tracheostomy, and our result is consistent with the literature. Although the timing of tracheostomy was long, no significant correlation was observed with mortality.

Keywords: Pediatric intensive care, tracheostomy, decannulation, prolonged mechanical ventilation

Öz

Amaç: Trakeostomi çocuk yoğun bakım ünitesinde (ÇYBÜ) sık uygulanan cerrahi girişimlerden biridir. Önceleri laringeal obstruksiyonu olan hastalarda acil tedavi yöntemi iken günümüzde daha çok elektif şartlarda uzamış mekanik ventilasyon süresi olan hastalarda uygulanmaktadır. Bu çalışmada, ÇYBÜ'mizde trakeostomi uygulanan hastaları, endikasyonları, ve komplikasyonları değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu retrospektif çalışma Şubat 2018'den Nisan 2022'ye kadar gerçekleştirildi. Veriler hasta kayıtlarından toplandı ve analiz edildi.

Bulgular: Kırk üç hasta çalışmaya alındı. Hastaların ortanca yaşı 5±4.99 (aralık 0-17 yaş) ve 30 hasta (%69.8) erkek idi. Dört yıllık çalışma döneminde trakeostomi oranı %2,4 ve dekanülasyon oranı %7 bulundu. En sık trakeostomi uygulama endikasyonu uzamış mekanik ventilasyondu (%88.3). Trakeostomi öncesi entübasyon süresi ortanca 68.33±27.22 (aralık 0-240) gündü. Çalışmada yoğun bakım izlem sürecinde cerrahi komplikasyon izlenmedi. Tüm hastalar yoğun bakımdan ev tipi mekanik ventilatör ile taburcu edildi. Taburculuk sonrası poliklinik kontrol sayısı ortancası 7.28±1.89 (aralık 3-10), yıllık kanül değişim sayısı ortancası 3.62±0.76 (aralık 1-5) idi. 14 hasta ÇYBÜ'den taburcu olduktan sonra kaybedildi. Ölüm zamanının ortancası ÇYBÜ' den taburculuk sonrası 30±13.97 (aralık 11-56) aydı. Hayatta kalan ve ölen hastalar yaş, mekanik ventilasyon süresi ve ÇYBÜ' de kalış süresine göre karşılaştırıldığında arada anlamlı fark bulunmadı (sırasıyla p=0.291, p=0.115 ve p=0.291).

Sonuç: Bizim çalışmamızda uzun mekanik ventilasyon süresi trakeostomi açılması için en sık endikasyon olup sonucumuz literatür ile uyumludur. Trakeostomi zamanlaması uzun olsa bile mortalite ile arada anlamlı ilişki görülmemiştir.

Anahtar Kelimeler: Çocuk yoğun bakım, trakeostomi, dekanulasyon, uzamış mekanik ventilasyon

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Received *(Geliş Tarihi)*: 05.09.2023 **Accepted *(Kabul Tarihi)*:** 30.09.2023

INTRODUCTION

Tracheotomy refers to a surgical incision in the trachea. Tracheostomy, on the other hand, is a surgical procedure in which a stoma is created between the trachea and the skin. Tracheostomies have been performed since ancient times for various clinical conditions. Although it was not incorporated into routine clinical practice until the 19th century, it later became an emergency treatment method for patients with acute laryngeal obstruction due to diphtheria. [1] Initially used as a last resort for acute airway obstruction, this method had a high mortality rate in the early period. However, with the introduction of standard procedures and increased support for follow-up treatment by Chevalier Jackson in the early 20th century, mortality and morbidity significantly decreased. [2, 3]

Following the Copenhagen poliomyelitis epidemic in 1952, tracheostomy became the standard procedure for virtually all patients with respiratory failure. [4] As modern medicine advanced, tracheostomy, which was initially used routinely in patients with upper airway obstruction due to diphtheria and epiglottitis, began to be employed for various indications. In both adults and children, tracheostomy is used for acute or chronic upper airway obstruction, facilitating patient care in cases requiring long-term ventilation support, protection from aspiration, prevention of laryngotracheal stenosis in patients requiring prolonged intubation, and aiding weaning from a ventilator by eliminating the dead space created by the endotracheal tube. Common indications for tracheostomy in children include congenital and acquired airway stenosis, neurological conditions requiring prolonged intubation, bilateral vocal cord failure, and laryngeal stenosis due to infectious upper respiratory tract infection.[5-8] The timing, indications, techniques, and home care conditions for tracheostomy vary widely.[9-11] The outcomes of tracheostomy generally depend on factors such as age, comorbidities, patient anatomy, experience of the unit, timing of tracheostomy, and techniques used. [12-14] In this study, we aimed to evaluate patients who underwent tracheostomy, indications, and complications in our single-center experience.

MATERIAL AND METHODS

This retrospective study was conducted from February 2018 through April 2022. The study included patients aged 1 month to 18 years who were followed up in the pediatric intensive care unit (PICU) and underwent tracheostomy for the first time. Patients who had previously undergone tracheostomy in another hospital or department, as well as those under 1 month and over 18 years of age, were excluded from the study. Data regarding demographics (age, gender, race, underlying disease, genetic diagnosis), tracheostomy indications, time elapsed until tracheostomy after the indication, factors affecting the time between the indication and the procedure, location of the operation (operating room / PICU bedside), procedure duration, postoperative complications, tube replacement frequency, and reasons, infection details, and mortality were recorded. Indications, timing, early and late complications, and tracheostomy outcomes were collected and analyzed. Indications, timing, early and late complications, and tracheostomy outcomes were collected and analyzed. Patients were followed up at the hospital every two months for at least 6 months after discharge.

The decision for tracheostomy was made by a pediatric intensivist for all patients. A pediatric surgeon performed all of the tracheostomy procedures. A pediatric surgeon conducted all tracheostomy procedures, determining the timing of the procedure after obtaining informed consent from the parents in collaboration with the intensivist. A standardized tracheostomy procedure was followed in all cases. Most tracheostomies were performed in the operating room, with only a few emergency cases being performed bedside in the PICU.

Parents and caregivers actively participated in the care of tracheostomized patients. They received education on routine tracheostomy care, including suctioning and tube changing through demonstrations. Information brochures on care were provided to patients. Given that the PICU comprised isolated rooms allowing parents to stay with the patient, suitable hours were arranged for educational sessions. Parents and caregivers were also trained on equipment use such as suction catheters, suction machines, and pressure setup before discharge.

Statistical Analysis

Statistical analysis was done using the SPSS 25.0 (Statistical Program Social Sciences) program. In the evaluation of the data, the frequencies and percentages were given for the qualitative (qualitative) data. From quantitative descriptive statistical methods, mean and standard deviation were used for normally distributed data, while median widths and averages were used for non-normally distributed data. Data were expressed as means (SD), medians (interquartile range [IQR]), and proportions as appropriate. Kolmogorov-Smirnov test was used to determine the normal distribution of the data. The Mann-Whitney U test was used for comparisons between two groups of quantitative variables that did not show normal distribution. For all tests, a p-value <0.05 was considered statistically significant.

RESULTS

A total of 3822 patients were admitted to the PICU during the 4 years. 1722 patients were followed up with a mechanical ventilator. When these patients were examined according to prolonged mechanical ventilation time, the number of intubated patients for more than 14 and 28 days were 664 and 94, respectively. Tracheostomy was performed in 43 (2.4%) patients out of 1722 intubated patients. Considering

the prolonged mechanical ventilation period, tracheostomy was performed in 6.4% of the patients who remained on mechanical ventilation for more than 14 days and in 45.7% of those who remained on mechanical ventilation for more than 28 days. Intubated patients followed by PICU are shown in **Figure**.

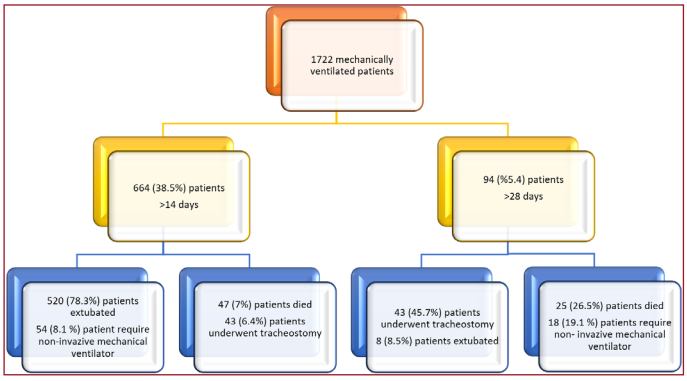

Figure: Detailed evaluation of the patients who were intubated in the PICU for 4 years, according to the length of stay on mechanical ventilator for 14 days and 28 days.

Of the 44 patients, 30 (69.8%) were male. The median age of the patients was 5±4.99 [Interquartile range (IQ) 0-17 years]. The median body weight of the patients was 18.51±4.99 (IQ range, 0-70) kilograms. There was a chronic disease in 38 patients (86.3%). Eleven patients (25.5%) had tracheostomy performed within the first year of life. The most common indication for tracheostomy was prolonged mechanical ventilation secondary to cerebral palsy and neuromuscular diseases. The clinical features of patients and tracheostomy indications are given in **Table 1**. Tracheostomy was performed in 39 (90.7%) patients in the operating room under elective conditions, and in three patients (1.3%) in the PICU due to emergency. The indication for tracheostomy was prolonged mechanical ventilation (PML) in 38 (88.4%) patients and anatomical defect in five (7%) patients. The distribution of the patients according to the underlying diseases is given in **Table 1**. The median duration of tracheostomy after admission to the PICU was 115.51±14.39 (IQ range, 0-70) days; it was 68.33±27.22 (range 0-240) (IQ range, 0-240) days after undergoing the mechanical ventilator. The reason for the late implementation of the tracheostomy was that the parents did not give their consent to the medical staff due to their anxiety and fear about tracheostomy care. Only 3 patients were accidentally decannulated in the early period, and other complications such as wound infection, bleeding, or trachea-innominate artery injury were not observed in the study. After discharge, wounds occurred at the entrance area in 3 patients and granulation tissue in 4 patients. The median length of stay in the PICU after tracheostomy was 31 days (IQ range, 9-182)

Table 1: Demographics and clinical features of patients who underwent tracheostomy

	N (%)
Gender	
Female	13 (30.2)
Male	30 (69.8)
Age	
< 1 year	11 (25.5)
1-5 years	18 (41.8)
> 5 years	14 (32.5)
Underlying chronic disease	38 (88.3)
Cerebral palsy	15 (34.8)
Neuromuscular disease- neurologic disorder	8 (18.6)
Diagnosed genetic disorder	5 (11.6)
Metabolic disorder	5 (11.6)
Congenital cardiac defect	3 (6.9)
Chronic lung disease (bronchopulmonary dysplasia, pulmonary alveolar proteinosis)	2 (4.6)
Previously healthy child	5 (11.6)
Traumatic craniofacial anomaly	3 (6.9)
Anatomical defect (laryngeal stenosis, thoracic tumor)	2 (4.6)
Tracheostomy Indications	
Prolonged mechanical ventilation	38 (88.4)
Upper airway obstruction	2 (4.6)
Traumatic craniofacial anomaly	3 (6.9)

All patients were discharged from the PICU. Only three (7%) patients were able to be decannulated at follow-up. The median number of one-year visits to the outpatient clinic for tracheostomy care in the post-discharge period was 7.2±1.8 (IQ range, 3-10), and the median number of one-year cannula replacements was 3.6±0.7 (IQ range, 1-5) times. In the study, 14 (32.6%) patients died, the median time of death was 30±13.9 (IQ range,11-56) months after tracheostomy placement. All patients died after discharge. Although the rate of patients who died in infancy was higher, there was no statistically significant difference. In the study, when the surviving and non-survived patients were compared according to their ages, length of stay in PICU, and mechanical ventilation periods, no statistically significant difference was found (p values p=0.102, p=0.291, p=0.115, respectively) (**Table 2**). The median survival time of 29 patients who survived after tracheostomy was 39.28±9.14 (IQ range, 16-54) months.

Table 2: Comparison of surviving and deceased patients by age, duration of mechanical ventilation, and length of stay in the PICU

	Total N (%)	Survived N (%)	Non-survived N (%)	p
Age				
0-2 years old	20 (46.5)	13 (65)	7 (35)	0.102
2-17 years old	23 (53.8)	16 (69.5)	7 (30.4)	
Duration of mechanical ventilation				
<28 days	4 (9.3)	13 (33.3)	1 (25)	0.115
>28 days	39 (90.6)	26 (66.6)	3 (75)	
Length of stay in PICU				
<21 days	2 (4.6)	1 (3.4)	1 (71.4)	0.291
>21 days	41(95.3)	28 (96.5)	13 (92.8)	

PICU: Pediatric intensive care unit

DISCUSSION

In recent years, there has been a notable increase in the rate of tracheostomies performed on children, a trend closely linked to advancements in neonatal and pediatric intensive care. While tracheostomy was initially employed as an emergency life-saving measure, a significant portion of tracheostomized

children now constitute a highly complex patient group heavily reliant on tracheostomy and associated medical technologies for their long-term survival. [1-5, 13] In our study, tracheostomy was carried out as an emergency treatment in only 6.9% of cases. The majority of patients underwent tracheostomy due to the necessity for prolonged mechanical ventilation. Notably, our study showed a smaller proportion of patients with upper airway obstruction compared to other studies (4.6%). [7,14]

All patients in our study were discharged from the PICU after undergoing tracheostomy. The discharge rate observed in our study was higher than reported in other studies.[14, 15, 16] The ability to discharge 45.7% of patients intubated for more than 28 days is of significant importance for PICU operations. This allows for the admission of new patients and aids in cost management, particularly in regions where specialized palliative care centers are scarce and there is a limited number of intensive care beds Presently, a distinct objective is to transition patients to palliative care centers by implementing tracheostomy at an early stage, particularly in cases of chronic diseases where significant improvement is not anticipated. This transition aims to alleviate PICU occupancy rates and optimize healthcare resource utilization.

The literature strongly advocates for performing tracheostomies in pediatric patients during the early stages of their care. Various publications emphasize that prolonged ventilation before tracheostomy is linked with increased morbidity and extended stays in the PICU. Early tracheostomy has been proposed to offer substantial benefits without affecting mortality rates. [17, 18] However, in this study, the timing of tracheostomies was notably delayed. The primary reason for this delay was the absence of a pediatric intensive care specialist during the initial year and the extended intubation periods experienced. This delay was attributed to the fear, panic, and anxiety of families in this regard. Educating families is crucial to mitigate these concerns. In developed countries, tracheostomy care relies on skilled multidisciplinary teams, encompassing physicians, nurses, respiratory physical therapists, speech therapists, dietitians, and psychologists, with extensive professional expertise. [19-21] In our country, specialized teams of this nature are lacking, leading families to feel uncomfortable and insecure about the procedure.

The majority of the cases in this study involved boys (69.8%) aligning with similar findings in other studies. [14, 19, 20] Existing literature notes that a significant proportion of patients undergoing tracheostomy are under the age of one. [14,19, 21,22] However, in our study, a lower number of infants were observed, with 74.3% of patients being over one year old. Several factors may contribute to this observation, including the patient population studied, the occurrence of tracheostomies in neonatal intensive care units for patients with congenital defects (thus not being included in our study), and cultural or ethnic reasons, which sometimes prompt families to consent to tracheostomy at a later stage.

In our study, the rate of the patients being decannulated was notably low compared to the other studies in Turkey. [17, 23-28] This discrepancy is believed to be attributed to the high number of patients with underlying chronic conditions in our study. The literature does not provide specific guidance on the duration between cannula changes in pediatric patients. However, it is generally deemed safe to change the cannula after the third day. [29, 30] Subsequently, we observed that the average time for cannula changes after discharge was notably prolonged.

In our study, all patients were discharged home with a home ventilator, and no serious complications were observed during the follow-up period in the intensive care unit. The absence of tracheostomy-related fatalities aligns with findings from comparable studies in our country. [16, 20, 27, 31] Prolonged mechanical ventilation remains the most common indication, consistent with other studies. [16, 20, 27, 28] Upon examining the underlying chronic conditions of our patients, a notable proportion had hypoxic-ischemic encephalopathy and cerebral palsy which significantly contributes to this trend. Comparing patients with survived and those who did not, there were no significant differences in terms of age, duration of mechanical ventilation, and length of stay in the PICU. Interestingly, despite the extensive tracheostomy use and prolonged PICU stay observed in our study, the lack of significant differences can be attributed to the relatively low incidence of sepsis due to resistant bacterial infections, a common complication of extended hospitalization. The isolated room set up in our PICU and the comprehensive care training of our medical team (including nurses and allied health personnel) also played a role. Additionally, families often refrained from giving informed consent for tracheostomy in patients with no life expectancy, regardless of the duration of mechanical ventilation.

Our study has some limitations. First, it is a single-center retrospective study. Second, the number of patients is insufficient to assess the outcome of patients in different subgroups (upper airway obstruction).

CONCLUSION

In conclusion, our study aligns with other research regarding tracheostomy indications and the patient population. Tracheostomy remains the primary option for patients with chronic underlying diseases who necessitate prolonged mechanical ventilation and need to be discharged from the PICU. Similar to previous studies, our findings demonstrate that tracheostomy, when performed under intensive care conditions, carries a low mortality and morbidity rate. A notable challenge in our study was the prolonged timing of tracheostomy and the extended length of stay in the PICU. This issue underscores the critical role of pediatric intensivists and their involvement in patient management. We believe that addressing this challenge requires proactive engagement with parents, encouraging them to consider tracheostomy.

This proactive approach can ensure better post-discharge healthcare team support, organized by healthcare providers, and educate parents on proper care for their children at home once the clinical situation has stabilized.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Mersin University Clinical Researches Ethics Committee (Date:15.12.2021. Decision Number: E-1854281).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Acknowledgment: The authors thank to the nurses and medical staff of the PICU and operating room department. We would like to thank the patients' families for allowing the information to be shared.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1355833
J Contemp Med 2023;13(5):1013-1017

Original Article / Orijinal Araştırma

The Effect of Entecavir and Tenofovir Disoproxil on Bone Mineral Density in Chronic Hepatitis B Treatment

Kronik Hepatit B Tedavisinde Entekavir ve Tenofovir Disoproksilin Kemik Mineral Yoğunluğuna Etkisi

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Abstract

Aim: Evaluation of the relationship between drugs and osteoporosis in patients receiving entecavir (ETV) or tenofovir disoproxil fumarate (TDF) treatment for chronic hepatitis B infection (CHB).

Material and Method: The study included patients who received ETV or TDF treatment for at least 12 months between 2016 and 2021 and underwent bone mineral densitometry (BMD) measurement at different times during the treatment period. Demographic characteristics of the patients and the association of antiviral drug use with osteopenia/osteoporosis were evaluated. retrospectively.

Results: The study included 170 patients, 92 (54.1%) of whom were male, with a mean age at diagnosis of 36.57±14.88 years. Of the patients, 24 (14.1%) were on ETV and 146 (85.9%) were on TDF. The mean age at BMD measurement was 48.62±13.4 years. The median time from diagnosis to BMD was 138.5 (15-373) months. Osteopenia/osteoporosis was found in 14 (15.2%) of male patients and 25 (32.1%) of female patients. The frequency of osteopenia/osteoporosis was significantly higher in women (p=0.011). There was no significant difference in the frequency of osteopenia/osteoporosis between ETV and TDF (p=0.112). Lumbar spine (LS) BMD was significantly higher in TDF users (p=0.043). While no patient had a BMD within 12 months of treatment initiation, 6 (3.5%) of the patients had a BMD within 24 months, 8 (4.7%) within 36 months and 25 (14.7%) within 60 months of treatment initiation.

Conclusion: There was no significant difference in the development of osteopenia/osteoporosis in patients using TDF and ETV. It was found that bone mineral measurements of patients with CHB were not performed regularly and appropriately.

Keywords: Chronic hepatitis B, osteoporosis, tenofovir disoproxil fumarate, entecavir.

Öz

Amaç: Kronik hepatit B enfeksiyonu (KHB) nedeniyle entekavir(ETV) veya tenofovir disoproksil fumarat (TDF) tedavisi alan hastalarda ilaçların osteoporoz ile ilişkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: 2016-2021 yılları arasında en az 12 ay boyunca ETV veya TDF tedavisi başlanan ve sonraki takiplerinde kemik mineral dansitometri (KMD) ölçümü yapılan hastaların demografik özellikleri ile antiviral ilaç kullanımının osteopeni/ osteoporoz ile ilişkisi retrospektif olarak değerlendirildi.

Bulgular: Çalışmaya 92'si (%54,1) erkek, ortalama tanı yaşı 36,57±14,88 yıl olan 170 hasta dâhil edildi. Hastaların 24'ü (%14,1) ETV, 146'sı (%85,9) ise TDF kullanıyordu. Ortalama KMD ölçüm yaşı 48,62±13,4 yıl idi. Tanıdan itibaren KMD'ye kadar geçen süre ortanca 138,5 (15-373) ay idi. Erkek hastaların 14'ünde (%15,2), kadın hastaların ise 25'inde (%32,1) osteopeni/osteoporoz saptanırken, kadınlarda osteopeni/osteoporoz sıklığı anlamlı olarak daha yüksek idi (p=0,011). ETV ve TDF arasında osteopeni/osteoporoz sıklığı açısından anlamlı farklılık izlenmedi (p=0,112). KMD parametrelerinde Lomber spine(LS) KMD TDF kullananlarda anlamlı olarak daha yüksek idi (p=0,043). Tedavi başlandıktan sonra 12 ay içinde hiçbir hastaya KMD istenmezken, hastaların 6 'sına (%3,5) tedavi başlandıktan sonraki 24 ay içinde, 8'ine (%4,7) 36 ay içinde, 25'ine de (%14,7) 60 ay içinde KMD istenmişti.

Sonuç: TDF ve ETV kullanan hastalarda osteopeni/osteoporoz gelişimi açısından anlamlı farklılık saptanmadı. KHB'si olan hastaların kemik mineral ölçümlerinin düzenli ve uygun bir şekilde yapılmadığı saptandı.

Anahtar Kelimeler: Kronik hepatit B, osteoporoz, tenofovir disoproksil fumarat, entekavir.

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Received *(Geliş Tarihi)*: 06.09.2023 **Accepted *(Kabul Tarihi)*:** 26.09.2023

INTRODUCTION

Despite an effective vaccination program, CHB infection continues to be a major global health problem, affecting nearly 300 million people and causing approximately 900,000 deaths annually due to cirrhosis and hepatocellular carcinoma (HCC), according to data released by the World Health Organization.[1]

Although hepatitis B surface antigen (HBsAg) seroconversion is expected in the treatment of CHB, treatment continues throughout the patient's life since seroconversion occurs at low rates. The aim of treatment is to prevent disease progression and the development of cirrhosis and hepatocellular carcinoma.[2-5]

Nucleos(t)it analogs such as ETV, TDF and tenofovir alafenamide fumarate (TAF) are used in treatment due to their high antiviral efficacy and favorable long-term safety profile.[2-5]

Hepatic osteodystrophy is a general term used to describe metabolic bone diseases that develop in patients with chronic liver disease. The definition of hepatic osteodystrophy includes both osteopenia and osteoporosis.[6] There are many factors that cause osteoporosis in liver diseases. Malnutrition due to impaired liver function, malabsorption and impaired vitamin D synthesis are the main factors. In addition, deficiency of albumin and binding globulins involved in vitamin D transport also contributes to the mechanism. Diuretics, steroids and antiviral drugs used in treatment are also suspected. Studies in animal models have shown that tenofovir, one of the antiviral drugs, decreases bone mineral density.[7,8]

In our study, we aimed to evaluate the relationship between antiviral drugs and osteopenia/osteoporosis and the status of screening examinations in patients receiving ETV or TDF treatment for CHB infection with real-life data.

MATERIAL AND METHOD

The study included patients aged 18 years and older who received ETV or TDF treatment for at least 12 months between 2016 and 2021 and had bone mineral densitometry (BMD) measurements during the treatment period.Patients using specific drug groups [such as glucocorticosteroids (5 mg prednisone or equivalent for at least 3 months), anticonvulsants, anticoagulants, long-term proton pump inhibitors], have hyperthyroidism, hyperparathyroidism, cirrhosis, and alcohol-dependent patients were excluded. (**Figure 1**). Patients' age at diagnosis, gender, menopausal state, chronic HBV medications, follow-up period and BMD results were evaluated retrospectively by scanning from the hospital electronic information system. HBV DNA was found to be <20 IU/ml in patients receiving antiviral treatment and the disease was considered inactive. Vitamin D levels were not included because of the long follow-up period.

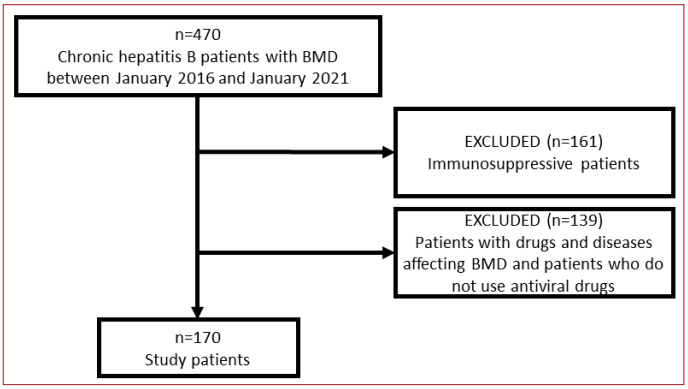

Figure 1. Flow chart of patients included in the study

BMD was measured by dual-energy X-ray absptiometry (DEXA). All DEXA measurements were made using the Hologic Discovery scanner and evaluated by the same person. T-score was used in postmenopausal women and men over 50 years of age, Z-score was used in premenopausal women and men under 50 years of age.T-score less than -2.5 standard deviation (SD) was defined as osteoporosis, between -1 and -2.5 SD as osteopenia and SD greater than -1 as normal. A Z score of -2 SD and below was considered as "lower than expected bone mass for chronological age/osteoporosis" and above -2 as "normal bone mass for chronological age/normal".[9]

Ethical Consideration

The study was carried out with the permission of Karadeniz Technical University Faculty of Medicine Ethics Committee (Date:13.01.2022 Decision no:315). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

SPSS Windows version 22 program was used for statistical tests. Continuous variables were evaluated in terms of normal distribution by histogram, Q-Q graph and Shaphiro-Wilk or Kolmogorov-Smirnov tests according to the number of variables. The normally distributed continuous variables were presented as mean±standard deviation throughout the study and independent-variables t-test was used to compare the two groups.

Other continuous variables were presented with median (minimum-maximum) values and the nonparametric Mann-Whitney U test was used to compare the groups.

Categorical variables were presented as frequencies and percentages, and Pearson Chi-square test or Fischer's exact probability test was used to compare the groups. Tests with a p value of 0.05 or less at the 95 percent confidence interval were considered statistically significant.

RESULTS

The study included 170 patients. 92 (54.1%) of the patients were male and 78 (45.9%) were female. The mean age at diagnosis was 36.57±14.88 years and the mean age at

BMD measurement was 48.62±13.4 years. The mean age at diagnosis and age at BMD assessment were lower in women than in men (p=0.014, p=0.004, respectively. Twelve (7.1%) of the patients at the time of diagnosis and 18 (10.6%) at the time of drug initiation were aged 60 and over. The median time from diagnosis to BMD was 138.5 (15-373) months. Of the patients, 24 (14.1%) were on ETV and 146 (85.9%) were on TDF. The median duration of TDF use was longer than ETV (p=0.001). Osteopenia/osteoporosis was found in 14 (15.2%) of male patients and 25 (32.1%) of female patients, and the frequency of osteopenia/osteoporosis was significantly higher in women (p=0.011) (**Table 1**).

Table 1. Demographic characteristics of the patients

Value		p
Male/Female, n (%)	92 (54.1) / 78 (45.9)	
Antiviral drug, n (%)		
ETVa	24 (14.1)	
TDFb	146 (85.9)	
≥ 60 years, n (%)		
Diagnosis	12 (7.1)	
Medication initiation	18 (10.6)	
Age (Diagnosis), mean± SD	36.57±14.88	
Male	39.14±14.75	0.014*
Female	33.54±14.55	
Age** (BMDc), mean±SD	48.62±13.4	
Male	51.35±13.36	0.004*
Female	45.41±12.81	
Osteopenia/osteoporosis, n (%)		
Male	14 (15.2)	0.011†
Female	25 (32.1)	

*:t Test, †: Chi-square test SD: Standard derivation,
**at diagnosis time, a :Entecavir , b :Tenofovir disoproxil fumarate, c :Bone mineral density

During the period from diagnosis to BMD, osteopenia or osteoporosis was detected in 9 (37.5%) patients on ETV and 30 (20.5%) patients on TDF, but there was no significant difference in the frequency of osteopenia/osteoporosis between drugs (p=0.11).

When BMD was analyzed, LS BMD was significantly higher in TDF users (p=0.043), while no significant difference was found in LS T/Z-score, Femoral Neck (FN) BMD, FN T/Z-score, Total Femur (TF) BMD and TF T/Z-score (p>0.05) (**Table 2**).

None of the patients had a BMD within 12 months of treatment initiation. 6 (3.5%), 8 (4.7%) and 25 (14.7%) patients had a BMD within 24, 36 and 60 months, respectively (**Table 2**).

DISCUSSION

TDF and ETV are antiviral drugs that have a high genetic barrier in CHB, reduce liver-related mortality and are recommended in first-line treatment.[2,10,11] In our study, we investigated the effect of antiviral drugs on BMD in patients receiving TDF or ETV treatment.

TDF use may cause osteoporosis through various pathways including the development of Fanconi syndrome and hypophosphatemic osteomalacia by accumulating in the proximal tubule and decreasing bone formation by decreasing osteoblast gene expression.[12-14] The decreasing effect of TDF on BMD has been demonstrated primarily in HIV patients and then in monoinfected CHB patients in various studies.[15-17]

In the study conducted by Wei et al.[18] in the USA examining the effect of ETV and TDF on BMD in patients using ETV or TDF, no increase in the risk of osteopenia/osteoporosis was found in the short and medium term. In our study, osteopenia/osteoporosis was found in 30 (20.5%) patients on TDF, while osteopenia/osteoporotikse was found in 9 (37.5%) patients on ETV, and no significant difference was found in the frequency of osteopenia/osteoporosis between the two drugs (p=0.112).

Table 2. Association of antiviral drugs with BMD

Value	ETVa	TDFb	p
BMD*, n (%)			
Normal	15 (62.5)	116 (79.5)	0.112†
Osteopenia/osteoporosis	9 (37.5)	30 (20.5)	
Gender, n (%)			
Male	13 (54.2)	79 (54.1)	1†
Female	11 (45.8)	67 (45.9)	
Duration of drug use, months mean±SD	37.42±28.65	57.97±28.02	0.001*
Age(Diagnosis), year	40.38±16.21	35.95±14.62	0.177*
BMD, diagnosis(month)	124.83±88.13	154.68±82.34	0.105*
LSc BMD,mean±SD	1.07±0.213	1.15±0.181	0.043*
LS T/Z-score, mean±SD	-0.5042±1.8066	0.0784±1.4071	0.073*
FNd BMD, mean± SD	0.9199±0.1869	0.9588±0.1513	0.262*
FN T/Z-score, mean±SD	-0.3833±1.4621	-0.1959±1.2227	0.500*
TFe BMD, median (iqr)	0.931 (0.16)	1.007 (0.22)	0.071 ‡
TF T/Z-score, mean± SD	-0.4042±1.519	-0.0055±1.197	0.148*
Time to BMD month			
12	0	0	
24	2 (8.3)	4 (2.7)	0.201†
36	4 (16.7)	4 (2.7)	0.015†
60	4 (16.7)	21 (14.4)	0.758†

*: t Test, †: Chi-square test , ‡: Mann-Whitney u test SD: Standard derivation, iqr: Interquertile range, * :Bone mineral density, a :Entecavir, b : Tenofovir disoproxil fumarate, c:Lomber spine, d :Femoral neck, e :Total femur

In the meta-analysis including 16 studies conducted by Yang et al. no significant difference was found in the incidence of osteoporosis/osteopenia between patients using TDF and ETV (p=0.13).[19] In our study, despite the longer duration of TDF use, LS BMD was higher than ETV (p=0.043), while no significant difference was found in L1-L4 T-score, FN BMD, FN T-score, TF BMD and TF T-score (p>0.05).

Tenofovir alafenamide (TAF) molecule, the new formulation of tenofovir, is thought to have less negative effects on bone health. In a double-blind randomized study by Seto et al.[20] it was found that patients who received TDF for 2 years had a greater decrease in hip and spine bone mineral density than patients who received TAF. Due to the long-term use of TDF, which is associated with a decrease in BMD, studies examining its effect on the development of osteopenia/osteoporosis are of special importance.

The EASL 2017 guideline recommends switching TDF to TAF or ETV in patients aged 60 years and older and in patients with existing bone disease (stress fractures, long-term use of corticosteroid drugs, osteoporosis) because of the high risk of side effects.[2] In our study, 18 (10.6%) of the patients were 60 years of age or older at the time of drug initiation, and 13 (72.2%) of these patients were started on TDF.

According to the Turkish Society of Endocrinology and Metabolism (TEMD) guideline, BMD measurement is recommended for every patient with a diagnosis of chronic liver disease. An evaluation should also be performed due to the additional risks that may occur on bone metabolism after the initiation of antiviral agents.[21] In our study, only 6 patients (3.5%) had BMD measurement within 24 months after initiation of treatment.

The most important limitations of our study are that it was retrospective and single centered. In addition, the number of patients on ETV and TDF is not evenly distributed.

The age at diagnosis is probably earlier, but the accepted date of diagnosis of the disease was taken as the date of first detection.

CONCLUSION

In conclusion, in our study, although the duration of TDF use was longer in patients receiving ETV or TDF treatment, no statistically significant difference was found in osteoporosis/osteopenia rates. More long-term and prospective studies are needed to examine the effects of antiviral treatments on the development of osteopenia/osteoporosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karadeniz Technical University Faculty of Medicine Ethics Committee (Date: 13.01.2022, Decision no: 315).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1342668
J Contemp Med 2023;13(5):1018-1023

Original Article / Orijinal Araştırma

Evaluation of the Quality and Reliability of YouTube Videos on Premature Ventricular Contraction

Prematüre Erken Kontraksiyon ile İlgili YouTube Videolarının Kalite ve Güvenilirliğinin Değerlendirilmesi

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Abstract

Aim: The internet is a popular and continually utilized platform to gain medical knowledge for patients and health professionals. This research aimed to evaluate the accuracy and quality of videos for premature ventricular contraction (PVC) on YouTube.

Material and Method: The keyword "premature ventricular contraction" was inputted into the YouTube search engine. The 60 most watched videos on YouTube were analyzed. Six of these were excluded from the study. A total of 54 patients were included in the study. General characteristics of the videos were recorded. Two specialist physicians reviewed all videos. GQS, DISCERN, and JAMA scoring systems were used to test the video quality and reliability. Video quality was divided into three groups according to the GQS score. Video characteristics were compared between quality groups.

Results: 37% of the videos posted were from doctors, and the most frequently seen content was related to general information about PVCs, accounting for 70.4%. There were 24 high-quality videos. The number of video comments (p=0.006), daily view rate (p=0.001), JAMA (p=<0.001), and DISCERN (p=<0.001) scores were increased in high-quality videos. The video source was divided into two groups: physicians and non-physicians. GQS (p=0.024) and DISCERN (p=0.047) scale scores were seen to be higher in doctors when evaluated as video sources.

Conclusion: YouTube provides an accessible and cost-effective platform for patients to learn about and comprehend their ailments. Using this platform by the right people can be a valuable patient resource for PVC.

Keywords: Premature ventricular contraction, Internet, YouTube, GQS

Öz

Amaç: İnternet, hastalar ve sağlık profesyonelleri için tıbbi bilgi edinmede popüler ve sürekli kullanılan bir platformdur. Bu araştırma, YouTube'daki prematüre ventriküler kontraksiyon (PVK) videolarının doğruluğunu ve kalitesini değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: YouTube arama motoruna "prematüre ventriküler kontraksiyon" anahtar kelimesi girilmiştir. YouTube'da en çok izlenen 60 video analiz edilmiştir. Bunlardan altısı çalışma dışı bırakıldı. Toplam 54 hasta çalışmaya dahil edildi. Videoların genel özellikleri kaydedildi. İki uzman hekim tüm videoları inceledi. Video kalitesini ve güvenilirliğini test etmek için GQS, DISCERN ve JAMA skorlama sistemleri kullanıldı. Video kalitesi GQS skoruna göre üç gruba ayrıldı. Video özellikleri gruplar arasında karşılaştırıldı.

Bulgular: Yayınlanan videoların %37'si doktorlara aittir ve en sık görülen içerik %70,4 ile PVK'ler hakkında genel bilgilerle ilgiliydi. Yüksek kaliteli 24 video vardı. Video yorum sayısı (p=0,006), günlük görüntüleme oranı (p=0,001), JAMA (p=<0,001) ve DISCERN (p=<0,001) puanları yüksek kaliteli videolarda arttığı saptandı. Video kaynağı iki gruba ayrılmıştır: hekimler ve hekim olmayanlar. GQS (p=0.024) ve DISCERN (p=0.047) ölçek puanlarının video kaynağı hekimlerde daha yüksek olduğu görülmüştür.

Sonuç: YouTube, hastaların hastalıklarını öğrenmeleri ve anlamaları için erişilebilir ve uygun maliyetli bir platform sağlar. Bu platformun doğru kişiler tarafından kullanılması PVK için değerli bir hasta kaynağı olabilir.

Anahtar Kelimeler: Prematüre erken kontraksiyon, internet, YouTube, GQS

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Received *(Geliş Tarihi)*: 14.08.2023 **Accepted *(Kabul Tarihi)*:** 11.09.2023

INTRODUCTION

Premature ventricular contractions (PVC) are irregular beats from the ventricles that are not part of the heart's usual conduction system.[1] It is frequently encountered in cardiac pathologies. Increased PVCs have been found in chronic diseases such as ischemic heart disease, heart failure, and hypertension.[2] Myocardial cell remodeling and scar formation lead to the development of PVCs. It has also been reported to occur in 40% to 90% of ordinary healthy people without any damage to the myocardium.[3] An increase in the number of PVCs can lead to heart failure or deterioration in the symptoms of heart failure. The incidence of idiopathic PVCs is high. Medical treatment and ablation therapy are at the forefront of symptomatic idiopathic PVCs. Patients refractory to medical therapy are ablated with the electrophysiologic study.[4] In general, cardiologists are not predisposed to progress in the more specific field of electrophysiology as the training is time-consuming and demanding. They are more inclined towards general cardiology and invasive procedures.

Today, it is common to use the internet to access health-related information, and it has been reported that 80% of Internet users access health-related information.[5] It has been shown that 75% of people with chronic diseases are influenced by internet-based health information in their treatment decisions.[6] One of the popular sources used for accessing health-related information is YouTube, but there are concerns about the quality and reliability of the information it contains. The information may be for advertising purposes and not reflect the truth. In addition, videos are prepared by experts in their field, and this causes information pollution. Some questionnaires assess the reliability and scientific content of information sources. Global Quality Score (GQS), DISCERN, and Journal of the American Medical Association (JAMA) are the most commonly used practical questionnaires and scales. These scales are tools that evaluate scientific articles and reveal their quality.[7] In this study, we aimed to investigate the quality and reliability of information by examining the most watched videos with PVCs on YouTube.

MATERIAL AND METHOD

This study analyzed the 60 most viewed videos on PVC using the search button on YouTube until May 2023. Fifty-four videos were included in the study (**Graph 1**.) Before keywords were entered, videos with ventricular extra beat, ventricular extrasystole, and PVC in the literature were scanned. The PVC, which had the highest follow-up rate, was determined as the keyword for the study. In English, PVC was searched on the YouTube video-sharing platform (https://www.youtube.com/). Browser search history was deleted before the keyword was searched, as past search results might influence the study. Videos were sorted according to the highest video view rates. The most watched videos were ranked first. Sixty videos on the first three pages of YouTube were analyzed. A playlist was created. Because it was anticipated that the search list results might change, all videos were evaluated and scored by two experts with backgrounds and experience in electrophysiology and arrhythmia.

Two investigators determined whether the videos should be included in the study. The exclusion criteria were as follows: videos unrelated to PVC, repetitive videos of the same content from publishers, videos published in languages other than English, videos with advertising content, and videos with poor audio and video quality. In addition, videos that require a membership to watch were not included in this study, and videos that are available for public use were evaluated. Ethics committee approval was not required since this research was not a study involving humans and animals.

Data of video

The upload date, total number of views, likes, comments, and video duration were recorded. The number of views per day was calculated as the total number of views divided by the total number of days on YouTube. Video sources were analyzed into four groups: Doctors, healthcare professionals, health information websites, and television programs. Regarding video content, general information, medical and ablation treatments were analyzed in three groups. The video's target audience was categorized into two groups: patients and healthcare professionals.

Evaluating video quality

Video quality was assessed based on the GQS, which has been widely used in previous studies. According to the GQS, low quality was assigned 1-2 points, intermediate quality was assigned 3 points, and high quality was assigned 4-5 points. Scoring was based on the information in the scale. The scale information is expressed as follows:

One point, video quality is low, information is missing and not beneficial for patients; 2 points, although some information is given, overall video quality is insufficient; 3 points, meaningful information about the subject is given but contains misleading information; 4 points, video quality, and fluency are good, in general, most of the information is correct but contains minor deficiencies. 5 points, there are no deficiencies in the fluency and quality of the video. It contains accurate information and is very useful for patients.[8]

Evaluation of video reliability

The modified DISCERN questionnaire has been used in previous studies to test the reliability of health information. It consists of five questions. Yes and no answers are scored 1 and 0, respectively. The survey questions are as follows: a) Is the purpose of the video clear and understandable? b) Is the source of information provided by experts in the field? c) Is the information unbiased and balanced? d) Are there additional sources of information for patient reference? e) Does it include ambiguous and controversial areas?[9]

JAMA is a survey by the American Medical Association testing the reliability of sources on health websites. It covers four items: Authorship, citation, patent rights, and currency. Each is scored 1 point. A high total score indicates high credibility.[10]

Statistical analysis

The analyses were evaluated in SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) 22 package program. Descriptive data were presented as n and % values for categorical data and mean ±standard deviation and median (minimum-maximum) values for continuous data. The Kolmogorov-Smirnov test evaluated the conformity of continuous variables to normal distribution. Video sources were categorized as doctors and non-doctors. Non-parametric Mann-Whitney U-test was used to compare these two groups. The Kruskal-Wallis test compared three groups since the GQS scale groups were not normally distributed. The Spearman correlation test was used to examine the relationship between continuous variables. Interobserver and intraobserver measurement variability, employing a limits of agreement method with Bland-Altman plots was evaluated in all video images. The statistical significance level was accepted as p<0.05 in the analysis.

RESULTS

A total of 60 videos were evaluated. Six videos were excluded from the study. The remaining 54 videos were included in the study (**Figure 1**). Doctors posted the most videos with PVCs (37%). The most common video content was general information about PVC, with a rate of 70.4%. The videos were directed at patients rather than health professionals. **Table 1** includes information on the GQS, JAMA, and DISCERN scales obtained from the videos, as well as the general characteristics of the video. **Figure 2** reflects the quality of the videos according to the GQS scale. The number of videos by year is shown in **Figure 3**.

Table 1. All features of the videos

	Number	%
Data source		
Doctors	20	37
Other health professionals	14	25.9
Health information sites	16	29.6
TV programs	4	7.4
Video content		
General information	38	70.4
Medical treatment	9	16.7
Ablation treatment	7	13
Target group		
Health professionals	24	44.4
Patients	30	55.6
	Mean ±SD	**Median (Min-max)**
GQS	3.17±0.96	3 (2-5)
JAMA	2.83±1.04	3 (1-4)
DISCERN	3.05±1.13	3 (1-5)
Number of views	75044.96±130810.35	29500 (6900-831120)
Number of views per day	45.19±53.83	19.93 (3.01-243.84)
Number of video Likes	873.90±1232.28	376.50 (6-6840)
Number of video comments	167±249.10	58 (0-1203)
Time elapsed since the video was uploaded (days)	2113.94±1422.46	1825 (126-5840)

Those in bold are p less than 0.05.

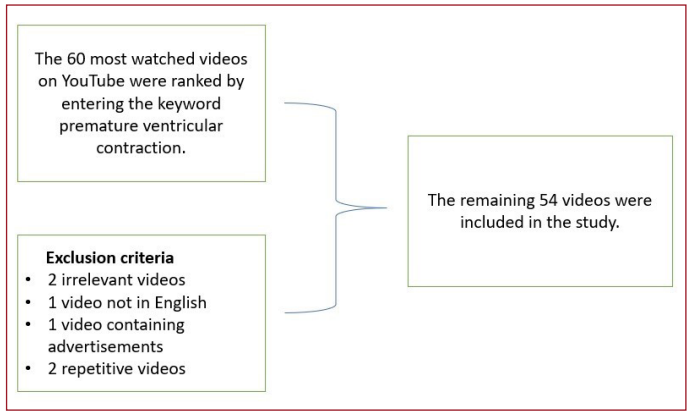

Figure 1: Flowchart showing the selection of YouTube videos

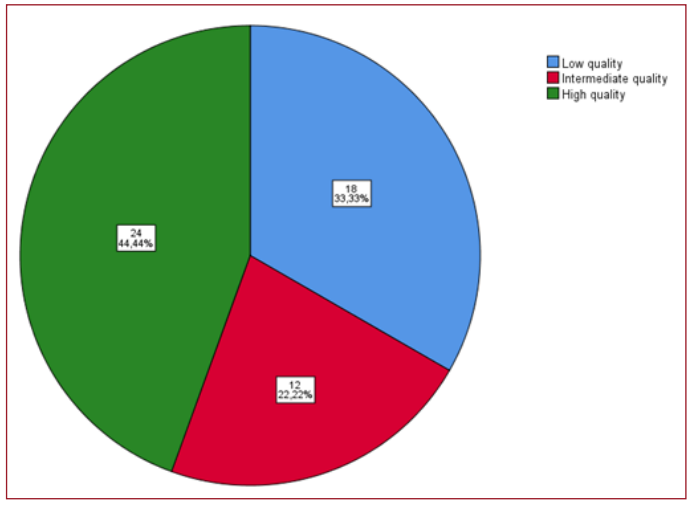

Figure 2: Quality classification of the analyzed videos

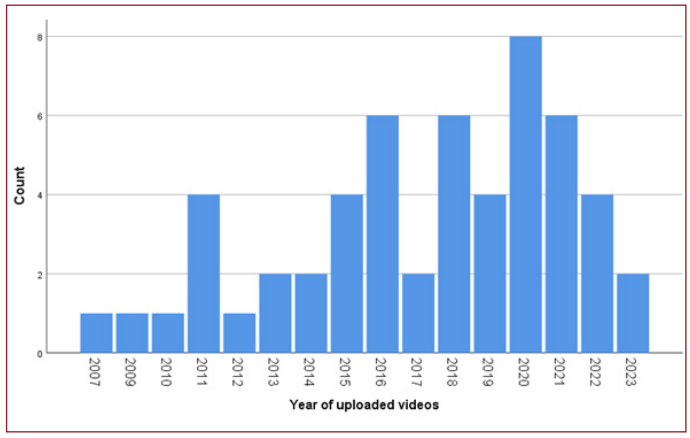

Figure 3: Distribution of analyzed videos by year

Videos were categorized into three groups according to the GQS scale. There were 24 high-quality videos. When the variables were analyzed between the three groups, significant differences were found in the number of video comments (p=0.006), daily viewing rate (p=0.001), JAMA (p=<0.001) and DISCERN (p=<0.001) scales (**Table 2**). Post-hoc analyses showed a statistically significant difference due to the high-quality group.

Table 2. Comparison of basic features according to quality groups

	Low quality N=18	Intermediate quality N=12	High quality N=24	p*
	Median (min-max)	Median (min-max)	Median (min-max)	
Video duration (min)	9.27 (0.33-64)	5.29 (0.50-70)	7.54 (1-29.49)	0.730
Number of views	32500 (11000-139000)	21500 (6900-204000)	54000 (8500-831120)	0.111
Number of views per day	18.67 (3.01-243.84)	11.34 (4.44-46.58)	30.68 (3.42-189.04)	0.001
Number of video likes	374.50 (6-3500)	215.50 (78-1300)	565.50 (36-6840)	0.056
Number of video comments	29 (0-380)	25.50 (4-811)	287 (0-1203)	0.006
Elapsed time (days)	1095 (147-4745)	2190 (365-4380)	2007.50 (126-5840)	0.605
JAMA	2 (1-4)	3 (1-4)	4 (1-4)	<0.001
DISCERN	2 (1-4)	3 (2-4)	4 (1-5)	<0.001

Those in bold are p less than 0.05.

The video source was revised into two groups: doctors and non-doctor. When the scales were compared between the groups, GQS (p=0.024) and DISCERN (p=0.047) scale scores were higher in doctors as video sources (**Table 3**). The JAMA (p=0.101) scale was similar between the groups. The correlation between the scales and variables was also analyzed. The highest correlation was found between JAMA and DISCERN (p<0.001, r=0.804). In addition, the number of comments and the GQS scale were correlated (p=0.001, r=0.450). The relationship between the scales and other parameters is shown in **Table 4**.

Table 4. Correlation of variables according to quality scales

		GQS	JAMA	DISCERN
JAMA	r	0.538		0.804
	p	<0.001		<0.001
DISCERN	r	0.767	0.804	
	p	<0.001	<0.001	
Video duration	r	0.023	-0.030	-0.017
	p	0.870	0.830	0.801
Number of views	r	0.169	0.153	0.144
	p	0.221	0.270	0.298
Number of views per day	r	0.158	0.168	0.222
	p	0.254	0.225	0.107
Number of video likes	r	0.154	0.110	0.076
	p	0.265	0.428	0.584
Number of video comments	r	0.450	0.117	0.219
	p	0.001	0.399	0.111
Elapsed time	r	0.083	0.064	0.020
	p	0.549	0.648	0.887

DISCUSSION

We are aware of our study as the first study evaluating the quality, reliability, and content of English YouTube videos related to PVC. Most of the videos analyzed in our study were general information, and the videos were prepared for healthcare professionals and patients in similar proportions. The majority of video sources (37%) were doctors. The higher quality videos were uploaded to YouTube by doctors than other video sources. Videos uploaded by doctors were found to have higher credibility. In addition, videos with many daily views and comments were better quality than the number of views.

PVC is an arrhythmia with a high incidence, even in healthy people. The fact that it is so common and that those who complain of palpitations learn about it through various platforms has led to the need to research this term. Youtube is the most common platform that provides easy access to the most information and visualization. YouTube is a beneficial platform for healthcare professionals, providing online lectures, and helping them better understand the term premature ventricular contraction, which they regularly encounter. One of the results of our study was the high percentage of general information. The reason for this is our assumption that they use the social platform to get information about diseases rather than treatment of the disease. In terms of treatment, except for herbal and preventive treatments, we can assume that they consult health institutions in cases that require medication or interventional procedures. We can say that they use the social platform to get preliminary information before going to health institutions.

Table 3. Comparison of key features by video Sources

	Doctor	Non-doctor	p*
	Median (Min-max)	Median (Min-max)	
Video duration (min)	8.56 (0.50-64)	5.73 (0.33-70)	0.227
Number of views	21500 (6900-149000)	38500 (11000-831120)	0.032
Number of views per day	13.92 (3.42-136.07)	21.83 (3.01-243.84)	0.781
Number of video likes	269.50 (80-3800)	498 (6-6840)	0.781
Number of video comments	114.50 (0-1203)	56 (0-811)	0.329
Elapsed time (days)	1825 (126-4380)	1825 (147-5840)	0.393
JAMA	3 (1-4)	3 (1-4)	0.101
DISCERN	4 (1-5)	2.50 (1-5)	0.047
GQS	4 (2-5)	3 (2-4)	0.024

Those in bold are p less than 0.05.

While there were fewer PVC-related videos in previous years, there was a particular increase in the following years. This may be attributed to Youtube not being actively used in previous years and the internet was not so widespread. However, when we looked at the year graph, we observed that the number of most viewed videos increased and decreased in a parabolic manner. The reason for this is that the quality and reliability of the videos increased, and the previously uploaded videos met the necessary needs of patients and healthcare professionals.

The internet has become an important source of access to information in the health field now. It has been shown that 87.5% of patients with some chronic diseases consulted the internet for information about their diseases before a doctor's appointment. An average of 8.7 million daily users use the internet to obtain medical information, more than daily visits to health professionals. However, approximately 75% of these users are reported to be concerned about the reliability of the information.[11] One of the most preferred websites by internet users is Youtube. This video-sharing site can potentially be a valuable source of health information. However, this platform raises concerns about disseminating false and misleading information because anyone can upload videos related to health and are not controlled. In various studies conducted in different disease groups, YouTube videos were reported as low-quality.[12,13] Therefore, healthcare professionals should be informed about the quality and content of online information.

In the literature, various studies evaluating the quality of health-related videos on the Youtube platform have obtained different results. When we look at the literature, the rate of high-quality videos varies from 5.4% to 65%.[14] In our study, 44.4% of the videos on PVC were high quality. Differences in the topics examined, video sources, and the number of videos examined may be the reason for the different results in the literature. Most of the information about PVC was general information. Catheter ablation therapy was mentioned the least. The reasons for this may include that catheter ablation is less commonly used, it is a relatively new treatment modality, and it does not appeal to a wide range of people.

In our study, high-quality videos were uploaded by physicians. Videos uploaded by physicians had higher JAMA and DISCERN scores than in other groups, and there was a significant difference. In various studies in the literature, the JAMA and DISCERN scores of videos uploaded by physicians were observed to be higher, and it was reported that the reliability of these videos was higher.[15] It can be concluded that it is more valuable and reliable for patients to consider the uploading source when using YouTube to obtain information. However, a study by Rice reported that most people who tried to obtain health-related information online ignored the information sources.[16] Therefore, physicians can create more reliable sources for informational purposes or advise patients to pay attention to the sources of videos.

We could not determine a significant correlation between the duration of the videos in our study and SCQ, JAMA, and DISCERN scores. Studies show high-quality videos are more prolonged than low-quality videos.[17] The subject is expected to be better explained and conveyed with increased duration. However, it has also been reported that the viewer's interest decreases with increasing video duration.[16] It is recommended that video uploaders maintain reasonable time supervision for high-quality videos. Furthermore, the number of views and likes received was not correlated with these scores. However, the number of comments was found to improve video quality. The number of comments increases engagement with videos. We can say that the high number of comments gives credibility to the videos and that the viewers unwittingly gravitate towards quality videos.

Our study has some limitations. However, we think it will contribute to the literature. The sample size of our study was small, and "premature ventricular contraction" was used as the search keyword on YouTube. Short videos watched on YouTube were excluded from the study because they contained advertisements and were less than 1 minute long. We analyzed 60 videos that appeared on the first three pages; other videos were not analyzed. Since YouTube is a dynamic platform, new videos are added, and the number of views, comments, and likes of existing videos, in a sense, video popularity is constantly changing. In addition, YouTube is a platform used for advertising purposes; the number of video views may vary due to the advertising effect. JAMA, DISCERN, and GQS were used in our study as in other studies in the literature. However, there is no precise method to evaluate health video content. The evaluation of the videos depends on the researcher and is subjective.

CONCLUSION

Patients suffering from palpitations are increasingly interested in online resources, including YouTube, as with many disease groups. YouTube provides an accessible and cost-effective platform for patients to learn about and comprehend their ailments. Using this platform by the right people can be a valuable patient resource. However, patients may watch low-quality videos and be misinformed due to the focus on video popularity and misdirection for advertising purposes. Approximately half of the videos in our study were uploaded by physicians, and physicians uploaded the most high-quality videos. It is crucial for physicians and academic institutions to increase their interest in this platform and for patients to access accurate and reliable information. In addition, attempts should be made to subject health-related information on this platform to an audit mechanism. In addition, an increase in the number of comments can affect video quality. A high number of comments arouses curiosity in viewers about the topic. Therefore, there is a need for videos that will impact all viewers and provide them with detailed information, leaving them open to questions. This can be very useful for individuals using the video for education.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was not required since this research was not a study involving humans and animals.

Informed Consent: Informed consent was not required.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1332759
J Contemp Med 2023;13(5):1024-1032

Original Article / Orijinal Araştırma

Evaluation of Hematological Biomarkers in Childhood Metabolic Dysfunction Associated Steatotic Liver Disease

Çocukluk Çağı Metabolik Disfonksiyon İlişkili Steatotik Karaciğer Hastalığında Hematolojik Biyobelirteçlerin Değerlendirilmesi

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Abstract

Aim: We aimed to investigate the clinical significance and diagnostic value of inflammation-based biomarkers in children with a diagnosis of Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD).

Material and Method: This study was carried out by retrospectively evaluating the files of patients followed up in the Department of Pediatric Hepatology at Selçuk University between July 2022 and January 2023.The study was completed with 120 patients with MASLD diagnosed according to the criteria of the AASLD and EASL, 80 healthy controls.Comparisons were made by calculating laboratory values and formulas through them.

Results:There were 50 (41.7%) girls and 70 (58.3%)boys in the patient group,and 40 girls (50.0%) and 40 boys (50.0%) in the control group.While 80 patients with Grade 0 detected in liver ultrasonography were taken as the control group; 102 (85%) Grade 1 and 18 (15%) Grade 2-3 patients were considered as the patient group.The values of the patients were compared with the values of healthy volunteers.When the WBC, neutrophil, lymphocyte, platelet, MHR, RPR, RLR, MPR, WMR, GPR, SII and FIB-4score values were compared according to liver grading, a correlation was found in the tests performed on the patients.

Conclusion: Our study suggests that the presence of MASLD should be investigated in individuals, and possible complications can be prevented with early diagnosis and treatment approaches.As a result, we think that the use of hematological biomarkers will be useful for the simple and rapid detection of patients with suspected MASLD and who need further examination and treatment.

Keywords: Metabolic dysfunction associated steatotic liver disease, biomarker, chıldren, fatty liver disease

Öz

Amaç: Çalışmamızda Metabolik Disfonksiyon İlişkili Steatotik Karaciğer Hastalığı (MASLD) tanılı çocuklarda inflamasyon temelli biyobelirteçlerin klinik önemi ve tanısal değerini araştırmayı amaçladık.

Gereç ve Yöntem: Bu Çalışma, Temmuz 2022-Ocak 2023 tarihleri arasında Selçuk Üniversitesi Çocuk Gastroenteroloji bölümünde takip edilen hasta dosyalarının retrospektif olarak değerlendirilmesi ile gerçekleştirilmiştir.AASLD ve EASL kriterlerine göre tanı konulan 120 MASL hastası ve 80 sağlıklı kontrol grubu ile çalışma tamamlanmıştır. Laboratuvar değerleri ve bunlar aracılığı ile formüller hesaplanarak karşılaştırmalar yapılmıştır.

Bulgular: Hasta grubunda 50 (%41,7) kız, 70 (%58,3) erkek ve kontrol grubunda ise 40 kız (%50,0), 40 erkek (%50,0) idi.Karaciğer Ultrasonografilerinde Grade 0 tespit edilen 80 hasta kontrol grubu; 102'si (%85) Grade 1 ve 18'i (%15) Grade 2-3 hasta grubu olarak kabul edildi. Hastaların değerleri, sağlıklı gönüllülerin değerleri ile karşılaştırıldı.Yapılan testlerde hastalarda WBC, nötrofil, lenfosit, platelet, MHO, RPO, RLO, MPO, WMO, GPO, Sİİ ve FIB-4 skor değerleri karaciğer Gradelendirilmesine göre karşılaştırıldığında korelasyon tespit edildi.

Sonuç: MASLD'ın erken tespiti için etkili bir izleme göstergesine acilen ihtiyaç duyulmaktadır. Yapmış olduğumuz bu çalışma, kişilerde MASL varlığının araştırılması gerektiğini, erken tanı ve tedavi yaklaşımları ile olası komplikasyonların önüne geçilebileceğini düşündürmektedir.Sonuç olarak MASLD'den şüphelenilen, ileri tetkik ve tedaviye ihtiyaç duyan hastaların basit ve hızlı bir şekilde tespiti için hematolojik biyobelirteçlerin kullanımı faydalı olacağı düşüncesindeyiz.

Anahtar Kelimeler: Metabolik disfonksiyon ilişkili steatotik karaciğer hastalığı, biyobelirteç, çocuklar, yağlı karaciğer hastalığı

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Received *(Geliş Tarihi)*: 25.07.2023 **Accepted *(Kabul Tarihi)*:** 05.09.2023

INTRODUCTION

Hepatic steatosis, hepatocyte damage, liver inflammation, and fibrosis, which were associated with overweight or obese people for many years, was published in 1980 by Jurgen Ludwig with the term "Non-Alcoholic Steatohepatitis".[1] It was considered that this definition did not fully elucidate the etiology, was stigmatizing, and contributed to inequality in healthcare. The term "Steatotic Liver Disease Associated with Metabolic Dysfunction" (MASLD) was suggested later in the article published in 2020 by Eslam et al.[2] The nomenclature was changed in 2023 by the Liver Diseases Research Association (AASLD) and the European Liver Diseases Research Association (EASL), predicting that it could improve awareness and patient identification.[3]

MASLD is a healthcare concern with increasing prevalence because of improved living conditions and sedentary lifestyle habits.[4,5] Its global prevalence is 20-50% in obese children and is the most common Chronic Liver Disease (CHD) on a global scale.[6,7] In our country, its prevalence was reported to be 23-62% in obese children.[8-10]

MASLD often has no symptoms but sometimes, liver enlargement may be the only finding on examination. For these reasons, the diagnosis of the disease is made with laboratory findings. Ultrasonography (USI) is among the basic methods employed to detect fatty liver.[3,11] Early detection and evaluation of MASLD and liver fibrosis, monitoring disease development, and choosing appropriate therapeutic modalities for patients are very important.[12,13] Liver biopsy is the gold standard for grading of liver fibrosis and clinical diagnosis. However, it is not always preferred in children because it is an invasive method. Increasing evidence shows that chronic inflammation is considered an important part of its pathophysiology.[14] It is possible to predict the presence and development of MASLD with inflammatory markers.[10,15-17]

In the present study, the researchers planned to investigate the clinical value of novel, non-invasive, and practical inflammatory biomarkers to assess the relationship between hematological biomarkers and MASLD in obese children and to predict the development of MASLD.

MATERIAL AND METHOD

The study was carried out with the permission of Selçuk University Local Ethics Committee (Date: 18.07.2023, Decision No: 2023/352). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 120 patients who were diagnosed with MASLD, detected to have adiposity on USI, with excluded autoimmune, metabolic, and infectious causes, and who were not known to have drug and toxin exposure, in the Pediatric Hepatology clinic of the Selçuk University between July 2022 and January 2023.[18] The control group consisted of 80 healthy children who met the inclusion criteria after semi-structured diagnostic interviews. All children were assessed and their gender and age characteristics were recorded. Body Weight (BW-kg), Height (cm), Body Mass Index (BMI), and Body Weight for Height (BWH) measurements were recorded for all patients.

Simultaneous complete blood counts and biochemistry samples with USI were taken from the system of the biochemistry laboratory of the Faculty Hospital were taken from the hospital system by using the Beckman Coulter AU5800, LH780 brand device. Hemoglobin (Hb), platelet distribution width (PDW), the mean platelet volume (MPV), mean corpuscular volume (MCV) and erythrocyte distribution width (RDW) values were recorded from the files. Alanine amino transferase (ALT), aspartate amino transferase (AST), GGT, total protein, albumin, cholesterol, HDLcholesterol, and LDLcholesterol values were assessed. Then, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), hemoglobin/RDW (HRR), RDW/platelet (RPR), RDW/lymphocyte (RLR), MPV/platelet (MPR), WBC/MPV (WMR), GGT/platelet ratio (GPR), and monocyte/HDL cholesterol (MHR) value and monocyte ratios were calculated. NPAR was calculated by using the formula of "Neutrophil percentage (%)x100/Albumin (g/dL), APRI score was obtained by AST/Platelet count.[18] The formula of [Age×AST(U/L)] / [Platelet count ×√ALT(U/l)][19] and Prognostic Nutritional Index (PNI) (10×Albumin [g/dL])+(0.005 xLymphocyte) were used for FIB-4 score.The SII values were calculated with the formula [SII=Neutrophil×Platelet/Lymphocyte]. The assessments were made according to Selçuk University Medical Faculty. Hematology Laboratory reference values for the present study population.

Liver USI examination was made by using a convex probe (Frequency 3.5-5.0MHz) and the Aplio500 US device (Toshiba Medical Systems, Japan) by the only pediatric radiologist of the hospital, who had 15 years of experience, blinded to the purpose of the study and the laboratory values of the patients. The degree of hepatosteatosis was classified as follows.No steatosis (Grade 0), Mild steatosis (Grade 1), Moderate-severe steatosis(Grade 2-3).[19]

Statistical Analysis

The data were entered into the SPSS 23.0 program. In the comparison of the numerical parameters in the two groups, the Student t-test was employed in those with normal distribution, and the Mann-Whitney U test was used in those who did not. The Kruskal-Wallis test was employed to compare median values in groups of more than two. The ANOVA Test was employed to compare the numerical parameters with normal distribution in more than two independent groups. Confidence intervals and odds ratios were calculated for hematological ratios with Binary Logistic Regression Analysis for MASLD development. The predictive power of indices in predicting disease was specificity, sensitivity, positive and negative predictive value, and Area Under the Curve (AUC). The highest Youden Index([Specificity+Sensitivity]-1) was set as the best possible cut-off point and $p<0.05$ was accepted as the significance level in all analyses.

RESULTS

A total of 200 patient were included in the present study (120 MASL patients of whom 80 were included in the healthy control group with Grade 0 in liver USI). 70 (58.3%) of the patients were male, 50 (41.7%) female. In the healthy control group, 40 (50.0%) were male and 40 (50.0%) were female.When the distribution according to gender was assessed in the patient and control groups, no statistically significant differences were detected (p:0.174). The demographic characteristics are given in **Table 1**.

When the hematological values were assessed, WBC, neutrophil, lymphocyte, platelet count, MPV, PCT, MHR, RPR, RLR, MPR, WMR, GPR, SII, and FIB-4 scores of the patients were compared, statistically significant differences were detected in the control and patient groups. No significant differences were detected between the control and patient groups in terms of MCV, RDW, NLR, PLR, LMR, HRR, PNI, NPAR, and APRI scores (**Table 2**).

When liver USIs were assessed, 80 (40.0%) of the patients were Grade 0 (Control Group), 102 (51%) were Grade 1, and 18 (9.0%) were Grade 2-3. When the patients' WBC, neutrophil, lymphocyte, platelet, MHR, RPR, RLR, MPR, WMR, GPR, SII, and FIB-4 scores were compared according to liver grading, statistically significant differences were detected. However, a statistically significant difference was detected in Hb, monocyte count, RDW, PCT, and MPV. No significant differences were detected between liver grading in terms of NLR, PLR, LMR, HRR, PNI, NPAR, and APRI scores (**Table 3**).

Table 1: The distribution of the demographic characteristics of the patients who participated in the study according to the patient and control groups

	Patient Group		Control Group		p
	n	%	N	%	
Gender					
Boy	70	58.3	40	50.0	0.174
Girl	50	41.7	40	50.0	
Age Group					
<10	21	60.0	14	40.0	
10.1-15.0	56	58.3	40	41.7	0.876
>15.1	43	62.3	26	37.7	
BMI					
<24.9	10	16.9	49	83.1	
25.0-29.9	37	78.7	10	21.3	<0.001
>30.0	35	76.9	4	23.1	

BMI: Body Mass Index.

Table 2: The distribution of the hematological values and indices of patients according to patient and control groups

	Patient Group		Control Group		p
	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	
WBC	8.29±1.98	8.16 (4.45 - 14.56)	7.15±1.88	6.85 (3.84 - 14.27)	<0.001
Neutrophil	4.5±1.57	4.25 (1.52 - 10.5)	3.7±1.12	3.59 (1.69 - 6.71)	<0.001
Lymphocyte	2.84±0.96	2.73 (0.36 - 7.57)	2.49±0.62	2.53 (1.19 - 4.07)	0.005
Hgb	13.99±1.38	13.8 (10.1 - 17.1)	13.69±1.27	13.6 (9.7 - 16.9)	0.131
Platelet	337.22±67.49	339.5 (171 - 502)	305.66±72.57	301 (152 - 531)	<0.001
Monocyte	0.61±0.17	0.6 (0.33 - 1.07)	0.57±0.16	0.53 (0.3 - 1.07)	0.062
MCV	81.76±5.67	81.95 (59 - 92.4)	82.18±4.77	82.6 (64.2 - 93.1)	0.920
RDW	13.48±1.34	13.2 (11.6 - 19.5)	13.2±1.12	13 (11.6 - 17.8)	0.117
PCT	0.33±0.07	0.33 (0.17 - 0.5)	0.31±0.07	0.3 (0.15 - 0.49)	0.024
MPV	9.82±1.02	9.7 (6.15 - 12)	10.13±0.94	9.9 (8.6 - 13.6)	0.025
NLR	1.856±1.465	1.519 (0.527 - 10.167)	1.584±0.641	1.48 (0.577 - 3.783)	0.396
MHR	0.015±0.005	0.013 (0.006 - 0.028)	0.012±0.005	0.011 (0.006 - 0.025)	<0.001
PLR	134.761±72.658	122.869 (26.42 - 744.444)	128.07±36.698	125 (63.415 - 283.673)	0.978
LMR	4.864±1.881	4.676 (0.632 - 15.771)	4.59±1.289	4.695 (2 - 7.682)	0.537
HRR	1.051±0.166	1.062 (0.564 - 1.379)	1.047±0.145	1.04 (0.567 - 1.395)	0.655
RPR	0.042±0.01	0.04 (0.027 - 0.078)	0.046±0.012	0.044 (0.027 - 0.082)	0.008
RLR	5.541±3.755	4.846 (1.77 - 37.778)	5.656±1.59	5.415 (2.948 - 10.672)	0.019
APRI Score	0.075±0.062	0.064 (0.026 - 0.503)	0.066±0.026	0.061 (0.024 - 0.16)	0.303
MPR	0.031±0.008	0.029 (0.015 - 0.057)	0.035±0.011	0.032 (0.018 - 0.078)	0.002
WMR	0.851±0.216	0.817 (0.464 - 1.512)	0.712±0.202	0.681 (0.385 - 1.586)	<0.001
GPR	0.078±0.083	0.056 (0.016 - 0.587)	0.041±0.017	0.038 (0.015 - 0.088)	<0.001
SII	609.425±402.946	524.669 (118.098 - 2660.62)	475.712±201.572	422.522 (172.921 - 1011.941)	0.010
PNI	46.629±3.495	47.012 (30.026 - 54.009)	46.781±2.566	47.007 (39.012 - 52.01)	0.671
FIB-4 Score	0.186±0.094	0.171 (0.041 - 0.659)	0.233±0.079	0.228 (0.083 - 0.446)	<0.001
NPAR	11.66±2.89	11.32 (5.64 - 26.03)	11.21±2.57	11.16 (5.07 - 19.03)	0.486

WBC:White Blood Cell, Hgb: Hemoglobine, MCV:Mean Corpuscular Volume, RDW: Red Cell Distrubition, PCT: Platelecrit; MPV: Mean Platelet Volume, NLR: neutrophil / Lymphocyte Ratio; MHO: Monocyte/HDL Ratio; PLO: Platelet/ Lymphocyte Ratio; LMO: Lymphocyte Monocyte Ratio; HRO: Hemoglobin/RDW Ratio ; RPO: RDW/Platelet Ratio; RLO: RDW/ Lymphocyte Ratio; APRI: AST/PLT; MPR: MPV/Platelet Ratio; WMO: WBC/MPV Ratio; SII: Systemic Immune Inflammation Index

When the ROC Analysis results of the hematological index values for the diagnostic value of MASLD were assessed, the cut-off value of the MHR Value was found to be 0.011, the diagnostic value was AUC 0.66 (0.583-0.746), the specificity was 60.80%, sensitivity was 73.50%. The positive likelihood ratio was calculated as 1.87.When the cut-off value of WMR value was taken as 0.812, the diagnostic value was AUC 0.699 (0624-0.744), and specificity was 77.20% with a sensitivity of 51.30%. The positive likelihood ratio was calculated as 2.25. ROC analysis results of hematological index values for the diagnostic value of patients with MASLD are given in **Table 4**.

Table 3: The comparison of patients' hematological index levels according to Liver Grading

	Grade 0 n:80 (%40.0)		Grade 1 n:102 (%51.0)		Grade 2-3 n:18 (%9.0)		p
	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	
Age	12.89±2.85	13.06 (7.1 - 17.02)	13.11±3.15	13.9 (6.4 - 17.8)	13.58±2.51	14.5 (8.9 - 17.45)	0.381
BW	55.21±16.85[a]	53.2 (22.8 - 88.6)	79.16±21.61[b]	82.1 (36 - 121)	97.15±38.55[c]	89.75 (52.5 - 152)	<0.001
BW Persentile	56.69±34.83[a]	62 (0.87 - 100)	97.07±6.83[b]	99.46 (55.57 - 100)	99.29±0.87[c]	99.75 (97.88 - 100)	<0.001
BW SDS	0.19±1.61[a]	0.26 (-3.37 - 3.8)	2.61±1.26[b]	2.35 (-0.11 - 6.75)	3.4±1.68[c]	2.81 (1.57 - 7.06)	<0.001
BMI	21.78±4.49[a]	21.12 (14.2 - 35.49)	30.22±5.32[b]	29.33 (21.9 - 46.49)	34.14±9.55[b]	31.2 (23.8 - 50.3)	<0.001
BMI Persentile	59.32±34.78[a]	73 (1 - 100)	96.65±5.75[b]	99 (71 - 100)	98.63±1.36[b]	98.5 (96 - 100)	<0.001
WBC	7.15±1.87[a]	6.85 (3.84 - 14.27)	8.37±2.04[b]	8.22 (4.45 - 14.56)	7.79±1.45[a]	7.56 (5.4 - 10.81)	<0.001
Neutrophil	3.69±1.11[a]	3.59 (1.69 - 6.71)	4.58±1.59[b]	4.30 (1.52 - 10.5)	3.98±1.33[a]	3.97 (1.91 - 7.45)	<0.001
Lymphocyte	2.48±0.62[a]	2.52 (1.19 - 4.07)	2.78±0.90[a]	2.66 (0.36 - 5.74)	3.17±1.2[b]	3.06 (1.58 - 7.57)	0.005
Monocyte	0.57±0.16	0.53 (0.3 - 1.07)	0.62±0.16	0.6 (0.33 - 1.02)	0.6±0.18	0.57 (0.38 - 1.07)	0.062
Hgb	13.69±1.27	13.6 (9.7 - 16.9)	14.04±1.4	13.9 (10.1 - 17.1)	13.63±1.21	13.55 (11.8 - 16.1)	0.070
RDW	13.19±1.12	13.0 (11.6 - 17.8)	13.52±1.42	13.2 (11.6 - 19.5)	13.26±0.77	13.1 (12.1 – 15.0)	0.083
Platelet	305.66±72.57[a]	301 (152 - 531)	340.18±69.8[b]	341 (171 - 502)	321.06±48.31[a]	321.5 (200 - 417)	<0.001
Platelecrite	0.31±0.07	0.30 (0.15 - 0.49)	0.33±0.08	0.33 (0.17 - 0.50)	0.32±0.05	0.32 (0.22 - 0.42)	0.104
MPV	10.13±0.93	9.9 (8.6 - 13.6)	9.78±1.02	9.7 (6.15 – 12.0)	9.98±0.96	9.8 (8.6 - 11.6)	0.099
NLR	1.58±0.64	1.47 (0.58 - 3.78)	1.94±1.55	1.55 (0.53 - 10.17)	1.37±0.64	1.26 (0.59 - 3.42)	0.396
MHR	0.012±0.004[a]	0.010 (0.006 - 0.025)	0.014±0.005[b]	0.013 (0.005 - 0.027)	0.014±0.003[b]	0.015 (0.008 - 0.019)	<0.001
PLR	128.07±36.7	125.0 (63.41 - 283.67)	138.63±76.49	128.08 (47.13-744.44)	112.82±39.84	105.30 (26.42-210.13)	0.978
LMR	4.59±1.29	4.69 (2.0 - 7.68)	4.69±1.57	4.60 (0.63 - 9.19)	5.77±2.99	5.08 (2.04 - 15.77)	0.537
HRR	1.047±0.144	1.039 (0.567 - 1.394)	1.054±0.171	1.066 (0.564 - 1.379)	1.033±0.133	1.022 (0.831 - 1.319)	0.655
RPR	0.045±0.011[a]	0.043 (0.026 - 0.081)	0.041±0.010[b]	0.039 (0.026 - 0.078)	0.042±0.007[b]	0.041 (0.029 - 0.067)	0.008
RLR	5.65±1.59[a]	5.42 (2.95 - 10.67)	5.71±4.01[a]	5.02 (2.25 - 37.78)	4.59±1.49[b]	4.39 (1.77 - 9.49)	0.019
WMR	0.711±0.202[a]	0.680 (0.385 - 1.585)	0.862±0.223[b]	0.826 (0.463 - 1.511)	0.784±0.151[b]	0.749 (0.533 - 1.129)	<0.001
MPR	0.035±0.011[a]	0.032 (0.017 - 0.078)	0.030±0.008[b]	0.029 (0.014 - 0.056)	0.032±0.007[b]	0.030 (0.022 - 0.055)	0.002
GPR	0.040±0.017[a]	0.037 (0.015 - 0.088)	0.070±0.069[b]	0.051 (0.016 - 0.450)	0.116±0.133[c]	0.081 (0.040 - 0.586)	<0.001
SII	475.71 ±201.57[a]	422.52 (172.92-1011.94)	635.12±417.33[b]	538.21 (146.29-2660.62)	451.87±251.8[a]	395.19 (118.1 - 1247.36)	0.010
PNI	46.78±2.56	47.01 (39.01 - 52.01)	46.73±3.62	47.01 (30.02 - 54.01)	46.03±2.66	45.16 (43.01 - 52.04)	0.671
APRI Score	0.07±0.03	0.06 (0.02 - 0.16)	0.07±0.07	0.06 (0.03 - 0.5)	0.07±0.03	0.06 (0.03 - 0.15)	0.303
FIB-4 Score	0.232±0.079[a]	0.227 (0.082-0.445)	0.189±0.099[b]	0.173 (0.041-0.659)	0.168±0.050[b]	0.159 (0.103-0.274)	<0.001
NPAR Score	11.21±2.57	11.16 (5.07-19.81)	11.80±2.98	11.50 (5.63-26.04)	10.88±2.22	11.11 (5.68-15.31)	0.426

BW: Body Weight ; BMI; Body Mass Index; SDS: Standart Deviation Score;WBC: White Blood Cell,;Hgb: Hemoglobine; RDW: Red Cell Distrubition; MPV: Mean Platelet Volume; NLR: Neutrophil / Lymphocyte Ratio; MHR: Monocyte/HDL Ratio; PLR: Platelet/ Lymphocyte Ratio; LMO: Lymphocyte /Monosit Ratio; HRR: Hemoglobin/RDW Ratio; RPR: RDW/Platelet Ratio; RLR: RDW/ Lymphocyte Ratio; APRI: AST/PLT; MPR: MPV/ Platelet Ratio; WMR: WBC/MPV Ratio; GPR: Granulocyte/Platelet Ratio, SII: Systemic Immune Inflammation Index.

Table 4: The ROC analysis results of the hematological values for the diagnostic value of MASLD patients

	AUC (%95 CI)	Cut Off	P	Sensitivity (%)	Spesifisity (%)	+LR	-LR	PPV (%)	NPV (%)	Accuracy (%)
WBC	0.675 (0.599-0.751)	8.09	<0.001	51.67	77.50	2.30	0.62	77.50	51.67	62.00
Neutrophil	0.659 (0.583-0.735)	3.87	<0.001	61.70	67.50	1.89	0.57	74.00	54.00	64.00
Lymphocyte	0.618 (0.540-0.696)	2.60	<0.001	59.20	60.00	1.47	0.68	68.93	49.48	52.35
Platelet	0.635 (0.556-0.715)	331.50	<0.001	54.20	68.80	1.73	0.67	72.22	50.00	52.85
MHR	0.665 (0.583-0.746)	0.011	<0.001	73.50	60.80	1.87	0.43	73.95	59.72	61.49
WMR	0.699 (0624-0.744)	0.812	<0.001	51.30	77.20	2.25	0.63	77.22	51.26	61.62
RPR	0.389 (0.310-0.468)	0.056	0.008	10.83	86.30	0.79	1.03	54.17	39.20	41.00
GPR	0.755 (0.681-0.829)	0.047	<0.001	66.67	73.85	2.84	0.45	79.52	59.26	69.51
MPR	0.370 (0.292-0.449)	0.025	0.002	88.60	11.40	0.84	2.41	55.90	21.62	49.49
SII	0.608 (0.529-0.687)	415.23	<0.001	70.85	50.00	1.42	0.58	68.00	53.33	62.50
FIB-4 Score	0.306 (0.232-0.381)	0.219	<0.001	22.80	66.20	0.41	1.75	38.03	27.56	31.31

AUC: Area under the curve; 95%CI: %95 confidence interval; Cut off: cut-off value; WBC: White Blood Cell; MHR: Monocyte/HDL Ratio; WMR: WBC/MPV Ratio; RPR: RDW/Platelet Ratio; GPR: Granulocyte/Platelet Ratio; MPR: MPV/Platelet Ratio; SII: Systemic Immune Inflammation Index.

Multivariate regression analysis of the hematological indices was made to predict MASLD. Parameters that constituted risk factors in the univariate analysis were put into the models and 3 different models were created in predicting the patients. Nagelkerke R Square was 70.30% in Model 1 obtained by using BMI, WMR, GPR, SII, and MPR parameters. The specificity was 83.3, the sensitivity was 88.0, and the accuracy was 85.9. The Multivariate Regression Analysis results of the Hematological Index values for the diagnostic value of patients with MASLD are given in **Table 5**.

DISCUSSION

MASLD is often associated with obesity, Type 2 Diabetes Mellitus (DM) and Metabolic Syndrome.[19-22] It is unclear which patients will remain with simple steatosis and which will progress to liver cirrhosis or have cardiovascular risk. For this reason, novel biomarkers are needed to show the association with poor prognosis in MASLD.

Studies conducted on hematological parameters are very few in the pediatric population. The potential role of hematological indices in hepatic steatosis has not been investigated adequately. It was argued that Platelet Index Values are associated with the presence, severity, and complications of insulin resistance closely.[23-29] Çiftçi et al study, MPV value was reported to be significantly lower in MASLD patients.[30-32] In the present study, the researchers detected a significantly lower MPV value in the MASLD group when compared to healthy controls.We attributed this to the small number of patients with severe fibrosis.

RDW is an indicator of deterioration during the maturation and differentiation of erythrocytes as a result of oxidative stress and chronic inflammation, and an increased RDW was reported in the literature in the presence of these conditions.[33-35] The RDW value associated with advanced fibrosis in patients with MASLD is elevated than in other liver diseases and this can be employed as indicators.[36-38] In the present study, no statistical significance was detected between the patient and control group in terms of RDW.

It is already known that increased WBC is a risk factor independent of metabolic factors. Lee et al. reported a positive correlation between the WBC count and the prevalence of MASLD and also showed that the elevated WBC count increased the risk of MASLD.[39-42] In the present study, WBC levels were found to be significantly elevated in the patient group when compared to the control group. The WBC level was significantly elevated in Grade 1 patients when compared to Grade 0 patients. When ROC Analysis was made for WBC values and when the cut-off value was taken as 8.09, AUC was calculated as 0.675 (0.599-0.751), specificity 77.50%, and sensitivity 51.67%. When multivariate regression analysis was assessed to predict patients with MASLD, WBC value was found to be an independent risk factor, but it was not statistically significant in model 2. We think that WBC levels may be good diagnostic biomarkers for MASLD patients.

Table 5: The Multivariate Regression Analysis results of the Hematological Index Values for the diagnostic value of MASLD patients

	MULTIVARIATE ANALYSIS							UNIVARIATE ANALYSIS	
	p	OR (%95 CI)	-2 Log likelihood	Nagelkerke R Square	Accuracy	Sensitivity	Spesifity	p	
MODEL 1									
BMI	<0.001	0.694 (0.590-0.817)	84.928	0.703	85.9	88.0	83.3	<0.001	0.678 (0.598-0.769)
WMR	0.050	42.170 (1.005-1769.8)						<0.001	0.030 (0.006-0.161)
GPR	0.003	1.27 (1.08-4.32)						<0.001	0.758 (0.598-0.987)
SII	0.196	0.998 (0.995-1.001)						<0.001	0.998 (0.997-1.00)
MPR	0.007	2.62 (1.48-4.64)						0.002	10.91 (1.10-108.18)
Constant	0.023								
MODEL 2									
BW SDS	<0.001	0.668 (0.563-0.792)	79.036	0.727	86.7	84.7	85.8	<0.001	0.249 (0.157-0.395)
WBC	0.187	1.280 (0.887-1.847)						<0.001	0.720 (0.607-0.854)
MHR	0.600	0.1 (0.01-7.51)						0.002	0.814 (0.745-0.947)
FIB-4	<0.001	9.19 (20.63-409.99)						<0.001	402.040 (11.867-13621.10
GPR	0.005	0.1 (0.02-0.25)						<0.001	0.758 (0.598-0.987)
Constant	<0.001								
MODEL 3									
BMI P	<0.001	0.900 (0.850-0.954)	82.651	0.707	86.6	93.3	82.5	<0.001	0.872 (0.823-0.925)
WMR	0.407	3.108 (0.213-45.41)						<0.001	0.030 (0.006-0.161)
GPR	<0.001	0.874 (0.812-0.954)						<0.001	0.758 (0.598-0.987)
FIB-4	0.024	21.06 (3.70-119.60)						<0.001	402.040 (11.867-13621.10
SII	0.072	0.997 (0.994-1.00)						<0.001	0.998 (0.997-1.00)
Constant	<0.001								

BMI: Body Mass Index; WMR: WBC/MPV Ratio; GPR: Granulocyte/Platelet Ratio; SII: Systemic Immune Inflammation Index; MPR: MPV/Platelet Ratio; BW: Body Weight;, SDS: Standart Deviation Score; WBC: White Blood Cell; MHR: Monocyte/HDL Ratio ; WMR: WBC/MPV Ratio.

Hepatocytes cause neutrophil accumulation as a result of oxidative stress and necrosis in the hepatic inflammatory process of MASLD.[43] In their study, Zhou concluded that neutrophil levels were elevated in the MASLD group compared to the control group.[44,45] In the present study, neutrophil and lymphocyte levels were detected to be significantly elevated in the MASLD patient group when compared to the healthy control group. Neutrophil levels were detected to be significantly elevated in our patients with Grade 1 steatosis when compared to Grade 0 patients. When the neutrophil and lymphocyte ROC analysis were made for the diagnostic value of patients with MASLD, the cut-off value was taken as 3.87 and 2.60, respectively, and the researchers detected high sensitivity and specificity. Based on the results of the present study, we think that neutrophil and lymphocyte levels can be employed together with other biomarkers in patients with MASLD.

The inflammatory response induces increased neutrophil and platelet counts with decreased lymphocyte count and makes their ratios a valuable tool to assess inflammatory status indirectly. Recently, biomarkers such as NLR, PLR, and LMR are employed as potential markers of inflammatory progression.[46,47] In the present study, we couldn't find a statistically significant relationship between NLR, PLR, LMR, and MASLD.

WMR was employed to predict thrombosis-related events, especially in cardio, cerebral, and peripheral vascular diseases.[48,49] Few studies were conducted in the past to determine the relationship between WMR and MASLD, and no studies were conducted in children. It was shown in a previous study that the group with apnea and MASLD had elevated WBC/MPV ratio values than those with MASLD alone, and the WBC/MPV ratio was an independent risk factor for MASLD.[50] In our study, a statistically significant relationship was detected between WMR and MASLD. According to USI, although no significant differences were detected between patients with Grade 1 and Grade 2-3 in terms of WMR levels, it was detected to be significantly lower in patients with Grade 0. When the ROC analysis was made for the value of the cut-off value for the WMR for the diagnostic value of patients with MASLD, it was detected that AUC was 0.699 (0624-0.744), specificity was 77.20%, and sensitivity was 51.30% when the cut-off value was taken as 0.812. WMR value, which is an independent risk factor in the regression analysis, was not significant in the multivariate analysis.

NPAR score is a biomarker that can be employed as an indicator of systemic inflammation.[51,52] Few studies assessed the predictive value of the NPAR score in MASLD or advanced liver fibrosis.[53] No association was detected between patients with MASLD and healthy controls in our study.

Recently, RPR is used as the preferred biomarker in various diseases with its ease of measurement and affordable cost, and it was employed to predict the severity of fibrosis in MASLD patients.[54] When ROC analysis was used for the RPR value for the diagnostic value of patients with MASLD when the cut-off value was determined as 0.056, it was determined that AUC was 0.389 (0.310-0.468), specificity was 86.30%, sensitivity was 10.83%. We think that it can be a good biomarker in predicting MASLD.

Considering the proinflammatory characteristics of monocytes and the anti-inflammatory characteristics of HDL-C, MHR was considered a novel systemic inflammatory marker.[55,56] It is not known whether MHR is associated with MASLD. Adult studies were conducted and there is no literature investigating the orrelation in children. In the present study, the researchers assessed whether the MHR value would be a good biomarker for predicting MASLD in pediatric patients. In a retrospective study, it was shown that there was a significant positive correlation between MHR and age, ALT, and HOMA-IR values.[57-59] The researchers found that the MHR levels were elevated in patients with MASLD compared to healthy controls. When ROC analysis was made for the MHR value to further investigate the diagnostic value of patients with MASLD when the cut-off value was taken as 0.011, it was detected that AUC was 0.665 (0.583-0.746), specificity was 60.80%, and sensitivity was 73.50%. However, although the MHO value was an independent risk factor in the univariate regression analysis, it was not significant in the multivariate analysis. In particular, we predict that each unit increase in the MHR value will cause an increased risk of MASLD by 1.87 times. We think that it can be used as a good biomarker to predict MASLD and its prognosis.

No study was detected in the literature investigating the relationship between SII and MASLD in children. In our study, it was detected that there were elevated levels of SII in patients with MASLD than in healthy controls. According to liver USI, SII levels were detected to be significantly elevated in patients with Grade 1 when compared to Grade 0 patients. To investigate the diagnostic value of patients with MASLD, the cut-off value for the SII value was 415 in the ROC analysis. To investigate the diagnostic value of patients with MASLD, when the cut-off value for the SII value was taken as 415.23 in the ROC analysis, the AUC was 0.608 (0.529-0.687), the specificity was 60.80%, and the sensitivity was 70.85%. In particular, it was determined that each unit increase in the SII value causes a 1.42-fold increase in the risk of MASLD. However, while the SII value was an independent risk factor in univariate regression analysis, it was not significant in multivariate analysis. We think that the SII value can be used as a good biomarker to predict MASLD and predict its prognosis.

Assessing the extent of liver fibrosis in MASLD patients accurately is crucial for prognosis and clinical decision-making.[60] Although biopsy is the accepted gold standard, its use is limited because of its invasiveness and difficulty in reproducing fibrosis monitoring. Because of these limitations, non-invasive tools were developed for use in the staging and follow-up of MASLD and liver fibrosis.[61] Biomarkers not only identify patients with MASLD noninvasively but also

contribute to assessing the severity of Steatohepatitis and fibrosis. In the present study, the researchers employed the GPR, APRI, and FIB-4 scoring systems employed for fibrosis scoring to predict MASLD.

In his study, Lemoine suggested the ratio of GPR, which has higher diagnostic performance than AST, which can routinely identify patients with fibrosis.[62,63] There is no study in the literature investigating the relationship between MASLD and GPR in predicting and predicting prognosis. In our study, we found the GPR level to be higher in patients with MASLD than in healthy controls. When the GPR levels were examined according to the liver grading, we found that the GPR level increased positively as the grade increased and it was statistically significant. To investigate the diagnostic value of patients with MASLD, ROC analysis was performed for the GPO value. When the cut-off value was taken as 0.047, the researchers found an AUC of 0.755 (0.681-0.829), specificity of 60.80%, and sensitivity of 66.67%. We predict that each unit increase in the GPR value will cause a 2.84-fold increase in the risk of MASLD. GPR value, which is an independent risk factor in univariate regression analysis to predict patients with MASLD, attracted our attention as a good biomarker in multivariate analysis.

After the APRI score was defined by Wai et al. its usability and suitability in various CHD were evaluated.[64] In the study conducted by Kruger et al. more positive results were obtained in the APRI score of patients with biopsy-diagnosed MASLD compared to other parameters. When the cut-off value for APRI was taken above 1.5, the AUROC value was 0.85, with 86% specificity, and 75% sensitivity.[65] In the present study, no significant differences were detected between the patient and healthy control groups in terms of APRI score.

The FIB-4 score, which was defined to assess the degree of fibrosis, was compared with other scoring systems in a study that included 576 patients who were diagnosed with MASLD by biopsy in 2012, and it was shown that FIB-4 detected more advanced fibrosis patients with 91% than other formulas.[66,67] In the present study, the researchers detected that MASLD patients had a lower FIB-4 score level than healthy controls. ROC analysis was made to predict patients. When the FIB-4 cut-off value was taken as 0.219, the researchers detected AUC 0.306 (0.232-0.381) with a specificity of 66.20% and sensitivity of 22.80%. Although the FIB-4 score was an independent risk factor in univariate regression analysis, it also contributed significantly to multivariate analysis. We think that it can be employed as a good biomarker to predict MASLD and predict prognosis.

There were several limitations in the present study. The study included a limited number of patients in one single healthcare center, and the diagnosis of MASLD was made by guided USI, and most of the patients did not have biopsy data. Because of the cross-sectional fashion of this retrospective study, the researchers were unable to identify causal relationships or long-term clinical outcomes. Prospective studies with a longer follow-up period are needed to confirm the results.

CONCLUSION

MASLD is a common disease has become an important healthcare concern. An effective monitoring indicator is urgently needed for early detection of MASLD. We think that using hematological biomarkers will be beneficial for the simple and rapid detection of suspected patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University Local Ethics Committee (Date: 18.07.2023, Decision No: 2023/352).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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