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The Effect of Manual Detorsion on Testicular Salvage Rates in Adult Testicular Torsion Patients: Single Center Experience

Erişkin Testis Torsiyonu Hastalarında Manuel Detorsiyonun Testis Kurtarma Oranlarına Etkisi: Tek Merkez Deneyimi

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ABSTRACT

Aim: The aim of this study was to reveal the effect of manual detorsion on testicular salvage rates and the factors affecting the success of manual detorsion in adult testicular torsion.
Material and Methods: The records of patients who applied to the emergency department with pre-diagnosis of acute scrotum were examined. A total of 62 adult patients diagnosed with testicular torsion were included in the study. Manual detorsion was attempted in all patients before surgery. Demographic characteristics of the patients, time from onset of scrotal pain to hospital admission (<24 hours/>24 hours), physical examination and ultrasonography findings, type of surgery performed, and long-term results were evaluated. The data were statistically compared between patients with manual detorsion considered successful and unsuccessful.
Results: Manual detorsion was considered successful in 36 (58.1%) patients and unsuccessful in 26 (41.9%) patients. Orchiopexy was performed in 35 (97.2%) of the successful patients and in 11 (42.3%) of the unsuccessful patients ($p<0.001$). When subgroup analysis was performed, although there was no significant difference in pain duration between patients with and without successful manual detorsion for patients with pain duration of less than 24 hours ($p=0.648$), there was a statistically significant difference in testicular salvage rates. While the rate of orchiectomy was 1/35 (2.9%) in patients with successful manual detorsion, this rate was 8/19 (42.1%) in unsuccessful patients ($p<0.001$).
Conclusion: Manual detorsion increases testicular salvage rates in adult patients diagnosed with testicular torsion, and it should be attempted especially in patients with pain duration less than 24 hours.
Keywords: Testicular torsion; manual detorsion; orchiopexy; orchiectomy.

ÖZ

Amaç: Bu çalışmanın amacı erişkin testis torsiyonunda manuel detorsiyonun testis kurtarma oranlarına etkisini ve manuel detorsiyonun başarısını etkileyen faktörleri ortaya koymaktır.
Gereç ve Yöntemler: Akut skrotum ön tanısı ile acil servise başvuru yapan hastaların kayıtları incelendi. Testis torsiyonu tanısı konulan 62 erişkin hasta çalışmaya dahil edildi. Hastaların tamamına cerrahi öncesinde manuel detorsiyon denendi. Hastaların demografik özellikleri, skrotal ağrının başlangıcından hastaneye başvuruya kadar geçen süreleri (<24 saat/>24 saat), fizik muayene ve ultrasonografi bulguları, uygulanan cerrahinin tipi ve uzun dönem sonuçları değerlendirildi. Elde edilen veriler manuel detorsiyonu başarılı ve başarısız kabul edilen hastalar arasında istatistiksel olarak karşılaştırıldı.
Bulgular: Manuel detorsiyon 36 (%58,1) hastada başarılı, 26 (%41,9) hastada ise başarısız olarak kabul edildi. Başarılı olan hastaların 35'inde (%97,2) ve başarısız olan hastaların ise 11'inde (%42,3) orşiopeksi uygulandı ($p<0,001$). Alt grup analizi yapıldığında, ağrı süresi 24 saatten daha kısa olan hastalarda, manuel detorsiyonu başarılı olan ve olmayan hastalar arasında ağrı süresi açısından anlamlı bir farklılık olmamasına rağmen ($p=0,648$), testis kurtarma oranları arasında istatistiksel olarak anlamlı bir farklılık mevcuttu. Başarılı manuel detorsiyon uygulanan hastalarda orşiektomi oranı 1/35 (%2,9) iken, başarısız olan hastalarda bu oran 8/19 (%42,1) olarak bulundu ($p<0,001$).
Sonuç: Testis torsiyonu tanısı alan erişkin hastalarda manuel detorsiyon testis kurtarma oranlarını artırmaktadır, özellikle 24 saatten az ağrı süresi olan hastaların tamamında denenmelidir.
Anahtar kelimeler: Testiküler torsiyon; manuel detorsiyon; orşiopeksi; orşiektomi.

INTRODUCTION

Testicular torsion is a disease that is characterized by rotation of the spermatic cord around itself, causes ischemic organ damage in the affected testis, and requires urgent diagnosis and treatment (1). It is the second most common cause of acute scrotum after acute epididymoorchitis. Since it is known that ischemic damage to the testicle is associated with the amount and duration of cord rotation, time is of critical importance in testicular torsion (1-4). Delay in diagnosis and detorsion of the affected spermatic cord results in high rates of orchiectomy (5-7).

The standard approach in the treatment of testicular torsion is surgical exploration (7). Manual detorsion performed before surgery is known to be a safe and noninvasive method that reduces the duration of testicular ischemia and increases the testicular salvage rate (7-10). Even when manual detorsion is partially successful, reducing testicular rotation may allow some perfusion and may result in a significant prognosis difference (4,10,11).

The literature about the effectiveness of manual detorsion is usually obtained from data of pediatric patients, rather than adult patients. In this study, we aimed to determine the effect of manual detorsion on testicular salvage rates in adult patients admitted to the emergency department with testicular torsion and also the factors affecting the success of manual detorsion.

MATERIAL AND METHODS

Following ethics committee approval (Adana City Training and Research Hospital Clinical Research Ethics Committee affiliated to Adana Governorship Provincial Health Directorate with reference number 2022/1765), the computer records and files of patients who applied to the emergency department with the diagnosis of acute scrotum between January 2010 and January 2020 were examined. Patients diagnosed with testicular torsion based on a history of testicular pain, physical examination findings, and color Doppler ultrasonography (CDUS) findings were included in our study. Patients diagnosed with acute scrotal causes other than testicular torsion, patients diagnosed with testicular torsion with missing data such as duration of pain, CDUS findings, degree of torsion during surgery, manual detorsion results, and follow-up records, and patients under 18 years of age were excluded from the study.

Manual detorsion was attempted in all patients with testicular torsion before surgical exploration. The procedure was performed from medial to lateral without spermatic cord block or sedation as standard. Detorsion was considered successful in patients with immediate relief of pain and whose testicular blood flow was obtained again on the control CDUS. In addition, the success of manual detorsion was evaluated with scrotal exploration after detorsion. Emergency scrotal exploration was performed without delay in patients with failed manual detorsion.

Viability of testicles was evaluated after spermatic cord detorsion and heat application during scrotal exploration. Orchiectomy was performed for necrotic testicles where tissue perfusion could not be achieved. Patients with good testicular viability underwent orchiopexy on the affected side and contralateral side.

Demographic characteristics of the patients, time from the onset of scrotal pain to hospital admission (<24 hours / >24 hours), physical examination and CDUS findings, pain relief after manual detorsion and CDUS findings, surgical findings, type of surgery performed, and long-term results were evaluated. The data were statistically compared between patients with manual detorsion considered successful and unsuccessful.

Atrophy/viable testicle evaluations in the postoperative period were performed with the results of CDUS and physical examination findings of patients at three-month intervals.

Statistical analysis

Data are expressed as n (%), mean±standard deviation, or median (interquartile range, IQR) [min-max] as appropriate. The normality assumption was checked with the Shapiro-Wilk test. The Mann-Whitney U test or Student's t-test was used for continuous variables. Pearson chi-square or Fisher's exact test was performed for categorical variables. Statistical analysis was performed using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY). A p value of <0.05 was considered statistically significant.

RESULTS

Our study consisted of 62 adult patients with a mean age of 24.0±6.9 years. While manual detorsion was considered successful in 36 (58.1%) of these patients, it was considered unsuccessful in 26 (41.9%) patients. Residual torsion was observed in all patients who were considered unsuccessful when scrotal exploration was subsequently performed. Orchiopexy was performed in 35 (97.2%) of the patients with successful manual detorsion, and in 11 (42.3%) of the unsuccessful patients ($p<0.001$). Median pain durations were 4.5 (range, 2-26) and 6 (range, 2-96) hours in the successful and unsuccessful groups, respectively ($p=0.042$). The clinical and demographic characteristics of the patients are shown in Table 1.

In addition, subgroup analysis was performed for patients according to the duration of pain as less than 24 hours and more than 24 hours. Manual detorsion was found to be successful in 35 (64.8%) of 54 patients whose pain duration was less than 24 hours. Although there was no significant difference in pain duration between those with and without successful manual detorsion among these patients ($p=0.648$), there was a statistically significant difference in testicular salvage rates. While the rate of orchiectomy was 1/35 (2.9%) in patients with successful manual detorsion, this rate was 8/19 (42.1%) in unsuccessful patients ($p<0.001$). Manual detorsion was found to be successful in only 1 (12.5%) of 8 patients with pain duration of more than 24 hours and orchiopexy was performed for this patient. Orchiectomy was performed in all 7 patients with failed manual detorsion. The subgroup analysis results of the patients are shown in Table 2.

DISCUSSION

The degree and duration of spermatic cord twist in testicular torsion is the most important factor in maintaining testicular viability (7,12). If not treated urgently, testicular infarction or atrophy develops during follow-up. The amount of rotation of the spermatic cord

Table 1. Clinical and demographic characteristics of patients

Manual Detorsion	**Success (n=36)**	**Failed (n=26)**	**p**
Age (years), mean±SD	23.5±5.7	24.7±8.4	0.505[T]
Findings, n (%)			
Abnormal horizontal position of the testis	29 (80.6)	20 (76.9)	0.729[¥]
Absent cremasteric reflex	20 (55.6)	14 (53.8)	0.894[¥]
Abnormal CDUS	36 (100)	26 (100)	-
Pain duration (hours), median (IQR) [min-max]	4.5 (4.8) [2-26]	6 (25) [2-96]	**0.042**[†]
Surgical type, n (%)			
Orchiopexy	35 (97.2)	11 (42.3)	**<0.001**[¥]
Orchiectomy	1 (2.8)	15 (57.7)	
Follow-up time (months), mean±SD	13.1±3.5	12.6±2.6	0.547[T]

SD: standard deviation, IQR: interquartile range, CDUS: color Doppler ultrasonography, T: Student's t test, †: Mann Whitney-U test, ¥: Chi-square test

Table 2. Subgroup analysis results of patients

Pain Duration	**<24 hours (n=54)**		**p**	**>24 hours (n=8)**		**p**
Manual Detorsion, n (%)	**Success 35 (64.8)**	**Failed 19 (35.2)**		**Success 1 (12.5)**	**Failed 7 (87.5)**	
Surgical type, n (%)						
Orchiopexy	34 (97.1)	11 (57.9)	**<0.001**[¥]	1 (100)	-	-
Orchiectomy	1 (2.9)	8 (42.1)		-	7 (100)	
Pain duration (hours), median (IQR) [min-max]	4 (4) [2-15]	5 (5) [2-12]	0.648[†]	26	36 (40) [28-96]	-
Testicular atrophy, n (%)	-	2 (10.5)	-	-	-	-
Degree of peroperative torsion, n (%)						
>360º	-	6 (31.6)	-	-	4 (57.1)	-
<360º	-	2 (10.5)		-	3 (42.9)	

IQR: interquartile range, †: Mann Whitney-U test, ¥: Chi-square test

and the delay in treatment are associated with testicular salvage rates and subsequent atrophy rates (10,11,13-15).

Patient history, physical examination findings, and CDUS come to the fore in the diagnosis of testicular torsion. All of our patients applied to the emergency department with the complaint of sudden onset testicular pain. As a physical examination finding, 79.0% of our patients had an abnormal horizontal position of the testicle and 54.8% had a loss of cremasteric reflex. Although there are many imaging methods that evaluate testicular vascularity, CDUS can be used safely for diagnosis because of its easy accessibility, cheap and fast results, the sensitivity of 63.6%-100%, and the specificity of 97-100%. Although better results were reported with high-resolution ultrasonography for the diagnosis of testicular torsion, its availability is not as common as CDUS (16). Therefore, CDUS has an important role in the diagnosis of testicular torsion and in the evaluation of the effectiveness of manual detorsion. After manual detorsion, restoration of normal blood flow in the affected testis should be demonstrated by ultrasonography (7,17). The patients in our study were diagnosed with testicular torsion based on history, physical examination, and CDUS findings.

Manual detorsion, first described by Nash in 1893, is known as a safe and noninvasive method that reduces testicular ischemia time and increases the rate of testicular salvage (7-10,18). After successful manual detorsion, the pain resolves in a short time (less than 5 minutes), testicular blood flow is restored on CDUS, and the testicle usually returns to its lower position in the scrotum (7,8). However, restoration of blood flow should be confirmed after this maneuver and orchiopexy should be applied under elective conditions (8,19). Local anesthesia or sedation is not performed during manual detorsion in our clinic, as the resolution of pain, which is an important parameter in determining the success of the detorsion maneuver, will be lost with anesthesia.

With manual detorsion, the aim is to temporarily alleviate testicular ischemic damage. The extent of ischemic damage increases with the degree of rotation of the spermatic cord. Therefore, even when the detorsion procedure is partially successful, reducing testicular rotation may allow some perfusion (4,10,11). Manual detorsion of the testis was shown to be associated with a significant reduction in the amount of testicular rotation evaluated intraoperatively (10). Although Dias Filho et al. (10) recommended that manual detorsion be performed only in patients with testicular pain of less than 24 hours, Vasconcelos-Castro et al. (7) showed that the advantage of manual detorsion was independent of the duration of pain and reported that it should be applied to all patients. In our study, manual detorsion was attempted in all patients, and when the patients who were considered successful were explored, residual torsion was not detected in any of them. In particular, our manual detorsion success rate and testicular salvage rates were found to be higher for patients whose pain duration did not exceed 24 hours. For this reason, we think that manual detorsion should be attempted, especially in patients whose pain duration is less than 24 hours. In addition, although the number of our patients is not high, we believe that surgical exploration may be appropriate without wasting time, due to the

decrease in the success rate of manual detorsion in patients with pain duration longer than 24 hours.
The limitations of our study are that it was designed retrospectively and manual detorsion was applied by different physicians over time. However, we think it will contribute to the literature since it is one of the few studies on testicular torsion in adult patients.

CONCLUSION

Manual detorsion increases testicular salvage rates in adult patients diagnosed with testicular torsion, and it should be attempted especially in all patients with pain duration of less than 24 hours. We believe that randomized prospective studies with larger numbers of patients will support our findings and increase the level of evidence.

Ethics Committee Approval: The study was approved by the Ethics Committee of Adana City Training and Research Hospital (10.02.2022, 1765).

Conflict of Interest: None declared by the authors.

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REFERENCES

1. Moore SL, Chebbout R, Cumberbatch M, Bondad J, Forster L, Hendry J, et al. Orchidopexy for testicular torsion: a systematic review of surgical technique. Eur Urol Focus. 2021;7(6):1493-503.
2. McLaren PSM. A systematic review on the utility of ultrasonography in the diagnosis of testicular torsion in acute scrotum patients. Radiography (Lond). 2021;27(3):943-9.
3. Syed MK, Al Faqeeh AA, Othman A, Hussein AA, Hussain S, Almas T, et al. The spectrum of testicular pathologies upon scrotal exploration for acute scrotum: a retrospective analysis. Cureus. 2020;12(10):e10984.
4. Visser AJ, Heyns CF. Testicular function after torsion of the spermatic cord. BJU Int. 2003;92(3):200-3.
5. Cost NG, Bush NC, Barber TD, Huang R, Baker LA. Pediatric testicular torsion: demographics of national orchiopexy versus orchiectomy rates. J Urol. 2011;185(6 Suppl):2459-63.
6. Jefferies MT, Cox AC, Gupta A, Proctor A. The management of acute testicular pain in children and adolescents. BMJ. 2015;350:h1563.
7. Vasconcelos-Castro S, Flor-de-Lima B, Campos JM, Soares-Oliveira M. Manual detorsion in testicular torsion: 5 years of experience at a single center. J Pediatr Surg. 2020;55(12):2728-31.
8. Cornel EB, Karthaus HF. Manual derotation of the twisted spermatic cord. BJU Int. 1999;83(6):672-4.
9. Demirbas A, Demir DO, Ersoy E, Kabar M, Ozcan S, Karagoz MA, et al. Should manual detorsion be a routine part of treatment in testicular torsion? BMC Urol. 2017;17(1):84.
10. Dias Filho AC, Oliveira Rodrigues R, Riccetto CL, Oliveira PG. Improving organ salvage in testicular torsion: comparative study of patients undergoing vs not undergoing preoperative manual detorsion. J Urol. 2017;197(3 Pt 1):811-7.
11. Tryfonas G, Violaki A, Tsikopoulos G, Avtzoglou P, Zioutis J, Limas C, et al. Late postoperative results in males treated for testicular torsion during childhood. J Pediatr Surg. 1994;29(4):553-6.
12. Drlík M, Kočvara R. Torsion of spermatic cord in children: a review. J Pediatr Urol. 2013;9(3):259-66.
13. Sessions AE, Rabinowitz R, Hulbert WC, Goldstein MM, Mevorach RA. Testicular torsion: direction, degree, duration and disinformation. J Urol. 2003;169(2):663-5.
14. Cummings JM, Boullier JA, Sekhon D, Bose K. Adult testicular torsion. J Urol. 2002;167(5):2109-10.
15. Lian BS, Ong CC, Chiang LW, Rai R, Nah SA. Factors predicting testicular atrophy after testicular salvage following torsion. Eur J Pediatr Surg. 2016;26(1):17-21.
16. Kalfa N, Veyrac C, Lopez M, Lopez C, Maurel A, Kaselas C, et al. Multicenter assessment of ultrasound of the spermatic cord in children with acute scrotum. J Urol. 2007;177(1):297-301.
17. Nussbaum Blask AR, Rushton HG. Sonographic appearance of the epididymis in pediatric testicular torsion. AJR Am J Roentgenol. 2006;187(6):1627-35.
18. Nash WG. Acute torsion of spermatic cord: reduction: immediate relief. BMJ. 1893;1(1684):742-3.
19. Ringdahl E, Teague L. Testicular torsion. Am Fam Physician. 2006;74(10):1739-43.

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Efficacy of Transarterial Chemoembolization with Drug-Eluting Beads in Hepatocellular Carcinoma: A Single-Center Experience

Hepatosellüler Karsinomda İlaç Yüklenebilir Mikroküreler ile Yapılan Transarteriyel Kemoembolizasyonun Etkinliği: Tek Merkez Deneyimi

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ABSTRACT

Aim: The aim of this study was to evaluate the efficacy of transarterial chemoembolization (TACE) with drug-eluting beads in hepatocellular carcinoma (HCC).
Material and Methods: Twenty-nine patients with HCC who were treated with TACE with drug-eluting beads between 2019 and 2021 were included in the study. The success of the TACE procedure was evaluated using pre- and post-operative contrast-enhanced computed tomography/magnetic resonance images. Patient characteristics, embolizing-bead sizes, procedure-related complications, and pre- and post-procedure alpha-fetoprotein (AFP) levels were recorded.
Results: The mean age of the patients was 65.6±10.4 years, and the objective response rate was 17.2% (5/29). 100-300 μm particles were used in 11 (37.9%) patients, and 300-500 μm particles were used in 18 (62.1%). The median target lesion number was 1 (range, 1-6). Six (20.7%) patients had non-target lesions. There were newly developed lesions in four (13.8%) patients. A significant decrease was found in the median target lesion size after (41; range, 0-116 mm) the procedure compared to the pre- (42; range, 22-188 mm) procedure ($p<0.001$). A significant difference was found between the median AFP levels before (343; range, 1.44-2000 ng/mL) and after (52; range, 0.95-1435 ng/mL) the procedure ($p<0.001$).
Conclusion: Since most patients with HCC are diagnosed in the intermediate stage, curative treatment is not possible. TACE is an important treatment option for the local control of the disease in this patient group. However, the success of TACE treatment may vary depending on the cancer stage, number of patients, follow-up period, and type and size of the microsphere used.
Keywords: Hepatocellular carcinoma; transarterial chemoembolization; drug-eluting beads.

ÖZ

Amaç: Bu çalışmanın amacı hepatosellüler karsinomda (HCC) ilaç salınımlı mikroküreler ile yapılan transarteriyel kemoembolizasyon (TAKE) tedavisinin etkinliğini değerlendirmektir.
Gereç ve Yöntemler: 2019 ve 2021 tarihleri arasında ilaç salınımlı mikroküreler ile TAKE uygulanan 29 HCC'li hasta çalışmaya dahil edildi. TAKE işleminin başarısı işlem öncesi ve sonrası kontrastlı bilgisayarlı tomografi ve manyetik rezonans görüntüleri ile değerlendirildi. Hasta karakteristikleri, embolizasyon için kullanılan mikroküre boyutları, işleme bağlı komplikasyonlar ve işlem öncesi ve sonrası alfa fetoprotein (AFP) düzeyleri kaydedildi.
Bulgular: Hastaların yaş ortalaması 65,6±10,4 yıldı ve objektif yanıt oranı %17,2 (5/29) idi. 11 (%37,9) hastada 100-300 μm ve 18 (%62,1) hastada 300-500 μm boyutlarında partikül kullanılmıştı. Ortanca hedef lezyon sayısı 1 (aralık, 1-6) idi. Altı (%20,7) hastada hedef olmayan lezyon mevcuttu. Dört (%13,8) hastada yeni gelişen lezyon mevcuttu. İşlem sonrası ortanca hedef lezyon boyutunda (41; aralık, 0-116 mm) işlem öncesi (42; aralık, 22-188 mm) ile karşılaştırıldığında anlamlı bir azalma olduğu saptandı ($p<0,001$). Ayrıca, işlem öncesi (343; aralık, 1,44-2000 ng/mL) ve işlem sonrası (52; aralık, 0,95-1435 ng/mL) ortanca AFP değerleri arasında anlamlı bir farklılık saptandı ($p<0.001$).
Sonuç: HCC hastalarının büyük bir kısmı intermediate evrede teşhis edildiğinden küratif tedavileri mümkün değildir. Bu hasta grubunda TAKE, hastalığın lokal kontrolünde önemli bir tedavi seçeneğidir. Bununla birlikte, TAKE tedavisinin başarısı kanser evresi, hasta sayısı, takip süresi ve kullanılan mikrokürenin tipi ve boyutuna göre değişkenlik gösterebilir.
Anahtar kelimeler: Hepatosellüler karsinom; transarteriyel kemoembolizasyon; ilaç salınımlı mikroküreler.

INTRODUCTION

Liver cancer is the sixth most frequently diagnosed cancer, and ranks fourth in cancer-related deaths (1). Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver (2).

The surgical treatment of liver tumors is an option with curative potential. However, only 20% of patients are suitable for surgical treatment (3). Most liver malignancies cannot be treated surgically due to the presence of comorbidities, multiple metastases, anatomical localization where resection is not possible, insufficient functional liver capacity, and tumor recurrence (4,5). Locoregional therapies are applied to patients who are not suitable for surgical treatment. Transarterial chemoembolization (TACE) and ablation are the most preferred locoregional therapy methods in this field (6-8). In HCC, the Barcelona Clinic Liver Cancer (BCLC) staging and treatment algorithm are used to guide treatment based on the tumor stage, liver functional status, physical condition, and cancer-related symptoms of patients. TACE treatment is applied in BCLC stage B HCC and causes necrosis in the tumor with arterial embolization and death of tumor cells through the cytotoxic effects of the chemotherapeutic drugs used. TACE can inhibit tumor progression and improve survival; therefore, it is considered a palliative treatment for BCLC stage B HCC (9). The current study aimed to evaluate the efficacy of TACE treatment with drug-eluting beads in HCC.

MATERIAL AND METHODS

After obtaining approval from the local ethics committee (Sakarya University, 02.02.2022, 102075), 29 patients with BCLC stage B HCC who were referred to our clinic at Sakarya University Training and Research Hospital for TACE treatment between 2019 and 2021 were retrospectively included in the study. The exclusion criteria were determined as uncorrected coagulopathy and pregnancy. Response to treatment was evaluated with contrast-enhanced computed tomography/magnetic resonance (CT/MR) images taken before (Figure 1.A) and after the procedure. Drug-eluting bead sizes, pre- and post-procedure alpha-fetoprotein (AFP) levels, and procedure-related complications were recorded.

TACE Procedure

With the patient under local anesthesia, a 5F vascular sheath was placed in the right common femoral artery under ultrasound guidance. Then, angiograms were obtained from the celiac artery and superior mesenteric artery to determine the origin of the hepatic artery with a 0.035" guide wire and Cobra/Simmons 1 (Tempo, Cordis, UK) catheter. After the celiac artery/superior mesenteric artery was catheterized, the origin of the feeding arteries of the lesions was determined on the angiograms (Figure 1.B). Subsequently, a microcatheter (Renegade, Boston Scientific, USA) was super selectively advanced to the feeding arteries of the tumor. A mixture of doxorubicin, drug-eluting embolizing particles (DC Bead, Boston Scientific, USA), and iohexol, a low-osmolarity contrast agent (Opaxol, Opakim, Turkey), was administered via the microcatheter. Embolizing injection was performed away from the origin of the gastroduodenal, right gastric, and cystic arteries. In order to prevent off-target embolization, the embolizing particle was injected slowly, and the procedure was terminated when stagnation developed (Figure1.C).

Analgesic and antiemetic treatments were administered during and/or after the procedure. The patients were non-invasively monitored with oxygen saturation and blood pressure measurements and electrocardiography throughout the procedure.

Imaging and Follow-up

Before and after (Figure 1.D) the TACE procedure, dual-phase (arterial and portal venous phase) contrast CT/MR images of the liver were obtained with the same protocol. Treatment efficacy was evaluated with contrast-enhanced CT/MR imaging at the first month.

The modified response evaluation criteria in solid tumors (mRECIST) criteria were used to assess the patients' response to treatment. For this purpose, HCC lesions were categorized as target, non-target, and newly developed. For a lesion to be classified as a target lesion, it should be suitable for repeated measurements, show an arterial enhancement pattern, and have at least one diameter that is ≥1 cm (10). The response of target and non-target lesions to TACE treatment according to the mRECIST criteria is summarized in Tables 1 and 2, respectively. The presence of a newly developed lesion of ≥1 cm with arterial hypervascularity and contrast washout in the portal venous or late phase indicates HCC without histopathology (10). If the newly developed lesions did not meet these criteria, it was decided whether HCC was present according to the follow-up examinations. The overall response of the patients to TACE therapy was determined by evaluating the target, non-target, and newly developed lesions together (Table 3).

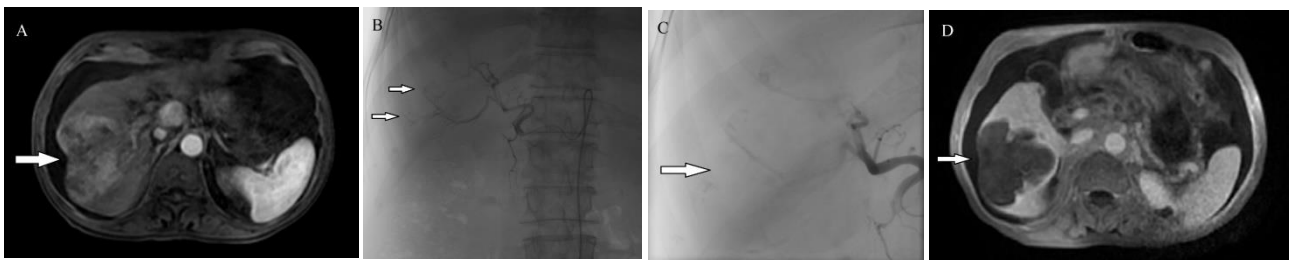

Figure 1. Radiological images of a 78-year-old male patient **A)** Contrast-enhanced abdominal magnetic resonance (MR) image shows hepatocellular carcinoma (HCC) with a diameter of 87 mm in the liver with contrast enhancement in the arterial phase. **B)** Angiography image shows the tumoral staining of HCC before embolization **C)** Angiography image after transarterial chemoembolization with drug-eluting beads shows occlusion and stagnation in the feeder artery of the tumor **D)** Contrast-enhanced MR image taken at the first postoperative month shows no contrast enhancement in the tumoral area, and the appearance is consistent with complete response

Table 1. Response of target lesions to transarterial chemoembolization (TACE) treatment according to the modified response evaluation criteria in solid tumors (mRECIST) criteria (10)

Treatment Response	Definition
Complete response	Disappearance of intra-tumoral arterial enhancement in all target lesions
Partial response	≥30% reduction in the sum of the longest diameters of all target lesions showing arterial enhancement
Stable disease	Cases that cannot be categorized as having partial response or progressive disease
Progressive disease	≥20% increase in the sum of the shortest diameters of all target lesions showing arterial enhancement

Table 2. Response of non-target lesions to transarterial chemoembolization (TACE) treatment according to the modified response evaluation criteria in solid tumors (mRECIST) criteria (10)

Treatment Response	Definition
Complete response	Disappearance of intra-tumoral arterial enhancement in all non-target lesions
Incomplete response/stable disease	Persistence of intra-tumoral arterial enhancement in one or more non-target lesions
Progressive disease	Emergence of one or more new lesions and/or definite progression of existing non-target lesions

Table 3. Overall response of patients with hepatocellular carcinoma (HCC) to transarterial chemoembolization (TACE) treatment according to the modified response evaluation criteria in solid tumors (mRECIST) criteria (10)

Target Lesion	Non-target Lesion	Newly developed Lesion	Overall Response
CR	CR	Absent	CR
CR	IR/SD	Absent	PR
PR	No PD	Absent	PR
SD	No PD	Absent	SD
PD	Any category	Any category	PD
Any category	PD	Any category	PD
Any category	Any category	Present	PD

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, IR: incomplete response

Statistical Analysis

Statistical analysis was performed using MedCalc (ver.12, Ostend, Belgium) software package. For the statistical analysis, categorical variables were presented as numbers and percentages, and continuous variables as median, quartiles, and minimum-maximum values for descriptive findings. Continuous variables were compared with Wilcoxon test according to their conformance to a normal distribution determined with the Shapiro-Wilk test. The statistical significance level was accepted as $p<0.05$.

RESULTS

Twenty-four (82.8%) patients were male and five (17.2%) were female. The mean age of the patients was 65.6±10.4 years. Before the TACE procedure, surgery was performed in two (6.9%) patients and microwave ablation (MWA) in three (10.3%). 100-300 μm particles were used in 11 (37.9%) patients and 300-500 μm particles in 18 (62.1%). The median number of target lesions was 1 (range, 1-6). Six (20.7%) patients had non-target lesions, and four (13.8%) had a newly developed lesion. The target lesion and overall treatment response are presented in Table 4. The objective response rate, which represents the percentage of patients with a complete or partial response, was determined as 17.2% (5/29).

A significant difference was found between the median AFP values before (343; range, 1.44-2000 ng/mL) and after (52; range, 0.95-1435 ng/mL) the procedure ($p<0.001$). In addition, there was a significant decrease in the median target lesion size after (41; range, 0-116 mm) the procedure compared to the pre- (42; range, 22-188 mm) procedure ($p<0.001$; Table 5).

Mild postembolization syndrome, which causes abdominal pain and nausea/vomiting, was observed in eight (27.6%) of the patients. Liver abscess developed in one (3.4%) patient after embolization.

Table 4. Treatment response of target lesions and overall treatment response

	Target Lesion Response	Overall Treatment Response
Complete response	1 (3.4%)	1 (3.4%)
Partial response	5 (17.2%)	4 (13.8%)
Stable disease	20 (69%)	17 (58.6%)
Progressive disease	3 (10.4%)	7 (24.2%)

Table 5. Serum AFP level and target lesion size comparison before and after the procedure

	Pre-procedure	Post-procedure	p
AFP (ng/mL)	343 (20.25-715.25) [1.44-2000]	52 (10.85-220) [0.95-1435]	**<0.001**
Target lesion size (mm)	42 (32.75-90.25) [22-188]	41 (22-79.25) [0-116]	**<0.001**

AFP: alpha-fetoprotein, descriptive statistics were reported as median (1^{st} quartile – 3^{rd} quartile) [minimum-maximum]

DISCUSSION

In this study, the efficacy of TACE therapy in BCLC stage B HCC was evaluated. In the literature, it has been reported that in the absence of vascular invasion and extrahepatic tumor spread, TACE may improve one- and two-year survival in patients with HCC who are not suitable for curative treatment (11). Conventional TACE involves the injection of a mixture of a chemotherapeutic agent and iodized oil. Many studies are being conducted to increase the efficacy of locoregional therapies and reduce the systemic toxicity of chemotherapeutic drugs. Drug-eluting beads are among the products developed for this purpose (11). In vitro studies and animal experiments have proven that TACE administered with drug-eluting beads is associated with a mild transient increase in liver enzymes, reduced plasma doxorubicin levels, and increased tumor necrosis (12-14). Therefore, in the current study, TACE was performed with drug-eluting beads (DC Beads, Boston Scientific, USA).

There are studies comparing the treatment efficacy and complication rates according to the size of drug-eluting beads (15). Higher coagulation necrosis and complete response rates, longer overall survival, less fibrosis, and postembolization syndrome have been reported in embolization procedures performed with 100-300 μm particles compared to those undertaken with larger particles (15). However, due to the risk of severe necrosis in normal liver tissue, advanced embolization with very small particles should be avoided (11). While no significant difference has been shown between large and small size particles in terms of drug release, it has been reported that small beads have a higher drug-eluting capacity due to their high surface area/volume ratio (15). Many factors such as tumor volume, size of the artery feeding the tumor, and tumor characteristics should be considered in the selection of the bead size to be used. In addition, the presence of an arteriovenous shunt is very important in this decision. Therefore, a careful examination of angiographic images is necessary before embolization in order to prevent serious complications. In the current study, the size of the drug-eluting beads used was 100-300 μm in 11 (37.9%) patients and 300-500 μm in 18 (62.1%).

The efficacy of TACE also depends on the arterial blood supply to the tumor, tumor size, and ultraselective positioning of the embolizing catheter, and it is almost impossible to achieve complete tumor necrosis with TACE alone. Residual tumor cells may cause local recurrence and distant metastasis (16,17). Studies have shown that the combination of TACE and local ablative treatments is much more successful than the use of either method alone (18,19). The synergistic effect of the combination of TACE and MWA/radiofrequency ablation (RFA) can be explained as follows: With TACE, hepatic arterial blood flow is decreased, the heat sink effect of vascular structures in local ablative treatments is reduced, and the thermal efficacy of MWA/RFA and the attainable intra-tumor temperature level are increased. Similarly, chemotherapeutic drugs used in TACE can increase the thermal sensitivity of tumor cells and thermal conductivity of MWA (20-22). Combined therapies can be used as an alternative method for the successful eradication of the tumor and maximum preservation of liver function (23). In the current study, before the TACE procedure, surgery was performed in two (6.9%) patients, and MWA was applied to three (10.3%), and TACE was planned when recurrence was observed. There was a significant decrease in the AFP values of the patients and the sum of the diameters of the target lesions compared to the pre-procedure evaluation. The objective response rate was determined as 17.2%, which was lower than previously reported rates of 51.6% (24) and 66.6-76.8% (25). These differences in clinical results can be due to various factors, such as the cancer stage, number of patients, follow-up period, and type and size of the beads used (25).

For TACE performed with drug-eluting beads in patients with HCC, the rate of major complications has been reported as 1.6-7.2% and that of minor complications as 30.2-67.6% (25). In the current study, mild postembolization syndrome, which causes abdominal pain and nausea/vomiting, was observed in 27.6% of the patients. In addition, liver abscess developed in one (3.4%) patient after embolization. A drainage catheter was placed in the abscess under ultrasound guidance, and the patient was treated with appropriate antibiotic therapy.

The limitations of this study can be listed as limited number of participants, its single-center nature, short follow-up period, and retrospective design.

CONCLUSION

Since most patients with HCC are diagnosed in the intermediate stage, curative treatment is not possible. TACE seems to be an important treatment option in the local control of the disease in this patient group. However, the success of TACE may vary depending on the cancer stage, number of patients, follow-up period, and type and size of the beads used. It is predicted that the newly developed agents and drug-eluting beads will increase the success of TACE treatment, and to achieve this, further large-scale and long-term studies are needed.

Ethics Committee Approval: The study was approved by the Ethics Committee of Sakarya University Faculty of Medicine (02.02.2022, 102075).

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

2. Bosetti C, Turati F, La Vecchia C. Hepatocellular carcinoma epidemiology. Best Pract Res Clin Gastroenterol. 2014;28(5):753-70.
3. Poulou LS, Botsa E, Thanou I, Ziakas PD, Thanos L. Percutaneous microwave ablation vs radiofrequency ablation in the treatment of hepatocellular carcinoma. World J Hepatol. 2015;18(8):1054-63.
4. Bipat S, van Leeuwen MS, Ijzermans JN, Comans EF, Planting AS, Bossuyt PM, et al. Evidence-base guideline on management of colorectal liver metastases in the Netherlands. Neth J Med. 2007;65(1):5-14.
5. Bilchik AJ, Wood TF, Allegra D, Tsioulias GJ, Chung M, Rose DM, et al. Cryosurgical ablation and radiofrequency ablation for unresectable hepatic malignant neoplasms: a proposed algorithm. Arch Surg. 2000;135(6):657-64.
6. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301-14.
7. Lanza E, Donadon M, Poretti D, Pedicini V, Tramarin M, Roncalli M, et al. Transarterial therapies for hepatocellular carcinoma. Liver Cancer. 2016;6(1):27-33.
8. Gruber-Rouh T, Naguib NN, Eichler K, Ackermann H, Zangos S, Trojan J, et al. Transarterial chemoembolization of unresectable systemic chemotherapy-refractory liver metastases from colorectal cancer: long-term results over a 10-year period. Int J Cancer. 2014;134(5):1225-31.
9. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19(3):329-38.
10. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30(1):52-60.
11. Grosso M, Vignali C, Quaretti P, Nicolini A, Melchiorre F, Gallarato G, et al. Transarterial chemoembolization for hepatocellular carcinoma with drug-eluting microspheres: preliminary results from an Italian multicentre study. Cardiovasc Intervent Radiol. 2008;31(6):1141-9.
12. Lewis AL, Gonzalez MV, Lloyd AW, Hall B, Tang Y, Willis SL, et al. DC bead: in vitro characterization of a drug-delivery device for transarterial chemoembolization. J Vasc Interv Radiol. 2006;17(2 Pt 1):335-42.
13. Hong K, Khwaja A, Liapi E, Torbenson MS, Georgiades CS, Geschwind JF. New intra-arterial drug delivery system for the treatment of liver cancer: preclinical assessment in a rabbit model of liver cancer. Clin Cancer Res. 2006;12(8):2563-7.
14. Lewis AL, Taylor RR, Hall B, Gonzalez MV, Willis SL, Stratford PW. Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. J Vasc Interv Radiol. 2006;17(8):1335-43.
15. Jia G, Van Valkenburgh J, Chen AZ, Chen Q, Li J, Zuo C, et al. Recent advances and applications of microspheres and nanoparticles in transarterial chemoembolization for hepatocellular carcinoma. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2022;14(2):e1749.
16. Zhou J, Liu Y, Ren Z, Zhang Y, Zhang M. Transarterial chemoembolization with gelatin sponge microparticles for barcelona clinic liver cancer Stage C and large hepatocellular carcinoma: Initial clinical experience. J Cancer Res Ther. 2017;13(5):767-72.
17. Li W, Man W, Guo H, Yang P. Clinical study of transcatheter arterial chemoembolization combined with microwave ablation in the treatment of advanced hepatocellular carcinoma. J Cancer Res Ther. 2016;12(Supplement):C217-20.
18. Hou YF, Wei YG, Yang JY, Wen TF, Xu MQ, Yan LN, et al. Combined hepatectomy and radiofrequency ablation versus TACE in improving survival of patients with unresectable BCLC stage B HCC. Hepatobiliary Pancreat Dis Int. 2016;15(4):378-85.
19. Katsanos K, Kitrou P, Spiliopoulos S, Maroulis I, Petsas T, Karnabatidis D. Comparative effectiveness of different transarterial embolization therapies alone or in combination with local ablative or adjuvant systemic treatments for unresectable hepatocellular carcinoma: A network meta-analysis of randomized controlled trials. PLoS One. 2017;12(9):e0184597.
20. Biederman DM, Titano JJ, Bishay VL, Durrani RJ, Dayan E, Tabori N, et al. Radiation segmentectomy versus TACE combined with microwave ablation for unresectable solitary hepatocellular carcinoma up to 3 cm: A propensity score matching study. Radiology. 2017;283(3):895-905.
21. Hu H, Chen GF, Yuan W, Wang JH, Zhai B. Microwave ablation with chemoembolization for large hepatocellular carcinoma in patients with cirrhosis. Int J Hyperthermia. 2018;34(8):1351-8.
22. Ako S, Nakamura S, Nouso K, Dohi C, Wada N, Morimoto Y, et al. Transcatheter arterial chemoembolization to reduce size of hepatocellular carcinoma before radiofrequency ablation. Acta Med Okayama. 2018;72(1):47-52.
23. Li X, Chen B, An C, Cheng Z, Han Z, Liu F, et al. Transarterial chemoembolization combined with microwave ablation versus microwave ablation only for Barcelona clinic liver cancer Stage B hepatocellular carcinoma: A propensity score matching study. J Cancer Res Ther. 2020;16(5):1027-37.
24. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010;33(1):41-52.
25. Nouri YM, Kim JH, Yoon HK, Ko HK, Shin JH, Gwon DI. Update on transarterial chemoembolization with drug-eluting microspheres for hepatocellular carcinoma. Korean J Radiol. 2019;20(1):34-49.

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Are High Urea Values before Intravenous Immunoglobulin Replacement a Risk Factor for COVID-19 Related Mortality?

İntravenöz İmmünoglobulin Replasmanı Öncesi Yüksek Üre Değerleri COVID-19'a Bağlı Mortalite için Bir Risk Faktörü müdür?

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ABSTRACT

Aim: This study aimed to examine the data of the coronavirus disease 2019 (COVID-19) patients treated with intravenous immunoglobulin (IVIG) treatment and to investigate the effects of the patients' clinical, laboratory, and treatment characteristics and risk factors for mortality.

Material and Methods: The study evaluated 81 adult COVID-19 patients who were hospitalized for the treatment of COVID-19 between April 2020 and September 2020 and were followed up, treated, and consulted in the immunology clinic for IVIG treatment, in a retrospective manner.

Results: The univariate analyses revealed that the duration of hospitalization in service, being intubated, duration of IVIG treatment, and the urea value before IVIG treatment were related to mortality in COVID-19 patients treated with IVIG treatment. As a result of multivariate analysis, being intubated and urea value before IVIG treatment were found to be independent risk factors for mortality (p=0.001 and p=0.009, respectively). It was found that for the 60 mg/dL level of urea value before IVIG treatment to predict mortality, the sensitivity was 46.2%, and the specificity was 35.5%. The area under the curve was found as 0.647; 95% confidence interval 0.518-0.776 (p=0.029).

Conclusion: The study found that urea values before IVIG treatment were a risk factor for mortality in patients who received IVIG treatment for COVID-19. This is important as it indicates that urea values should be closely monitored in patients given IVIG treatment for COVID-19. It also suggests that when resources are limited and risk stratification is required in COVID-19 patients, urea values can be helpful.

Keywords: SARS-CoV-2; immunoglobulin; mortality; blood urea nitrogen; COVID-19.

ÖZ

Amaç: Bu çalışmanın amacı, intravenöz immünoglobulin (IVIG) tedavisi ile tedavi edilen koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) hastalarının verilerini incelemek ve hastaların klinik, laboratuvar ve tedavi özellikleri ile mortalite için risk faktörlerinin etkilerini araştırmaktır.

Gereç ve Yöntemler: Çalışmada, Nisan 2020 ile Eylül 2020 tarihleri arasında COVID-19 tedavisi için hastaneye yatırılan ve IVIG tedavisi için immünoloji kliniğinde takip, tedavi ve konsülte edilen 81 erişkin COVID-19 hastası geriye dönük olarak değerlendirilmiştir.

Bulgular: Tek değişkenli analizler, IVIG tedavisi ile tedavi edilen COVID-19 hastalarında hastanede yatış süresi, entübe olma, IVIG tedavi süresi ve IVIG tedavisi öncesi üre değerinin mortalite ile ilişkili olduğunu gösterdi. Çok değişkenli analiz sonucunda, entübe olma ve IVIG tedavisi öncesi üre değeri mortalite için bağımsız risk faktörleri olarak bulundu (sırasıyla, p=0,001 ve p=0,009). Mortaliteyi öngörmek için IVIG tedavisi öncesi 60 mg/dL üre değeri için duyarlılık %46,2 ve özgüllük ise %35,5 olduğu bulundu. Eğri altında kalan alan 0,647; %95 güven aralığı ise 0,518-0,776 olarak bulundu (p=0,029).

Sonuç: Çalışmada, COVID-19 nedeniyle IVIG tedavisi alan hastalarda IVIG tedavisi öncesi üre değerlerinin mortalite için bir risk faktörü olduğu bulundu. Bu, COVID-19 için IVIG tedavisi verilen hastalarda üre değerlerinin yakından izlenmesi gerektiğini göstermesi açısından önemlidir. Ayrıca, COVID-19 hastalarında kaynaklar sınırlı olduğunda ve risk sınıflandırması gerektiği durumlarda, üre değerlerinin yardımcı olabileceğini göstermektedir.

Anahtar kelimeler: SARS-CoV-2; immunoglobulin; mortalite; kan üre nitrojen; COVID-19.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has affected the whole world in economic, social, spiritual, and many other areas, particularly in the field of health, since December 2019, when it was first described (1,2). As the disease is highly contagious, the virus spread worldwide in a short time and caused one of the most catastrophic pandemics in human history (3). Although there are some vaccines to reduce virus transmission and develop protection against it, it is obvious that vaccinating all the people in the world will not be possible in a short term. Although it has been more than one year since the World Health Organization (WHO) accepted COVID-19 as a pandemic, there is still no effective treatment. Until now, many treatment options, particularly antimalarial drugs and antivirals, systemic corticosteroids, tocilizumab, anakinra, conventional plasma therapy, and intravenous immunoglobulin (IVIG) therapy, have been tried in the form of monotherapy or combinations for treating COVID-19, there is still no consensus on its treatment (4-7). For this reason, it becomes crucial that the physicians interested in COVID-19 treatment share all the data they acquire, particularly in vulnerable patient groups, to reduce morbidity and mortality. Regarding COVID-19 treatment management, many countries have created their treatment protocols, and many associations have published guidelines for its treatment. COVID-19 treatment in Turkey has been primarily applied in line with the Ministry of Health protocols. In general, the patients positive for SARS-CoV-2 polymerase chain reaction (PCR) were put on hydroxychloroquine and favipiravir treatment at appropriate doses. Patients who did not benefit from these treatments and/or had underlying risk factors were hospitalized. In addition to respiratory support treatments, patients were treated with conventional plasma, systemic steroid therapy, immunomodulatory therapies such as tocilizumab and anakinra, and IVIG treatment, whichever appropriate, as line therapies (8). IVIG was administered as per the clinical immunologists' opinions and in the proper dose and time intervals.

Considering that pulmonary lesions in COVID-19 are caused by viral infiltrates and inflammatory response, IVIG treatment provides inflammatory cytokine balance, inhibits auto-reactive T cells, reduces antibody production from CD19+ B cells, and reduces macrophage activity. The IVIG treatment is thought to provide a regression in pulmonary lesions, reducing the need for mechanical ventilation, length of hospital stay, and mortality rates in these patients (9,10). Therefore, this study aimed to retrospectively examine the data of patients who reported to the immunology clinic for IVIG treatment in a tertiary referral hospital and who were hospitalized, followed up, and treated for COVID-19. The study also investigated the effects of the patients' clinical, laboratory, and treatment characteristics and risk factors for mortality in patients with COVID-19 treating with IVIG treatment.

MATERIAL AND METHODS

The study included adult COVID-19 patients who were hospitalized for the treatment of COVID-19 in a tertiary referral hospital (University of Health Science Konya Education and Research Hospital) between April 2020 and September 2020 and were followed-up, treated, and consulted in the immunology clinic for IVIG treatment in a retrospective manner. A review of medical records (including information on age, sex, and disease duration) was undertaken. Venous blood samples for biochemical analyses were drawn after at least ten hours of fasting, early in the morning. All biochemical analyses were conducted in the Central Biochemistry Laboratory of the Konya Education and Research Hospital. Laboratory measurements of the patients at the first admission to the hospital, at the time of hospitalization, and before IVIG treatment were used.

Complete blood counts were performed using Sysmex XN-10 (Sysmex Corporation, Kobe, Japan) analyzers with the fluorescent flow cytometry method. Serum creatinine levels were measured using the Jaffe method. Quantitative determination of serum IgG, IgM, IgA, and IgE was done through particle-enhanced immunonephelometry using the Siemens BN II/BN ProSpec system (Erlangen, Germany).

The follow-up period of all patients started with their hospitalization. For the patients who died, the number of days between the date of hospitalization and death was accepted as the follow-up period. The duration of follow-up was calculated by confirming whether the discharged patients were alive or not through the Republic of Turkey Death Reporting System, two weeks after discharge. For patients who died within two weeks of discharge, the follow-up period was accepted as the number of days between the date of hospitalization and death. For patients who lived more than two weeks after discharge, the follow-up period was calculated by adding 14 days to the number of days they stayed in the hospital.

IVIG treatment dose was calculated from a total dose of 2 gr/kg. The total dose was given to the patients in 3-5 days. Dose adjustment in obese patients was based on ideal body weight. In order not to cause renal burden, a 10% concentration of IVIG preparations that do not contain maltose and sucrose were preferred.

The time until hospitalization, resulting from the emergence of SARS-CoV-2-related symptoms such as fever, cough, and body pain, was considered the duration of illness. The duration of the follow-up in the service was specified as the day of hospitalization and the follow-up period in the intensive care unit (ICU) as the duration of intensive care hospitalization. All patients in the study received IVIG treatment. Some patients were followed only in the service and received IVIG treatment in the service. Some patients received IVIG treatment in the ICU. Patients who received IVIG treatment in the service and those who received IVIG treatment in the first 24/48 h after their admission to intensive care were specified as the IVIG treatment ICU first 24/48 h.

The systemic inflammatory index (SII) was calculated by the formula platelet x neutrophil/lymphocyte counts. The SARS-CoV-2 diagnosis was established with the detection of the SARS-CoV-2 genome via the PCR method from the nasopharyngeal sample (nasal swab) in patients with symptoms suggestive of SARS-CoV-2 infection such as fever, cough, shortness of breath, joint and body pain, and/or viral infiltration on lung imaging (PA chest radiography or lung tomography).

The permission for the study was obtained from the Republic of Turkey, Ministry of Health Scientific Research Platform. In addition, an ethics committee approval was obtained from Karatay University Ethics Committee (with the decision dated 09.02.2021, and numbered 2020/021). The study was conducted as per the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using the SPSS version 22.0 software package (IBM Corp., Armonk, NY, USA). The normality of the data was tested with the Kolmogorov-Smirnov test. Normally distributed variables were presented as mean±standard deviation, and data that were not normally distributed were expressed as median, interquartile range, and minimum-maximum. Descriptive data were presented as frequencies and percentages and compared using the chi-square test or Fisher's exact test. Comparisons between baseline characteristics were performed by independent samples t or Mann-Whitney U tests, where appropriate. Independent predictors for mortality were determined using Cox regression analysis with the backward: Wald model. Receiver operator characteristics (ROC) curve analysis was used to determine the most appropriate cut-off for the urea level. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 81 patients, 27 (33.3%) female and 54 (66.7%) male, were included in the study. The median age of the patients was 71 (range, 41-94) years. During the follow-up, the mortality rate was 64.2% (n=52). The rate of intubated patients was 45.7% (n=37). The median follow-up period was 19 (range, 1-60) days. The duration of hospitalization was 16 (range, 1-44) days, and the duration of hospitalization in intensive care was 10 (range, 0-31) days. All patients received hydroxychloroquine and favipiravir treatment during their follow-up. In addition, IVIG treatment was given to all patients. While 35 (43.2%) patients received tocilizumab treatment, 15 (18.5%) patients received conventional plasma and 33 (40.7%) patients received pulse steroid treatment. Fifty (61.7%) of the patients in the first 24 h of their admission to intensive care and 52 (64.2%) of the patients in the first 48 h of their admission to intensive care received IVIG treatment.

There was no statistically significant difference between the patients who died during their follow-up and the patients who survived in terms of age, gender, tocilizumab treatment, conventional plasma treatment, and the number of days of hospitalization in the service. We observed significant differences in terms of intubated patient ratio, pulse steroid therapy, white blood cell count on hospitalization, platelet count on hospitalization, lymphocyte percentage before IVIG treatment, C-reactive protein (CRP) values on hospitalization and before IVIG treatment, urea values before IVIG treatment, SII levels on hospitalization and before IVIG treatment, and neutrophil to lymphocyte ratio (NLR) levels before IVIG treatment. The demographic, laboratory and clinical characteristics of the patients have been summarized in Table 1, Table 2, Table 3, and Table 4.

Table 1. Baseline demographic and clinical parameters of the study group

Variable	Non-survivor (n=52)	Survivor (n=29)	p	Total (n=81)
Gender, n (%)				
Male	35 (67.3)	19 (65.5)	0.870	54 (66.7)
Female	17 (32.7)	10 (34.5)		27 (33.3)
Age (years)	72.5 (59.5-77) [41-94]	70 (59-76) [46-78]	0.391	71 (60-76.5) [41-94]
Follow up time (day)	20 (12.25-28.75) [1-38]	16 (12-28) [3-60]	0.745	19 (12-28.5) [1-60]
Duration of illness (day)	7 (5-10) [3-10]	7 (5-8) [3-8]	0.846	7 (5-8.50) [3-10]
Duration of hospitalization (day)	17 (10-27) [1-38]	16 (12-28) [3-44]	0.557	16 (10.5-27) [1-44]
Duration of inpatient service (day)	7 (3-9) [0-31]	10 (3-14.5) [0-21]	0.055	7 (3-11) [0-31]
Duration of intensive care (day)	10 (5-19) [0-31]	13 (6.75-16.5) [2-21]	0.509	10 (5-17) [0-31]
Intensive care, n (%)	48 (92.3)	18 (62.1)	**0.001**	66 (81.5)
Intubation, n (%)	34 (65.2)	3 (10.3)	**0.001**	37 (45.7)
Comorbidity, n (%)	40 (76.9)	20 (69.0)	0.433	60 (74.1)

Descriptive statistics were reported as median (1st quartile - 3rd quartile) [minimum - maximum] for numerical variables

Table 2. Treatment parameters of the study group

Variable	Non-survivor (n=52)	Survivor (n=29)	p	Total (n=81)
Convalescent plasma, n (%)	9 (17.3)	6 (20.7)	0.707	15 (18.5)
Pulse steroid therapy, n (%)	28 (53.8)	5 (17.2)	**0.001**	33 (40.7)
Tocilizumab treatment, n (%)	19 (36.5)	16 (55.2)	0.105	35 (43.2)
IVIG treatment at least 3 days, n (%)	42 (80.8)	26 (89.7)	0.296	68 (84)
IVIG treatment in first 24 h, n (%)	30 (57.7)	20 (69.0)	0.317	50 (61.7)
IVIG treatment in first 48 h, n (%)	32 (61.5)	20 (69.0)	0.504	52 (64.2)
Duration of IVIG treatment (day)	3 (3-4) [1-5]	3 (3-5) [2-5]	0.069	3 (3-5) [1-5]
IVIG dose (gr/day)	40 (35-50) [25-50]	40 (35-50) [30-50]	0.832	40 (35-50) [25-50]

IVIG: intravenous immunoglobulin, descriptive statistics were reported as median (1st quartile - 3rd quartile) [minimum - maximum] for numerical variables

Table 3. Laboratory parameters of the study group

Variable	Non-survivor (n=52)	Survivor (n=29)	p	Total (n=81)
WBC count ($\times 10^9$ /L)				
On hospitalization	8185 (5995-11170) [1176-27350]	5820 (4345-9040) [2630-20110]	**0.020**	7960 (5280-10460) [1176-27350]
Before IVIG treatment	11955 (7687-17342) [430-27290]	8190 (5435-10695) [1220-25920]	**0.008**	9570 (7430-15685) [430-27290]
Lymphocyte percentage ($\times 10^9$ /L)				
On hospitalization	9.95 (6.10-15.675) [2.20-30.00]	12.10 (7.70-24.45) [3.00-33.10]	0.081	10.90 (6.25-17.15) [2.20-33.10]
Before IVIG treatment	3.35 (2.375-6.00) [0.80-46.50]	5.60 (4.05-10.80) [2.60-35.70]	**0.001**	4.30 (2.90-4.30) [0.80-46.50]
Neutrophil percentage ($\times 10^9$ /L)				
On hospitalization	86.4 (77.8-90.8) [56.4-96.6]	75.0 (63.3-87.0) [26.1-94.2]	**0.001**	84.5 (74.0-89.5) [26.1-96.6]
Before IVIG treatment	93.2 (90.8-94.3) [70.9-97.4]	89.8 (81.0-92.8) [41.9-95.7]	**0.020**	92.0 (86.0-94.1) [41.9-97.4]
Platelet count ($\times 10^3$)				
On hospitalization	205 (165.5-269.5) [71-372]	166 (131.5-214.5) [75-422]	**0.030**	186 (147-258) [71-442]
Before IVIG treatment	242 (158.0-346.2) [75-512]	231 (170.5-299.5) [27-401]	0.395	232 (162-313) [27-512]
Fasting blood glucose (mg/dL)				
On hospitalization	154 (117.75-215.75) [84-361]	122 (97.5-167) [75-480]	**0.034**	140 (103-191) [75-480]
Before IVIG treatment	172 (118.50-215.50) [88-344]	141 (119-229) [77-263]	0.195	157 (115-215) [77-344]
Urea (mg/dL)				
On hospitalization	42.5 (32-62) [15-256]	41 (29-70.5) [17-180]	0.863	42 (30.5-66.5) [15-256]
Before IVIG treatment	57.5 (46-92) [33-230]	44 (36.5-72) [17-79.1]	**0.029**	55 (42.5-77.5) [17-230]
Creatine (mg/dL)				
On hospitalization	1.04 (0.90-1.26) [0.58-6.87]	1.02 (0.85-1.24) [0.60-2.20]	0.629	1.03 (0.90-1.91) [0.58-6.87]
Before IVIG treatment	0.89 (0.75-1.13) [0.52-2.60]	0.87 (0.71-1.02) [0.50-1.22]	0.544	0.89 (0.75-1.05) [0.50-2.60]
IgG (mg/dL), on hospitalization	10.60 (6.72-11.50) [5.9-13.8]	7.69 (3.29-10.02) [0.0-16.1]	0.136	8.59 (5.75-10.85) [0.0-16.1]
IgM (mg/dL), on hospitalization	0.42 (0.36-0.67) [0.20-1.88]	0.60 (0.38-0.85) [0.17-1.21]	0.573	0.44 (0.39-0.73) [0.17-1.88]
IgA (mg/dL), on hospitalization	2.52 (2.15-3.53) [0.37-7.62]	2.45 (1.25-2.89) [0.24-3.32]	0.198	2.50 (1.86-2.94) [0.24-7.62]

IVIG: intravenous immunoglobulin, WBC: white blood cell, Ig: immunoglobulin, descriptive statistics were reported as median (1st quartile - 3rd quartile) [minimum - maximum] for numerical variables

Table 4. Inflammatory parameters of the patients

Variable	Non-survivor (n=52)	Survivor (n=29)	p	Total (n=81)
CRP (mg/L)				
On hospitalization	124 (47-159) [3-415]	66 (35.9-102.0) [8.5-317]	**0.015**	91.2 (41.5-146.8) [3.0-415]
Before IVIG treatment	82 (13-128) [3.1-297]	21 (6.1-65.1) [3.1-197]	**0.012**	47.0 (8.6-120.5) [3.1-297]
SII				
On hospitalization	1953.0 (1024.6-3393.4) [254.2-11059.8]	823.1 (432.3-2684.9) [352.9-12962.4]	**0.016**	1558.8 (670.4-3128.3) [254.2-12962.4]
Before IVIG treatment	6676.9 (2890.1-10383.1) [657.7-22356.5]	3567.0 (1494.1-546.1) [1354.7-13441.4]	**0.013**	4897.3 (2119.3-8419.5) [657.7-22356.5]
NLR				
On hospitalization	9.06 (5.30-14.73) [1.93-42.21]	6.12 (2.94-11.83) [1.86-30.72]	0.075	8.26 (4.45-14.38) [1.86-42.21]
Before IVIG treatment	27.81 (14.44-38.01) [2.33-126.31]	16.15 (7.64-23.27) [5.80-27.66]	**0.001**	19.39 (11.12-32.73) [2.33-126.31]

CRP: C-reactive protein, SII: systemic inflammatory index, NLR: neutrophil to lymphocyte ratio, IVIG: intravenous immunoglobulin, descriptive statistics were reported as median (1st quartile - 3rd quartile) [minimum - maximum] for numerical variables

The univariate analyses revealed that the duration of hospitalization in service, being intubated, duration of IVIG treatment, and the urea value before IVIG treatment were related to mortality in patients treated with IVIG treatment (p=0.043, p=0.001, p=0.074, and p=0.004, respectively). As a result of multivariate analysis, being intubated and urea value before IVIG treatment were found to be independent risk factors for mortality (p=0.001 and p=0.009, respectively, Table 5).

It was found that for the 60 mg/dL level of urea value before IVIG treatment to predict mortality in COVID-19 patients receiving IVIG treatment, the sensitivity value was 46.2%, and the specificity was 35.5%. The area under the curve (AUC) was found 0.647 with a 95% confidence interval (CI) of 0.518-0.776 (p=0.029, Figure 1).

Table 5. Independent risk factors for mortality

Variable	HR (95% CI)	p
Intubation	0.389 (0.218 - 0.693)	**0.001**
Urea, before IVIG treatment	1.009 (1.002 - 1.017)	**0.009**

IVIG: intravenous immunoglobulin, HR: hazard ratio, CI: confidence interval

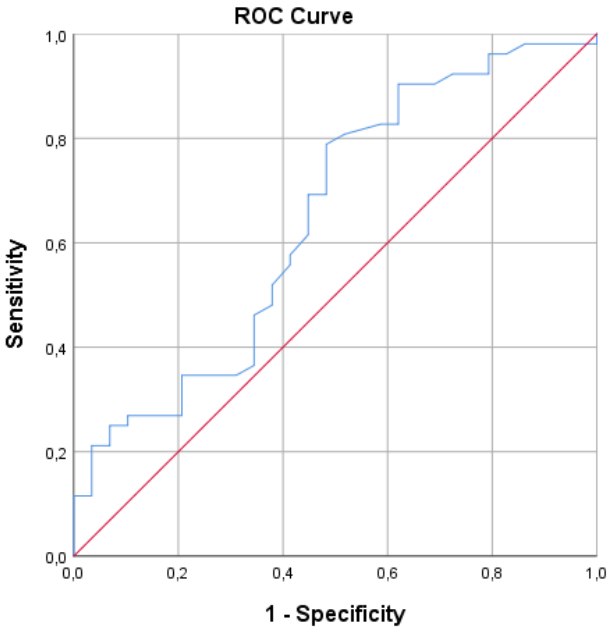

Figure 1. ROC curve of urea level before IVIG treatment

DISCUSSION

The SARS-CoV-2 virus has caused one of the most severe pandemics in human history and has put a lot of pressure, particularly on healthcare systems, since March 2020, when it was declared as a pandemic by WHO. The virus has caused the deaths of approximately 3 million people in nearly one year since its outbreak (2,11). At present, there is no globally accepted treatment scheme for treating patients hospitalized for COVID-19. Therefore, it is crucial to determine the prognostic factors in vulnerable patient groups and to develop treatment modalities specific to patient groups according to these factors to reduce mortality and morbidity. In line with this opinion, this study found that being intubated and urea values before IVIG treatment are independent risk factors for COVID-19-related mortality in patients hospitalized for COVID-19 and given IVIG treatment.

Acute renal failure development has been reported in 7% of COVID-19 patients (12,13). In addition, renal failure has been reported to increase COVID-19-related hospital deaths in mortality studies (14-19). Cheng et al. (15) showed an increase in blood urea nitrogen (BUN) that increased mortality 3.97 times in COVID-19 patients. Another study reported that the hospitalization BUN and D-dimer levels were associated with mortality, and BUN values of ≥4.6 mmol/L included a high risk for hospital deaths (14). In another study, 6.29% of COVID-19 patients showed an increase in BUN, and increased basal BUN and creatinine values were reported to cause high mortality (17). Ng et al. (18) reported that being intubated and BUN values are risks for hospital mortality in patients with end-stage renal disease and COVID-19. Although the increase in BUN after SARS-CoV-2 is frequent, the reason for this increase is not clear. Renal epithelial cells contain angiotensin-converting enzyme 2 (ACE2) receptors that are 100 times more intense than respiratory epithelial cells; SARS-CoV-2 is internalized to renal cells and may cause renal function loss with a cytopathic effect (15,20). It has been suggested that this may increase the absorption of BUN from the renal tubules by activating the renin-angiotensin-aldosterone system (20). Although IVIG treatment is often used as one of the last treatment options in patients who do not respond to other treatments, IVIG treatment itself may be associated with renal damage (13). On the other hand, the increase in BUN levels in COVID-19 patients may be an indicator of kidney dysfunction and an increased inflammatory state. The renal load caused by increased catabolism, hypovolemia-induced renal hypoperfusion, sepsis, drugs used in the treatment of COVID-19 such as steroid therapy, and rhabdomyolysis may also cause an increase in BUN. Although creatinine, another indicator of renal damage, was not found to be a predictor of mortality in this study, the fact that BUN is predictive of mortality suggests that BUN increases due to inflammatory conditions rather than a renal-induced reason and that increased inflammatory processes play a role in making BUN a risk factor for mortality. Another situation supporting this hypothesis is that inflammatory markers of the patients who died before IVIG treatment were prominently higher and statistically significant than those of alive patients. As the most common cause of mortality in COVID-19 is a respiratory failure caused by cytokine storm, the majority of patients (81.5%) in the present study had to be followed up in the ICU due to deterioration in their clinical condition. IVIG treatment is one of the last options in COVID-19 patients who are unresponsive to other therapies and whose cytokine storms are not controlled. It was thought that these patients face an intense inflammatory process, which causes an increase in BUN.

The retrospective design, relatively small size of study group, lack of evaluation of other renal markers such as proteinuria and hematuria, and lack of knowledge of what happened in the post-follow-up period form the main limitations of this study.

CONCLUSION

The study found that urea values before IVIG treatment were a risk factor for mortality in patients who received IVIG treatment for COVID-19. This is important as it indicates that BUN values should be closely monitored in patients given IVIG treatment for COVID-19. It also suggests that when resources are limited and risk stratification is required in COVID-19 patients, BUN values can be helpful.

Ethics Committee Approval: The study was approved by the Ethics Committee of KTO Karatay University Faculty of Medicine (09.02.2021, 21).

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REFERENCES

1. Liu X, Liu C, Liu G, Luo W, Xia N. COVID-19: Progress in diagnostics, therapy and vaccination. Theranostics. 2020;10(17):7821-35.
2. Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: a global health crisis. Physiol Genomics. 2020;52(11):549-57.
3. Ferrer R. [COVID-19 Pandemic: the greatest challenge in the history of critical care]. Med Intensiva (Engl Ed). 2020;44(6):323-4. Spanish.
4. Asselah T, Durantel D, Pasmant E, Lau G, Schinazi RF. COVID-19: Discovery, diagnostics and drug development. J Hepatol. 2021;74(1):168-84.
5. Echeverría-Esnal D, Martin-Ontiyuelo C, Navarrete-Rouco ME, De-Antonio Cuscó M, Ferrández O, Horcajada JP, et al. Azithromycin in the treatment of COVID-19: a review. Expert Rev Anti Infect Ther. 2021;19(2):147-63.
6. Stasi C, Fallani S, Voller F, Silvestri C. Treatment for COVID-19: An overview. Eur J Pharmacol. 2020;889:173644.
7. Wang MY, Zhao R, Gao LJ, Gao XF, Wang DP, Cao JM. SARS-CoV-2: Structure, biology, and structure-based therapeutics development. Front Cell Infect Microbiol. 2020;10:587269.
8. Demirbilek Y, Pehlivantürk G, Özgüler ZÖ, Alp Meşe E. COVID-19 outbreak control, example of ministry of health of Turkey. Turk J Med Sci. 2020;50(SI-1):489-94.
9. Mazeraud A, Gonçalves B, Aegerter P, Mancusi L, Rieu C, Bozza F, et al. Effect of early treatment with polyvalent immunoglobulin on acute respiratory distress syndrome associated with SARS-CoV-2 infections (ICAR trial): study protocol for a randomized controlled trial. Trials. 2021;22(1):170.
10. Xie Y, Cao S, Dong H, Li Q, Chen E, Zhang W, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. J Infect. 2020;81(2):318-56.
11. Hadian M, Mazaheri E, Jabbari A. Different approaches to confronting the biological epidemic; prevention tools with an emphasis on COVID-19: A systematized study. Int J Prev Med. 2021;12:127.
12. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020;98(1):209-18.
13. Orbach H, Katz U, Sherer Y, Shoenfeld Y. Intravenous immunoglobulin: adverse effects and safe administration. Clin Rev Allergy Immunol. 2005;29(3):173-84.
14. Cheng A, Hu L, Wang Y, Huang L, Zhao L, Zhang C, et al. Diagnostic performance of initial blood urea nitrogen combined with D-dimer levels for predicting in-hospital mortality in COVID-19 patients. Int J Antimicrob Agents. 2020;56(3):106110.
15. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97(5):829-38.
16. Liu Q, Wang Y, Zhao X, Wang L, Liu F, Wang T, et al. Diagnostic performance of a blood urea nitrogen to creatinine ratio-based nomogram for predicting in-hospital mortality in COVID-19 patients. Risk Manag Healthc Policy. 2021;14:117-28.
17. Liu YM, Xie J, Chen MM, Zhang X, Cheng X, Li H, et al. Kidney function indicators predict adverse outcomes of COVID-19. Med (N Y). 2021;2(1):38-48.e2.
18. Ng JH, Hirsch JS, Wanchoo R, Sachdeva M, Sakhiya V, Hong S, et al. Outcomes of patients with end-stage kidney disease hospitalized with COVID-19. Kidney Int. 2020;98(6):1530-9.
19. Shao M, Li X, Liu F, Tian T, Luo J, Yang Y. Acute kidney injury is associated with severe infection and fatality in patients with COVID-19: A systematic review and meta-analysis of 40 studies and 24,527 patients. Pharmacol Res. 2020;161:105107.
20. Nogueira SÁR, Oliveira SCS, Carvalho AFM, Neves JMC, Silva LSVD, Silva Junior GBD, et al. Renal changes and acute kidney injury in COVID-19: a systematic review. Rev Assoc Med Bras (1992). 2020;66(Suppl 2):112-7.

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Comparison of Tocilizumab and Anakinra in the Treatment of COVID-19: A Single-Center Experience

COVID-19 Tedavisinde Tocilizumab ve Anakinra'nın Karşılaştırılması: Tek Merkez Deneyimi

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ABSTRACT

Aim: The aim of this study was to examine whether a difference between endotracheal intubation, non-invasive mechanical ventilation, high flow oxygen therapy requirements and 28-day mortality rate in severe and critical coronavirus disease 2019 (COVID-19) patients receiving anakinra and tocilizumab treatment.

Material and Methods: A total of 70 patients infected with COVID-19, who were treated with tocilizumab and anakinra from April 2020 to March 2021 at Karabük Training and Research Hospital, were recruited in this retrospective study. Data on patient demographics, comorbidities, treatments, clinical outcomes of the patients' and hemogram findings were retrieved from hospital records.

Results: The mean age of the patients was 61.34±11.8 years. Of the 70 patients, 12 (17.1%) were female and 58 (82.9%) were male. Severe and critical COVID-19 cases were evident in 48 (68.6%), and 22 (31.4%) patients, respectively. The mortality rate in 28 days was not statistically significantly different between the tocilizumab and anakinra groups (p=0.999). Both the necessity of high flow oxygen therapy and non-invasive mechanical ventilation were lower in the tocilizumab group than in the anakinra group (p<0.001, and p=0.002, respectively), while there was no statistically significant difference in the necessity of intubation between the two groups (p=0.999). The length of stay was also significantly shorter in the tocilizumab group (p=0.027).

Conclusion: High flow oxygen therapy, non-invasive mechanical ventilation requirements, and length of stay were significantly lower than anakinra in the tocilizumab group. Excessive inflammatory response with cytokine storm features causes severe disease course and worsens prognosis in COVID-19.

Keywords: Anakinra; COVID-19; tocilizumab.

ÖZ

Amaç: Bu çalışmanın amacı anakinra ve tocilizumab tedavisi alan ağır ve kritik koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) hastalarında; endotrakeal entübasyon, non-invaziv mekanik ventilasyon, yüksek akım oksijen tedavisi gereksinimleri ve 28 günlük mortalite oranları arasında bir farklılık olup olmadığının araştırılmasıdır.

Gereç ve Yöntemler: Bu geriye dönük çalışmaya, Nisan 2020 ile Mart 2021 tarihleri arasında Karabük Eğitim ve Araştırma Hastanesi'nde tocilizumab ve anakinra ile tedavi edilmiş olan COVID-19 ile enfekte 70 hasta dahil edildi. Hastaların demografik özellikleri, komorbiditeler, tedaviler, hastaların klinik sonuçları ve hemogram bulguları ile ilgili veriler hastane kayıtlarından alındı.

Bulgular: Hastaların ortalama yaşı 61,34±11,8 yıl idi. 70 hastanın 12 (%17,1)'si kadın ve 58 (%82,9)'i erkekti. Ağır ve kritik COVID-19 vakası sırasıyla 48 (%68,6) hastada ve 22 (%31,4) hastada görüldü. Tocilizumab ve anakinra grupları arasında; 28 gündeki mortalite oranı istatistiksel olarak anlamlı şekilde farklı değildi (p=0,999). Yüksek akım oksijen tedavisi ve non-invaziv mekanik ventilasyon gereksinimlerinin her ikisi de tocilizumab grubunda anakinra grubundan daha düşük (sırasıyla p<0,001 ve p=0,002) iken entübasyon ihtiyacı bakımından iki grup arasında istatistiksel olarak anlamlı bir farklılık yoktu (p=0,999). Tocilizumab grubunda hastanede kalış süresi de anlamlı olarak daha kısaydı (p=0,027).

Sonuç: Tocilizumab grubunda yüksek akım oksijen tedavisi, non-invaziv mekanik ventilasyon gereksinimleri ve hastanede kalış süresi anakinra grubuna göre anlamlı derecede daha düşüktür. COVID-19'da sitokin fırtınası, aşırı inflamatuar yanıt, ciddi hastalık seyrine neden olmakta ve prognozu kötüleştirmektedir.

Anahtar kelimeler: Anakinra; COVID-19; tocilizumab.

INTRODUCTION

Worldwide, more than 112 million cases of coronavirus and 3.8 million deaths have been reported (1). Nowadays only glucocorticoids are known to decrease mortality rates among severe coronavirus disease 2019 (COVID-19) infections (2,3). The corticosteroids' mechanism in critically ill patients is decreasing an excessive host inflammatory response which is responsible for serious illness and death from COVID-19.

Interleukin-1 and interleukin-6 are cytokines that are released into infection and stimulate acute-phase and fever responses (3,4). Anakinra is a recombinant monoclonal antibody and a slightly modified version of the human interleukin-1 receptor antagonist protein which received approval to treat rheumatoid arthritis, idiopathic pulmonary fibrosis and auto-inflammatory diseases such as the Familial Mediterranean Diseases (5,6). Tocilizumab is another monoclonal antibody that inhibits both membrane-bound and soluble interleukin-6 receptors (7). It is used to treat diseases such as rheumatoid arthritis and systemic-onset juvenile idiopathic arthritis (7). In the COVID-19 pandemic, anakinra and tocilizumab are used for the purpose of decreasing and managing host inflammatory responses in clinics worldwide (8,9). However, there is an inadequate number of research into severe COVID-19 patients between anakinra and tocilizumab usage that investigate the mortality rates from COVID-19. We aimed to investigate the mortality rate and mortality at day twenty-eighth of COVID-19 patients whose treatment includes anakinra and tocilizumab according to patients' genders, ages, other diseases, blood test results, and necessity of non-invasive mechanical ventilation (NIMV) or endotracheal intubation.

MATERIAL AND METHODS

Study Design and Participants

The patients infected with COVID-19, who were treated with tocilizumab and anakinra from April 2020 to March 2021 at Karabük Research and Training Hospital, were recruited in this retrospective study. All patients were anonymous.

The study was approved by both the Ministry of Health and the Local Ethics Committee (Karabük University Ethics Committee, dated June 2, 2021 and numbered 579). The patients were given an informed consent form and their written consent was obtained.

Procedures

Data on patient demographics (age, gender), comorbidities, treatments, clinical outcomes of the patients' blood biochemistry, and hemogram findings were retrieved from hospital records. Diabetes, hypertension, chronic renal failure, heart failure, chronic lung disease, and malignancy were noted in the patients. Only those treated with tocilizumab and anakinra while they were hospitalized were included in the study.

Eligibility criteria for tocilizumab and anakinra administration were: a diagnosis of COVID-19 confirmed upon reverse-transcriptase polymerase chain reaction (RT-PCR) positivity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on nasopharyngeal swab; hyper-inflammation defined as an elevation in either C-reactive protein (CRP) or ferritin, in the presence of increased lactate dehydrogenase (LDH); severe respiratory involvement defined by typical radiological findings at chest X-Ray and /or computed tomography scan (10).

The severity of the COVID-19 was classified into four types: mild, moderate, severe, and critical (11). The serum levels of CRP, complete blood count, D-dimer, ferritin, and LDH were observed before tocilizumab and anakinra administration. The levels of pulse oxygen were observed before and after tocilizumab and anakinra administration. Hospitalization day, high flow oxygen therapy (HFOT) and mechanical ventilator needs, and mortality rate were evaluated in patients receiving tocilizumab and anakinra treatment.

Statistical Analysis

Statistical analysis was done with SPSS v.22.0. Normality assumption was examined with the Shapiro-Wilk test. Independent samples t-test or Mann-Whitney U test was used to compare groups whenever appropriate. Pearson chi-square or Fisher's exact test was used to analyze categorical variables. Data are presented as mean, standard deviation, or median (interquartile range) [min-max] for numerical variables, and as the number and percentage for categorical variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

Of the 70 patients, 12 (17.1%) were female and 58 (82.9%) were male. The mean age of the patients was 61.34±11.8 years. Severe and critical COVID-19 cases were evident in 48 (68.6%), and 22 (31.4%) patients, respectively. All patients received high-dose steroids (250 mg/day). At the same time, 66 (94.3%) patients were treated with favipiravir. Considering biological agents 30 (42.9%) patients were treated with anakinra and 40 (57.1%) patients were treated with tocilizumab.

Comparisons of the patients receiving tocilizumab and anakinra revealed no statistically significant difference in age (p=0.271) and gender distribution (p=0.927). While chronic lung disease in the anakinra group was higher than in the tocilizumab group (n=13, 43.3% vs. n=7, 17.5%, respectively, p=0.018), there was no statistically significant difference between the groups in terms of diabetes mellitus (p=0.766), hypertension (p=0.580), chronic kidney disease (p=0.573), malignancy (p=0.420), and congestive heart failure (p=0.283, Table 1).

According to the disease severity, while 31 (64.6%) of the 48 patients with the severe disease received tocilizumab, and 17 (35.4%) received anakinra, of the 22 patients with the critical disease, 9 (40.9%) received tocilizumab, and 13 (59.1%) received anakinra (p=0.074).

Laboratory Results

When laboratory results of the tocilizumab and anakinra groups were compared; no statistically significant difference was found between the groups in terms of the CRP (p=0.233), D-dimer (p=0.075), LDH (p=0.194), procalcitonin (p=0.127) and hemoglobin (p=0.571) values. While ferritin (p=0.022), white blood cell count (p<0.001), and platelet count (p<0.001) were higher, a lower level of lymphocytes (p=0.013) was found in the anakinra group. Although the SpO_2 value was higher in the tocilizumab group before treatment (p<0.001), it was similar in groups after the treatment (p=0.234, Table 2).

Clinical Outcomes

The mortality rate in 28 days was not statistically significantly different between the tocilizumab and anakinra groups (p=0.999). Both the necessity of HFOT and NIMV were lower in the tocilizumab group than in the anakinra group (p<0.001, and p=0.002, respectively), while there was no statistically significant difference in the necessity of intubation between the two groups (p=0.999). The length of stay was also significantly shorter in the tocilizumab group (p=0.027, Table 3).

DISCUSSION

In this study, no significant difference was found between tocilizumab and anakinra groups in 28 days of mortality and intubation need. But; HFOT and NIMV requirements, and length of stay were significantly lower than anakinra in the tocilizumab group.

Observational studies have suggested that anakinra and tocilizumab are effective in reducing mortality and/or intubation in patients with severe COVID-19 (12,13). These good results led to this clinical trial, which suggests that tocilizumab, was administered very early in hospitalized patients with COVID-19 infection.

The first clinical experience of tocilizumab in COVID-19 patients have been reported at the end of 2020 in the Lancet Rheumatol (14). After that report, a single-center study including 100 unmatched COVID-19 patients with mechanical ventilation, showed an improvement in the respiratory severity using a disease-specific scale and a decrease in laboratory inflammation parameters after two intravenous administrations of tocilizumab (15). In another retrospective analysis, tocilizumab at the median dose of 5.7 mg/kg showed a significant reduction in invasive mechanical ventilation needs on day 14 (16). A retrospective study conducted on 29 patients treated with high-dose anakinra compared to 16 control, showed that high-dose anakinra was associated with a higher survival rate at 21 days with a reduction in CRP and with progressive improvement results of PaO_2/FiO_2 (17). Whereas in our study there was no reported clinical side effect of anakinra and tocilizumab.

In May 2021, Coloretti et al. (18) reported clinical results in an intensive care unit (ICU) admitted patients requiring mechanical ventilation for acute respiratory distress syndrome (ARDS) due to COVID-19. It was shown that both anakinra and tocilizumab seem to be well tolerated in hospital survival rates. In our study, the survival rates and toleration of medications are similar to the study by Coloretti et al. (18).

Anakinra and tocilizumab increase survival rates in COVID-19 patients. Both medicines decrease the severity and mortality of COVID-19. However, there is no clinical difference in mortality rates between anakinra and tocilizumab. One in 40 patients who received tocilizumab and one in 30 patients who received anakinra were dead until day 28.

Table 1. Demographic and clinical characteristics

	Tocilizumab (n=40)	Anakinra (n=30)	p
Age (years), mean±SD	62.7±11.1	59.5±12.7	0.271
Gender, n (%)			
Male	33 (82.5)	25 (83.3)	0.927
Female	7 (17.5)	5 (16.7)	
Diabetes mellitus, n (%)	12 (30.0)	10 (33.3)	0.766
Hypertension, n (%)	20 (50.0)	17 (56.7)	0.580
CLD, n (%)	7 (17.5)	13 (43.3)	**0.018**
CKD, n (%)	1 (2.5)	2 (6.7)	0.573
CHF, n (%)	7 (17.5)	2 (6.7)	0.283
Malignancy, n (%)	0 (0.0)	3 (10.0)	0.420

CLD: chronic lung disease, CKD: chronic kidney disease, CHF: congestive heart failure

Table 3. Comparison of clinical outcomes in groups

	Tocilizumab (n=40)	Anakinra (n=30)	p
Mortality in 28 days	1 (2.5)	1 (3.3)	0.999
Need for HFOT	2 (5)	13 (43.3)	**<0.001**
Need for NIMV	0 (0)	7 (23.3)	**0.002**
Need for intubation	3 (7.5)	2 (6.7)	0.999
Length of stay	13.5 (6.5) [5-56]	18 (17) [5-37]	**0.027**

HFOT: high flow oxygen therapy, NIMV: non-invasive mechanical ventilation

Table 2. Comparison of laboratory parameters in groups

	Tocilizumab (n=40)	Anakinra (n=30)	p
Ferritin (ng/mL)	1100 (1197) [160-1650]	1552 (571) [188-6797]	**0.022**
CRP (mg/L)	150.5 (111) [19-308]	164 (49) [67-331]	0.233
D-dimer (ng/mL)	1.46 (1.95) [0.31-24]	2.1 (4.5) [0.3-18]	0.075
LDH (U/L)	473 (208) [228-817]	537 (237) [240-930]	0.194
Procalcitonin (ng/mL)	0.09 (0.12) [0.01-5.3]	0.17 (0.25) [0.01-23.48]	0.127
WBC ($x10^3$, µl/mL)	10 (4.3) [2.5-19]	15 (8.3) [7.6-35.8]	**<0.001**
Platelets ($x10^3$, µL)	220 (112) [74-410]	328 (144) [110-959]	**<0.001**
Lymphocytes (µL)	735 (295) [290-2090]	555 (415) [180-5770]	**0.013**
Hemoglobin (g/dL)	13.4 (1.4) [9-16]	13.5 (2) [8.3-15.4]	0.571
SpO_2 (%), before treatment	88 (4.2) [80-96]	82 (6) [60-97]	**<0.001**
SpO_2 (%), after treatment	95 (3) [90-97]	94.5 (3) [90-97]	0.234

CRP: C-reactive protein, LDH: lactate dehydrogenase, WBC: white blood cell, SpO_2: peripheral oxygen saturation

Another study from Spain suggests that the use of anakinra in patients with moderate hyper inflammation associated with severe COVID-19 pneumonia after previous failure of corticosteroids alone or with tocilizumab therapy may be an alternative in the management of these patients, and may prevent deaths (19). However, in our study, there is no significant difference between the tocilizumab and anakinra groups in 28 days of mortality. But; HFOT and NIMV requirements were significantly lower than anakinra in the tocilizumab group.

In February 2021 a meta-analysis of non-randomized cohort studies across comparative reported that anakinra was safe and associated with significant reductions in both mortality and the need for mechanical ventilation (20).

A letter to editor analysis of non-randomized cohort studies is the first to investigate the effect of anakinra versus tocilizumab on the risk for COVID-19 death, showing a clear benefit of IL-1 versus IL-6 inhibition (21). According to our study, we have no evidence to verify this proposition.

One limitation of this study was the small patient population and was single-centered. The higher patient of chronic lung diseases in the anakinra group and the high ferritin value, which is one of the poor prognostic laboratory factors, may have affected our results.

CONCLUSION

High flow oxygen therapy, NIMV requirements, and length of stay were significantly lower than anakinra in the tocilizumab group. Excessive inflammatory response with cytokine storm features causes severe disease course and worsens the prognosis in COVID-19. Studies including larger numbers of patients are needed to comment on the efficacy of anti-inflammatory treatments.

Ethics Committee Approval: The study was approved by the Non-Invasive Clinical Research Ethics Committee of Karabük University (02.06.2021, 579).

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REFERENCES

1. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). 2022 Feb 5. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.
2. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA. 2020;324(13):1330-41.
3. Erçen Diken Ö, Yıldırım F, Yıldız Gülhan P, Özkaya Ş, Şimşek M, Yücel C, et al. Corticosteroid use in COVID-19 pneumonia. Tuberk Toraks. 2021;69(2):217-26.
4. Argüder E, Yanık Üstüner G, Ekici R, Kılıç H, Erten Ş, Karalezli A. Tuberculosis risk in patients with rheumatologic disease treated with biologic drugs. Tuberk Toraks. 2020;68(3):236-44.
5. Fleischmann RM, Schechtman J, Bennett R, Handel ML, Burmester GR, Tesser J, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. Arthritis Rheum. 2003;48(4):927-34.
6. Yalçın Kehribar D, Özgen M. The experience of interleukin-1 inhibition in patients with familial Mediterranean fever. J Exp Clin Med. 2021;38(1):27-31.
7. Yakar Hİ, Pazarlı AC, İnönü Köseoğlu H, Kanbay A. The effect of tocilizumab on severe COVID-19 infection: Review of current evidence. Tuberk Toraks. 2021;69(1):74-83.
8. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. N Engl J Med. 2021;384(1):20-30.
9. Franzetti M, Forastieri A, Borsa N, Pandolfo A, Molteni C, Borghesi L, et al. IL-1 receptor antagonist anakinra in the treatment of COVID-19 acute respiratory distress syndrome: A retrospective, observational study. J Immunol. 2021;206(7):1569-75.
10. Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: advances in diagnosis and treatment. JAMA. 2018;319(7):698-710.
11. Xu YH, Dong JH, An WM, Lv XY, Yin XP, Zhang JZ, et al. Clinical and computed tomographic imaging features of novel coronavirus pneumonia caused by SARS-CoV-2. J Infect. 2020;80(4):394-400.
12. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci. 2020;117(20):10970-5.
13. Navarro-Millán I, Sattui SE, Lakhanpal A, Zisa D, Siegel CH, Crow MK. Use of anakinra to prevent mechanical ventilation in severe COVID-19: A case series. Arthritis Rheumatol. 2020;72(12):1990-7.
14. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, et al. Tocilizumab in patients with severe COVID19: a retrospective cohort study. Lancet Rheumatol. 2020;2(8):e474-84.
15. Knorr JP, Colomy V, Mauriello CM, Ha S. Tocilizumab in patients with severe COVID-19: A single-center observational analysis. J Med Virol. 2020;92(11):2813-20.
16. Alattar R, Ibrahim TBH, Shaar SH, Abdalla S, Shukri K, Daghfal JN, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. J Med Virol. 2020;92(10):2042-9.
17. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute

respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol. 2020;2(6):e325-31.
18. Coloretti I, Busani S, Biagioni E, Venturelli S, Munari E, Sita M, et al. Effects of cytokine blocking agents on hospital mortality in patients admitted to ICU with acute respiratory distress syndrome by SARS-CoV-2 infection: retrospective cohort study. Multidiscip Respir Med. 2021;16(1):737.
19. Aomar-Millán IF, Salvatierra J, Hernández-Quero J. Anakinra after treatment with corticosteroids alone or with tocilizumab in patients with severe COVID-19 pneumonia and moderate hyperinflammation. A retrospective cohort study: reply. Intern Emerg Med. 2021;16(4):1105-6.
20. Pasin L, Cavalli G, Navalesi P, Sella N, Landoni G, Yavorovskiy AG, et al. Anakinra for patients with COVID-19: a meta-analysis of non-randomized cohort studies. Eur J Intern Med. 2021;86:34-40.
21. Patoulias D, Dimosiari A, Michailidis T. Anakinra or tocilizumab for prevention of COVID-19 death? A big dilemma. Eur J Intern Med. 2021;90:107-8.

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Effects of Laboratory Parameters on Tear Tests and Optical Coherence Tomography Findings in Pediatric Celiac Disease

Çocuk Çölyak Hastalarında Laboratuvar Parametrelerinin Göz Yaşı Testleri ve Optik Koherens Tomografi Bulguları Üzerindeki Etkisi

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ABSTRACT

Aim: The aim of this study was to evaluate the tear parameters and optical coherence tomography (OCT) findings in children with celiac disease (CD) and to investigate the relationship between these findings and laboratory data.
Material and Methods: The study included 100 eyes of 50 CD patients as well as 110 eyes of 55 healthy subjects with no ocular pathology as a control group. Best corrected visual acuity was evaluated, baseline tear volume was estimated using standard Schirmer's test, and fluorescein tear film break-up time (TBUT) was determined for all participants. Pupillary dilation was induced and macular sections and optic disc sections were obtained with OCT.
Results: The patient and control groups showed no statistically significant differences in terms of age and gender distribution (p=0.490, and p=0.930, respectively). Mean Schirmer's test measurement was significantly lower in the CD patients compared to the control group (14.07±5.14 mm vs. 20.20±3.93 mm, p<0.001). TBUT was also shorter in the CD patients compared to the control subjects (10.86±3.51 s vs. 15.25±2.49 s, p<0.001). Mean total retinal thickness and outer retinal thickness values were significantly lower in the patient group than in the control group (p<0.001, for both parameters). In addition, the mean retinal nerve fiber layer (RNFL) thickness measurement was significantly thinner in the patient group than in the control group (p<0.001).
Conclusion: In the presented study, it was observed that macular and RNFL thickness were decreased in children with CD compared to the control group, and tear tests were also impaired.
Keywords: Celiac disease; laboratory parameters; tear film; optical coherence tomography; pediatric patients.

ÖZ

Amaç: Bu çalışmanın amacı çölyak hastalığı (ÇH) olan çocuklarda gözyaşı parametreleri ve optik koherens tomografi (OKT) bulgularını değerlendirmek ve bu bulgular ile laboratuvar verileri arasındaki ilişkiyi araştırmaktır.
Gereç ve Yöntemler: Çalışmaya ÇH nedeniyle takip edilen 50 hastanın 100 gözü ile herhangi bir oküler patolojisi olmayan 55 sağlıklı katılımcının 110 gözü dahil edildi. Tüm katılımcıların en iyi düzeltilmiş görme keskinliği değerlendirildi, standart Schirmer testi kullanılarak gözyaşı miktarı belirlendi ve floresein ile gözyaşı kırılma zamanı (GKZ) belirlendi. Pupiller dilatasyon sağlandıktan sonra maküla kesitleri ve optik disk kesitleri OKT cihazı ile alındı.
Bulgular: Yaş ve cinsiyet dağılımı bakımından hasta ve kontrol grupları arasında istatistiksel olarak anlamlı farklılık yoktu (sırasıyla, p=0,490 ve p=0,930). Ortalama Schirmer testi değeri kontrol grubu ile karşılaştırıldığında ÇH hastalarında anlamlı olarak daha düşüktü (14,07±5,14 mm'ye karşı 20,20±3,93 mm, p<0,001). Ayrıca GKZ değeri sağlıklı katılımcılar ile karşılaştırıldığında ÇH hastalarında anlamlı olarak daha kısaydı (10,86±3,51 s'ye karşı 15,25±2,49 s, p<0,001). Ortalama total retina kalınlığı ve dış retina kalınlığı değerleri hasta grubunda kontrol grubuna göre anlamlı olarak daha düşüktü (her iki parametre için p<0,001). Ayrıca, ortalama retina sinir lifi (ORSL) kalınlığı kontrol grubu ile karşılaştırıldığında hasta grubunda anlamlı olarak daha inceydi (p<0,001).
Sonuç: Sunulan bu çalışmada ÇH olan çocuklarda maküla ve ORSL kalınlığının kontrol grubuna göre azaldığı ve gözyaşı testlerinin de bozulduğu görülmüştür.
Anahtar kelimeler: Çölyak hastalığı; laboratuvar parametreleri; gözyaşı filmi; optik koherens tomografi; çocuk hastalar.

Presented as an oral presentation at the 51st Annual Meeting of ESPGHAN (May 9-12, 2018; Geneva, Switzerland).

INTRODUCTION

Celiac disease (CD) is an autoimmune disease of the small intestine that occurs in genetically predisposed individuals due to the ingestion of gluten-containing foods (1). It was first described by Samuel Gee in 1888, and the importance of gluten ingestion in its pathophysiology emerged in 1953 (2,3). Gluten ingestion causes intestinal mucosal damage and malabsorption of nutrients in these patients. Onset can occur in childhood or adulthood and the disease is a lifelong condition (4). The prevalence of CD varies regionally, with reports ranging from 0.47% to 1% (5,6). Although the classical findings involve the gastrointestinal tract, CD is recognized as a syndrome that can affect various systems and manifest along a broad clinical spectrum (7). The main reason for this is that pediatric patients present with milder and extraintestinal findings (8-11). These patients seem to be more prone to certain ocular conditions, especially dry eye, cataract, retinopathy, orbital myositis, uveitis and they may develop ocular involvement as an extraintestinal manifestation (12).

The present study was conducted to evaluate tear parameters and optical coherence tomography (OCT) findings in CD patients and to investigate the relationship between these findings and laboratory parameters.

MATERIAL AND METHODS

This study was designed as a prospective, randomized controlled study, and approval was obtained from the Mersin University Clinical Research Ethics Committee (dated 11.05.2017, numbered 153) prior to initiating the study. The study was conducted in accordance with the 1997 Declaration of Helsinki and informed consent forms were obtained from the parents of the patients included in the study.

One hundred eyes of 50 patients who were being followed up for CD in the Division of Pediatric Gastroenterology comprised the patient group. Patients with systemic disease other than CD and diagnosed with ocular disease other than dry eye were excluded from the study. The control group included 110 eyes of 55 healthy subjects with no ocular pathology other than a refractive error (-6.00 diopters (D) to 4.00 D.). All patients underwent best corrected visual acuity assessment, followed by Schirmer tear test II (5 minutes) under topical anesthesia to determine baseline tear quantity and fluorescein dye test to determine tear film break-up time (TBUT). After slit-lamp examination, 1% tropicamide was instilled to dilate the pupils and 9x9 mm macular sections and 6x6 mm optic disc sections were taken with a spectral domain OCT device (Nidek RS 3000; Nidek Co. Ltd, Aichi, Japan) capable of modal image acquisition from 53,000 different points. The macular sections were evaluated based on the ETDRS map, while the peripapillary retinal nerve fiber layer (RNFL) thickness was evaluated separately on the map in clock hours. In addition, inner retinal thickness (IRT; from the RNFL to the posterior of the outer plexiform layer) and outer retinal thickness (ORT; posterior of the outer plexiform layer to the posterior retinal pigment epithelium) using the software included in the device. All OCT images were acquired at the same time in the morning (10-12 am) by the same experienced technician and scans were repeated when necessary. The body mass index (BMI) of CD patients was calculated, and their hematocrit, ferritin, vitamin B12, folate, vitamin D, albumin, total cholesterol, and triglyceride levels in venous blood samples drawn after night fasting for at least 12 hours were recorded. The samples were analyzed by using fully automatic analyzers in the centralized laboratory. Lipid profile and albumin measures were done by spectrophotometric methods. Ferritin, vitamin B12, and folate measures were done by ELISA method, and 25 (OH) vitamin D measure was done by liquid chromatography-mass spectrometry technique. We compared the tear and OCT data of the CD patients with those of the healthy subjects, and also evaluated the relationship between the patients' ocular data and laboratory parameters.

Statistical Analysis

Normality of the data distributions was tested for each group using the Shapiro-Wilk test. Normally distributed parameters were summarized with the descriptive statistics mean and standard deviation. Categorical variables were expressed using the descriptive statistics number and percentage. The Student's t-test was used to compare the means of the parameters between the patient and control groups, and the Pearson correlation coefficient was used to evaluate the relationships between the parameters. All data analyses were performed using the SPSS v.11.5 package program, and $p<0.05$ was considered significant.

RESULTS

The patient and control groups showed no statistically significant differences in terms of gender distribution and age ($p=0.930$ and $p=0.490$, respectively). The mean follow-up period of the patients was 3.58±2.04 years. It was observed that vitamin D levels were below the normal limit in the patients.

Mean Schirmer's test measurement was significantly lower in the CD patients compared to the control group (14.07±5.14 mm vs. 20.20±3.93 mm, $p<0.001$). TBUT was also shorter in the CD patients compared to the control group (10.86±3.51 s vs. 15.25±2.49 s, $p<0.001$, Table 1). Schirmer's test results were not significantly associated with laboratory data; however, TBUT was significantly correlated with vitamin D ($r=0.250$, $p=0.021$) and total cholesterol ($r=-0.220$, $p=0.041$) levels.

Total retinal thickness (TRT) values were significantly lower in the CD patients compared to the control group (252.33±21.66 μm vs. 262.58±17.63 μm, $p<0.001$, Figure 1). The CD patient group also showed significantly lower ORT values compared to the control group (196.69±14.93 μm vs. 214.87±11.84 μm, $p<0.001$). The separate retinal thickness values in the inner and outer rings and the data on the relationship of retinal layers with systemic data were presented in Table 2 and Table 3, respectively.

RNFL thickness was significantly thinner in the patient group compared to the control group ($p<0.001$). Significant correlations were observed between cup/disc ratio and vitamin B12 ($r=-.0450$, $p<0.001$) and triglyceride ($r=0.310$, $p=0.004$) levels, as well as between RNFL and ferritin ($r=0.540$, $p<0.0001$) levels. Cup/disc ratio data and segmental RNFL measurements were summarized in Table 4.

Table 1. Comparison of age, gender, and tear parameters

	Control (n=55)	Patient (n=50)	p
Gender, n (%)			
Male	18 (32.7)	16 (32.0)	0.930
Female	37 (67.3)	34 (68.0)	
Age (years)	12.82±3.58	12.34±3.58	0.490
Schirmer (mm)	20.20±3.93	14.07±5.14	**<0.001**
TBUT (sec)	15.25±2.49	10.86±3.51	**<0.001**

TBUT: tear film break-up time

Table 2. Comparison of retinal thickness parameters

	Control (n=55)	Patient (n=50)	p
TRT (µm)	262.58±17.63	252.33±21.66	**<0.001**
CRT (µm)	227.68±15.38	223.63±17.80	0.078
IRT (µm)	28.58±5.88	27.24±6.43	0.110
ORT (µm)	214.87±11.84	196.69±14.93	**<0.001**
External Ring			
Superior	303.42±12.85	301.34±17.05	0.320
Temporal	292.49±14.33	287.85±17.94	**0.039**
Inferior	299.06±15.16	294.11±16.27	**0.023**
Nasal	318.85±12.77	315.44±18.25	0.120
Internal Ring			
Superior	341.86±17.28	334.69±23.63	**0.014**
Temporal	329.93±16.87	319.66±18.72	**<0.001**
Inferior	332.59±33.55	328.64±21.14	0.310
Nasal	339.56±18.62	333.67±17.50	**0.019**

TRT: total retinal thickness, CRT: central retinal thickness, IRT: inner retinal thickness, ORT: outer retinal thickness

DISCUSSION

Studies have demonstrated altered tear parameters and ocular surface changes in CD (13,14). The results of the present study are consistent with the literature, but in contrast to previous studies, we investigated the association between tear parameters and laboratory results. Although it was observed that no relationship between Schirmer's test results and laboratory parameters, TBUT was correlated with vitamin D and total cholesterol levels. A positive correlation between TBUT and systemic vitamin D levels has also been reported by Jin et al (15). In the present study, TBUT was positively correlated with systemic vitamin D levels in patients with CD. In contrast, it was detected that a negative correlation between TBUT and total cholesterol level. This is consistent with existing knowledge that increased systemic cholesterol alters lipid profiles in meibomian gland secretions, which increases the probability of developing dry eye (16).

In the present study, CD patients had lower TRT, CRT, IRT, ORT, and RNFL values compared to the control group. Different from previous studies, we have measured these layers separately to understand which layer causes thinning. We think that deficiency of the micronutrients or cross reaction of the autoantibodies may be the cause of the retinal layers thinning. At the same time, children with CD exhibited a significantly higher cup/disc ratio when compared to the control group.

Aksoy et al. (17) reported a negative correlation between serum ferritin levels and peripapillary RNFL thickness in

Table 4. Comparison of optic nerve parameters

	Control (n=55)	Patient (n=50)	p
C/D ratio	0.28±0.13	0.41±0.12	**<0.001**
RNFL	109.15±9.94	100.11±13.85	**<0.001**

C/D ratio: cup/disc ratio, RNFL: retinal nerve fiber layer

Table 3. Correlations between retinal thickness parameters and laboratory findings

	Central Retinal Thickness		Total Retinal Thickness		Inner Retinal Thickness		Outer Retinal Thickness	
	r	p	r	p	r	p	r	p
Ferritin	-0.200	0.070	-0.140	0.180	0.160	0.340	-0.230	**0.035**
B12	0.210	0.054	0.140	0.180	-0.100	0.340	0.310	**0.004**
D Vitamin	0.270	**0.012**	0.140	0.190	0.060	0.540	0.220	**0.039**
Total Cholesterol	-0.300	**0.006**	-0.260	**0.017**	-0.040	0.720	-0.280	**0.008**
Triglyceride	-0.340	**0.001**	-0.220	**0.041**	-0.060	0.550	-0.350	**0.001**

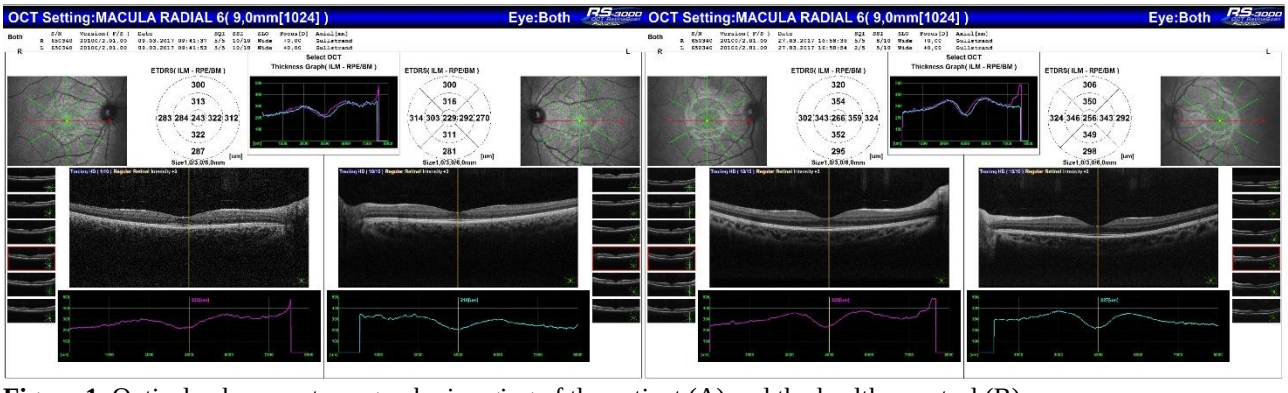

Figure 1. Optical coherence tomography imaging of the patient (A) and the healthy control (B)

children with iron deficiency and thalassemia major. In the present study, serum ferritin levels were negatively correlated with ORT and positively correlated with RNFL in children with CD. In contrast to the findings of Aksoy et al. (17), our results indicate that serum ferritin levels in patients with CD do not affect IRT but are inversely associated with ORT. The discrepancies between these results may be due to the evaluation of different patient groups. Furthermore, it is important to note that the ferritin levels observed in the current patient series were within normal limits.

A study evaluating patients with vitamin B12 deficiency revealed a positive correlation between peripapillary RNFL thickness and serum vitamin B12 levels (18). In the same study, however, RNFL thickness measurements were not associated with serum folate levels. In the present study, there were positive correlations between serum B12 vitamin levels and ORT, and between serum folate levels and IRT. There was also a negative correlation between serum B12 level and cup/disc ratio. Vitamin B12 deficiency is known to potentially lead to optic neuropathy and optic atrophy, which may explain this relationship between cup/disc ratio and serum vitamin B12 levels (19). However, it should be noted that the B12 and folate levels of the patients included in the study were within normal limits, and these findings may be related to the laboratory data or to the natural disease course in patients with CD.

Graffe et al. (20) demonstrated a positive association between serum vitamin D levels and CRT in the elderly. In contrast, Uro et al. (21) reported that vitamin D level was positively associated with ganglion cell complex thickness, but not with RNFL thickness. In the present study, we found that serum vitamin D levels were positively correlated with CRT and ORT but were not associated with optic nerve parameters in CD patients. These findings are similar to those in the literature.

One of the interesting findings of the present study is the negative correlation between total cholesterol and triglyceride levels and CRT, TRT, and ORT. There are studies in the literature with different results regarding the effect of blood lipid profile on OCT results (22-25). The present study suggests that serum lipid profile has different effects on these parameters in CD patients than those reported in the literature. Atherosclerosis begins in childhood even during the intrauterine period. Lipid accumulation in the aorta can be seen at the age of 3 years. We think that high cholesterol and triglyceride levels may accelerate the ischemic process and be subclinically reflected as thinning in the OCT measurements (26).

CONCLUSION

Tear parameters and OCT measurements may be altered in patients with CD. For this reason, it should be kept in mind that celiac patients should be followed up closely and subclinical eye involvement may occur. Therefore, monitoring of patients with OCT is more important for follow-up rather than diagnosis. Furthermore, the results of this study suggest that tear parameters and OCT measurements are associated with systemic variables. For this reason, systemic parameters of the patients should be closely monitored by gastroenterology specialists and nutritional parameters should be replaced. Hereby, subclinical eye involvement may be prevented.

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REFERENCES

1. Jimenez J, Loveridge-Lenza B, Horvath K. Celiac disease in children. Pediatr Clin North Am. 2021;68(6):1205-19.
2. Cabanillas B. Gluten-related disorders: Celiac disease, wheat allergy, and nonceliac gluten sensitivity. Crit Rev Food Sci Nutr. 2020;60(15):2606-21.
3. Dicke WK, Weijers HA, van de Kamer JH. Coeliac disease. II. The presence in wheat of a factor having a deleterious effect in cases of coeliac disease. Acta Paediatr (Stockh). 1953;42(1):34-42.
4. Trancone R, Jabri B. Celiac disease and gluten sensitivity. J Intern Med. 2011;269(6):582-90.
5. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. Am J Gastroenterol. 2012;107(10):1538-44.
6. Dalgic B, Sari S, Basturk B, Ensari A, Egritas O, Bukulmaz A, et al. Turkish Celiac Study Group. Prevalance of celiac disease in healthy Turkish school children. Am J Gastroenterol. 2011;106(8):1512-7.
7. Parzanese I, Qehajaj D, Patrinicola F, Aralica M, Chiriva-Internati M, Stifter S, et al. Celiac disease: From pathophysiology to treatment. World J Gastrointest Pathophysiol. 2017;8(2):27-38.
8. Rampertab SD, Pooran N, Brar P, Singh P, Green PH. Trends in the presentation of celiac disease. Am J Med. 2006;119(4):355.e9-14.
9. Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, et al. The Oslo definitions for coeliac disease and related terms. Gut. 2013;62(1):43-52.
10. Durazzo M, Ferro A, Brascugli I, Mattivi S, Fagoonee S, Pellicano R. Extra-intestinal manifestations of celiac disease: What should we know in 2022? J Clin Med. 2022;11(1):258.
11. Whyte LA, Jenkins HR. The epidemiology of coeliac disease in South Wales: A 28-year perspective. Arch Dis Child. 2013;98(6):405-7.
12. Fousekis FS, Katsanos A, Katsanos KH, Christodoulou DK. Ocular manifestations in celiac disease: an overview. Int Ophthalmol. 2020;40(4):1049-54.
13. Karatepe Hashas AS, Altunel O, Sevinc E, Duru N, Alabay B, Torun YA. The eyes of children with celiac diease. J AAPOS. 2017;21(1):48-51.

14. Uzel MM, Citirik M, Kekilli M, Cicek P. Local ocular surface parameters in patients with systemic celiac disease. Eye (Lond). 2017;31(7):1093-8.
15. Jin KW, Ro JW, Shin YJ, Hyon JY, Wee WR, Park SG. Correlation of vitamin D levels with tear film stability and secretion in patients with dry eye syndrome. Acta Ophthalmol. 2017;95(3):e230-5.
16. Rathnajumar K, Ramachandran K, Baba D, Ramesh V, Anebaracy V, Vidhya R, et al. Prevalence of dry eye disease and its association with dyslipidemia. J Basic Clin Physiol Pharmacol. 2018;29(2):195-9.
17. Aksoy A, Aslan L, Aslankurt M, Eser O, Garipardic M, Okumuş S, et al. Retinal fiber layer thickness in children with thalessemia major and iron deficiency anemia. Semin Ophthalmol. 2014;29(1):22-6.
18. Türkyılmaz K, Öner V, Türkyılmaz AK, Kırbaş A, Kırbaş S, Şekeryapan B. Evaluation of peripapillary nevre fiber layer thickness in patients with vitamin B12 deficiency using spectral domain optical coherence tomography. Curr Eye Res. 2013;38(6):680-4.
19. Larner AJ. Visual failure caused by vitamin B12 deficiency optic neuropathy. Int J Clin Pract. 2004;58(10):977-8.
20. Graffe A, Beauchet O, Fantino B, Milea D, Annweiler C. Vitamin D and macular thickness in the elderly: an optical coherence tomography study. Invest Ophthalmol Vis Sci. 2014;55(8):5298-303.
21. Uro M, Beauchet O, Cherif M, Graffe A, Milea D, Annweiler C. Age-related vitamin D deficiency is associated with reduced macular ganglion cell complex: a cross-sectional high-definition optical coherence tomography study. PLoS One. 2015;10(6):e0130879.
22. Benarous R, Sasongko MB, Qureshi S, Fenwick E, Dirani M, Wong TY, et al. Differential association of serum lipids with diabetic retinopathy and diabetic macular edema. Invest Ophthalmol Vis Sci. 2011;52(10):7464-9.
23. Davoudi S, Papavasileiou E, Roohipoor R, Cho H, Kudrimoti S, Hancock H, et al. Optical cohrence tomography characteristics of macular edema and hard exudates and their association with lipid serum levels in type 2 diabetes. Retina. 2016;36(9):1622-9.
24. Sasaki M, Kawashima M, Kawasaki R, Uchida A, Koto T, Shinoda H, et al. Association of serum lipids with macular thickness and volume in type 2 diabetes without diabetic macular edema. Invest Ophthalmol Vis Sci. 2014;55(3):1749-53.
25. Kardys A, Weinstock-Guttman B, Dillon M, Masud MW, Weinstock N, Mahfooz N, et al. Cholesterol affects retinal nevre fiber layer thickness in patients with multiple sclerosis with optic neuritis. Eur J Neurol. 2013;20(9):1264-71.
26. Stenbes WE. The lipid hypothesis and the role hemodynamics in atherogenesis. Prog Cardiovacs Dib. 1990;33(2):119-36.

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Clinical Results of Surgical Treatment of Giant Lipomas: A Single-Center Experience

Dev Lipomların Cerrahi Tedavisi Sonrası Klinik Sonuçlar: Tek Merkez Deneyimi

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ABSTRACT

Aim: Lipomas are benign tumors, and generally present as small lesions. However, giant lipomas are less frequent. There are only a few studies regarding the surgical treatment of giant lipomas. Marginal or wide resection is usually performed; however, there is no standard surgical approach. The aim of this study was to evaluate clinical results after surgical treatment of giant lipomas and to present a differential diagnosis of lipomatous lesions.
Material and Methods: A total of 42 cases (24 female, 18 male) admitted to our clinic between 2015 and 2020 due to giant lipoma with at least 10 cm dimensions were included in this study. A preoperative biopsy was performed for all cases. All patients were undergone wide excision followed by postoperative histopathological examination.
Results: The mean age was 57.5±12.9 years. The median follow-up was 35 months. Anatomic localization was thigh in 16 (38.1%) patients, shoulder in 7 (16.7%) patients, hip in 5 (11.9%) patients, back in 4 (9.5%) patients, arm in 9 (21.4%) patients, and the iliac region in 1 (2.4%) patient. Wide resection was performed, and final pathology was consistent with lipoma in all cases. There was no complication except in one patient who had transient neuropraxia after removing a giant lipoma at the proximal femur. At the latest follow-up, all cases were asymptomatic with no recurrence.
Conclusion: Preoperative biopsy and wide resection should be preferred for the diagnosis and treatment of giant lipomas. Wide resection may prevent a recurrence. Routine follow-up is necessary to detect possible malign transformation.
Keywords: Giant lipoma; wide resection; benign tumors.

ÖZ

Amaç: Lipomlar iyi huylu tümörlerdir ve genellikle küçük lezyonlar olarak ortaya çıkar. Ancak dev lipomlar daha az sıklıkta görülür. Dev lipomların cerrahi tedavisi ile ilgili çok az sayıda çalışma bulunmaktadır. Marjinal veya geniş rezeksiyon genellikle uygulanmaktadır; ancak standart bir cerrahi yaklaşım yoktur. Bu çalışmanın amacı, dev hücreli lipomların cerrahi tedavisi sonrası klinik sonuçlarını değerlendirmek ve lipomatöz tümörlerin ayırıcı tanısını sunmaktır.
Gereç ve Yöntemler: Bu çalışmaya 2015 ve 2020 yılları arasında en az 10 cm çapında dev lipom nedeniyle kliniğimize başvuran toplam 42 olgu (24 kadın, 18 erkek) dahil edildi. Tüm olgulara ameliyat öncesi biyopsi uygulandı. Tüm hastalara geniş eksizyon yapıldıktan sonra postoperatif histopatolojik inceleme yapıldı.
Bulgular: Ortalama yaş 57,5±12,9 yıl idi. Ortanca takip süresi 35 aydı. Anatomik yerleşim 16 (%38,1) hastada uyluk, 7 (%16,7) hastada omuz, 5 (%11,9) hastada kalça, 4 (%9,5) hastada sırt, 9 (%21,4) hastada kol, 1 (%2,4) hastada iliak bölge idi. Geniş rezeksiyon yapıldı ve nihai patoloji sonucu tüm hastalarda lipom ile uyumluydu. Proksimal femurda yerleşimli dev lipomun çıkarılmasından sonra bir hastada geçici nöropraksi görülmesi dışında başka bir komplikasyona rastlanmadı. Son kontrolde, tüm hastalar asemptomatikti ve nüks görülmedi.
Sonuç: Dev lipomların teşhisinde ameliyat öncesi biyopsi ve tedavisinde geniş rezeksiyon tercih edilmelidir. Geniş rezeksiyon rekürrensi önleyebilir. Muhtemel malign transformasyonun tespit edilmesi için rutin takip gereklidir.
Anahtar kelimeler: Dev lipom; geniş rezeksiyon, iyi huylu tümör.

INTRODUCTION

Lipomas are the most common benign mesenchymal tumors. Its prevalence is 2.1 per 1000 people. Most of the lipomas are located in the subcutaneous tissue and present as a small mass, usually less than 2-3 cm. A giant lipoma refers to a lesion that should be at least 10 cm in axial or coronal dimension or weigh a minimum of 1000 g. These types of lipomas can cause compression to adjacent anatomic structures (1). Giant lipomas are rarely presented in the English-speaking literature, with usually case reports or series (1-9). The choice to prefer wide or marginal resection is variable (10).

They may be predisposed to diagnostic challenges both radiologically and pathologically. Differential diagnoses from sarcoma are of utmost importance to put forward the appropriate treatment strategy. So, in this manuscript, we aimed to present our patients treated surgically for their giant cell lipomas between 2015 and 2020 in a tertiary reference center of orthopedic oncology center in the light of current literature and to present a differential diagnosis of lipomatous lesions which have been very rarely presented in the English-speaking literature.

MATERIAL AND METHODS

Our study cohort consisted of 42 patients who were surgically treated for their giant lipomas with a size of more than 10 cm in appendicular and axial skeleton between the dates of 2015 and 2020 in a tertiary orthopedic oncology referral center (Istanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital) detected from the musculoskeletal oncology database of our pathology unit. All lesions were undergone preoperative biopsy and wide excision followed by postoperative histopathological examination. This study was approved by the ethics committee of the İstanbul Medeniyet University (dated 16.06.2021, numbered 319). Age, gender, anatomical localization, histopathological features of the lesions, and follow-up time were noted. All patients had a preoperative X-ray and magnetic resonance imaging (MRI) examination. The diagnosis was confirmed with a preoperative biopsy in all of our patients. Patients were followed up every six months for the first two years and then yearly with contrast-enhanced MRI examination for recurrence.

All patients with at least one year of follow-up and adequate radiologic imaging were included in the study.

Surgical Technique

In all cases, wide resection was performed to decrease the recurrence rate with a cuff of normal tissue surrounding the tumoral lesion with paying attention to neurovascular structures. We opt not to perform marginal resection which involves dissection and removal of the tumor through the pseudocapsule or peritumoral reactive tissue (11).

Statistical Analysis

Descriptive statistics were given as mean, standard deviation, and minimum-maximum values for numerical variables. Categorical variables were summarized as numbers and percentages.

RESULTS

The study included 42 cases, 24 (57.1%) of whom were female, and 18 (42.9%) were male. The mean age of the patients was 57.5±12.9 (range, 28-87) years. The median follow-up was 35 (range, 2-66) months. Anatomic localization of the lesions were thigh in 16 (38.1%) patients, shoulder in 7 (16.7%) patients, hip in 5 (11.9%) patients, back in 4 (9.5%) patients, arm in 9 (21.4%) patients, and the iliac region in 1 (2.4%) patient. Preoperative tru-cut biopsy was performed in all patients due to the size of the lesions.

Wide resection was performed in all patients. There was no complication except in one patient who had neuropraxia of the femoral nerve after removing a giant lipoma at the proximal femur.

Postoperative histopathological examination was also performed for all patients confirming the diagnosis.

A representative case was demonstrated in Figure 1. The intraoperative view demonstrates the lesion abutting the radial nerve (Figure 1a). After resection, the macroscopic view demonstrated well-circumscribed tumors with a uniform glistening yellow to pale cut surface (Figure 1b).

Histological examination of lipomas is a well-differentiated lipomatous proliferation composed of mature adipocytes. Fibrous septa may be present, but atypical hyperchromatic stromal cells are absent (Figure 1c). Fat necrosis and dystrophic calcification, especially in large deep-seated tumors, may be seen (Figure 1d). Lipomas which contain nodules of metaplastic bone or cartilage are termed osteolipoma or chondrolipoma. Immunohistochemical examination shows positive staining with sS-100 and HMGA 2. No staining was detected with MDM2 and CDK4.

Demographic and clinical findings of the cases including the localization and size of the tumoral lesions were given in Table 1 and Table 2.

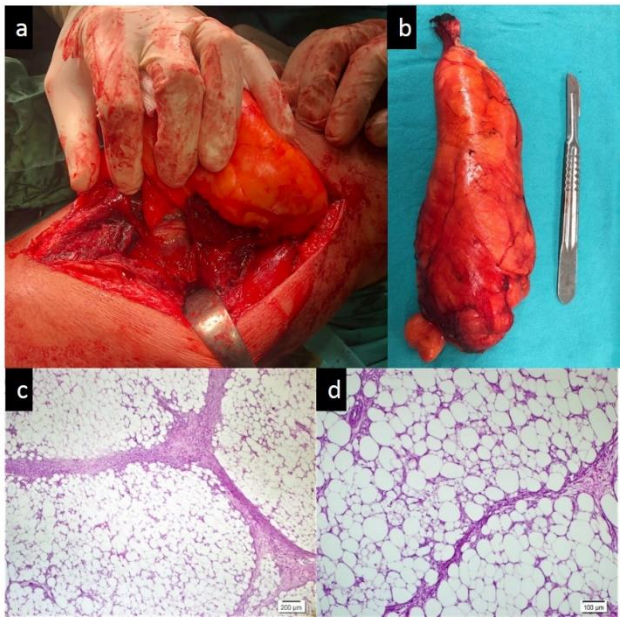

Figure 1. a) The lesion is abutting the radial nerve. **b)** Macroscopic view demonstrates well-circumscribed tumors with a uniform glistening yellow to pale cut surface. **c)** Microscopic view shows the giant lipoma composed of multiple lobules of mature fat cells separated by fibrous septa. (Hematoxylin and Eosin (H&E) x100) **d)** Fat necrosis and rare macrophage are present (H&E x200)

Table 1. Demographic and clinical findings of cases in lower extremity and iliac region

Case	Age	Gender	Localization	Size
1	62	Female	Right thigh	17x13x9
2	50	Male	Right hip	23x2x3
3	72	Female	Right hip	10x7x5
4	65	Female	Left hip	15x3x2
5	65	Male	Right hip	18x12x6
6	28	Female	Left thigh	14x15x8
7	41	Female	Left thigh	12x12x6
8	68	Male	Left iliac	11x9x2.5
9	53	Male	Left thigh	12x9x8
10	87	Female	Left thigh	24x13x8
11	66	Male	Right thigh	16x11x5
12	58	Female	Right thigh	17x11x6
13	78	Male	Left thigh	13x7x5
14	78	Female	Right thigh	21x24x7
15	70	Female	Right thigh	15x11x6
16	51	Female	Left hip	17x16x6
17	52	Male	Left thigh	13x6x5
18	46	Female	Right thigh	10x5x3
19	55	Female	Right thigh	15x8x7
20	57	Female	Left thigh	20x9.5x6
21	54	Female	Left thigh	13x10x6
22	68	Male	Left thigh	13x8x4

Table 2. Demographic and clinical findings of cases in upper extremity and back

Case	Age	Gender	Localization	Size
1	44	Male	Right shoulder	10x3x3
2	49	Male	Left arm	10x2x4
3	55	Female	Right shoulder	15x14x5
4	40	Female	Left arm	10x7x2.5
5	43	Female	Right shoulder	11x10x1
6	52	Male	Back	14x11x3
7	48	Male	Right shoulder	10x10x4
8	59	Male	Left shoulder	11x8x2
9	69	Male	Back	12x7x5
10	50	Male	Right arm	11x7x3
11	50	Female	Left arm	11x7x4.5
12	52	Male	Right shoulder	10.5x9x7
13	64	Male	Right arm	16x9x5.5
14	59	Female	Back	11x5.5x3
15	89	Female	Left arm	13x12x7
16	58	Female	Right arm	10x8x5
17	64	Female	Right arm	10x6x3.5
18	55	Female	Back	12x11x6
19	33	Female	Left arm	11.5x10.5x5
20	59	Male	Right shoulder	11.5x10.5x5

DISCUSSION

Lipoma is the most frequently detected soft tissue tumor of mesenchymal origin and is composed of mature adipocytes cells. Although the exact etiology of lipomas is unknown, genetic disorders like Gardner syndrome, chromosomal abnormalities, hypercholesterolemia, obesity, and trauma are among the suggested underlying causes (12). Hypercholesterolemia, obesity, and trauma may be especially associated with subcutaneous lipomas (13).

Lipomas usually manifest as thinly encapsulated, rounded mass varying in size (median 3 cm). However, a size larger than 10 cm is extremely uncommon (13,14). Giant lipomas have been described in various parts of the body, including the thigh, buttock, scapular region, and abdomen, usually as case reports or series. As sizes greater than 5 cm usually have been associated with an increased risk factor for malignancy, we opt to perform a preoperative biopsy in all our cases (15,16).

Göçer et al. (5) presented 17 cases who underwent total excision due to giant lipoma at the upper extremity. The mean follow-up was 42 months and there was one case with recurrence. He concluded that in large deep located lesions with a heterogeneous appearance on MRI, clinical information should be detailed to the pathologist for differential diagnosis.

Although some authors advocate using a 5 cm size as defining the giant cell lipoma, we prefer to use the cut-off value of 10 cm (1,5,17) as atypic lipomas/well-differentiated liposarcomas are usually more than 10 cm in diameter (18).

Aside from cosmetic problems, giant lipomas may cause neurovascular compression in upper and lower extremities as in our representative case. Gungor et al. (19) presented a giant thigh lipoma. The mass was measured as 10x14x23 cm, which abutted the femoral neurovascular bundle. After the biopsy confirmed lipoma, en-bloc resection was performed. At 24 months of follow-up, there was no recurrence. Pakanati et al. (6) presented a 25x20 cm giant lipoma located at the thigh which was excised. The final report was angiolipoma. The patient had no recurrence detected at the last follow-up.

Morales et al. (7) performed wide excision on a giant thigh lipoma in a 25-year-old female. As clinical and radiological findings were suggestive of lipoma, no biopsy was performed. He outlined that excision of giant lipomas should be performed with at least one cm of margin to decrease the risk of local recurrence.

Clesham et al. (20) excised a lipoma in a 65-year-old man which was causing median nerve compression. 2 weeks after excision, the neurological complaints resolved. Toft F. (21) in a recent study obtained satisfactory results 6 weeks after excision of a giant lipoma which was located at biceps brachii. He emphasized that management guidelines were inconsistent in these tumors. Giant lipomas however may cause a diagnostic challenge and be confused with atypical lipomatous tumors or other liposarcomas. A definitive diagnosis of giant cell lipoma can only be made by histopathological examination (22).

Although very rare, they may also transform into liposarcoma. Microscopically, lipomas present with well-defined masses consisting of mature adipocytes. There are also different subtypes like angiolipoma, fibrolipoma, spindle cell lipoma, pleomorphic lipoma, chondroid lipoma, and fibrohistiocytic lipoma other than typical lipomas (10).

Histopathologic findings that differentiate atypical lipomas/well-differentiated liposarcomas from lipomas are the location, size, and immunohistochemical features. Atypical lipomatous tumors tend to be in the deep tissues and retroperitoneum. Its diameter is usually greater than 10

cm, and its microscopic sections contain bands of hyalinized connective tissue, atypical nuclei, and lipoblasts. Immunohistochemically, p16, MDM2, and CDK4 are usually positive (23,24).

As another entity, lipomatosis is usually seen in childhood. It consists of diffuse lipomatous proliferation without a capsule. These help to differentiate lipomatosis from lipomas (25).

Only one patient had a spindle cell lipoma in our patient cohort with giant lipomas, and the remaining were classical subtypes. Spindle cell lipoma is a very rare benign lipomatous neoplasm composed of mature adipose tissue, ropey collagen, and bland spindle cells. They usually present as a subcutaneous mass and predilection to localize at the posterior neck, shoulder, and back region (26).

Radiologically, lipomas are usually less than 10 cm and usually have no or few thin (less than 2 cm) septa, with no or minimal contrast enhancement and no or minimal T2 signal foci detected with MRI examination, however giant lipomas may mimic liposarcomas (27).

Definitive treatment of giant cell lipoma is surgical excision after the diagnosis is usually confirmed with a biopsy as in our patient cohort as they may have overlapping features with other lesions like atypic lipomas both histopathologically and radiologically. Intralesional resection should be avoided whenever possible to prevent recurrence and the possibility of transforming to liposarcoma in the future.

CONCLUSION

Histopathological examination with preoperative biopsy is the key to diagnoses of giant cell lipomas, although MRI examinations are usually sensitive for detecting lipomas but less than 10 cm. Consultation with an experienced musculoskeletal pathologist should be carried out in case of any doubt for diagnosis. Immunohistochemical stains with CDK4 and MDM2 may further help to differentiate atypical lipomas which are usually larger than 10 cm from giant lipomas. Fluorescence in situ hybridization (FISH) analyses may increase the diagnostic accuracy in selected cases.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of İstanbul Medeniyet University (16.06.2021, 319).

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REFERENCES

1. Johnson CN, Ha AS, Chen E, Davidson D. Lipomatous soft-tissue tumors. J Am Acad Orthop Surg. 2018;26(22):779-88.
2. Litchinko A, Cherbanyk F, Menth M, Egger B. Giant gluteal lipoma surgical management. BMJ Case Rep. 2019;12(8):e229842.
3. Ramirez-Montaño L, Lopez RP, Ortiz NS. Giant lipoma of the third finger of the hand. Springerplus. 2013;2(1):164.
4. Szewc M, Gawlik P, Żebrowski R, Sitarz R. Giant lipoma in the fronto-temporo-parietal region in an adult man: Case report and literature review. Clin Cosmet Investig Dermatol. 2020;13:1015-20.
5. Göçer H, Dabak N, Çıraklı A. Giant lipomas of the upper extremity. Acta Oncol Turc. 2016;49(3):192-6.
6. Pakanati R, Gogineni RC, Ede NB. Recurrent giant intermuscular lipoma of thigh. J NTR Univ Health Sci. 2019;8(3):219-21.
7. Morales Morales CA, González Urquijo M, Morales Flores LF, Sánchez Gallegos MN, Rodarte Shade M. Giant intramuscular thigh lipoma: A case report and review of literature. Int J Surg Case Rep. 2021;82:105885.
8. Aydoğdu E, Yıldırım S, Eker G, Aköz T. Giant lipoma of the back. Dermatol Surg. 2004;30(1):121-2.
9. Gondowardojo YRB, Argie D, Arifin MZ. Giant lower back lipoma in pediatric : a case report. Bali Med J. 2017;6(3):554-6.
10. Zenginkinet T, Okay E, Çelik A, Toksöz Yıldırım AN, Öztürk MB. Clinical results after surgical treatment of spindle cell lipomas. Duzce Med J. 2021;23(3):258-62.
11. Endo M, Lin PP. Surgical margins in the management of extremity soft tissue sarcoma. Chin Clin Oncol. 2018;7(4):37.
12. Niranjan A, Mutreja J. Review on lipoma and case studies. Eur J Mol Clin Med. 2020;7(6):1336-42.
13. Cribb GL, Cool WP, Ford DJ, Mangham DC. Giant lipomatous tumours of the hand and forearm. J Hand Surg Br. 2005;30(5):509-12.
14. Salam GA. Lipoma excision. Am Fam Physician. 2002;65(5):901-4.
15. Silistreli OK, Durmuş EU, Ulusal BG, Oztan Y, Görgü M. What should be the treatment modality in giant cutaneous lipomas? Review of the literature and report of 4 cases. Br J Plast Surg. 2005;58(3):394-8.
16. Celik C, Karakousis CP, Moore R, Holyoke ED. Liposarcomas: Prognosis and management. J Surg Oncol. 1980;14(3):245-9.
17. Abdulsalam T, Osuafor CN, Barrett M, Daly T. A giant lipoma. BMJ Case Rep. 2015;2015:bcr2015212030.
18. Fisher SB, Baxter KJ, Staley CA 3rd, Fisher KE, Monson DK, Murray DR, et al. The general surgeon's quandary: Atypical lipomatous tumor vs lipoma, who needs a surgical oncologist? J Am Coll Surg. 2013;217(5):881-8.
19. Gungor M, Sir E, Aksoy A, Agirbas S. Giant lipoma extending into two thigh canals: A case report. Acta Orthop Traumatol Turc. 2017;51(3):270-2.
20. Clesham K, Galbraith JG, Ramasamy A, Karkuri A. Giant lipoma of the hand causing median nerve compression. BMJ Case Rep. 2017;2017:bcr2017220056.

21. Toft F. Surgical resection of a giant intramuscular lipoma of the biceps brachii: a case report and review of the literature. Arch Orthop Trauma Surg. 2022;142(3):373-9.
22. Lee YJ, Jeong YJ, Lee JH, Jun YJ, Kim YJ. Liposarcoma in the axilla developed from a longstanding lipoma. Arch Plast Surg. 2014;41(5):600-2.
23. Altun E, Yüksel S, Kaygusuz G, Yıldız HY. Diagnostic importance of clinicopathologic features and p16, CD34, MDM2 expression in differential diagnosis of adipocytic tumors. Acta Orthop Traumatol Turc. 2020;54(1):59-65.
24. Nagano S, Yokouchi M, Setoguchi T, Ishidou Y, Sasaki H, Shimada H, et al. Differentiation of lipoma and atypical lipomatous tumor by a scoring system: Implication of increased vascularity on pathogenesis of liposarcoma. BMC Musculoskelet Disord. 2015;16(1):36.
25. Sheybani EF, Eutsler EP, Navarro OM. Fat-containing soft-tissue masses in children. Pediatr Radiol. 2016;46(13):1760-73.
26. Bancroft LW, Kransdorf MJ, Peterson JJ, Sundaram M, Murphey MD, O'Connor MI. Imaging characteristics of spindle cell lipoma. AJR Am J Roentgenol. 2003;181(5):1251-4.
27. Knebel C, Neumann J, Schwaiger BJ, Karampinos DC, Pfeiffer D, Specht K, et al. Differentiating atypical lipomatous tumors from lipomas with magnetic resonance imaging: A comparison with MDM2 gene amplification status. BMC Cancer. 2019;19(1):309.

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Relationship between the Empathy of Emergency Personnel and Their Approach to Acute Stroke Patients

Acil Servis Personelinde Empati ve Akut İnmeli Hastalara Yaklaşımları Arasındaki İlişki

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ABSTRACT

Aim: The aim of this study was to investigate the relationship between the empathy level of emergency department physicians and nurses and the referral of patients for intravenous thrombolytic and/or endovascular thrombectomy treatment.

Material and Methods: This cross-sectional study was carried out with the emergency department physicians and nurses of hospitals that did not have a stroke clinic in Bursa in July 2019, and included 198 emergency personnel. Participants' sociodemographic characteristics, professional working conditions, and stroke history in their immediate environment (friends and family) were recorded and empathy level was measured. The health professions version of the Jefferson Scale of Empathy was used in the assessment of empathy status among emergency physicians and nurses.

Results: The mean empathy score of the study group, by the Jefferson scale of empathy, was found 98.63±14.83 points. In this study, no significant relationship was found between the empathy score and the number of referrals (p=0.962). The total empathy score did not differ by the role of the participants in the hospital (p=0.161) or observation of stroke cases in their family or their friends (p=0.694). Healthcare professionals who had received emergency education (p<0.001), were older (p<0.001), spent more time in their profession (p=0.005), and had observed stroke cases in their family or friends (p=0.005) transferred more stroke cases.

Conclusion: This study suggests that interventions for increasing the empathy levels of emergency medicine specialists and nurses will not have a general effect on the referral of acute stroke cases for intravenous thrombolytic and endovascular thrombectomy treatment.

Keywords: Empathy; acute stroke; emergency medicine specialists and nurses.

ÖZ

Amaç: Bu çalışmanın amacı, acil servis hekimleri ve hemşirelerinin empati düzeyleri ile intravenöz trombolitik ve/veya endovasküler trombektomi tedavisi için hastaların sevk edilmesi arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler: Kesitsel tipteki bu çalışma Bursa'da inme kliniği olmayan hastanelerin acil servis hekimleri ve hemşireleri ile Temmuz 2019 tarihinde gerçekleştirilmiş ve çalışmaya toplam 198 acil servis personeli dahil edilmiştir. Katılımcıların sosyodemografik özellikleri, mesleki çalışma koşulları ve kendi yakın çevrelerindeki (aile ve arkadaşlar) inme öyküleri sorgulanarak kaydedildi ve empati düzeyleri ölçüldü. Acil servis hekimleri ve hemşirelerinin empati durumlarının değerlendirilmesinde Jefferson empati ölçeğinin sağlık çalışanları versiyonu kullanıldı.

Bulgular: Çalışma grubunun Jefferson empati ölçeği ile elde edilen ortalama empati skoru 98,63±14,83 puan olarak bulundu. Bu çalışmada empati puanı ile sevklerin sayısı arasında herhangi bir anlamlı ilişki bulunmadı (p=0,962). Toplam empati puanı, katılımcıların hastanedeki rolüne (p=0,161) veya ailelerinde ya da arkadaşları arasında inme vakası görülmesine (p=0,694) göre de bir farklılık göstermedi. Acil eğitimi almış olan (p<0,001), daha yaşlı olan (p<0,001), mesleğinde daha fazla zaman geçirmiş olan (p=0,005) ve ailesinde veya arkadaşlarında inme vakası gözlemlemiş olan (p=0,005) sağlık çalışanlarının daha fazla inme vakası sevk ettiği görüldü.

Sonuç: Bu çalışma, acil servis hekimleri ve hemşirelerinin empati düzeylerini artırmaya yönelik müdahalelerin, akut inme olgularının intravenöz trombolitik ve endovasküler trombektomi tedavisi için sevkinde genel bir etkiye sahip olmayacağını düşündürmektedir.

Anahtar kelimeler: Empati; akut inme; acil servis hekimleri ve hemşireler.

INTRODUCTION

Cerebrovascular disease is one of the most common causes of permanent disability and death in the world (1). Implementation of intravenous alteplase (intravenous thrombolytic therapy) within the first 4.5 hours in appropriate patients with acute ischemic stroke both ameliorates the clinical outcome of these patients and affects their survival (1-3). Endovascular thrombectomy is recommended in proximal artery occlusions with a low response rate to intravenous thrombolytic treatment (4-6). The concept "time is brain" emphasizes the importance of time in acute stroke treatment (7). Both intravenous thrombolytic therapy and endovascular thrombectomy should be implemented within a short therapeutic time window and better clinical outcomes are achieved in a case with earlier implementation (8,9). Therefore, early diagnosis of these patients and their rapid arrival to the stroke clinic is very important.

Empathy, which describes the ability to understand a patient's feelings and thoughts (10), can be an important factor affecting clinical outcomes, especially in patients in which swift action is necessary, such as those with stroke. It has been reported that increased empathy level in healthcare professionals is associated with better clinical outcomes and low burnout. Higher levels of empathy in healthcare professionals increase patients' belief, treatment compliance, and satisfaction, reduce anxiety, affect litigation decisions and reduce the frequency of exhaustion and complications (11-15). Interestingly, it has also been reported that the number of donor notifications is higher in the presence of intensive care nurses with high empathy levels (16).

In close cooperation with neurologists, emergency physicians and nurses are of vital importance in the rapid and accurate recognition of symptoms in stroke patients, in the prompt completion of triage, in the conduct of radiological and laboratory examinations, and in the implementation of early basic treatment protocols (1-3,5,17). In the hospital, emergency physicians and nurses, who are the first contact point of the patient, act as a team in the rapid transfer of appropriate acute stroke patients to the stroke center and their access to acute stroke treatments. Therefore, it is important to evaluate the effects of empathy levels among emergency physicians and nurses on outcomes related to the management of stroke patients.

The aim of the study was to evaluate the relationship between the empathy level of nurses and emergency physicians and the referral of acute stroke patients to comprehensive stroke units for intravenous thrombolytic and/or endovascular thrombectomy treatment.

MATERIAL AND METHODS

This cross-sectional study was carried out with the emergency physicians (emergency medicine specialists, emergency practitioners) and nurses of hospitals that did not have a stroke clinic in Bursa, Turkey. All participants had to have been employed for at least 6 months at the time of study conduct, July 2019. This study was approved by the Clinical Research Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital (Date: 10 July 2019, No: 2011-KAEK-25 2019/07-26), and necessary permissions were obtained to conduct the study. The study was carried out in accordance with the Declaration of Helsinki.

Bursa Yüksek İhtisas Training and Research Hospital had been running a comprehensive stroke unit for two years at the time of the conduct of this research. Intravenous thrombolytic therapy and/or endovascular thrombectomy in the emergency departments of other hospitals in Bursa are considered appropriate for acute ischemic stroke cases, which are referred to our center. Within the scope of the study, we interviewed emergency physicians and nurses of 13 hospitals that referred acute stroke cases to this stroke unit for further treatment.

The questionnaire used in the study included questions about sociodemographic characteristics, professional working conditions, stroke history in participants' immediate environment (family and friends), and evaluation of empathy level.

The Jefferson Scale of Physician Empathy (JSPE) version of the Jefferson Empathy Scale (JSE), developed to measure empathy in medical and health professional groups, was used (10). The Turkish validity and reliability of the JSE was performed by Öztürk et al. (16) The JSE includes 20 items answered on a 7-point Likert type scale, with positively worded questions scored as "strongly disagree=1" to "strongly agree=7", while negatively worded questions are inversely scored "strongly disagree=7" to "strongly agree=1". Possible scores vary between 20 and 140 points with higher scores showing greater levels of empathy (10).

After detailed information about the purpose and scope of the study was given to all health personnel eligible for the study (26 emergency medicine specialists, 160 emergency practitioners, and 386 nurses), verbal and written consent was obtained from those who agreed to participate (13 emergency medicine specialists, 50 emergency practitioners, 135 nurses). Health personnel in the research group were asked to complete the questionnaire.

Statistical Analysis

The data were analyzed using the IBM SPSS software (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). The Shapiro-Wilk test was used to assess whether the data followed a normal distribution. Categorical variables were given as number and percentage, and continuous variables as mean±standard deviation or median (min-max). According to the normality test results, Kruskal-Wallis, Mann-Whitney U, or independent samples t tests were used to compare the groups. Categorical variables were compared by the Pearson chi-square and Fisher's exact test. The reliability of the JSE scale was evaluated using Cronbach's alpha coefficient. The correlation between JSE score and age, professional experience, and the monthly shift was analyzed, and the Spearman correlation coefficient was calculated. A p-value of <0.05 was considered statistically significant.

RESULTS

The study group consisted of 198 individuals, 115 (58.1%) were females and 83 (41.9%) were males. Of the study group, 13 (6.6%) were emergency medicine specialists, 50 (25.3%) were emergency practitioners, and 135 (68.1%) were nurses. The mean empathy score of the research

group, as measured by JSE, was 98.63±14.83 points. The scores obtained from the 'perspective taking', 'compassionate care', and 'standing in the patient's shoes' sub-dimensions were 54.83±8.62, 34.36±8.11, and 9.44±3.04 points, respectively. No significant relationship was found between the empathy levels of the health personnel in the study and variables including gender (p=0.908), hospital position (p=0.161), stroke history in the family & friends (p=0.694), and stroke referral (p=0.962, Table 1). There was a very weak negative correlation between total empathy score and the number of shifts per month (r_s=-0.170, p=0.017) while no significant correlation was found for age (r_s=0.050, p=0.524), and professional experience (r_s=0.040, p=0.628). Both the gender (p=0.624) and the number of monthly shifts (p=0.458) were not associated with stroke referral. The median age of healthcare professionals who referred patients to the comprehensive stroke unit was significantly higher than those who did not (32 vs. 26 years, p<0.001). Professional experience was found to be significantly longer among health personnel who had referred patients compared to those who had not (10 vs. 4 years, p=0.005). All (n=13) emergency medicine specialists, 64% (n=32) of emergency practitioners, and 47.4% (n=64) of nurses had referred patients for stroke, and thus, the distribution of professions in the referral and non-referral groups demonstrated a significant difference (p<0.001). The frequency of referral by healthcare professionals with stroke history among family & friends was also significantly higher than those without (69.2% vs. 30.8%, p=0.005, Table 2).

DISCUSSION

In this study, possible relationships between the empathy levels of emergency physicians and nurses and their referral of patients for intravenous thrombolytic and/or endovascular thrombectomy treatment methods were investigated. Our results revealed that being an emergency medicine specialist or emergency practitioner (relative to nurses as the reference category) and age (higher age) were independently associated with requesting a stroke-related referral; however, empathy level was not associated with the likelihood of referral.

Previous studies proved that higher scores of empathy were associated with better clinical outcomes in various conditions and diseases. It was observed that diabetes control was better with high empathy scores of physicians (12). Hypertension control has also been demonstrated to be better in the presence of primary care physicians that had higher empathy scores (18). In our study, we could not observe a relationship between empathy score and patient referral for stroke.

Table 1. Relationship between empathy score and characteristics of the participants

Gender	**Female (n=115)**	**Male (n=83)**	**p**
	98.76±13.99 (55-138)	98.46±15.99 (62-124)	0.908[a]
Role in the hospital	**Specialist (n=13)**	**Practitioner (n=50)**	**Nurse (n=135)**	**p**
	107.08±16.01 (77-138)	98.84±13.57 (66-128)	97.82±15.04 (55-125)	0.161[b]
Stroke history in the family & friends	**Yes (n=65)**	**No (n=133)**	**p**
	99.23±15.08 (55-138)	98.35±14.75 (62-128)	0.694[c]
Stroke referral	**Yes (n=109)**	**No (n=89)**	**p**
	98.71±15.34 (62-138)	98.55±14.25 (55-125)	0.962[c]

Descriptive statistics were presented as mean±standard deviation (min-max), [a]: Mann-Whitney U test, [b]: Kruskal-Wallis test, [c]: Independent Samples t test

Table 2. Factors affecting stroke referral

Stroke referral	**Yes (n=109)**	**No (n=89)**	**p**
Gender*, n (%)			
Female	65 (56.5%)	50 (43.5%)	0.624[a]
Male	44 (53.0%)	39 (47.0%)	
Age (years), median (min-max)	32 (22-57)	26 (20-55)	**<0.001[b]**
Professional experience (years), median (min-max)	10 (1-33)	4 (1-32)	**0.005[b]**
Number of monthly shifts, median (min-max)	10 (0-16)	10 (0-18)	0.458[b]
Role in the hospital*, n (%)			
Emergency medicine specialist	13 (100%)	0 (0.0%)	**<0.001[a]**
Emergency practitioner	32 (64.0%)	18 (36.0%)	
Nurse	64 (47.4%)	71 (52.6%)	
Stroke in the family & friends*, n (%)			
Yes	45 (69.2%)	20 (30.8%)	**0.005[a]**
No	64 (48.1%)	69 (51.9%)	

*: percentage values were calculated within rows, [a]: chi-square test, [b]: Mann-Whitney U test

The mean total empathy score was reported as 104.56±16.17 in a study performed with Turkish medicine students (19), whereas in a study performed with intensive care nurses in Türkiye, the mean total empathy score was reported to be 98.97±12.40 (16). On the other hand, the mean total empathy score was 106±16.5 in a study with oncology nurses (20). The total mean empathy score was 112.8±10.2 in a study performed with family medicine doctors (21), similarly, in our study, the mean JSE of the participants was 98.63±14.83.

In our study, no relationship was detected between gender and the empathy scores of the participants. In the literature, a higher level of empathy was frequently detected in female physicians and medical students compared to their male counterparts (19,22,23). In contrast to studies showing that senior and older physicians showed higher scores of empathy (13,24), no correlation was detected in our study between the age and empathy scores of physicians or nurses.

An inverse correlation was detected in our study between the number of monthly shifts and total empathy score. In a study with emergency medicine specialists, it was observed that good quality of life was associated with a higher empathy level (25). As the healthcare staff's quality of life decreases with an increasing number of shifts, the total empathy score may decrease. This finding indicates that the empathy levels of emergency staff can be increased at a meaningful degree if the number of monthly shifts could be reduced, which would, in turn, translate into a better quality of care provided to patients.

The age and professional experience of healthcare personnel who transferred patients to the stroke center were found to be significantly higher in this study. Emergency medicine specialists declared that more acute stroke cases were transferred to the stroke clinics during their shifts for thrombolytic or endovascular thrombectomy compared to emergency practitioners and nurses. Also, it is important to note that the patient referral rate in the healthcare personnel who experienced a stroke in their family & friends was found to be higher. No difference was detected among groups in terms of gender. This outcome led us to think that emergency education, age, and professional experience, and observation of stroke in the family & friends were more effective in patient referral compared to empathy score.

Total empathy score did not vary with the role of the participants in the hospital or the presence of stroke in the family and among friends. We saw that specialist training, age (possibly associated with professional experience), and presence of stroke history among family & friends were associated with increased referrals. However, empathy level was not a factor associated with the likelihood of referral in our group of healthcare employees. We hope that these results will contribute to the literature since there has been no study analyzing the relationship between empathy levels of emergency physicians and nurses of hospitals and referrals for acute stroke treatment.

Strengths and Limitations

This was a small sample size study that was limited to our province. Thus, we cannot generalize its results. For this reason, large-scale, multi-centered studies could provide a better assessment of the relationship between empathy and referral of acute stroke patients in the emergency department. Besides this, as several factors may have an effect on the transfer of these patients, especially stroke characteristics (e.g. stroke severity), patient characteristics (e.g. comorbidities), timing (stroke onset, potential time of the transfer to the secondary hospital, etc.), more studies are needed to stratify for these factors. In addition, nurses are not directly authorized for the referral of patients but they have an influence in accelerating the triage of acute stroke patients in the emergency department and guiding physicians' referral of patients indirectly. This can also be considered as a limitation of our study.

CONCLUSION

The findings of this study suggest that interventions for increasing the empathy levels of emergency medicine specialists and nurses will not have an increasing effect on the referral of acute stroke cases for intravenous thrombolytic and endovascular thrombectomy treatment. Transfer of appropriate patients to related hospitals by increasing the number of emergency medicine specialists in the emergency departments and providing in-service training to increase experience appear to be more promising for potentially increasing access to these treatments.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital (10.07.2019, 07-26).

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REFERENCES

1. Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, et al. Update on the global burden of ischemic and hemorrhagic stroke in 1990-2013: The GBD 2013 Study. Neuroepidemiology. 2015;45(3):161-76.
2. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333(24):1581-7.
3. Wahlgren N, Ahmed N, Dávalos A, Hacke W, Millán M, Muir K, et al. Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. Lancet. 2008;372(9646):1303-9.
4. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372(24):2285-95.
5. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid

endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):1019-30.
6. Goyal M, Menon BK, Van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723-31.
7. Saver JL. Time is brain--quantified. Stroke. 2006;37(1):263-6.
8. Khatri P, Abruzzo T, Yeatts SD, Nichols C, Broderick JP, Tomsick TA. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. Neurology. 2009;73(13):1066-72.
9. Meretoja A, Keshtkaran M, Saver JL, Tatlisumak T, Parsons MW, Kaste M, et al. Stroke thrombolysis: save a minute, save a day. Stroke. 2014;45(4):1053-8.
10. Hojat M, Gonnella JS, Nasca TJ, Mangione S, Vergare M, Magee M. Physician empathy: definition, components, measurement, and relationship to gender and specialty. Am J Psychiatry. 2002;159(9):1563-9.
11. Derksen F, Bensing J, Lagro-Janssen A. Effectiveness of empathy in general practice: a systematic review. Br J Gen Pract. 2013;63(606):e76-84.
12. Hojat M, Louis DZ, Markham FW, Wender R, Rabinowitz C, Gonnella JS. Physicians' empathy and clinical outcomes for diabetic patients. Acad Med. 2011;86(3):359-64.
13. Wang H, Kline JA, Jackson BE, Laureano-Phillips J, Robinson RD, Cowden CD, et al. Association between emergency physician self-reported empathy and patient satisfaction. PLoS One. 2018;13(9):e0204113.
14. Smith DD, Kellar J, Walters EL, Reibling ET, Phan T, Green SM. Does emergency physician empathy reduce thoughts of litigation? A randomised trial. Emerg Med J. 2016;33(8):548-52.
15. Yuguero O, Ramon Marsal J, Esquerda M, Vivanco L, Soler-González J. Association between low empathy and high burnout among primary care physicians and nurses in Lleida, Spain. Eur J Gen Pract. 2017;23(1):4-10.
16. Ozturk M, Demirci H. Turkish validation of the Jefferson scale of empathy for nurses seeking kidney donations in intensive care units. Aging Male. 2020;23(5):564-70.
17. Sharobeam A, Jones B, Walton-Sonda D, Lueck CJ. Factors delaying intravenous thrombolytic therapy in acute ischaemic stroke: a systematic review of the literature. J Neurol. 2021;268(8):2723-34.
18. Yuguero O, Marsal JR, Esquerda M, Soler-González J. Occupational burnout and empathy influence blood pressure control in primary care physicians. BMC Fam Pract. 2017;18(1):63.
19. Ozcakir A, Ediz B, Bilgel N. The relationship between subjective well-being and empathy among Turkish medical students. MedEdPublish. 2016;5:59.
20. Kesbakhi MS, Rohani C, Mohtashami J, Nasiri M. Empathy from the perspective of oncology nurses. J Compassionate Health Care. 2017;4:7.
21. Penšek L, Selič P. Empathy and burnout in Slovenian family medicine doctors: the first presentation of Jefferson scale of empathy results. Zdr Varst. 2018;57(3):155-65.
22. Hojat M, Gonnella JS. Eleven years of data on the Jefferson scale of empathy-medical student version (JSE-S): proxy norm data and tentative cutoff scores. Med Princ Pract. 2015;24(4):344-50.
23. Hojat M, Gonnella JS, Nasca TJ, Mangione S, Veloksi JJ, Magee M. The Jefferson scale of physician empathy: further psychometric data and differences by gender and specialty at item level. Acad Med. 2002;77(10 Suppl):S58-60.
24. Wolfshohl JA, Bradley K, Bell C, Bell S, Hodges C, Knowles H, et al. Association between empathy and burnout among emergency medicine physicians. J Clin Med Res. 2019;11(7):532-8.
25. Seo JW, Park KH, Park HY, Sun KH, Park SY, Kim TH, et al. Empathy and quality of life in Korean emergency physicians. J Korean Soc Emerg Med. 2016;27(2):150-6.

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Endovascular Treatment of Acute Renal Artery Hemorrhages: Efficacy and Effect on Renal Functions

Akut Renal Arter Kanamalarında Endovasküler Tedavi: Etkinliği ve Böbrek Fonksiyonlarına Etkisi

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ABSTRACT

Aim: The aim of this study was to investigate the efficacy and complications of endovascular treatment of acute renal artery hemorrhage and the etiology of the condition.
Material and Methods: Twenty-two patients who underwent endovascular embolization with renal acute artery hemorrhage between 2016 and 2020 were evaluated retrospectively. Etiologies of the acute renal artery hemorrhage were investigated. Laboratory and clinical follow-up information were analyzed for the efficacy and the complication of the treatment. The serum creatinine levels of the patients before and after the procedure were compared.
Results: Selective renal artery embolization procedures were performed in a total of 22 patients. Of the 22 patients, 10 (45.5%) were male and 12 (54.5%) were female. The patients' ages ranged from 5 to 79 years, and the mean age of the patients was 51.5±18.6 years. Clinical success was achieved in 91.7% of embolization procedures. A statistically significant increase was seen in the serum creatinine levels of the patients after the procedure compared to 24 hours before the angiography procedure (median: 0.97 vs. 0.93, p=0.046). No significant change was observed in serum blood urea nitrogen and the estimated glomerular filtration rate levels (p=0.338, and p=0.067, respectively). Acute renal failure and postembolization syndrome were observed in only one patient as complications. The complication rate was found to be 4.5%.
Conclusion: Selective embolization of the renal artery has high clinical success in acute renal artery hemorrhages without impairing renal function. The treatment has advantages such as no need for general anesthesia, and low complication rates.
Keywords: Embolisation; bleeding; endovascular; renal angiography; renal artery.

ÖZ

Amaç: Bu çalışmanın amacı akut renal arter kaynaklı hemorajilerin endovasküler tedavisinin etkinliğini ve komplikasyonlarını ile kanamaya neden olan etiyolojiyi araştırmaktır.
Gereç ve Yöntemler: 2016 ve 2020 yılları arasında akut renal arter kanaması nedeni ile endovasküler embolizasyon yapılan yirmi iki hasta geriye dönük olarak değerlendirildi. Akut renal arter hemorajisinin etiyolojisi araştırıldı. Tedavinin etkinliği ve gelişen komplikasyonlar için laboratuvar ve klinik takip bilgileri analiz edildi. Hastaların işlem öncesi ve işlem sonrası serum kreatinin düzeyleri karşılaştırıldı.
Bulgular: Toplam 22 hastaya selektif renal arter embolizasyonu işlemi uygulandı. Bu 22 hastanın 10 (%45,5) tanesi erkek ve 12 (%54,5) tanesi kadın idi. Hastaların yaşları 5 ile 79 yıl arasında değişmekteydi ve hastaların ortalama yaşı 51,5±18,6 yıl olarak saptandı. Embolizasyon işlemlerinin %91,7'sinde klinik başarı sağlandı. Hastaların işlem sonrasındaki serum kreatinin düzeylerinde, anjiyografi işleminden 24 saat öncesine göre istatistiksel olarak anlamlı bir artış görüldü (ortanca: 0,97'ye karşı 0,93; p=0,046). Serum kan üre nitrojeni ve tahmini glomerüler filtrasyon hızı düzeylerinde anlamlı bir değişiklik gözlenmedi (sırasıyla p=0,338 ve p=0,067). Komplikasyon olarak sadece bir hastada akut böbrek yetmezliği ve postembolizasyon sendromu izlendi. Komplikasyon oranı %4,5 olarak bulundu.
Sonuç: Akut renal arter kanamalarında renal arterin selektif embolizasyonu renal fonksiyonlarda bozulmaya neden olmadan yüksek bir klinik başarıya sahiptir. Tedavinin genel anesteziye gerek olmaması ve düşük komplikasyon oranları gibi avantajları vardır.
Anahtar kelimeler: Embolizasyon; kanama; endovasküler; renal anjiyografi; renal arter.

INTRODUCTION

The kidneys are one of the organs with a high blood supply. Although hemorrhages originating from the renal artery are not frequently seen, they can be life-threatening. The most common reasons include spontaneous rupture of renal tumors, trauma, and iatrogenic causes. Renal artery bleeding for iatrogenic reasons may be associated with major surgical procedures or may occur after minimally invasive procedures such as nephrostomy or renal biopsy. Most minor bleeding resolves with a conservative approach but a very small proportion may require an interventional procedure (1).

Although surgical procedures such as partial nephrectomy or radical nephrectomy have a place in the treatment of acute hemorrhages of renal artery origin, the less invasive method of selective renal artery embolization has started to be used in treatment more frequently. Despite the advantage of being able to make a pathological diagnosis by obtaining a specimen in surgical treatment, there are advantages to endovascular treatment such as a shorter stay in hospital and most importantly, greater protection of the nephron (2). However, complications can be observed in endovascular embolization such as non-target embolizations and associated nephron loss (3).

We aimed to investigate the efficacy and complications of endovascular treatment of acute renal artery hemorrhage and the etiology of the condition. We also investigated the effect of the procedure on renal functions.

MATERIAL AND METHODS

Approval for the study was granted by the Hatay Mustafa Kemal University Non-interventional Clinical Research Ethics Committee (dated 17.06.2021, and numbered 16). Patients who underwent renal artery embolization in the Hatay Mustafa Kemal University Interventional Radiology Unit were evaluated retrospectively. Acute renal artery hemorrhages causing impaired hemodynamics and laboratory results were accepted as inclusion criteria. Elective renal embolizations, such as unruptured angiomyolipoma or renal cell carcinoma, were excluded from the study. After inclusion and exclusion criteria 22 patients who underwent super-selective renal artery embolization between 2016 and 2020 in the Hatay Mustafa Kemal University Interventional Radiology Unit were included in the study.

The etiologies causing the hemorrhages were investigated. To evaluate the success of the treatment, the laboratory and clinical follow-up data were examined at least 6 months after the procedure. Patients with follow-up of less than one month were excluded from the study. The embolising agent and methods used in treatment were recorded. The pre and post-procedure urea and creatinine values of the patients were compared. Thus, the patients were evaluated in respect of acute renal failure which can develop secondary to endovascular treatment.

Before the angiography procedure, the extent of bleeding was investigated by abdominal computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US) examinations. Renal artery images were obtained in all patients with a 5 French (Fr) diagnostic catheter entered via the femoral route. One vial of contrast agent (Kopaq, 350 mg/mL, Onko-Kocsel, Istanbul, Turkey) was diluted 1/2 with physiological saline for angiography. After the determination of pathologies causing the hemorrhage (pseudoaneurysm, arteriovenous fistula, tumoral vascularity), this localization was super selectively entered with a 1.9 Fr or 2.4 Fr microcatheter. Depending on the pathology causing the bleeding, particle embolising agent (Embozene, CeloNova Biosciences, Newnan, Georgia, USA), liquid embolising agents (Lipiodol, Guerbet, Princeton, USA) or detachable microcoil (Blockade/Balt, Montmorency, France) were used (Figure 1).

Blood samples were taken from the patients within 24 hours before the angio and 24 hours after the procedure, and comparisons were made of blood urea nitrogen (BUN) and creatinine values and the estimated glomerular filtration rate (eGFR) calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Statistical Analysis

Data obtained in the study were analyzed statistically using IBM SPSS v.25 software. The conformity of continuous variables to normal distribution was assessed with visual (histogram) and analytical methods (Shapiro-Wilk test, Kolmogorov-Smirnov test). As variables did not show normal distribution, the descriptive statistics were stated using median, interquartile range, and minimum-maximum values. The Wilcoxon signed ranks test was applied in the comparisons of continuous variables not showing normal distribution measured at different time points. Correlations between numerical variables were evaluated using Spearman rank correlation analysis. A value of $p<0.05$ was accepted as statistically significant.

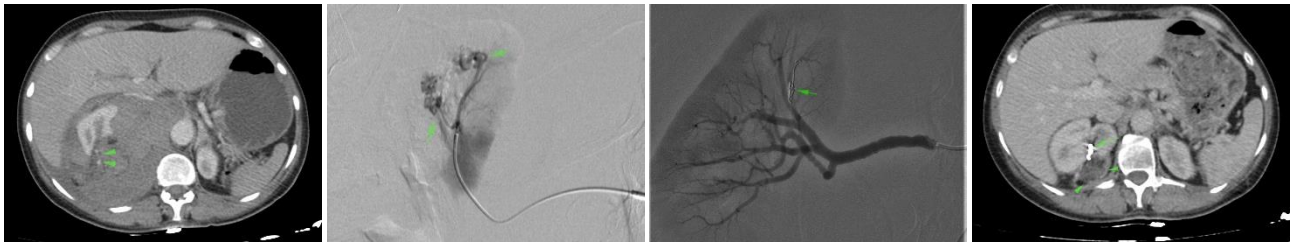

Figure 1. A) Axial section CT image of the patient admitted to the emergency department with acute abdominal pain. A large hematoma with active extravasation in the upper pole of the right kidney (arrows) is observed. **B)** In the renal artery angiography examination performed under emergency conditions; super selective images taken from the upper pole of the right renal artery show tumoral vascularity (arrows) due to angiomyolipoma in the upper pole of the right kidney. **C)** Postembolization angiography image showed the tumor was embolized completely with the coil (arrows) super selectively. **D)** In the control CT image of the patient 3 months later, it is seen that the coils (arrows) in the right kidney near the angiomyolipoma (arrowheads) and the hematoma disappeared after the embolization procedure.

RESULTS

In the Interventional Radiology Unit between 2016 and 2020, selective renal artery embolization procedures were applied to a total of 22 patients. The patients' ages ranged from 5 to 79 years, and the mean age of the patients was 51.5±18.6 years. Of the 22 patients, 10 (45.5%) were male and 12 (54.5%) were female. Of the 22 patients, the etiology of the hemorrhage was determined as ruptured angiomyolipoma in 9 (40.9%), percutaneous stone surgery in 6 (27.2%), percutaneous nephrostomy in 1 (4.5%), open stone surgery in 1 (4.5%), polycystic kidney disease in 1 (4.5%), and blunt trauma in 4 (18.2%).

Of the 4 patients with continuing hemorrhage, the procedure was converted to nephrectomy in 2 (9.1%). One of the patients who underwent nephrectomy had bleeding due to open stone surgery and the other due to angiomyolipoma rupture. Although the renal artery branches that cause bleeding in these patients were embolized super selectively, there was a decrease in hemoglobin values in the follow-up of the patients. However, both patients did not accept the re-embolization procedure. In the other 2 (9.1%) patients, the patient with polycystic kidney disease and a patient with abundant bleeding associated with iatrogenic causes, the embolization procedure was repeated and the bleeding was brought under control. Renal artery hemorrhages were treated with super-selective embolization in 22 of 24 procedures, with a clinical success of 91.7%. In one patient with tuberosclerosis and giant angiomyolipoma covering both kidneys, the serum creatinine level was high (1.8 mg/dl) at the start of the procedure, and after the procedure, acute kidney failure developed which required hemodialysis. During the subsequent follow-up, there was seen no longer a need for dialysis. In the same patient, pain and subfebrile fever lasting less than 24 hours were observed associated with the postembolisation syndrome. Acute renal failure was not observed in any other patient. The complication rate of the whole cohort was determined to be 4.5%. The etiologies of the patients, the embolic agents used, clinical success, and complications are shown in Table 1.

Angiography findings were seen as tumoral vascularity in 9 (40.9%) patients, active extravasation in 1 (4.5%) patient, pseudoaneurysm in 5 (22.7%) patients, arteriovenous fistula in 2 (9%) patients, and pseudoaneurysm together with arteriovenous fistula in 4 (18.2%) patients (Table 2). Accessory renal artery was not observed in any patient.

As findings suggestive of hemorrhage were not observed on the first angiography of the patient with polycystic kidney disease, Technetium-labelled (Tc-99m) erythrocyte scintigraphy was applied to the superior or

Table 2. Angiography findings in renal artery hemorrhages

Angiography findings	n (%)
Pseudoaneurysm	5 (22.7)
Arteriovenous fistula	2 (9.1)
Tumoral vascularity	9 (40.9)
Extravasation	1 (4.5)
Empiric	1 (4.5)
Pseudoaneurysm + Arteriovenous fistula	4 (18.2)

Table 1. Summary of patient characteristics, procedure details, and complications

No	Age/Gender	History	Embolic Agent	Additional Intervention	Clinical Success	Complication
1	41/M	PKD	Coils, 2nd time coils	TAE (4 days after 1st TAE)	Yes (2nd time)	No
2	60/F	Ruptured AML	Particles 100-200 µm	No	Yes	No
3	76/M	PNL	Coils	No	Yes	No
4	79/F	PNL	Coils	No	Yes	No
5	58/M	PN	Coils	No	Yes	No
6	73/F	PNL	Coils	No	Yes	No
7	68/F	Ruptured AML	Particles 200-400 µm	No	Yes	No
8	27/F	PNL	Coils	No	Yes	No
9	24/M	Blunt trauma	Coils	No	Yes	No
10	48/F	Ruptured AML	Particles 200-400 µm, Coils	No	Yes	No
11	37/M	Blunt trauma	Coils	No	Yes	No
12	51/M	Open stone surgery	Coils	Yes (Nephrectomy)	No	No
13	51/F	Ruptured AML	Particles 200 µm, Coils	No	Yes	No
14	59/M	Ruptured AML	Particles 400 µm, Coils	No	Yes	No
15	54/F	Ruptured AML	Particles 400 µm, Coils	Yes (Nephrectomy)	No	No
16	42/M	Tuberous sclerosis	Particles 400 µm, Coils	No	Yes	Yes (PES, AKI)
17	32/M	Blunt trauma	Coils	No	Yes	Yes
18	74/M	PNL	Lipiodol-glue	No	Yes	No
19	56/F	Ruptured AML	Particles 200 µm, Coils	No	Yes	No
20	63/F	Ruptured AML	Lipiodol-glue	No	Yes	No
21	5/F	Blunt trauma	Coils	No	Yes	No
22	55/F	PNL	Coils, 2nd time lipiodol-glue	TAE (8 days after 1st TAE)	Yes (2nd time)	Yes (AKI)

M: male, F: female, AKI: acute kidney injury, AML: angiomyolipoma, PES: postembolisation syndrome, PKD: polycystic kidney disease, PN: percutaneous nephrostomy, PNL: percutaneous nephrolithotomy, TAE: transarterial embolization

inferior pole localization of the bleeding kidney. According to the scintigraphy result, empirical embolization was performed without angiography findings of the pole of the bleeding kidney. No hemorrhage was observed during the follow-up of this patient.

A statistically significant increase was seen in the serum creatinine levels of the patients after the procedure compared to 24 hours before angiography (p=0.046). The change in serum creatinine levels after the angiography procedure showed no significant difference according to the patients' genders (p=0.488) and was not correlated with age (r_s=-0.233, p=0.296). No significant change was observed in serum BUN (p=0.338) and eGFR (p=0.067) levels (Table 3).

Table 3. Comparison of renal function tests of the cases before and after angiography

	Pre-Angiography	Post-Angiography	p
BUN, mg/dl	15.60 (12.00-16.20) [8.0-56.0]	13.90 (9.10-15.01) [8.4-52.0]	0.338
Creatinine, mg/dl	0.93 (0.67-1.16) [0.42-5.88]	0.97 (0.69-1.40) [0.41-6.09]	**0.046**
eGFR, ml/min	82.00 (61.28-103.55) [9.77-164.39]	77.82 (54.00-103.05) [9.36-164.39]	0.067

BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, continuous variables were expressed as the median (25^{th} - 75^{th} quartiles) [minimum-maximum] values

DISCUSSION

In this study, we aimed to investigate the efficacy and complications of endovascular treatment of acute renal artery bleeding and the etiology of the condition. We also investigated the effects of super-selective renal artery embolization on kidney functions. The clinical success of selective renal artery embolization has been reported to be 85%-94% (4,5). Clinical success was achieved in 91.6% who underwent embolization in this study. This rate is similar to other studies in the literature. Although 4 of the patients had recurrent bleeding after the first procedure, clinical success was achieved by re-embolization in only 2 of these patients. A nephrectomy was performed in the remaining 2 patients. One of the patients who underwent nephrectomy had bleeding due to open stone surgery and the other due to angiomyolipoma rupture. Although the renal artery branches that cause bleeding in these patients were embolized super selectively, there was a decrease in hemoglobin values in the patients' follow-up. However, both patients did not accept the re-embolization procedure. We attribute the failure of the first procedure to the fact that vasospasm developing secondary to acute bleeding prevents the visibility of the bleeding arteries. Acute renal failure and postembolization syndrome were observed in only one patient as complications. The complication rate was found to be 4,5%. The most frequently seen complication is a post-embolization syndrome which progresses with pain, fever, and nausea (5). The majority of complications associated with renal artery embolization are self-limiting without the need for additional treatment. Although uncommon, arterial dissection, abscess formation and urinary infection, hypertension, and renal dysfunction are other complications which may be seen after embolization (2). In a previous study that investigated complications associated with renal artery embolization, the procedure was reported to be safe in respect of renal function disorder and hypertension (3).

Reasons for hematuria of renal artery origin include iatrogenic causes such as nephrostomy, biopsy, percutaneous stone surgery, and partial nephrectomy; abdominal trauma, and tumor ruptures, primarily angiomyolipoma. Hemorrhages associated with renal artery injuries are seen with clinical and laboratory findings such as side pain, hematuria, tachycardia, and falls in hemoglobin and blood pressure levels (2). When these hemorrhages are not treated, they can be life-threatening (6).

The prevalence of minimally invasive kidney surgery also increases the frequency of post-surgical renal artery injuries (6). While the majority of renal artery hemorrhages associated with surgical procedures such as percutaneous stone surgery and partial nephrectomy are self-limiting, approximately 5% of these will require an interventional procedure (6,7). Selective renal artery embolization is a safe and effective method in the treatment of post-surgical bleeding (8). In a study, a success rate of 95% was achieved after endovascular treatment of 22 patients with renal artery injury after percutaneous stone surgery (9). Of the 22 patients who received endovascular treatment in this study, iatrogenic causes were determined in 8 (%36.3).

Urinary system injuries occur in approximately 10% of abdominal traumas (10). It has been reported that approximately 10% of renal traumas may require an embolization procedure and up to 5% progress to nephrectomy (11). Renal artery embolization has high success rates, especially in low-grade kidney trauma (2). Endovascular treatment is recommended if active renal artery bleeding is detected in grade II and III kidney injuries according to the American Association for Surgery of Trauma (AAST) scoring (12). Even in hemodynamically unstable patients, super-selective renal artery embolization may be one of the treatment modalities of choice in experienced centers (13). The rates of post-traumatic nephrectomy have been reported to be between 5-12% in different studies (14,15). Endovascular treatments with super-selective approaches can preserve more nephrons, while high clinical success can be achieved. It was reported in a study that compared nephrectomy and angioembolisation, that endovascular embolization treatments are an effective and safe method in patients with high-grade kidney injuries (16). In the current study, renal artery injury associated with trauma was determined in 4 (18.1%) patients. Clinical success has been achieved in all trauma patients treated endovascularly.

Angiomyolipoma rupture is prominent in the etiology of renal artery hemorrhages. Although there are no clear data about the frequency of angiomyolipoma hemorrhage, rates of 0.4%-2.5% have been reported in the literature (17,18).

Spontaneous perirenal hemorrhage was reported to be caused by angiomyolipoma at the rate of approximately 20-40% and by renal cell carcinoma at approximately 25-35% (19). In the current study, angiomyolipoma rupture was determined to be the cause of hemorrhage in 9 (40.9%) patients. In a study which compared 42 patients treated with surgery with 17 patients treated with embolization, it was reported that 60% (25/42) of the surgically treated patients progressed to radical nephrectomy and 40% (17/42) to partial nephrectomy (20). Clinical success was achieved in 8 (88.9%) of 9 patients with bleeding due to angiomyolipoma rupture.

Surgical treatment is among the options for the treatment of hemorrhages of renal artery origin. Radical nephrectomy is an extremely invasive method in the treatment of renal artery origin hemorrhages, which are usually associated with benign causes. Although surgical treatment has the advantage of being able to make a pathological diagnosis by taking a specimen, endovascular treatment has started to be more preferred in renal artery injuries as there is less renal parenchyma loss (21,22). In a previous study, it was reported that selective renal artery embolization should be the treatment method first selected for hemorrhages that are not self-limiting or that are life-threatening (3). This method also has the advantages of being minimally invasive, not requiring general anesthesia, having fewer complications, and providing greater protection of the nephron (4,23).

Renal dysfunction does not occur when 34% of the total embolized area is exceeded. (24). There are also studies that have emphasized that in patients where there are concerns of acute renal failure, the chance of endovascular treatment should not be delayed (24). In the current study, although there was a slight increase in the creatinine values after the procedure compared to before (from 0.93 to 0.97), no significant difference was observed in the eGFR measurements, which are an important marker of kidney function. A patient with tuberous sclerosis (patient no. 16) with giant angiomyolipomas covering both kidneys developed acute renal failure requiring hemodialysis after the procedure. However, this patient had elevated creatinine levels (1.8 mg/dl) before the procedure. On the 9th day of follow-up, the creatinine levels had decreased to the pre-procedure levels and there was no longer any requirement for hemodialysis. As giant angiolipomas were covering almost all the renal parenchyma in both kidneys, this was accepted as a predisposing factor for renal failure in this patient. Acute renal failure was not observed in any other patient in this series.

Our study has some limitations such as the small number of patients and its retrospective nature. While investigating the effect of endovascular treatment on kidney functions as blood tests were used, separate information about the functions of the right and left kidneys could not be obtained.

CONCLUSION

Selective embolization of the renal artery has high clinical success rates in the treatment of acute renal artery hemorrhages. There are also the advantages of there being no requirement for general anesthesia, low complication rates, and the potential for greater protection of the nephron.

Ethics Committee Approval: The study was approved by the Non-interventional Clinical Research Ethics Committee of Hatay Mustafa Kemal University (17.06.2021, 16).

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REFERENCES

1. Poyraz N, Balasar M, Gökmen İE, Koç O, Sönmez MG, Aydın A, et al. Clinical efficacy and safety of transcatheter embolization for vascular complications after percutaneous nephrolithotomy. Wideochir Inne Tech Maloinwazyjne. 2017;12(4):403-8.
2. Muller A, Rouvière O. Renal artery embolization-indications, technical approaches and outcomes. Nat Rev Nephrol. 2015;11(5):288-301.
3. Sam K, Gahide G, Soulez G, Giroux MF, Oliva VL, Perreault P, et al. Percutaneous embolization of iatrogenic arterial kidney injuries: safety, efficacy, and impact on blood pressure and renal function. J Vasc Interv Radiol. 2011;22(11):1563-8.
4. Öcal O, Puhr-Westerheide D, Mühlmann M, Deniz S, Fabritius MP, Weinhold P, et al. iRESCUE - Interventional embolization of Renal artEries after SurgiCal or traUmatic injury with hEmorrhage. Eur J Radiol. 2021;136:109540.
5. Murray TE, Doyle F, Lee M. Transarterial embolization of angiomyolipoma: a systematic review. J Urol. 2015;194(3):635-9.
6. Inci K, Cil B, Yazici S, Peynircioglu B, Tan B, Sahin A, et al. Renal artery pseudoaneurysm: complication of minimally invasive kidney surgery. J Endourol. 2010;24(1):149-54.
7. Jain S, Nyirenda T, Yates J, Munver R. Incidence of renal artery pseudoaneurysm following open and minimally invasive partial nephrectomy: a systematic review and comparative analysis. J Urol. 2013;189(5):1643-8.
8. Hong Y, Xiong L, Ye H, An L, Huang X, Xu Q. Outcome of selective renal artery embolization in managing severe bleeding after percutaneous nephrolithotomy. Urol Int. 2020;104(9-10):797-802.
9. Jinga V, Dorobat B, Youssef S, Radavoi GD, Braticevici B, Filipoiu F, et al. Transarterial embolization of renal vascular lesions after percutaneous nephrolithotomy. Chirurgia (Bucur). 2013;108(4):521-9.
10. Morey AF, Brandes S, Dugi DD 3rd, Armstrong JH, Breyer BN, Broghammer JA, et al. Urotrauma: AUA guideline. J Urol. 2014;192(2):327-35.
11. Sauk S, Zuckerman DA. Renal artery embolization. Semin Intervent Radiol. 2011;28(4):396-406.
12. Salcedo A, Ordoñez CA, Parra MW, Osorio JD, Leib P, Caicedo Y, et al. Damage Control for renal trauma:

the more conservative the surgeon, better for the kidney. Colomb Med (Cali). 2021;52(2):e4094682.
13. Bryk DJ, Zhao LC. Guideline of guidelines: a review of urological trauma guidelines. BJU Int. 2016;117(2):226-34.
14. Salem MS, Urry RJ, Kong VY, Clarke DL, Bruce J, Laing GL. Traumatic renal injury: Five-year experience at a major trauma centre in South Africa. 2020;51(1):39-44.
15. Sarang B, Raykar N, Gadgil A, Mishra G, Wärnberg MG, Rattan A, et al. Towards Improved Trauma Care Outcomes TITCO-India. Outcomes of renal trauma in Indian urban tertiary healthcare centres: a multicentre cohort study. World J Surg. 2021;45(12):3567-74.
16. Sarani B, Powell E, Taddeo J, Carr B, Patel A, Seamon M, et al. Contemporary comparison of surgical and interventional arteriography management of blunt renal injury. J Vasc Interv Radiol. 2011;22(5):723-8.
17. Bhatt JR, Richard PO, Kim NS, Finelli A, Manickavachagam K, Legere L, et al. Natural history of renal angiomyolipoma (AML): most patients with large AMLs >4cm can be offered active surveillance as an initial management strategy. Eur Urol. 2016;70(1):85-90.
18. Ouzaid I, Autorino R, Fatica R, Herts BR, McLennan G, Remer EM, et al. Active surveillance for renal angiomyolipoma: outcomes and factors predictive of delayed intervention. BJU Int. 2014;114(3):412-7.
19. Liu L, Wu R, Xia Y, Wang J, Xiong Y, Qu Y, et al. A preliminary study on classification and therapeutic strategies for spontaneous perirenal hemorrhage. Int J Surg. 2018;54(Pt A):86-91.
20. Faddegon S, So A. Treatment of angiomyolipoma at a tertiary care centre: the decision between surgery and angioembolization. Can Urol Assoc J. 2011;5(6):E138-41.
21. Regine R, Palmieri F, De Siero M, Rescigno A, Sica V, Cantarela R, et al. Embolization of traumatic and non-traumatic peripheral vascular lesions with Onyx. Interv Med Appl Sci. 2015;7(1):22-9.
22. Sayani R, Azeemuddin M, ul Haq T, Hamid RS, Salam B. An institutional review of transarterial embolization in haemorrhagic urological emergencies. J Pak Med Assoc. 2012;62(2):107-11.
23. Strobl FF, D'Anastasi M, Hinzpeter R, Franke PS, Trumm CG, Waggershauser T, et al. Renal pseudoaneurysms and arteriovenous fistulas as a complication of nephron-sparing partial nephrectomy: technical and functional outcomes of patients treated with selective microcoil embolization during a ten-year period. Rofo. 2016;188(2):188-94.
24. Piasecki P, Ząbkowski T, Brzozowski K, Narloch J, Zięcina P, Dziuk M, et al. The assessment of the risk of acute kidney injury in patients undergoing an urgent endovascular treatment due to severe renal bleeding. Cardiovasc Intervent Radiol. 2018;41(3):398-405.

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The Relationship of Thyroid Hormone Levels and Motor Symptoms in Parkinson's Disease

Parkinson Hastalığında Motor Semptomların Tiroid Hormon Seviyeleri ile İlişkisi

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ABSTRACT

Aim: This study aimed to investigate the relationship between thyroid hormone levels and the motor symptoms of Parkinson's patients.
Material and Methods: Neurology clinic logs of the patients diagnosed with Parkinson's disease and whose thyroid function tests were measured between 01.01.2018 and 01.04.2021 were selected. Those with primary thyroid hormone disorder were excluded. Motor symptom stages were determined according to the modified Hoehn and Yahr scale (mHYS) by records. According to the thyroid function test results, whether there was a difference in motor symptoms, duration of the disease, and effects of the drugs were examined.
Results: Of the 93 patients included in the study, 53 (57.0%) were male and 40 (43.0%) were female. The median age of the patients was 71 years. The motor symptoms of the patients were classified as stage 1 in 21 (22.6%), stage 1.5 in 18 (19.4%), stage 2 in 29 (31.2%), stage 2.5 in 13 (14.0%), stage 3 in 4 (4.3%), stage 4 in 6 (6.5%), and stage 5 in 2 (2.2%) patients. The median levels of TSH, fT3, and fT4 were 2.075 uIU/ml, 2.925 ng/dl, and 1.235 ng/dl, respectively. There was no significant correlation between the mHYS stages of the patients and TSH (r=-0.148, p=0.164), fT3 (r=-0.073, p=0.623), and fT4 levels (r=0.075, p=0.491).
Conclusion: There was no relationship between the severity of motor symptoms and hormone levels in patients with normal thyroid functions. Thyroid dysfunction may mimic many motor findings, but they do not affect the severity of motor findings in Parkinson's patients.
Keywords: Parkinson's disease; motor symptoms; thyroid functions.

ÖZ

Amaç: Bu çalışmanın amacı Parkinson hastalarının tiroid hormon seviyeleri ile motor semptomları arasındaki ilişkisinin araştırılmasıdır.
Gereç ve Yöntemler: 01.01.2018 ve 01.04.2021 tarihleri arasında Parkinson hastalığı tanısı almış olan ve tiroid fonksiyon testleri ölçülmüş olan hastaların nöroloji kliniği kayıtları seçildi. Primer tiroid hormon bozukluğu tanısı olanlar dışlandı. Kayıtlar incelenerek modifiye Hoehn ve Yahr ölçeğine (modified Hoehn and Yahr scale, mHYS) göre motor semptom evreleri belirlendi. Tiroid fonksiyon test sonuçlarına göre motor semptomlarda fark olup olmadığı, hastalık süresi ve ilaçların etkileri incelendi.
Bulgular: Çalışmaya dahil edilen 93 hastanın 53'ü (%57,0) erkek ve 40'ı (%43,0) kadın idi. Hastaların medyan yaşı 71 yıl idi. Hastaların motor semptomları 21 (%22,6) hastada evre 1, 18 (%19,4) hastada evre 1.5, 29 (%31,2) hastada evre 2, 13 (%14,0) hastada evre 2.5, 4 (%4,3) hastada evre 3, 6 (%6,5) hastada evre 4 ve 2 (%2,2) hastada evre 5 olarak sınıflandırıldı. Medyan TSH, fT3 ve fT4 düzeyleri sırasıyla 2,075 uIU/ml, 2,925 ng/dl ve 1,235 ng/dl idi. Hastaların mHYS evreleri ile TSH (r=-0,148; p=0,164), fT3 (r=-0,073; p=0,623) ve fT4 (r=0,075; p=0,491) düzeyleri arasında anlamlı bir korelasyon yoktu.
Sonuç: Tiroid fonksiyonları normal olan hastalarda motor semptomların şiddeti ve hormon seviyeleri arasında bir ilişki yoktur. Tiroid fonksiyon bozuklukları Parkinson hastalarındaki birçok motor bulguyu taklit edebilir, fakat motor bulgularının şiddetini etkilememektedir.
Anahtar kelimeler: Parkinson hastalığı; motor semptomlar; tiroid fonksiyonları.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative and progressive disease characterized clinically by bradykinesia, resting tremor, impaired postural reflexes, and rigidity (1). The essential criteria were determined by the Movement Disorders Association as bradykinesia with at least one of rigidity or resting tremor (2).

PD significantly impairs quality of life and prevents activities of daily living. The differential diagnosis of the disease involves some difficulties. These markers are easily accessible parameters and may be effective in differential diagnosis and in changing the severity of motor symptoms.

Thyroid hormones (TH) are formed by the binding of iodine to the amino acid tyrosine. The most synthesized hormone of the gland is thyroxine (T4), and the most active hormone is triiodothyronine (T3). For the continuity of metabolic events in the body, TH must be secreted continuously in a controlled manner (3). The efficacy of thyroxine is very doubtful and according to many researchers, it is seen as a precursor of T3. The main TH secreted by the thyroid gland is T4. Only 20% of the total plasma T3 is secreted by the thyroid gland, and the remaining 80% is formed as a result of deiodination of T4 in the periphery. Most of the T3 and T4 in plasma circulate bound to proteins. A smaller portion is free. They are the only free fractions that enter the cell and show bioactivity. Mutual adjustment with thyroid stimulating hormone (TSH) is also carried out by these free hormones (3).

Findings such as rigidity, bradykinesia, hypomemia, hypophonia, swallowing disorders, peripheral edema, respiratory problems, dementia symptoms, depression, sleep disorders, fatigue, weakness, constipation, orthostatic hypotension, sexual dysfunction seen in PD may also occur due to hypothyroidism. Tremor, anxiety disorders, panic disorder, excessive sweating, cramps, and paresthesia symptoms seen in PD are signs and symptoms that can also be seen in hyperthyroidism (4). Therefore, thyroid dysfunctions detected in the early period in PD patients will enable to distinguish similar signs and symptoms encountered in the clinic.

Although the relationship between PD and TH has been scientifically interesting and researched, studies have generally focused on the common features of diseases and the evaluation of impaired hormone levels, and the effect of TH levels on symptoms of PD has not been studied at a level to reach definitive conclusions (5).

In this study, we aimed to investigate whether TH levels are effective on motor symptoms in PD patients and to comment on whether the evaluation of thyroid function tests is necessary in the follow-up of PD.

MATERIAL AND METHODS

The study was carried out on the patient registration system data of Çanakkale Onsekiz Mart University Hospital. Ethics committee approval was obtained for the study from Çanakkale Onsekiz Mart University Ethics Committee for Clinical Studies with the decision number 08-02, dated November 03, 2021. The study population consisted of the patients included in the hospital registration system, and all existing records included.

Thyroid function test levels of those who were diagnosed with PD in the Neurology Clinic of Çanakkale Onsekiz Mart University Hospital between 01/01/2018 and 01/04/2021 were collected from the patient registry system. Those with a diagnosis of primary TH disorder were excluded. The oldest date was taken if thyroid function tests were measured more than once. Information on patients' motor symptom status, duration of illness, and medications were also collected from the hospital registry system.

Within the specified date range, 125 records matching the diagnostic features and thyroid function tests were examined. Thirty-two of the records (1 due to a past thyroid operation, 10 due to mismatch of diagnosis (3 secondary Parkinsonism (medication-induced), 1 vascular Parkinsonism, 6 Parkinson-plus syndromes), and 21 due to missing and inconsistent data were excluded from the study set. A total of 93 records were included in the study.

The modified Hoehn and Yahr scale (mHYS) is a widely used clinical rating scale for the coarse assessment of motor functions in PD. The scale provides a simple staging of the severity of bilateral motor involvement and the impairment of gait and balance. The scale was modified to include stages on the bilaterality of dysfunctions (6). Simple and easy to apply, it detects typical progressive motor deterioration patterns independent of patients' treatment. Progression in stages is associated with motor decline, deterioration in quality of life, and dopaminergic loss. It does not provide information on specific aspects of motor deficiency as well as non-motor aspects of PD (6). By examining the records of the patients, motor symptom stages were determined according to the mHYS.

Thyroid function tests of all patients were measured in the biochemistry laboratory of the hospital by electrochemiluminescence immunoassay (ECLIA) method on Roche Cobas 6000 (Roche Diagnostics, Mannheim, Germany) with the same brand kits. Laboratory normal standards are 0.27-4.20 uIU/ml for TSH, 2.00-4.40 ng/dl for free T3 (fT3), and 0.93-1.70 ng/dl for free T4 (fT4).

Statistical Analysis

The statistical analyses were performed with IBM SPSS Statistics for Windows, version 22. Assumptions of normality were controlled with the Kolmogorov-Smirnov test and non-parametric tests were used since none of the variables fit the normal distribution. Descriptive statistics were presented as the frequencies and percentages for categorical data, and with median, interquartile range, and minimum-maximum for numerical data. Mann-Whitney U and Spearman correlation tests were used for analyses. $p<0.05$ was accepted as the significance level.

RESULTS

Of the 93 patients included in the study, 53 (57.0%) were male and 40 (43.0%) were female. The median age of the patients was 71 (range, 39-89) years. Descriptive characteristics of the patients were given in Table 1. The median age of males was not significantly different from that of females (72 vs. 70, U=1559.0, p=0.052).

The median disease duration of the 93 patients included in the study was 4 (range, 1.5-22) years. The number of drugs used by patients was (minimum 1, maximum 4), one for 35 (37.6%) of them, two for 41 (44.1%) of them, three for 14 (15.1%) of them, and four drugs for 3 (3.2%) of them.

Fifty-seven (61.3%) of the patients were receiving levodopa treatment. There was no significant difference between the genders in terms of disease duration and the number of drugs (U=1048.5, p=0.496, and U=970.0, p=0.339, respectively). There was no significant correlation between the age of the patients, the duration of the disease, and the number of drugs they used (r=-0.056, p=0.588 and r=-0.057, p=0.587, respectively). There was a moderate positive correlation between the duration of the disease and the number of drugs used (r=0.316, p=0.002).
The motor symptoms were classified as stage 1 in 21 (22.6%), stage 1.5 in 18 (19.4%), stage 2 in 29 (31.2%), stage 2.5 in 13 (14.0%), stage 3 in 4 (4.3%), stage 4 in 6 (6.5%), and stage 5 in 2 (2.2%) patients according to the mHYS. There was no significant difference between the genders in terms of disease motor symptom stage (U=988.5, p=0.569). There was no significant correlation between the ages of the patients and the stage of motor symptoms (r=0.042, p=0.688). The motor symptom stage has a moderate positive correlation with the disease duration (r=0.430, p<0.001) and a weak positive correlation with the number of drugs used (r=0.242, p=0.019). Motor symptom stages were significantly higher in patients using Levopoda (U=630.0, p=0.001).
The descriptive statistics of TSH, fT3, and fT4 levels according to the patient records examined were given in Table 2. There was no significant difference between the genders in terms of TSH, fT3, and fT4 levels (U=1649.5, p=0.522, U=303.5, p=0.051, and U=1709.0, p=0.991, respectively). There was no significant correlation between the ages of the patients and their TSH and fT4 levels (r=-0.017, p=0.855, and r=0.016, p=0.861, respectively), while fT3 has a weak negative correlation with the age of patients (r=-0.272, p=0.037). There was no significant correlation between disease duration and TSH, fT3, and fT4 levels (r=-0.006, p=0.953, r=0.064, p=0.664, and r=0.096, p=0.374, respectively).
There was no significant correlation between the number of drugs used and TSH, fT3 and fT4 levels (r=-0.079, p=0.464, r=0.274, p=0.066, and r=0.051, p=0.643, respectively). Mean TSH, fT3 and fT4 levels were not significantly different between patients using and not using levodopa (U=873.5, p=0.645, U=209.5, p=0.242, and t=752.5, p=0.341, respectively).
The TSH values of the patients according to the mHYS motor symptom stages are given in Figure 1. There was no significant correlation between motor symptom stages and TSH, fT3, and fT4 levels (r=-0.148, p=0.164, r=-0.073, p=0.623, and r=0.075, p=0.491, respectively).

DISCUSSION

PD is usually observed in middle and advanced age and starts at the age of 50-60 on average and progresses over a period of 10-20 years. The annual incidence of PD is between 4.5-21/100000 (7). The diagnosis is principally clinical (2). The heterogeneous clinical picture includes motor subtypes as 'tremor dominant', 'postural instability and gait difficulty', or 'indeterminate'. The main clinical features of the disease can be listed as rigidity, flexion posture, loss of postural reflexes, resting tremor, bradykinesia, and the phenomenon of freezing (2).
Neuronal cell loss and appearance of Lewy bodies in substantia nigra are known as pathological determinants of sporadic PD. Nigrostriatal dopaminergic loss has been shown to be closely related to the severity of the classical motor findings especially bradykinesia and rigidity (9). The etiopathogenesis of selective loss of dopamine neurons in PD is still unclear. However, growing evidence suggests that oxidative stress and inflammation play an important role in the degeneration of dopaminergic neurons in PD (10). Possible mechanisms are associated with vascular risk factors, mitochondrial dysfunction, genetic, environmental factors, apoptosis, and oxidative stress (11). Non-motor symptoms observed in IPD are anxiety, sexual dysfunction, sleep disorders, cognitive dysfunction, apathy, depression, and psychosis, and sometimes they may cause more problems than non-motor symptoms (12).
Thyroid diseases are the most common endocrine disorders associated with PD. Bradykinesia and hypomimia, which are also observed in Parkinson's patients, may mask hypothyroid symptoms. Hyperthyroidism may worsen tremor and mask the levodopa response. It has been reported that both subclinical and clinical hypo- and hyperthyroidism occur

Table 1. Descriptive characteristics of the patients

Gender, n (%)	
Male	53 (57.0%)
Female	40 (43.0%)
Age (years)	71 (66-78) [39-89]
Disease duration (years)	4 (3-6) [1.5-22]
Number of drugs, n (%)	
1 drug	35 (37.6%)
2 drugs	41 (44.1%)
3 drugs	14 (15.1%)
4 drugs	3 (3.2%)
Levodopa treatment, n (%)	57 (61.3%)

Descriptive statistics were presented as median (25^{th}-75^{th} percentile) [min-max]

Table 2. Descriptive statistics of TSH, fT3, and fT4 levels

	Median	Q1-Q3	min-max
TSH (uIU/ml), (n=92)	2.075	1.21-2.69	0.218-7.99
fT3 (ng/dl), (n=46)	2.925	2.51-3.17	1.75-4.18
fT4 (ng/dl), (n=85)	1.235	1.12-1.39	0.798-1.79

TSH: thyroid stimulating hormone, fT3: free triiodothyronine, fT4: free thyroxine, Q1-Q3: 25^{th}-75^{th} percentile

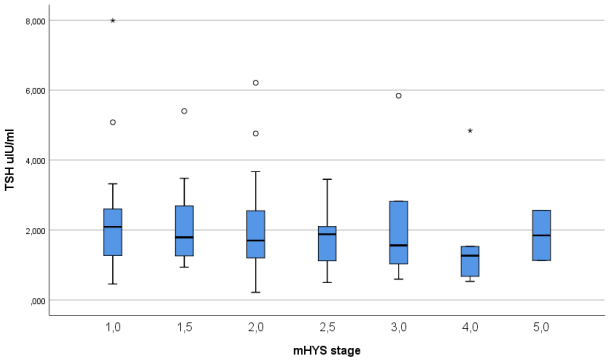

Figure 1. The TSH values of the patients according to the mHYS motor symptom stages
TSH: thyroid stimulating hormone, mHYS: modified Hoehn and Yahr scale

with PD. Thyroid hormones are important in the development and functioning of many organ systems, including the central nervous system. Thyroid function in advanced ages has been associated with the neurodegeneration process (13). High TH levels can cause oxidative stress by increasing basal metabolism and oxygen consumption. These effects are most pronounced in metabolically active organs such as the brain and have adverse effects on neuronal integrity (14).

Oxidative stress is important in the apoptosis of dopaminergic neurons and in the pathogenesis of PD. Increased oxidative stress is a risk factor for dopaminergic neuron degeneration in the early stages of PD (15). There is a mutual interaction between dopamine and thyrotropic hormone levels. Central dopamine deficiency in PD directly or indirectly leads to hormonal secretion disorders in the hypothalamo-pituitary pathway. Under normal conditions, dopamine modulates the hypothalamo-pituitary axis, increasing growth hormone secretion and decreasing prolactin secretion. Decreased prolactin levels also cause changes in TSH secretions (16). It has been reported that TSH levels can be decreased after levodopa treatment in Parkinson's patients, and low TSH levels detected in some PD patients were thought to be secondary to levodopa treatment (17). Even with significant fluctuations in circulation, brain T4 and T3 concentrations remain within a narrow range. This suggests that even slight changes in T4 may have consequences on CNS function (18).

The most common endocrine disorder associated with PD is thyroid disease. In addition to the fact that both hyperthyroidism and hypothyroidism are reported more frequently in PD patients than in healthy individuals, slightly increased fT4 levels are also observed in the early stages of the disease. The negative correlation between fT3 level and PD disease severity has been interpreted as patients with low fT3 levels may have a higher risk of developing serious disease. No results have been reported regarding the relationship of thyroid function to PH severity and motor symptoms in euthyroid patients (19).

Hypothyroidism is associated with PD motor symptom severity. fT3 levels have been shown to be lower in patients with the akinetic-rigid motor subtype than in patients with the tremor-predominant or mixed subtype. Patients with low thyroid hormone levels have symptoms of PD such as rigidity, hypokinesia, facial hypommia, and voice abnormalities. Hyperthyroidism exhibits clinical signs such as tremor, sweating, and weight loss experienced by many Parkinson's patients while exacerbating symptoms such as tremor and dyskinesia (20).

In this study, it was found that TH level did not affect the severity of motor findings in Parkinson's patients. This study gave us the opportunity to evaluate the effect of thyroid functions on PD motor symptoms from a different perspective. In many previous studies, the effects of thyroid dysfunctions on PD clinical findings were investigated and significant findings were obtained. In this study, the relationship between motor findings and thyroid function values in patients with normal thyroid function was investigated and it was found that it was not clinically related.

The main limitation of the study is that it was conducted in a cross-sectional design based on a single measurement. Therefore, the results do not reflect any changes that patients will experience throughout their disease process. Since the data belong to a single clinical center and representative power is not certain, care should be taken in generalizing the results. The study was carried out retrospectively using the available data from the hospital registry system. In this way, it was possible to evaluate the natural clinical course of the disease in the general clinical setting.

CONCLUSION

Although thyroid dysfunction is observed in more than 10% of Parkinson's patients, this rate was not different from the general population. Studies have generally focused on whether the frequency of thyroid dysfunction is different between Parkinson's patients and control groups. In this study, the relationship between normal differences in thyroid functions and motor functions in Parkinson's patients was investigated. Although thyroid dysfunctions and Parkinson's disease have similarities in the pathogenic mechanisms, causing difficulties in the clinical presentation and differential diagnosis, our results have shown that the differences in thyroid hormone levels that do not reach the level of disorder do not have a counterpart in the Parkinson's disease clinic. The main difference of this study from previous studies on this subject is that patients with normal thyroid hormone function were evaluated. These results revealed that when there is no clinical symptom in the follow-up of PD, control of thyroid hormone levels has no clinical benefit and the importance of hormone disorder is limited in the diagnostic work-up.

Ethics Committee Approval: The study was approved by the Clinical Researches Ethics Committee of Çanakkale Onsekiz Mart University (03.11.2021, 08/02).

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REFERENCES

1. Aygun D, Akpinar CK, Yon S, Onar MK. Effect of clinical autonomic dysfunction on cognitive functions in Parkinson’s disease. Dicle Med J. 2017;44(3):225-31.
2. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson’s disease. Mov Disord. 2015;30(12):1591-601.
3. Feldman AZ, Shrestha RT, Hennessey JV. Neuropsychiatric manifestations of thyroid disease. Endocrinol Metab Clin North Am. 2013;42(3):453-76.
4. Hayes MT. Parkinson's Disease and parkinsonism. Am J Med. 2019;132(7):802-7.

5. Mohammadi S, Dolatshahi M, Rahmani F. Shedding light on thyroid hormone disorders and Parkinson disease pathology: mechanisms and risk factors. J Endocrinol Invest. 2021;44(1):1-13.
6. Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, et al. Movement disorder society task force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord. 2004;19(9):1020-8.
7. Simon DK, Tanner CM, Brundin P. Parkinson disease epidemiology, pathology, genetics, and pathophysiology. Clin Geriatr Med. 2020;36(1):1-12.
8. Odabaş FÖ, Uca AU. The evaluation of quality of life of relatives caring for patients with Parkinson's disease. Dicle Med J. 2018;45(2):201-8.
9. Bülbül NG, Akbostancı MC. [Parkinson's disease and prodromal symptoms]. Parkinson Hast Harek Boz Derg. 2017;20(1-2):28-32. Turkish.
10. Yazar T, Olgun Yazar H. [Evaluation of C-reactive protein/albumin ratio according to stage in patients with idiopathic Parkinson disease]. Turk J Neurol. 2019;25(3):123-8. Turkish.
11. Geyik S, Yiğiter R, Akgül GP, Elçi MA, Ekmekyapar Fırat Y. [The relationship between Parkinson's disease and mean platelet volume]. Parkinson Hast Harek Boz Derg. 2016;19(1-2):31-4. Turkish.
12. Gürbüz M, Akdağ G, Arıcı Düz Ö, Özer F, Çokar Ö, Hanoğlu L. [Relation of apathy to motor and non-motor findings in Parkinson's disease]. Med Bull Haseki. 2019;57(2):129-34. Turkish.
13. Pasqualetti G, Pagano G, Rengo G, Ferrara N, Monzani F. Subclinical hypothyroidism and cognitive impairment: systematic review and meta-analysis. J Clin Endocrinol Metab. 2015;100(11):4240-8.
14. Villanueva I, Alva-Sánchez C, Pacheco-Rosado J. The role of thyroid hormones as inductors of oxidative stress and neurodegeneration. Oxid Med Cell Longev. 2013;2013:218145.
15. Wei Z, Li X, Li X, Liu Q, Cheng Y. Oxidative stress in Parkinson's Disease: a systematic review and meta-analysis. Front Mol Neurosci. 2018;11:236.
16. Kimber J, Watson L, Mathias CJ. Neuroendocrine responses to levodopa in multiple system atrophy (MSA). Mov Disord. 1999;14(6):981-7.
17. Gupta A, Haboubi N, Thomas P. Screening for thyroid dysfunction in the elderly. Arch Intern Med. 2001;161(1):130.
18. Stern RA, Davis JD, Rogers BL, Smith KER, Harrington CJ, Ott BR, et al. Preliminary study of the relationship between thyroid status and cognitive and neuropsychiatric functioning in euthyroid patients with Alzheimer dementia. Cogn Behav Neurol. 2004;17(4):219-23.
19. Tan Y, Gao L, Yin Q, Sun Z, Man X, Du Y, et al. Thyroid hormone levels and structural parameters of thyroid homeostasis are correlated with motor subtype and disease severity in euthyroid patients with Parkinson's disease. Int J Neurosci. 2021;131(4):346-56.
20. Kim JH, Lee HS, Ahn JH, Oh JK, Chang IB, Song JH, et al. Association between thyroid diseases and Parkinson's disease: a nested case-control study using a national health screening cohort. J Parkinsons Dis. 2021;11(1):211-20.

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While the Laparoscopic Appendectomy Is the Gold Standard in the Treatment of Acute Appendicitis, What Should Be the Preference for Closure of the Appendix Stump?

Akut Apandisit Tedavisinde Laparoskopik Apendektomi Altın Standart Olurken, Apendiks Kökünün Kapatılmasında Tercih Ne Olmalı?

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ABSTRACT

Aim: While laparoscopic appendectomy is the gold standard in the treatment of acute appendicitis, there is no consensus on reliable closure of the appendix stump. The aim of this study was to examine appendiceal stump closure techniques and their reliability during laparoscopic appendectomy.

Material and Methods: Between January 2019 and August 2021, 692 patients who underwent laparoscopic appendectomy with the diagnosis of acute appendicitis were included in the study. Demographic characteristics, length of hospital stay, pathology, appendix stump closure methods, operation time, complications, and cost results were analyzed retrospectively.

Results: Intracorporeal knotting (ICK) was used in 66.9% (n=463), and endoclip (EC) was used in 33.1% (n=229) of the patients. There was no statistically significant difference between the two groups in terms of length of hospital stay (p=0.054). While the mean operative time was 55.1±15.6 minutes in the ICK group, it was 45.7±16.5 minutes in the EC group (p<0.001). The general complication rate was 1.7% (n=12). While the complication rate was 2.2% (n=10) in ICK group, it was 0.9% (n=2) in EC group (p=0.354). While pericecal hematoma and ileus were seen only in the ICK group, the fistula was seen only in the EC group. EC was found to be more costly than ICK (p<0.001).

Conclusion: It was concluded that closure of the appendix stump with an EC in patients who underwent laparoscopic appendectomy is more useful, regardless of the severity of appendicitis, with a shorter operation time and shorter length of hospital stay, low complication rate, and ease of application.

Keywords: Appendectomy; laparoscopic surgery; postoperative complications.

ÖZ

Amaç: Akut apandisit tedavisinde laparoskopik apendektomi altın standart olurken, apendiks kökünün güvenilir bir şekilde kapatılması konusunda ise bir fikir birliği yoktur. Bu çalışmanın amacı laparoskopik apendektomi sırasında apendiks güdüğü kapatma tekniklerinin ve bu tekniklerin güvenilirliğinin incelenmesidir.

Gereç ve Yöntemler: Ocak 2019 ile Ağustos 2021 tarihleri arasında, akut apandisit tanısı ile laparoskopik apendektomi yapılmış olan 692 hasta bu çalışmaya dahil edildi. Demografik özellikler, hastanede kalış süresi, patoloji, apendiks kök kapatma yöntemleri, ameliyat süresi, komplikasyonlar ve maliyet sonuçları geriye dönük olarak analiz edildi.

Bulgular: Hastaların %66,9'unda (n=463) intrakorporeal düğümleme (intracorporeal knotting, ICK) yapılırken, %33,1'inde (n=229) ise endoklip (endoclip, EC) uygulandı. Hastanede kalış süresi bakımından iki grup arasında istatistiksel olarak anlamlı bir farklılık yoktu (p=0,054). Ortalama ameliyat süresi ICK grubunda 55,1±15,6 dakika iken, EC grubunda ise 45,7±16,5 dakika idi (p<0,001). Genel komplikasyon oranı %1,7 (n=12) idi. Komplikasyon oranı ICK grubunda %2,2 (n=10) iken, EC grubunda ise %0,9 (n=2) idi (p=0,354). Periçekal hematom ve ileus sadece ICK grubunda görülürken, fistül ise sadece EC grubunda görüldü. EC, ICK'ye göre daha maliyetli olarak bulundu (p<0,001).

Sonuç: Apandisit şiddeti ne olursa olsun, laparoskopik apendektomi yapılan hastalarda apendiks kökünün EC ile kapatılmasının, daha kısa ameliyat süresi ve daha kısa hastanede kalış süresi, düşük komplikasyon oranı ve uygulama kolaylığı ile daha faydalı olduğu sonucuna ulaşılmıştır.

Anahtar kelimeler: Apendektomi; laparoskopik cerrahi; postoperatif komplikasyonlar.

INTRODUCTION

Acute appendicitis (AA) is currently, as it has been in the past, the most common reason for acute abdominal pain in every age group. The lifetime risk of AA is 8.6% for males and 6.7% for females (1). Whilst 10% of the emergency department visits are abdominal pain, 1.9% of these cases are AA. Although the method of treatment for AA is a medical treatment for selected cases, the most common procedure is appendectomy (2). During appendectomy, the state of the appendix stump and its closure technique plays an important role in the safety of the appendix stump.

From the 19th century until recently, appendectomy was performed using the incision technique described by McBurney where the appendix stump is closed using non-absorbable sutures. Since the start of the practice of laparoscopic appendectomy (LA) in 1980, it has almost become the gold standard with its low surgical site infections, low postoperative pain, short length of stay (LOS) in hospital, and early back to work durations.

With that being said, techniques for closing the appendix stump vary. The most commonly employed closure techniques are endostapler, endoloop, intracorporeal knotting (ICK), titanium clips, polymeric clips, and electrothermal devices. Whilst endoloop and endoclip (EC) are similarly low-cost, lower operation durations have been detected in cases where the closure was made using an EC. Endostapler has the lowest perioperative complication rate (3.56%); however, its' usage is restricted by its' high cost. Postoperative complication rate and the length of hospital stay were detected to be similar for all stump-closure techniques (4). In this study, we aimed to retrospectively examine the ICK and EC results of the LAs we have performed in our clinic in the last two years.

MATERIAL AND METHODS

Our study started after the ethics committee approval of the University of Health Sciences Prof. Dr. Cemil Taşçıoğlu City Hospital Ethics Committee, dated 08.11.2021 and numbered 384. The patients with an AA diagnosis to whom LA was applied in our hospital's (University of Health Sciences, Prof. Dr. Cemil Taşçıoğlu City Hospital, İstanbul, Türkiye) emergency surgery department between the dates of 01.01.2019 and 01.08.2021 were included in the study. The patients who were subjected to open surgery and medical treatment and the patients whose stumps were closed by endoloop or stapler were excluded from the study. As a result, 692 patients were included in the study (Figure 1).

The demographic data of the patients, such as age and gender, the appendix closure techniques, the operation duration, the LOS, costs, and the morbidity and mortality rates were evaluated. The results of the closure techniques were compared statistically.

Laparoscopic appendectomy was performed with the Hasson technique with supraumbilical 10 mm, left-bottom quadrant, and suprapubic 5 mm trocars. Intra-abdominal pressure was set to 12 mmHg with CO_2 insufflation. Mesoappendix was separated from the appendix using electrocautery devices. As for the closure technique, the type of the EC used was polymeric hem-o-lock (Figure 2), the ICK was double-layered, and the suture material was 2-0 silk or 2-0 prolene (Figure 3).

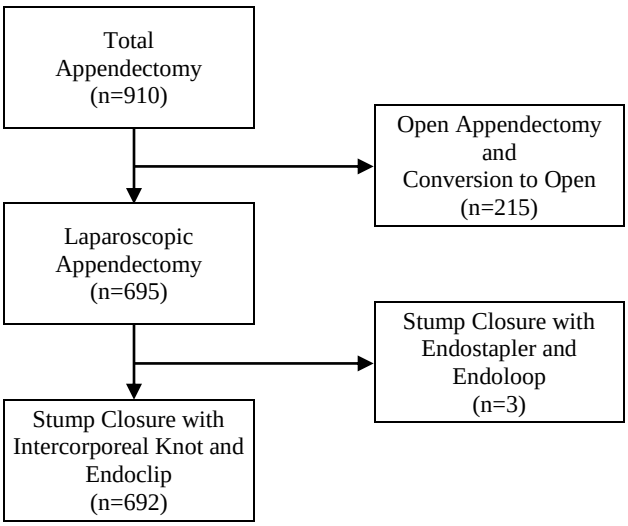

Figure 1. Including and excluding criteria of the study

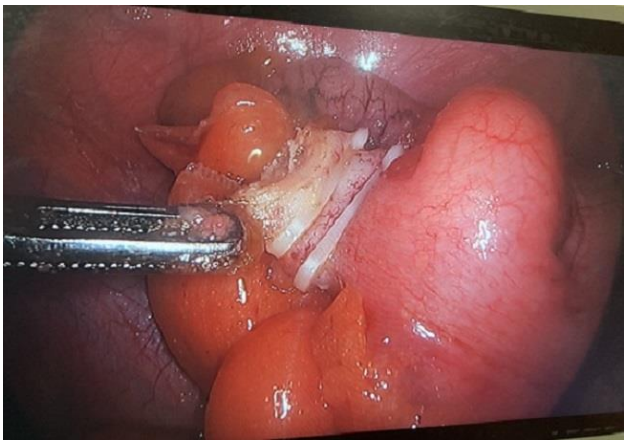

Figure 2. Endoclip

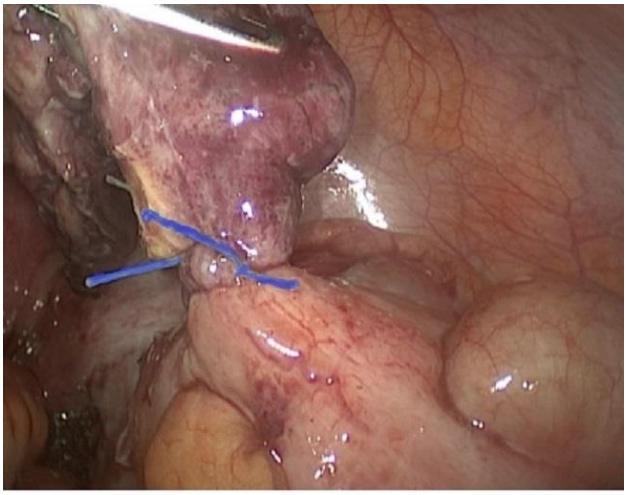

Figure 3. Intracorporeal knotting

Statistical Analysis

The statistical analysis was performed with SPSS v.22.0 (IBM Corp., Armonk, NY, USA). The normality tests were performed by the Kolmogorov-Smirnov test, and skewness and kurtosis values were also controlled. The

mean±standard deviation, median, minimum-maximum, frequency, and percentage values were used in the descriptive statistics. Intergroup analyses were performed with the independent samples t or the Mann-Whitney U test depending on the normality. Categorical data were evaluated with Pearson's chi-square and Fischer's exact test. $p<0.05$ was accepted as significant.

RESULTS

Of the 692 patients, 67.6% (n=468) that were included in the study were male, and %32.4 (n=224) were female. The mean age was 32.6±13.1 years, and the median LOS was detected as 1 (range, 0-14) days. Whilst the most common postoperative appendix pathology was phlegmonous appendicitis (Figure 4) with 86.1% (n=596), perforated appendicitis was observed in 12.7% (n=88) of the cases.

As the stump closure technique, ICK was performed for 66.9% (n=463), and EC was used for 33.1% (n=229) of the patients. The mean operation duration was 52.6±16.4 minutes. The general complication rate was 1.7% (n=12), and the mortality rate was zero. The most common morbidity was intra-abdominal abscess with 0.9% (n=6). The median cost was detected as 1526 (range, 931-4300) Turkish Liras (TL). The demographic and clinical characteristics of the patients were presented in Table 1.

As for the comparison of the stump closure techniques, while 67.4% (n=312) of the patients were male in the ICK group, 68.1% (n=156) of the patients were male in the EC group. No statistically significant difference in gender was found between the groups (p=0.846). The mean age was 31.8±12.6 years in the ICK group, and it was 33.9±13.9 years in the EC group. There was a statistically significant difference in the mean age between the groups (p=0.046). The median LOS was detected as 1 (range, 0-14) days for the ICK group and as 1 (range, 0-6) days for the EC group. There was no statistically significant difference in LOS between the two groups (p=0.054). For both groups, the most common pathology was detected as phlegmonous appendicitis. There was no statistically significant difference in pathology between the two groups (p=0.886). Operation duration was detected as 55.1±15.6 minutes for the ICK group and as 45.7±16.5 for the EC group. There was a statistically significant difference in the operation duration between the groups ($p<0.001$). The median cost was 1423 (range, 931-3808) TL for the ICK group and 1663 (range, 1127-4300) TL for the EC group. There was a statistically significant difference in cost between the groups ($p<0.001$). Whilst there was a complication in 2.2% (n=10) of the patients in the ICK group, the rate of complication was 0.9% (n=2) in the EC group. There was no significant difference in the number of complications between the groups (p=0.354). The comparison of the techniques were presented in Table 2. Among complication types (n=12), the most common one was intra-abdominal abscess with 50% (n=6). Rates of pericecal hematoma, ileus, fistula, and port site hernia were %16.7 (n=2), %16.7 (n=2), %8.3 (n=1), and %8.3 (n=1), respectively.

DISCUSSION

Laparoscopic appendectomy has become the gold standard due to low postoperative pain, early back to work, low surgical site infection, low postoperative adhesive ileus, and better cosmetic results. On top of these, due to the fact that it allows for more exploration, the laparoscopic approach is an important differential diagnostic tool for diseases that are confused with AA such as pelvic inflammatory disease, inflammatory bowel disease, tumor, diverticulitis, ovarian cyst, and ectopic pregnancy (5). Closure of the appendix stump is important for avoiding complications such as postoperative fistula, peritonitis, and intra-abdominal sepsis. For the closure, endostapler, endoloop, intracorporeal or extracorporeal suture, titanium or polymer EC, or tissue sealer devices are used (6).

Makaram et al. (4) have reported the mean age of the patients who have been subjected to ICK as 29.6 years and as 30.95 years for the patients who have been subjected to EC in their review article. In their study, there was no statistically significant difference in the compared stump closure techniques, age, and gender. In our study, EC was performed, statistically significantly, on older patients.

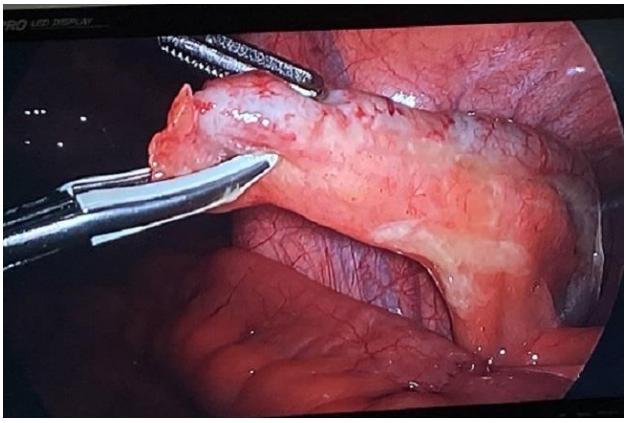

Figure 4. Phlegmonous appendicitis

Table 1. Demographic and clinical characteristics

Age (years), mean±SD	32.6±13.1
Gender, n (%)	
Male	468 (67.6)
Female	224 (32.4)
LOS (days), median (min-max)	1 (0-14)
Pathology, n (%)	
Phlegmonous	596 (86.1)
Perforated	88 (12.7)
Plastron	8 (1.2)
Type of stump closure, n (%)	
Intracorporeal knot	463 (66.9)
Endoclip	229 (33.1)
Duration of Surgery (minute), mean±SD	52.6±16.4
Complication, n (%)	
No	680 (98.3)
Yes	12 (1.7)
Type of Complication, n (%)	
Intraabdominal abscess	6 (0.9)
Pericecal hematoma	2 (0.3)
Ileus	2 (0.3)
Fistula	1 (0.1)
Port site hernia	1 (0.1)
Cost (TL), median (min-max)	1526 (931-4300)

SD: standard deviation, LOS: length of stay, TL: Turkish lira

Table 2. Comparison of the stump closure techniques

	Intracorporeal Knot (n=463)	Endoclip (n=229)	p
Age (years), mean±SD	31.8±12.6	33.9±13.9	**0.046**
Gender, n (%)			
Male	312 (67.4)	156 (68.1)	0.846
Female	151 (32.6)	73 (31.9)	
LOS (days), median (min-max)	1 (0-14)	1 (0-6)	0.054
Pathology, n (%)			
Phlegmonous	398 (86.0)	198 (86.5)	0.886
Perforated	59 (12.7)	29 (12.6)	
Plastron	6 (1.3)	2 (0.9)	
Duration of Surgery (minute), mean±SD	55.1±15.6	45.7±16.5	**<0.001**
Complication, n (%)			
No	453 (97.8)	227 (99.1)	0.354
Yes	10 (2.2)	2 (0.9)	
Type of Complication, n (%)			
Intraabdominal abscess	5 (1.1)	1 (0.4)	0.595
Pericecal hematoma	2 (0.4)	0 (0.0)	
Ileus	2 (0.4)	0 (0.0)	
Fistula	0 (0.0)	1 (0.4)	
Port site hernia	1 (0.2)	0 (0.0)	
Cost (TL), median (min-max)	1423 (931-3808)	1663 (1127-4300)	**<0.001**

SD: standard deviation, LOS: length of stay, TL: Turkish lira

In the literature, although it has been reported that LA was superior in LOS compared to open appendectomy, no difference in LOS has been reported for different appendix stump closure techniques. In the review article written by Makaram et al. (4), the mean LOS for ICK was reported as 2.2 (range, 0.8-2.8) days and as 2.2 (range, 0.8-4.0) days for EC. In our study, even though the LOS was relatively longer for the patients that underwent EC compared to the ones that underwent ICK, the difference was not statistically significant.

Appendix stump closure technique carries more importance for complications in complicated appendicitis cases. According to the comparative study conducted by Durán Muñoz-Cruzado et al. (7), endostapler was used in 51.1% of the complicated AA cases, whereas it was used in 16.5% of the non-complicated cases. According to the study conducted by Lasek et al. (8), 69.1% of the patients for whom EC was used, 26.2% of those for whom endostapler was used, and 33.3% of those for whom endoloop was used had gangrenous appendicitis. In the same study, it has been reported that 17.82% of the patients for whom EC was used, 21.72% of those for whom endostapler was used, and 5.76% of those for whom endoloop was used had perforated/auto-amputated appendicitis. In our study, for different appendicitis severities, no difference between stump closure techniques was observed. ICK was performed as the stump closure technique for 67% (59/88) of the perforated appendicitis cases and for 75% (6/8) of the plastron appendicitis cases.

The operation duration is an important consideration, and in a general sense, open operations take shorter than laparoscopic operations (9). Similarly, for stump closure techniques, it is preferred that the selected technique does not lengthen the operation duration even further. In the study conducted by Ateş et al. (10), it was reported that the mean operation duration was 62.8±15.4 minutes for ICK applications and 41.2±12.2 minutes for titanium EC applications and that this difference was statistically significant. In their review study, Makaram et al. (4) reported a mean operation duration of 68.2 (61.9-79.6) minutes for ICK and 47.7 (31.1-66) minutes for EC applications. In our study, the general mean operation duration for LA was detected to be 52.6±16.4 minutes. The duration was 55.1±15.6 minutes for ICK applications and 45.7±16.5 minutes for EC applications. Hence, according to our evaluations, as a stump closure technique, EC carries an advantage over ICK in that it provides shorter operation durations.

The occurrence of postoperative complications is another important consideration in the comparison of stump closure techniques. In their study, Makaram et al. (4) reported a postoperative complication rate of 7.83% for ICK and 2.09% for polymeric EC. In polymeric EC applications, while intra-abdominal abscess was observed in 0.37%, surgical site infection in 2.29%, and hematoma in 0.89% of the cases, ileus or peritonitis was not detected in any of the cases. As for the ICK applications, intra-abdominal abscess was observed in 1.67%, surgical site infection in 1.81%, hematoma in 0.83%, ileus in 1.43%, and peritonitis in 0.7% of the cases. In our study, the general LA postoperative complication rate was detected as 1.7%. This rate was detected as 2.2% for ICK and 0.9% for EC applications. Hence, according to our evaluations, whilst the occurrence of postoperative complications, especially intra-abdominal abscess, hematoma, and ileus turned out to be less likely for EC, one patient who developed fistula was also in the EC group.

Like most of the aforementioned factors, the cost of the operation is also an important consideration. In the studies evaluating the cost of LA stump closure techniques, the costs were evaluated based on the materials used for the investigated techniques, and the costs were detected as 380 USD for stapler, 70 USD for endoloop, 2 USD for ICK

with silk suture, and 3 USD for metallic EC (11). At the same time, in the study conducted by Bali et al. (12), the mean cost of ICK was reported as 675 TL, and the mean cost of stump closure with endoloop was reported as 768 TL (12). In our study, we detected that EC had a higher cost for the hospital compared to ICK.

CONCLUSION

In conclusion, laparoscopic appendectomy is accepted as the gold standard in the treatment of acute appendicitis. We evaluated the ICK and EC techniques for the closure of the appendix stump. According to our evaluations, the use of EC in the treatment of acute appendicitis can be preferred as an appendiceal stump closure technique, regardless of the severity of appendicitis, owing to its shorter operation time and shorter hospital stay, low complication risk, and ease of application. However, more high-quality prospective randomized studies are needed for the use of ECs to be accepted as a standard.

Ethics Committee Approval: The study was approved by the Ethics Committee of Prof. Dr. Cemil Taşçıoğlu City Hospital (08.11.2021, 384).

Conflict of Interest: None declared by the authors.

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Author Contributions: Idea/Concept: MY; Design: MY; Data Collection/Processing: MY; Analysis/Interpretation: MY; Literature Review: MY; Drafting/Writing: MY; Critical Review: AA.

REFERENCES

1. Snyder MJ, Guthrie M, Cagle S. Acute appendicitis: Efficient diagnosis and management. Am Fam Physician. 2018;98(1):25-33.
2. Karakaş DÖ, Yeşiltaş M, Gökçek B, Eğin S, Hot S. Is language disability a risk factor for complicated appendicitis? A retrospective cohort study. J Surg Med. 2020;4(8):631-5.
3. Wagner M, Tubre DJ, Asensio JA. Evolution and current trends in the management of acute appendicitis. Surg Clin North Am. 2018;98(5):1005-23.
4. Makaram N, Knight SR, Ibrahim A, Patil P, Wilson MSJ. Closure of the appendiceal stump in laparoscopic appendectomy: A systematic review of the literature. Ann Med Surg (Lond). 2020;57:228-35.
5. Lucchi A, Berti P, Grassia M, Siani LM, Gabbianelli C, Garulli G. Laparoscopic appendectomy: Hem-o-lok versus Endoloop in stump closure. Updates Surg. 2017;69(1):61-5.
6. Mayir B, Ensari CÖ, Bilecik T, Aslaner A, Oruç MT. Methods for closure of appendix stump during laparoscopic appendectomy procedure. Ulus Cerrahi Derg. 2015;31(4):229-31.
7. Durán Muñoz-Cruzado V, Anguiano-Diaz G, Tallón Aguilar L, Tinoco González J, Sánchez Arteaga A, Aparicio Sánchez D, et al. Is the use of endoloops safe and efficient for the closure of the appendicular stump in complicated and uncomplicated acute appendicitis? Langenbecks Arch Surg. 2021;406(5):1581-9.
8. Lasek A, Wysocki M, Mavrikis J, Myśliwiec P, Bobowicz M, Dowgiałło-Wnukiewicz N, et al. Comparison of stump closure techniques during laparoscopic appendectomies for complicated appendicitis - results from Pol-LA (Polish laparoscopic appendectomy) multicenter large cohort study. Acta Chir Belg. 2020;120(2):116-23.
9. Lippert H, Koch A, Marusch F, Wolff S, Gastinger I. [Open vs. laparoscopic appendectomy]. Chirurg. 2002;73(8):791-8. German.
10. Ates M, Dirican A, Ince V, Ara C, Isik B, Yilmaz S. Comparison of intracorporeal knot-tying suture (polyglactin) and titanium endoclips in laparoscopic appendiceal stump closure: a prospective randomized study. Surg Laparosc Endosc Percutan Tech. 2012;22(3):226-31.
11. Gonenc M, Gemici E, Kalayci MU, Karabulut M, Turhan AN, Alis H. Intracorporeal knotting versus metal endoclip application for the closure of the appendiceal stump during laparoscopic appendectomy in uncomplicated appendicitis. J Laparoendosc Adv Surg Tech A. 2012;22(3):231-5.
12. Bali İ, Karateke F, Özyazıcı S, Kuvvetli A, Oruç C, Menekşe E, et al. Comparison of intracorporeal knotting and endoloop for stump closure in laparoscopic appendectomy. Ulus Travma Acil Cerrahi Derg. 2015;21(6):446-9.

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Comparison of Tension Band Wiring Method Applied with K-wire or Cannulated Screw in Mayo 2A Olecranon Fracture Fixation: A Biomechanical Study

Mayo 2A Olecranon Kırık Tespitinde K-teli veya Kanüllü Vida ile Uygulanan Gergi Bantlama Metodunun Karşılaştırması: Biyomekanik Çalışma

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ABSTRACT

Aim: The study aimed to compare the biomechanical stability and strength of the tension band wiring method used to treat mayo 2A olecranon fractures with Kirschner (K)-wire or cannulated screw configurations.
Material and Methods: A total of 24 anatomical ulna models (Sawbones Model 1004, Pacific Research Laboratories, Vashon Island, WA) used in the study were divided into two equal groups of 12, tension band fixation with K-wire (Group 1) and tension band fixation with cannulated screw (Group 2), and groups were compared. The mechanical comparison was performed with a universal measuring machine (Shimadzu Autograph 50 kN; Shimadzu Corp).
Results: Fixation methods comparison (K-wire/cannulated screw) were the main factors that determined the stability and the strength of the internal fixation. The median flexion strength of Group 1 was 107.92 (range, 94.22-121.72) N, and that of Group 2 was 109.67 (range, 105.07-113.86) N. The median varus strength of Group 1 was 100.02 (range, 83.24-102.18) N, and that of Group 2 was 76.32 (range, 68.44-78.43) N. Varus strength and stiffness were significantly higher in the K-wire group than in the cannulated screw group (both p values were <0.001). No significant differences were detected between the groups regarding flexion strength and stiffness (both p values were 0.999).
Conclusion: Although no significant differences were detected between the two fixations in flexion bending cyclic loading, a significantly more stable fixation was achieved in tension banding applied with K-wire in varus bending cyclic loading. No reduction loss was detected during cyclic loading tests in either technique.
Keywords: Olecranon fracture fixation; tension banding; displaced transverse olecranon fracture.

ÖZ

Amaç: Bu çalışmanın amacı mayo 2A olekranon kırıklarının tedavisinde kullanılan gergi bantlama metodunun Kirschner (K)-teli veya kanüllü vida ile konfigürasyonlarının biyomekanik stabilitesini ve gücünü karşılaştırmaktı.
Gereç ve Yöntemler: Çalışmada kullanılan toplam 24 anatomik ulna modeli (Sawbones Model 1004, Pacific Research Laboratories, Vashon Island, WA), K-teli ile gergi bant tespiti (Grup 1) ve kanüllü vida ile gergi bant tespiti (Grup 2) olmak üzere 12'şerli iki eşit gruba ayrıldı ve gruplar karşılaştırıldı. Mekanik karşılaştırma evrensel bir ölçüm makinesi (Shimadzu Autograph 50 kN; Shimadzu Corp) ile uygulandı.
Bulgular: Fiksasyon yöntemleri karşılaştırması (K-teli/kanüllü vida), internal fiksasyonun stabilitesini ve gücünü belirleyen ana faktörlerdi. Grup 1'in ortanca fleksiyon mukavemeti 107,92 (aralık, 94,22-121,72) N ve Grup 2'nin 109,67 (aralık, 105,07-113,86) N idi. Grup 1'in ortanca varus mukavemeti ise 100,02 (aralık, 83,24-102,18) N ve Grup 2'nin 76,32 (aralık, 68,44-78,43) N idi. Varus mukavemeti ve sertliği K-teli grubunda kanüllü vida grubuna göre anlamlı şekilde daha yüksekti (her iki p değeri <0,001). Fleksiyon mukavemeti ve sertliği açısından gruplar arasında anlamlı bir farklılık saptanmadı (her iki p değeri 0,999).
Sonuç: Fleksiyon bending siklik yüklenmede iki tespit arasında anlamlı bir farklılık saptanmazken, varus bending siklik yüklenmede K-teli ile uygulanan gergi bantlamada anlamlı şekilde daha stabil bir tespit sağlandı. Her iki teknikte de siklik yükleme testleri sırasında herhangi bir redüksiyon kaybı görülmedi.
Anahtar kelimeler: Olekranon kırık fiksasyonu; gergi bantlama; deplase transvers olekranon kırığı.

INTRODUCTION

Olecranon fractures are intra-articular fractures accounting for approximately 10% of all upper extremity fractures (1,2). The impaction of the distal humerus, a direct trauma mechanism, often leads to a comminuted fracture pattern, and triceps traction, which is an indirect mechanism, leads to a simple-transverse fracture pattern (3). Anatomical reduction is necessary for olecranon fractures to prevent the development of post-traumatic arthritis and restore the former functionality of the triceps muscle (4). Also, it is essential to provide a stable fixation in which anatomical reduction is protected from the elbow's early flexion and extension movements.

In olecranon fractures, triceps' re-fixation with interfragmentary screws, Kirschner (K)-wires, or cannulated screw supported tension band wiring method (TBWM), plate-screw fixation, or bone fragment excision are among the fixation methods defined previously (5). TBWM is a reliable and widely used fixation method, especially in displaced transverse olecranon fractures. Although clinical and biomechanical studies regarding standard TBWM report excellent results, problems such as K-wires coming back, loss of reduction, and soft tissue irritation are still observed (6). In recent years, various methods have been proposed to develop TBWM, one of which is the Arbeitsgemeinschaft für Osteosynthesefragen (AO) tension band technique first performed with two K-wires sent intramedullary. Then it was changed to pass the distal volar cortex of the coronoid process. It was reported that the approach made by crossing the coronoid cortex reduces the rates of skin rebound and unsuccessful fixation (7). However, the implantation of K-wires through the anterior cortex of the coronoid process may restrict forearm rotation, increasing the risk of heterotopic ossification and neurovascular damage (8,9). Although there is evidence regarding successful clinical outcomes of different fixation methods used for olecranon fractures, the best fracture fixation technique is still a matter of debate (10).

The present study aimed to compare the biomechanical stability and strength of the TBWM used to treat Mayo 2A olecranon fractures with a K-wire or cannulated screw configuration.

MATERIAL AND METHODS

The approval for the study was obtained from the local Non-Interventional Clinical Studies Ethics Committee of Marmara University. Estimating that a minimum difference of 1 unit and a deviation of 0.5 units in the flexion and varus bending measurements would be clinically meaningful, the effect size was calculated as d=2. To achieve 80% power (β=0.20) at the α=0.05 level, six subjects were required in each group. Power analysis was performed using the G∗Power (v.3.1.9.2) program. A single orthopedic surgeon performed the entire procedure on each model. The osteotomy models and fixations were performed at the Department of Orthopedics and Traumatology of Marmara University. The biomechanical tests were performed at Dokuz Eylül University Biomechanics Laboratory.

A total of 24 anatomical ulna models divided into two equal groups of 12 were used in the study (Sawbones, model #1004 synthetic bone, Pacific Research Laboratories, Vashon Island, Washington, USA). Two groups were compared in the study; Group 1: tension band fixation with K-wire (1.6 mm diameter; TST Medical, Istanbul, Turkey) and Group 2; tension band fixation with a cannulated screw (6.5 mm diameter; TST Medical, Istanbul, Turkey). Two parallel K-wires or one cannulated screw in the same direction were inserted into the ulna distal anterior cortex proximal to the olecranon from previously determined standard locations. Fixation was completed in 8 configurations by passing a flexible cerclage wire (1.2 mm diameter; TST Medical, Istanbul, Turkey) through the tunnel opened in the ulnar dorsal cortex at a distance of 6.5 cm from the tip of the olecranon proximally behind the K-wire or cannulated screw and distally. For the cerclage tension, three full turns of tension were applied with the help of pliers with a knotting technique in the system whose void was taken (7). The schematization of the fracture line modeling and standardized entrance and exit locations to be used in detection in Group 1 were given in Figure 1. The schematization of the fracture line modeling and standardized entrance and exit points to be used in Group 2 were given in Figure 2.

Then, each sawbones was embedded in a plastic template containing liquid epoxy resin designed to hold it rigidly and was allowed to harden. Mechanical analysis was performed by fixing the plastic mold to a cylindrical metal with a mechanical clamping system.

The mechanical comparison was made with a universal measuring machine (Shimadzu® Autograph AG-IS 5 kN, Load Cell: SLBN5KN, Shimadzu Co., Kyoto, Japan; Figure 3). The models were tested in 50 cycles. For each sample, six models were used in ulna bending mechanical loading, and the force required to be applied at 0.5 mm/sec speed and 0-5 mm displacement were calculated for each configuration. The stiffness was calculated based on the slope of the force-displacement curve of five cycles for flexion-varus measurements. The stiffness value was calculated with Microsoft Excel (Microsoft Corp., Redmond, WA) software (N/mm).

Statistical Analysis

The IBM SPSS Statistics v.22 (IBM Corp.; Armonk, NY, USA) program was used for statistical analyses. According to the Shapiro-Wilk test, the quantitative variables were not normally distributed. The data were expressed as medians and interquartile ranges. The Mann-Whitney U test determined the differences in applied displacement force and stiffness between osteotomy groups. A p-value of <0.05 was considered statistically significant.

RESULTS

K-wire or screw application were the main factors that determined the stability and strength of the internal fixation. Mean flexion-varus bending cyclic load values were shown in Table 1. Varus bending cyclic load values in Group 1 were significantly higher than in Group 2 (p<0.001). No significant differences were detected between the groups in flexion bending cyclic load values (p=0.999). The mean stiffness values developed against flexion-varus bending cyclic loading applied in all osteotomy models were shown in Table 2. Stiffness values under varus bending cyclic load in Group 1 were significantly higher than in Group 2 (p<0.001). No significant differences were

detected between the groups in stiffness values under flexion bending cyclic load (p=0.999). Neither group detected no pin loosening or reduction loss during cyclic loading tests.

DISCUSSION

The TBWM for olecranon fractures provides a stable fixation allowing early mobilization. Continuous advances in the TBWM technique have significantly reduced failure rates on fixation and postoperative complication rates in olecranon fractures (11). Many authors published reports of various bicortical-localized K-wire or screwed configurations (12,13). This study aimed to determine whether the tension band fixation applied with bicortical K-wire or cannulated screw is equivalent in terms of strength and stability in Mayo 2A olecranon fractures. Although no significant differences were detected between the two fixations in flexion bending cyclic loading, the tension banding applied with K-wire in varus bending cyclic loading provided a significantly more stable fixation.

K-wires can be sent intramedullary-distally along the long axis of the ulna in the tension banding technique or can be sent obliquely-bicortical towards the anterior cortex of the ulna. In their study, Mullett et al. (14) explained the clinical and biomechanical results, and they showed that the bicortical method has a much lower complication rate than the intramedullary method. The need for implant removal is five times less. They showed that the bicortical method was significantly more stable in biomechanics. In the present study, we applied the bicortical method in both fixation techniques in line with the existing literature.

Cerclage in a circular configuration may provide insufficient stabilization in the tension banding technique, which may fail fixation because of early loosening. In their study that compared the fixation methods of olecranon fractures, Wang et al. (15) showed that the circular configuration and fixation had the lowest fixation strength, and eight wirings and screw fixation had similar fixation strength. In the present study, we preferred the Cerclage application in the eight configurations in the tension banding method.

In Jones et al.'s (16) study, the transcortical screw provided a more stable fixation under cyclic loading than the K-wire tension banding method. Hutchinson et al. (17), in another study, compared four olecranon fixation methods. They showed that adding a tension band system to intramedullary cancellous screw fixation increased stability, and intramedullary cancellous fixation supported by this tension band was more stable than tension band fixation with bicortical or intramedullary K-wire. Unlike Hutchinson et al. (17), Carofino et al. (18) simulated the strength of standing up from a chair with a high load and showed that the K-wire tension band system provides better stability than the intramedullary screw tension band system. No significant differences were detected in the present study under flexion bending and cyclic load. We found that the K-wire tension band system was more stable under varus cyclic loading, similar to Carofino et al.'s (18) study.

Biomechanical studies are conducted with materials such as sawbones, cadavers, and animal bones. Although it is possible to make consistent evaluations in biomechanical

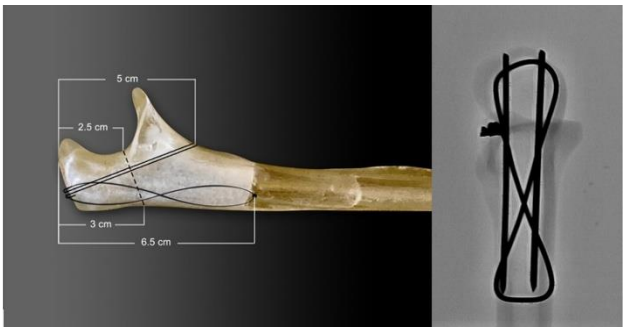

Figure 1. Mayo 2A olecranon fracture fixation with K-wire, a) Diagram view b) Anteroposterior (AP) X-ray view

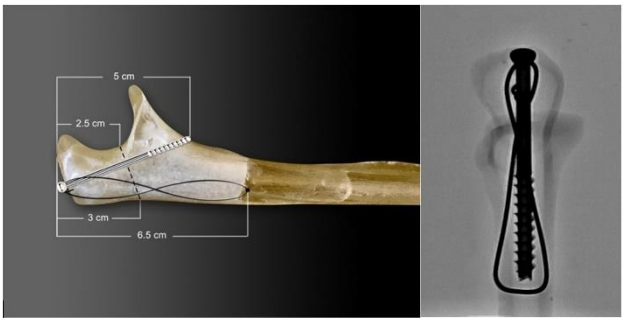

Figure 2. Mayo 2A olecranon fracture fixation with cannulated screw, a) Diagram view b) Anteroposterior (AP) X-ray view

Figure 3. Biomechanical testing of a Sawbone® with Mayo 2A olecranon fracture fixation

Table 1. Comparison of bending cyclic load values

	K-wire	Cannulated Screw	p
Flexion Bending (N)	107.92 (96.52-119.55) [94.22-121.72]	109.67 (107.45-111.18) [105.07-113.86]	0.999
Varus Bending (N)	100.02 (87.44-100.35) [83.24-102.18]	76.32 (72.93-77.22) [68.44-78.43]	<0.001

K-wire: Kirschner wire, descriptive statistics were given as median (25^{th}-75^{th} percentile) [min-max]

Table 2. Comparison of stiffness values against cyclic load

	K-wire	Cannulated Screw	p
Flexion Stiffness (N/mm)	21.58 (19.29-23.93) [18.83-24.51]	21.98 (21.45-22.30) [20.97-22.74]	0.999
Varus Stiffness (N/mm)	19.99 (17.47-20.12) [16.64-20.59]	15.25 (14.60-15.44) [13.83-15.70]	<0.001

K-wire: Kirschner wire, descriptive statistics were given as median (25^{th}-75^{th} percentile) [min-max]

studies by using cadavers, the use of cadavers is limited because of the lack of a sufficient number of cadavers, exposure to the effects of a wide age range, body structure, different health conditions, and specimen with no appropriate bone density (19). Although sawbones models do not represent the mechanical properties of cadaver bone, relative mechanical stability can be tested under consistency because all conditions are the same in mechanical testing, except for the fixation technique (20). In the present study, we preferred sawbones for olecranon mayo type 2A fracture modeling.

Our study had some limitations. The combined forces of compression, distraction, bending, and rotation in olecranon fracture could not be simulated at the fracture line, which could be caused by the potential deforming or stabilizing forces of the muscles around the elbow affecting the possible results. Although a natural fracture cannot be accurately reproduced in a single experimental model or biomechanical study, the data obtained can provide new insights into the treatment of fractures in general, especially in metal implants for fixation, to help surgeons make choices when dealing with real situations. Aside from biomechanical evaluations, there may be differences in surgical technique, ease of application, wound healing, surgical time, and fixation difficulty. A clinical study that will evaluate these will contribute to the literature.

CONCLUSION

According to the biomechanical analyses, K-wire configured tension banding provided significantly better stability in varus cyclic loading. However, no significant differences were detected between the two groups in flexion loadings.

Ethics Committee Approval: The study was approved by the Ethics Committee for Non-Invasive Clinical Studies of Marmara University (25.02.2021, 23).

Conflict of Interest: None declared by the authors.

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REFERENCES

1. Veillette CJ, Steinmann SP. Olecranon fractures. Orthop Clin North Am. 2008;39(2):229-36.
2. Powell AJ, Farhan-Alanie OM, Bryceland JK, Nunn T. The treatment of olecranon fractures in adults. Musculoskelet Surg. 2017;101(1):1-9.
3. Newman SD, Mauffrey C, Krikler S. Olecranon fractures. Injury. 2009;40(6):575-81.
4. Chalidis BE, Sachinis NC, Samoladas EP, Dimitriou CG, Pournaras JD. Is tension band wiring technique the "gold standard" for the treatment of olecranon fractures? A long term functional outcome study. J Orthop Surg Res. 2008;3:9.
5. Rantalaiho IK, Miikkulainen AE, Laaksonen IE, Äärimaa VO, Laimi KA. Treatment of displaced olecranon fractures: a systematic review. Scand J Surg. 2021;110(1):13-21.
6. Claessen FM, Braun Y, Peters RM, Dyer G, Doornberg JN, Ring D. Factors associated with reoperation after fixation of displaced olecranon fractures. Clin Orthop Relat Res. 2016;474(1):193-200.
7. Carter TH, Molyneux SG, Reid JT, White TO, Duckworth AD. Tension-band wire fixation of olecranon fractures. JBJS Essent Surg Tech. 2018;8(3):e22.
8. Parker JR, Conroy J, Campbell DA. Anterior interosseus nerve injury following tension band wiring of the olecranon. Injury. 2005;36(10):1252-3.
9. Shimura H, Nimura A, Fujita K, Kaburagi H. Comparison of the efficacy of the tension band wiring with eyelet wire versus anatomical locking plate fixation for the treatment of displaced olecranon fractures. J Orthop Surg (Hong Kong). 2021;29(3):23094990211059231.
10. Snoddy MC, Lang MF, An TJ, Mitchell PM, Grantham WJ, Hooe BS, et al. Olecranon fractures: factors influencing re-operation. Int Orthop. 2014;38(8):1711-6.
11. Chan KW, Donnelly KJ. Does K-wire position in tension band wiring of olecranon fractures affect its complications and removal of metal rate? J Orthop. 2015;12(2):111-7.
12. Midtgaard KS, Frihagen F, Dornan GJ, Coucheron M, Fossåen C, Grundel D, et al. Predicting secondary surgery after operative fixation of olecranon fractures: a model using data from 800 patients. JSES Int. 2021;5(5):948-53.
13. Lu QF, Tang GL, Zhao XJ, Zhang WJ, Guo SG, Wang HZ. Tension band wiring through double-cannulated screws as a new internal fixation method for treatment of olecranon fractures: a randomized comparative study. Acta Orthop Traumatol Turc. 2015;49(6):654-60.
14. Mullett JH, Shannon F, Noel J, Lawlor G, Lee TC, O'Rourke SK. K-wire position in tension band wiring of the olecranon-a comparison of two techniques. Injury. 2000;31(6):427-31.
15. Wang W, Wu G, Shen F, Zhang Y, Liu X. A biomechanical experiment and clinical study of the use of figure of eight plus circular wiring fixation for the treatment of olecranon fractures. Exp Ther Med. 2012;4(6):1081-6.
16. Jones TB, Karenz AR, Weinhold PS, Dahners LE. Transcortical screw fixation of the olecranon shows equivalent strength and improved stability compared with tension band fixation. J Orthop Trauma. 2014;28(3):137-42.
17. Hutchinson DT, Horwitz DS, Ha G, Thomas CW, Bachus KN. Cyclic loading of olecranon fracture fixation constructs. J Bone Joint Surg Am. 2003;85(5):831-7.

18. Carofino BC, Santangelo SA, Kabadi M, Mazzocca AD, Browner BD. Olecranon fractures repaired with FiberWire or metal wire tension banding: a biomechanical comparison. Arthroscopy. 2007;23(9):964-70.
19. Acevedo JI, Sammarco VJ, Boucher HR, Parks BG, Schon LC, Myerson MS. Mechanical comparison of cyclic loading in five different first metatarsal shaft osteotomies. Foot Ankle Int. 2002;23(8):711-6.
20. Kılıç B, Çalışkan M, Agar A, Uzun B, Ertem F, Gülabi D, et al. Comparison of two different screw trajectories in the treatment of oblique scaphoid fractures: A mechanical study on composite bone models. Jt Dis Relat Surg. 2021;32(2):377-82.

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The Relationship of Liver Stiffness with Liver Size, Age, Gender, and Body Mass Index in Child and Adult Age Groups by 2-D Shear Wave Elastography

Çocuk ve Erişkin Yaş Gruplarında Karaciğer Elastisitesinin Karaciğer Boyutu, Yaş, Cinsiyet ve Beden Kitle İndeksi ile İlişkisinin 2-D Shear Wave Elastografi ile Değerlendirilmesi

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ABSTRACT

Aim: The study aimed to evaluate the normal liver stiffness value (LSV) with shear wave elastography (SWE) in children and adults, and reveal the relationship between LSV and age, gender, body mass index (BMI), and liver size.
Material and Methods: A total of 173 healthy volunteers, 92 female and 81 male, aged between 4 and 50 years were included in this study. LSV measurements were performed in the supine position during normal breathing and from the right intercostal space where the acoustic window is best. The mean of the five valid measurements was accepted as the mean LSV. The relationship between the mean LSV and age, gender, liver size, and BMI was evaluated.
Results: There was a moderate positive correlation between LSV and age ($p<0.001$, $r=0.609$), LSV and BMI ($p<0.001$, $r=0.512$), and LSV and liver size ($p<0.001$, $r=0.485$). However, the multivariate linear regression analysis revealed that the effects of liver size and gender on LSV were not significant ($p=0.091$, and $p=0.759$, respectively), while the effects of age and BMI were significant ($p<0.001$, and $p=0.019$, respectively).
Conclusion: 2-D SWE is an effective imaging method to evaluate LSV both in children and adults. LSV increases with increasing age and BMI, however, it is not affected by gender and liver size. The normal LSV obtained in the present study can be used as reference values in the evaluation of various liver diseases with 2-D SWE.
Keywords: Liver; shear wave elastography; ultrasonography.

ÖZ

Amaç: Bu çalışma çocuklarda ve erişkinlerde normal karaciğer elastisite değerinin (liver stiffness value, LSV) shear wave elastografi (SWE) ile değerlendirilmesini ve LSV ile yaş, cinsiyet, beden kitle indeksi (BKİ) ve karaciğer boyutu arasındaki ilişkinin ortaya koyulmasını amaçlamaktadır.
Gereç ve Yöntemler: Bu çalışmaya yaşları 4 ve 50 yıl arasında olan, 92 kadın ve 81 erkek olmak üzere toplam 173 sağlıklı gönüllü dahil edilmiştir. LSV ölçümleri supin pozisyonda, normal nefes alma esnasında sağ interkostal aralıktan, akustik pencerenin en iyi olduğu aralıktan yapıldı. Beş güvenli ölçümün ortalaması ortalama LSV değeri olarak kabul edildi. Ortalama LSV ile yaş, cinsiyet, karaciğer boyutu ve BKİ arasındaki ilişki değerlendirildi.
Bulgular: LSV ile yaş arasında ($p<0,001$; $r=0,609$), LSV ile BKİ arasında ($p<0.001$; $r=0,512$) ve LSV ile karaciğer boyutu arasında ($p<0,001$; $r=0,485$) pozitif yönlü orta dereceli bir ilişki saptanmıştır. Ancak multivariate lineer regresyon analizi karaciğer boyutunun ve cinsiyetin LSV üzerine etkisinin anlamlı olmadığını (sırasıyla $p=0,091$ ve $p=0,759$), yaş ve BKİ'nin etkisinin ise anlamlı olduğunu ortaya çıkarmıştır (sırasıyla $p<0,001$ ve $p=0,019$).
Sonuç: 2-D SWE hem çocuklarda hem de erişkinlerde LSV'nin değerlendirilmesinde etkili bir görüntüleme yöntemidir. LSV yaş ve BKİ arttıkça artış göstermekte, bununla birlikte, cinsiyet ve karaciğer boyutundan etkilenmemektedir. Mevcut çalışmada elde edilen normal LSV çeşitli karaciğer hastalıklarının 2-D SWE ile değerlendirilmesinde referans değerler olarak kullanılabilir.
Anahtar kelimeler: Karaciğer; shear wave elastografi; ultrasonografi.

INTRODUCTION

Shear wave elastography (SWE) is an ultrasound (US) based non-invasive imaging method used in clinical practice to detect and grade liver fibrosis resulting from various etiological factors. The introduction of SWE into clinical use has led to a significant decrease in the rate of liver biopsies performed to evaluate liver fibrosis (1). There are several ultrasound-based elastography methods to assess liver fibrosis. These include transient elastography (TE), and acoustic radiation force impulse (ARFI). Two ARFI techniques are clinically available: point SWE (p-SWE) and 2-D SWE (2).

2-D SWE is an imaging method that quantifies the elasticity of tissue by measuring the speed of shear waves induced in the tissue by acoustic push pulses, generating 2-D quantitative images of shear wave speed. 2-D SWE displays 2-D color images of shear wave speed in a region of interest (ROI). The ROI can be adjusted in size and position, and the tissue stiffness can be obtained at any location within the ROI, as shear wave speed (m/s), or converted to Young's modulus (kPa) (3).

Although the reliability is high due to high inter- and intra-observer agreement in SWE, recent studies have reported high intersystem variability and overlapping in reference values (1,4-8).

Despite the abundance of studies on the evaluation of liver parenchymal pathologies with SWE (1,2,9,10), the literature involves fewer studies examining the normal liver stiffness value (LSV) in both adult and child age groups (3,11-14). However, determining the normal LSV reference values for each new elastography technique is crucial to increasing the diagnostic efficiency of SWE in various liver diseases (14,15). In addition, the high intersystem variability makes it necessary to determine the normal reference values well and therefore requires more studies involving different devices and SWE techniques that evaluate normal parenchyma. To the best of our knowledge, there is no study in the literature evaluating LSV both in children and adults together in the same study, examining at the same time the relationship between liver size and LSV. For all these reasons, this study aimed to evaluate the normal LSV with 2-D SWE in children and adults to determine the normal reference values and reveal the relationship between LSV and age, gender, body mass index (BMI), and liver size.

MATERIAL AND METHODS

Study Group

The study was approved by the Clinical Researches Ethics Committee of Tokat Gaziosmanpaşa University Faculty of Medicine (06.02.2020/20-KAEK-019). The participants were selected among the patients who were referred to the Radiology Department of Tokat Gaziosmanpaşa University Hospital from March 2020 to July 2021 for routine Abdominal US examination. It included healthy volunteers, without any history or suspicion of chronic liver disease, liver fibrosis, liver congestion, acute hepatitis and infiltrative liver diseases, hepatic and splenic inflammation, those with elevated liver enzymes, hepatomegaly, hepatosteatosis, viral hepatitis, portal hypertension, portal vein or bile duct dilatation, autoimmune or metabolic disease, focal liver lesion, or another disease. The participants consisted of those with normal values as defined by the World Health Organization criteria. The relationship of LSV with age, gender, BMI, and liver size was investigated.

2-D SWE Measurements

SWE measurements were performed by a radiologist with Logiq E9 XDclear, GE Healthcare, Milwaukee; WI ultrasonography device using C1-6-D XDclear 1-6 MHz convex probe. SWE measurements were performed in the supine position, during normal breathing, while the right arm was at maximum abduction, and from the right intercostal space at the location of the best acoustical window. The transducer was perpendicular to the liver capsule. The rectangular box was placed 1.5 to 2.0 cm below the liver capsule to avoid reverberation artifacts, and it did not contain vessels and bile ducts. The SWE images were obtained in the form of homogeneous color-coding filling inside the rectangle (16). LSV was calculated in kPa by placing an ROI drawn in the largest possible diameter into the rectangular box (Figure 1). Five valid measurements were conducted. Median LSV, interquartile range (IQR), and IQR/median ratio were calculated for each patient based on the five valid measurements. The average of these five values was determined as the mean LSV. In addition, the IQR/median value of the five values was calculated and patients with an IQR/median ratio of over 30% were not included in the study. The liver size measurements were performed in the supine position with the right arm at maximum abduction, and the patient deeply breathing, from the right midclavicular line, extending from the hepatic dome to the lower hepatic margin as a sonographic measurement parameter (17). All measurements were recorded to the nearest millimeter.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation, and categorical variables were expressed as frequency and percentage. Independent sample t-test and one-way analysis of variance were used to compare the normal-distribution continuous data between/among groups. For post hoc comparisons between the pair-wise groups, the Tukey HSD test was used. The chi-square test was used to compare the categorical data between/among groups. Pearson's correlation coefficient was used for correlation between variables. A multivariate linear regression model was implemented to determine the relationships between age, gender, BMI and liver size, and LSV. A p-value of <0.05 was considered significant. Statistical analyses were performed using IBM SPSS v.20 statistical package.

RESULTS

The study involved a total of 173 volunteers. They were divided into two groups: those <18 and ≥ 18 years of age, which formed the first classification of age groups. They were further split into five groups: those aged 4-9 years, 10-18 years, 19-28 years, 29-38 years, and 39-50 years, and this classification constituted the second classification of age groups. We investigated whether there was a difference in LSV between the groups. In both classifications, there was no significant difference in gender between the groups ($p=0.730$, and $p=0.261$, respectively). Characteristics of the study group were presented in Table 1.

When LSV was evaluated in the general study group in terms of gender, the mean LSV was 5.49±0.87 kPa in females and 5.33±0.89 kPa in males, and there was no statistically significant difference in LSV in terms of gender (p=0.238, Table 2).

Table 3 demonstrates the comparison of the age groups by the first classification of age into two groups, as <18 and ≥18 years of age. Accordingly, LSV was 4.95±0.73 kPa in the group aged <18 years and 5.70±0.85 kPa in the group aged ≥18 years, and the difference between the groups was statistically significant (p<0.001). The differences between the two groups both in BMI (p<0.001) and in liver size (p<0.001) were also statistically significant.

Table 4 presents the comparison of BMI, liver size, and LSV in the age groups by the second classification of age into five groups, as 4-9, 10-18, 19-28, 29-38, and 39-50 years of age. Accordingly, the general comparison revealed that the difference in LSV between all age groups was statistically significant (p<0.001). When the age groups by the second classification were compared among themselves, the differences between the following age groups were significant according to the post hoc test results: 4-9 years and 10-18 years, 29-38 years, and 39-50 years; 10-18 years and 4-9 years, 29-38 years, and 39-50 years; 19-28 years and 29-38 years and 39-50 years; 29-38 years and all age groups; 39-50 years and all age groups; and LSV increased with age. The differences between the five groups were also significant in BMI (both p<0.001) and liver size (p<0.001).

According to Pearson's correlation coefficient, there was a moderate positive correlation between LSV and age (p<0.001, r=0.609), LSV and BMI (p<0.001, r=0.512), and LSV and liver size (p<0.001, r=0.485) in the general group. In the group aged <18 years, there was a weak positive correlation between LSV and age (p=0.002, r=0.380), and LSV and BMI (p=0.003, r=0.362), as well as a moderate positive correlation between LSV and liver size (p=0.001, r=0.405). In the group ≥18 years of age, we found a moderate positive correlation between LSV and age (p<0.001, r=0.613) and LSV and BMI (p<0.001, r=0.491), and a weak positive correlation between LSV and liver size (p=0.003, r=0.287).

The multivariate linear regression analysis revealed that the effects of gender (p=0.759) and liver size (p=0.091) on LSV were not statistically significant while the effects of age (p<0.001) and BMI (p=0.019) were statistically significant. A one-unit increase in age causes an increase of 0.029 units in LSV, and a one-unit increase in BMI causes an increase of 0.052 units in LSV, both statistically significant (p<0.001, and p=0.019, respectively). Age is the variable that contributed to the model the most (Beta=0.412, p<0.001). The results of multivariate linear regression analysis were presented in Table 5.

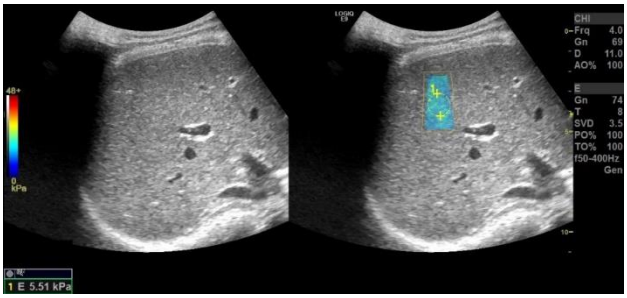

Figure 1. Measurement of normal liver parenchyma with 2-D SWE obtained from a 36-year-old female patient

Table 1. Characteristics of the study group

Characteristics	**(n=173)**
Gender, n (%)	
Female	92 (53.2)
Male	81 (46.8)
Age Groups, n (%)	
4-17	66 (38.2)
18-50	107 (61.8)
Age Groups, n (%)	
4-9	26 (15.0)
10-18	41 (23.7)
19-28	33 (19.1)
29-38	51 (29.5)
39-50	22 (12.7)
Age (year)	24.51±12.47 (4-50)
BMI (kg/m^2)	21.28±3.11 (14.10-26.40)
Liver Size (mm)	133.55±18.99 (86-160)
LSV (kPa)	5.41±0.88 (3.29-7.10)

BMI: body mass index, LSV: liver stiffness value, descriptive statistics of the continuous variables were expressed as mean±standard deviation (min-max)

Table 2. Comparison of the study group by gender

	Female (n=92)	**Male (n=81)**	**p**
Age (year)	25.76±12.37	23.10±12.51	0.162
BMI (kg/m^2)	21.64±2.81	20.88±3.39	0.110
Liver Size (mm)	134.26±18.14	132.75±20.00	0.604
LSV (kPa)	5.49±0.87	5.33±0.89	0.238

BMI: body mass index, LSV: liver stiffness value, descriptive statistics of the continuous variables were expressed as mean±standard deviation (min-max)

Table 3. Comparison of the age groups by first classification

	4-17 (n=66)	**18-50 (n=107)**	**p**
BMI (kg/m^2)	19.33±3.71	22.48±1.85	**<0.001**
Liver Size (mm)	119.12±15.28	142.46±15.24	**<0.001**
LSV (kPa)	4.95±0.73	5.70±0.85	**<0.001**

BMI: body mass index, LSV: liver stiffness value, descriptive statistics of the continuous variables were expressed as mean±standard deviation (min-max)

Table 4. Comparison of the age groups by second classification

	4-9 (n=26)	**10-18 (n=41)**	**19-28 (n=33)**	**29-38 (n=51)**	**39-50 (n=22)**	**p**
BMI (kg/m^2)	15.7±1.16^a	21.78±2.76^{bc}	21.58±2.04^c	22.88±1.64^b	22.8±1.54^{bc}	**<0.001**
Liver Size (mm)	107.85±11.65^a	126.78±12.75^b	139.97±16.14^c	142.53±15.99^c	146.14±11.95^c	**<0.001**
LSV (kPa)	4.65±0.79^a	5.17±0.62^b	5.11±0.88^{ab}	5.78±0.67^c	6.38±0.58^d	**<0.001**

BMI: body mass index, LSV: liver stiffness value, descriptive statistics of the continuous variables were expressed as mean±standard deviation (min-max), different superscripts (a, b, c, d) in the same row indicate a statistically significant difference between the groups

Table 5. Results of multivariate linear regression analysis

Model	Unstandardized Coefficients		Standardized Coefficients	p
	B	SE	Beta	
Age (year)	0.029	0.006	0.412	**<0.001**
BMI (kg/m^2)	0.052	0.022	0.185	**0.019**
Liver Size (mm)	0.006	0.004	0.132	0.091
Gender	-0.032	0.105	-0.018	0.759

Dependent variable: liver stiffness value, BMI: body mass index, SE: standard error

DISCUSSION

To the best of our knowledge, the present study is the first study evaluating adult and child groups together with the same technical equipment and method, comparing LSV in children and adult groups and examining the relationship between liver size and liver stiffness.

Normal LSVs vary according to the elastography method used in both children and adults (3,14). Mulabecirovic et al. (14) adopted TE as a reference and used 2-D SWE and p-SWE techniques in healthy individuals aged 20-70 years. They reported that the mean LSV was 4.5±0.8 kPa with 2-D SWE, 4.2±1.1 kPa with TE, and 4.1±0.8 kPa with p-SWE. They stated that the values were higher with 2-D SWE than that with TE. Bende et al. (3) revealed that the average LSV was 5.9±1.2 kPa in males and 4.7±1.2 kPa in females with 2-D SWE, and the values were lower compared with those obtained with TE in the study. In our study, the values obtained in the adult age group are similar to that of other 2-D SWE techniques mentioned in the literature and similarly higher than the values obtained with TE (3,14).

In the childhood age group, Yang et al. (11) found the normal LSV to be 6.3±1.1 kPa and 6.2±1.1 kPa in segments V and VI, respectively, in their study with 2-D SWE in school children. Eiler et al. (18) reported the mean LSV as 1.16±0.14 m/sec with point SWE in healthy children aged 0-17 years. In the study by Lewindon et al. (12) in children aged 0-18 years, they found LSV with TE 3.5±0.5 kPa in the 0-2 year-old group, 3.8±0.3 kPa in the 3-5 year-old group, 4.1±0.2 kPa in the 6-11 year-old group, and 4.5±0.2 kPa in the 12-18 year-old-group. Tokuhara et al. (13) divided children aged 1-18 years into three groups; 1-5 years, 6-11 years, and 12-18 years of age. The LSV they found with TE was 3.4 (2.3-4.6) kPa in the pre-school group, 3.8 (2.5-6.1) kPa in the primary school age group, and 4.1 (3.3-7.9) kPa in the adolescent group. In the child age group, the closest technique to that in our study is that in the study of Yang et al. (11) and the values obtained in both studies are similar.

There are several studies examining the relationship of LSV with age and gender in the child age group. Similar to ours, most of them found an increase between age and LSV (12,13); however, one study reported no relationship between age and LSV (18). Another one stated that LSV increased between the ages of 6-9 years and plateaued between the ages of 10-15 years (11).

There was no relationship between childhood gender and LSV in most studies similar to our study (11-13,19). However, one study reported the values to be lower in females (18).

Some studies examining the relationship between age and LSV in adult patients found the effect of age on LSV to be not significant (14,20), while some others reported that LSV increased with age (3,21). We found a positive correlation between age and LSV in the adult group, and the effect of age on LSV was significant in the multiple regression analysis. In addition, LSVs were higher in the adult age group compared to the child group. To our knowledge, the present study is the first that compared LSV in child and adult age groups.

The relationship between gender and LSV in adult patients is controversial. While some researchers claim that there are higher values in males (14,21,22), some studies report the difference between genders to be not significant, similar to ours (3,20,23).

A meta-analysis of large series conducted with TE examined the relationship between BMI and LSV and investigated the normal and fibrosis-related LSV and the factors affecting it. The study found the mean, lower, and upper limit values of the normal LSV to be 4.61 (4.51-4.71) kPa in those with BMI <30 kg/m^2, and 4.46 (3.96-4.96) kPa in those with BMI>30 kg/m^2, respectively (20). A study not involving obese patients in the adult age group found the difference not significant in the comparison of the groups with a BMI of 18.0-25.0 kg/m^2 and a BMI of 25-30 kg/m^2, and suggested that BMI did not affect LSV (14). A study targeting the childhood age group reported no relationship between BMI and LSV in children with normal BMI (19). However, we found a positive correlation between BMI and LSV both in the general group and the groups aged <18 and ≥18 years. We also found the effect of BMI on LSV significant in the multiple regression analysis.

We believe that the current study is the first that shows the relationship between liver size and LSV. Although we found a moderate positive correlation between liver size and LSV in both the general group and the groups aged <18 and ≥18 years, the effect of liver size on LSV was not significant in the multiple regression analysis.

Our study has some limitations worth mentioning. Firstly, the measurements were made by a single radiologist. However, the values included five measurements obtained following the validation criteria specified in the materials and method section. In addition, patients with an IQR/median ratio of over 30% were not included in the study. Many studies show that intra- and inter-observer compatibility is remarkable in 2-D SWE (14,24). Secondly, the number of patients is relatively small. Studies involving a higher number of patients can be conducted in the upcoming period.

CONCLUSION

2-D SWE is an effective imaging method to evaluate LSV in both child and adult age groups. Normal LSV presented in this study can be used as reference values in the evaluation of various liver diseases with 2-D SWE. While there is a positive correlation between LSV and age, and BMI, there is no significant correlation between LSV and gender and liver size.

Ethics Committee Approval: The study was approved by the Clinical Researches Ethics Committee of Tokat Gaziosmanpaşa University (06.02.2020, 019).

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REFERENCES

1. Ferraioli G. Review of liver elastography guidelines. J Ultrasound Med. 2019;38(1):9-14.
2. Barr RG. Ultrasound of diffuse liver disease including elastography. Radiol Clin North Am. 2019;57(3):549-62.
3. Bende F, Mulabecirovic A, Sporea I, Popescu A, Sirli R, Helge O, et al. Liver stiffness by 2-D shear wave elastography in a healthy cohort. Ultrasound Med Biol. 2018;44(2):332-41.
4. Felicani C, De Molo C, Stefanescu H, Conti F, Mazzotta E, Gabus V, et al. Point quantification elastography in the evaluation of liver elasticity in healthy volunteers: a reliability study based on operator expertise. J Ultrasound. 2018;21(2):89-98.
5. Barr RG. Liver elastography still in its infancy. Radiology. 2018;288(1):107-8.
6. Ryu H, Ahn SJ, Yoon JH, Lee JM. Reproducibility of liver stiffness measurements made with two different 2-dimensional shear wave elastography systems using the comb-push technique. Ultrasonography. 2019;38(3):246-54.
7. Ryu H, Ahn SJ, Yoon JH, Lee JM. Inter-platform reproducibility of liver stiffness measured with two different point shear wave elastography techniques and 2-dimensional shear wave elastography using the comb-push technique. Ultrasonography. 2019;38(4):345-54.
8. Alrashed AI, Alfuraih AM. Reproducibility of shear wave elastography among operators, machines, and probes in an elasticity phantom. Ultrasonography. 2021;40(1):158-66.
9. Wu JF, Song SH, Lee CS, Chen HL, Ni YH, Hsu HY, et al. Clinical predictors of liver fibrosis in patients with chronic hepatitis B virus infection from children to adults. J Infect Dis. 2018;217(9):1408-16.
10. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology. 2019;156(5):1264-81.e4.
11. Yang H, Sun Y, Tang Y, Lu Y, Hu B, Ying T. Shear-wave elastography of the liver in a healthy pediatric population. J Clin Ultrasound. 2020;48(3):139-44.
12. Lewindon PJ, Balouch F, Pereira TN, Puertolas-Lopez MV, Noble C, Wixey JA, et al. Transient liver elastography in unsedated control children: Impact of age and intercurrent illness. J Paediatr Child Health. 2016;52(6): 637-42.
13. Tokuhara D, Cho Y, Shintaku H. Transient elastography-based liver stiffness age-dependently increases in children. PLoS One. 2016;11(11):e0166683.
14. Mulabecirovic A, Mjelle AB, Gilja OH, Vesterhus M, Havre FR. Liver elasticity in healthy individuals by two novel shear-wave elastography systems-Comparison by age, gender, BMI, and number of measurements. PLoS One. 2018;13(9):e0203486.
15. Dong Y, Sirli R, Ferraioli G, Sporea I, Chiorean L, Cui X, et al. Shear wave elastography of the liver - review on normal values. Z Gastroenterol. 2017;55(2):153-66.
16. Grgurevic I, Puljiz Z, Brnic D, Bokun T, Heinzl R, Lukic A, et al. Liver, and spleen stiffness and their ratio assessed by real-time two dimensional-shear wave elastography in patients with liver fibrosis and cirrhosis due to chronic viral hepatitis. Eur Radiol. 2015;25(11):3214-21.
17. Borner N, Schwerk WB, Braun B. Leber. In: Braun B, Gunther R, Schwerk WB, editors. Ultraschalldiagnostik: Lehrbuch und Atlas. Landsberg: Ecomed; 1987. p.1-18. German.
18. Eiler J, Kleinholdermann U, Albers D, Dahms J, Hermann F, Behrens C, et al. Standard value of ultrasound elastography using acoustic radiation force impulse imaging (ARFI) in healthy liver tissue of children and adolescents. Ultraschall Med. 2012;33(5):474-9.
19. Sun PX, Tong YY, Shi J, Zhang H, Liu SJ, Du J. Normal values of shear wave velocity in liver tissue of healthy children measured using the latest acoustic radiation force impulse technology. World J Clin Cases. 2019;7(21):3463-73.
20. Bazerbachi F, Haffar S, Wang Z, Cabezas J, Arias-Loste MT, Crespo J, et al. Range of normal liver stiffness and factors associated with increased stiffness measurements in apparently healthy individuals. Clin Gastroenterol Hepatol. 2019;17(1):54-64.e1.
21. Roulot D, Costes JL, Buyck JF, Warzocha U, Gambier N, Czernichow S, et al. Transient elastography as a screening tool for liver fibrosis and cirrhosis in a community-based population aged over 45 years. Gut. 2011;60(7):977-84.
22. Colombo S, Belloli L, Zaccanelli M, Badia E, Jamoletti C, Buonocore M, et al. Normal liver stiffness and its determinants in healthy blood donors. Dig Liver Dis. 2011;43(3):231-6.
23. Madhok R, Tapasvi C, Prasad U, Gupta AK, Aggarwal A. Acoustic radiation force impulse imaging of the liver: measurement of the normal mean values of the shearing wave velocity in a healthy liver. J Clin Diagn Res. 2013;7(1):39-42.
24. Kim DW, Suh CH, Kim KW, Pyo J, Park C, Jung SC. Technical performance of two-dimensional shear wave elastography for measuring liver stiffness: a systematic review and meta-analysis. Korean J Radiol. 2019;20(6):880-93.

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Evaluation of Clinical Features and Treatment Results of Pediatric Patients With Pre-Diagnosis of COVID-19

COVID-19 Ön Tanısı Olan Çocuk Hastaların Klinik Özellikleri ile Tedavi Sonuçlarının Değerlendirilmesi

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ABSTRACT

Aim: The epidemiological characteristics and modes of transmission of coronavirus disease 2019 (COVID-19) in children are not yet fully understood. In this study, it was aimed to evaluate clinical, laboratory, and radiological findings and treatment approaches in patients with negative and positive PCR tests among those with suspected COVID-19 retrospectively.
Material and Methods: This study was conducted with 317 patients under 18 years of age, who received outpatient or inpatient treatment with a pre-diagnosis of COVID-19. All patients were assessed for clinical course, disease severity, comorbidity, demographic characteristics, laboratory and radiodiagnostic tests, treatment characteristics, and outcomes.
Results: The PCR test was positive in 133 (42%) and negative in 184 (58%) of the patients with suspected COVID-19. There was a history of contact in 78 (58.6%) and 51 (27.7%) of the PCR-positive and negative patients, respectively ($p<0.001$). While the PCR-negative group had a higher rate of hospitalization ($p=0.020$), hospital stay was longer in PCR-positive cases ($p=0.037$). The white blood cell count ($p=0.001$), platelet count ($p=0.037$), neutrophil count ($p=0.015$), and lactate level ($p=0.025$) were significantly lower in the PCR-positive group.
Conclusion: Early detection and isolation of children with symptoms suggestive of COVID-19 are important to limit the spread of the disease. It can be challenging initially to clinically understand whether the case has COVID-19, especially in pediatric patients. PCR test is the gold standard in the diagnosis of COVID-19. Considering the prevalence, severity, and complications of the outbreak, it would be a proper approach to initially evaluate suspected patients as COVID-19 patients.
Keywords: COVID-19; childhood; SARS-CoV-2.

ÖZ

Amaç: Çocuklarda koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19)'un epidemiyolojik özellikleri ve bulaşma yolları henüz tam olarak anlaşılamamıştır. Bu çalışmada, COVID-19 şüphesiyle takip edilen PCR testi negatif ve pozitif olan hastalarda klinik, laboratuvar ve radyolojik bulgular ve tedavi yaklaşımlarının geriye dönük olarak değerlendirilmesi amaçlanmıştır.
Gereç ve Yöntemler: Bu çalışma, COVID-19 ön tanısı ile ayaktan veya yatarak tedavi gören 18 yaş altı 317 hasta ile yapılmıştır. Tüm hastalar klinik seyir, hastalık şiddeti, ek hastalıkları, demografik özellikler, laboratuvar ve radyodiagnostik testler, tedavi özellikleri ve sonuçları açısından değerlendirildi.
Bulgular: COVID-19 şüphesi olan hastaların 133'ünde (%42) PCR testi pozitif ve 184'ünde (%58) negatifti. PCR pozitif ve negatif hastaların sırasıyla 78'inde (%58,6) ve 51'inde (%27,7) temas öyküsü vardı ($p<0,001$). PCR-negatif grupta hastaneye yatış oranı daha yüksek iken ($p=0,020$), PCR-pozitif grupta hastanede kalış süresi daha uzundu ($p=0,037$). Beyaz kan hücresi sayısı ($p=0,001$), trombosit sayısı ($p=0,037$), nötrofil sayısı ($p=0,015$) ve laktat düzeyi ($p=0,025$) PCR pozitif grupta anlamlı düzeyde düşüktü.
Sonuç: COVID-19'u düşündüren semptomları olan çocukların erken tespiti ve izolasyonu, hastalığın yayılmasını sınırlamak için önemlidir. Özellikle pediatrik hastalarda vakanın COVID-19 olup olmadığını klinik olarak anlamak başlangıçta zor olabilir. PCR testi COVID-19 tanısında altın standarttır. Salgının yaygınlığı, şiddeti ve komplikasyonları göz önüne alındığında şüpheli hastaları başlangıçta COVID-19 hastası gibi değerlendirmek uygun bir yaklaşım olacaktır.
Anahtar kelimeler: COVID-19; çocukluk çağı; SARS-CoV-2.

INTRODUCTION

In December 2019, cases of pneumonia of unknown etiology began to occur in Wuhan, Hubei province of China (1). The disease rapidly spread to other parts of China and several countries across the world. Later, a new member of the enveloped RNA coronavirus family was identified in bronchoalveolar lavage fluid samples collected from a patient in Wuhan and was accepted as the causative agent of this disease by the Chinese Center for Disease Control and Prevention (2). The World Health Organization (WHO) named this virus as the 2019 novel coronavirus (2019-nCoV) and the disease as coronavirus disease 2019 (COVID-19).

The first case detected in Europe was reported in France on January 24, 2020, followed by case reports in many European countries (3). Turkey reported its first case of COVID-19 on March 10, 2020 (4).

The first pediatric case diagnosed with COVID-19 was reported in Shenzhen on January 20, 2020 (5). After this date, cases have been increasingly reported worldwide. The epidemiological characteristics and modes of transmission of COVID-19 in children are not yet fully understood. Center for Disease Control and Prevention has reported that only 2% of cases occur in individuals younger than 19 years (6). According to United States data, pediatric patients account for 1.7% of the cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (7). These data suggest that children are less affected by 2019-nCoV, unlike other viruses. Clinical findings in pediatric patients are atypical and relatively milder than in adult patients. Children are mostly asymptomatic. Some cases have upper respiratory symptoms such as fever, dry cough, malaise, runny nose, and nasal congestion. Gastrointestinal symptoms such as abdominal pain, nausea-vomiting, and diarrhea may also be observed (8).

Although COVID-19 is diagnosed according to certain criteria, it can be challenging to diagnose the disease in PCR-negative patients. Even if there is a strong clinical suspicion, it is important to have other criteria for diagnosis in PCR test negativity. The present study evaluated clinical, laboratory, and radiological findings and treatment approaches in patients with negative and positive PCR test results among those with suspected COVID-19. The COVID-19-related findings were comparatively evaluated according to the laboratory and clinical characteristics of the patients.

MATERIAL AND METHODS

This single-centered retrospective study was conducted with 317 patients under 18 years of age, who received outpatient or inpatient treatment with a pre-diagnosis of COVID-19. This study was approved by the Ethics Committee of Düzce University (07.12.2020, 258). The study included both patients with a positive PCR test and patients tested for suspected SARS-CoV-2 and had a negative PCR test. The medical records of the patients were reviewed. Patients above 18 years of age, with inaccessible files or with severely incomplete data were excluded from the study. All patients were assessed for epidemiological and demographic characteristics, laboratory and radiodiagnostic tests, and treatment characteristics and outcomes. In addition, fever, cough, tachypnea, tachycardia, hypoxia, sore throat, fatigue, myalgia, headache, vomiting, diarrhea, and loss of smell were examined. Complete blood count, serum biochemical tests, myocardial enzymes, coagulation tests, erythrocyte sedimentation rate, and C-reactive protein (CRP) levels of the patients were evaluated. Patients with respiratory complaints or suspected pneumonia on physical examination received PA chest X-ray and those with unexplained respiratory findings or poor clinical course received lung computed tomography (CT) as an additional test.

Patients with at least one of the conditions such as hypoxia (oxygen saturation <92%), tachypnea, loss of consciousness, coma, convulsions, dehydration, feeding difficulties, vomiting, diarrhea, findings of myocardial injury, elevated liver enzymes, coagulation disorders, and rhabdomyolysis were admitted to the hospital. Among these patients, those without any improvement upon treatment and with worsening general condition were admitted to the intensive care unit. The treatment protocol for inpatients included general supportive treatment, monitoring of lung, liver, kidney, and heart functions, fever management, and oxygen delivery at a rate of 2-4 l/min via nasal cannula, systemic corticosteroids, and inhaled corticosteroids for patients with a saturation of <92%. Patients with indications were initiated on oseltamivir therapy and/or antibiotherapy (Ceftriaxone/Cefotaxime/Azithromycin). Azithromycin was added to the treatment of outpatients in the presence of secondary bacterial infection.

Polymerase Chain Reaction (PCR) Method

Combined nasopharyngeal-oropharyngeal swab, sputum, or tracheal aspirate samples were collected from suspected cases of COVID-19. The samples were sent to the laboratory under appropriate conditions in a viral transport medium, where they were processed in the biosafety cabinet. Nucleic acid extractions were performed manually using Bio-speedy viral nucleic acid extraction buffer (Bioeksen R&D Technologies, Turkey). PCR testing was then performed using a SARS-CoV-2 (2019-nCoV) RT-qPCR detection kit (Bioeksen R&D Technologies, Turkey) and Montania® Real-Time PCR instruments (Anatolia Geneworks, Turkey). PCR test results were evaluated and reported by the same laboratory manager.

Statistical Analysis

The distribution of the data was analyzed by the Kolmogorov-Smirnov test, and the Independent Samples t-test or the Mann-Whitney U test were used to compare the groups, depending on the distribution. Categorical variables were analyzed by Pearson chi-square, Fisher's exact, or Fisher-Freeman-Halton tests, depending on the expected count. Correlations among quantitative variables were examined by Pearson or Spearman correlation analysis, depending on the distribution of the variable. Descriptive statistics of the data were expressed as mean±standard deviation or median, quartiles, and minimum-maximum values, while categorical variables were summarized as frequency and percentage. Statistical analyses were performed using IBM SPSS v.22 software. The statistical significance level was considered as a p value of less than 0.05.

RESULTS

Among 317 children included in the study, the PCR test was positive in 133 (42%) and negative in 184 (58%). There was no significant difference in age (p=0.529) and gender (p=0.854) between PCR-positive and negative patients. There was a history of contact in 27.7% (n=51) and 58.6% (n=78) of PCR-negative and positive patients, respectively (p<0.001). The PCR-negative group had a higher rate of hospitalization (p=0.020). On the other hand, hospital stay was longer in PCR-positive cases than in negative ones (p=0.037). Oral, IV, or inhaled treatment was required in 59.8% (n=110) and 57.1% (n=76) of PCR-negative and positive cases, respectively (Table 1).

The comparison of the patients' clinical findings revealed that fever was more common in PCR-positive patients, while there was no significant difference in pulmonary involvement, cough, tachypnea, tachycardia, hypoxia, sore throat, fatigue, myalgia, headache, GI involvement findings, and additional chronic diseases between the groups. The PCR-positive and negative cases had similar comorbidity rates. These comorbidities were asthma, epilepsy, familial Mediterranean fever, hyperthyroidism, congenital adrenal hyperplasia, obesity, scoliosis, Tip 1 diabetes mellitus, prematurity, and cerebral palsy.

Peribronchial infiltration and consolidation were observed as chest X-ray findings, and the findings in positive and negative cases were similar. The lung tomography findings of ground glass, consolidation, empyema, and atelectasis were also similar in both groups of patients.

The white blood cell (WBC) count (p=0.010), platelet count (p=0.037), neutrophil count (p=0.015), and lactate level (p=0.025) were statistically significantly lower in the PCR-positive group (Table 2).

Age and the occurrence of disease symptoms (sore throat, myalgia, headache, and loss of smell) were positively correlated in PCR-positive patients (r=0.384, p=0.034). However, this correlation was not found in PCR-negative patients. Similarly, it was observed that the frequency of symptoms increased with increasing age in PCR-positive patients. On the other hand, both WBC (r=-0419, p<0.001) and lymphocyte counts (r=-0578, p<0.001) decreased with increasing age in PCR-positive COVID-19 patients.

Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, one of the important complications of the disease, was detected in three of the PCR-positive patients, while only two of them required hospitalization. All of the outpatients and inpatients recovered. These patients were excluded from the study.

The presence of additional chronic diseases is a risk factor for COVID-19. Depending on the severity of the disease, it can directly affect mortality and morbidity. The comparison of the patients related to additional chronic diseases was presented in Table 3.

When the symptoms and findings of the patients were evaluated by gender, sore throat was more common in females, while creatine kinase (CK) level was higher in males. Regarding all other parameters, there was no significant difference in gender between the two groups.

DISCUSSION

COVID-19 is an important disease that has affected the whole world and caused serious mortality and morbidity. Information about the occurrence and course of the disease in children has yet to be revealed. The present study assessed clinical and laboratory characteristics, treatment methods, and other disease-related factors in PCR-positive and negative cases among pediatric patients with suspected COVID-19 who presented with acute upper or lower respiratory tract infection symptoms.

Table 1. Demographic and clinical characteristics of PCR-positive and PCR-negative patients

	PCR-positive (n=133)	PCR-negative (n=184)	p
Age (year), mean±SD	8.66±6.18	8.24±5.76	0.529
Gender, n (%)			
Male	65 (48.9)	88 (47.8)	0.854
Female	68 (51.1)	96 (52.2)	
History of patient contact, n (%)	78 (58.6)	51 (27.7)	**<0.001**
Hospitalization rate, n (%)	4 (3.0)	17 (9.2)	**0.028**
Length of hospital stay (day), median (IQR) [min-max]	11 (13) [4-18]	3 (4) [1-11]	**0.037**
Fever, n (%)	72 (54.1)	71 (38.6)	**0.006**
Cough, n (%)	39 (29.3)	44 (23.9)	0.280
Tachypnea, n (%)	6 (4.5)	7 (3.8)	0.754
Tachycardia, n (%)	2 (1.5)	2 (1.1)	0.743
Hypoxia, n (%)	3 (2.3)	4 (2.2)	0.961
Comorbidity, n (%)	19 (14.3)	27 (14.7)	0.923
X-Ray, n (%)			
Normal	101 (75.9)	144 (78.3)	0.447
Peribronchial infiltration	30 (22.6)	33 (17.9)	
Consolidation	2 (1.5)	6 (3.3)	
Empyema	0 (0.0)	1 (0.5)	
Medication (n=76 vs n=111), n (%)			
Antibiotic	64 (84.2)	103 (92.8)	0.148
Antibiotic + Antiviral	10 (13.2)	6 (5.4)	
Corticosteroid	1 (1.3)	2 (1.8)	
Corticosteroid + Acetyl salicylic acid	1 (1.3)	0 (0.0)	

SD: standard deviation, IQR: interquartile range

Table 2. Laboratory parameters of PCR-positive and PCR-negative patients

	PCR-positive (n=133)	PCR-negative (n=184)	p
WBC (10^3/ul), median (IQR) [min-max]	7.2 (4.4) [2.7-21.6]	8.6 (6.0) [2.1-25.1]	**0.001**
RBC (10^6/ul), mean±SD	4.61±0.53	4.66±0.52	0.441
RDW (%), mean±SD	13.91±1.68	14.03±1.78	0.611
Platelet (10^3/ul), median (IQR) [min-max]	269 (107) [68-624]	282 (108) [107-633]	**0.037**
Lymphocyte (10^3/ul), median (IQR) [min-max]	1.86 (1.69) [0.4-7.11]	2.14 (1.85 [0.3-8.24]	0.654
Neutrophil (10^3/ul), median (IQR) [min-max]	4.21 (3.70) [0.39-13.02]	4.70 (5.83) [0.62-22.52]	**0.015**
NLR, median (IQR) [min-max]	1.79 (2.03) [0.12-18.06]	2.28 (4.17) [0.02-58.61]	0.195
PLR, median (IQR) [min-max]	128.83 (93.99) [27.71-480]	128.91 (134.33) [30.07-580]	0.690
Uric acid (mg/dl), mean±SD	3.95±1.13	3.73±1.37	0.245
CRP (mg/dl), median (IQR) [min-max]	0.39 (0.71) [0.06-18.97]	0.35 (2.41) [0.01-25.90]	0.935
Urea (mg/dl), mean±SD	20.68±7.35	22.00±7.43	0.195
BUN (mg/dl), mean±SD	9.91±3.52	10.42±3.42	0.288
Creatinine (mg/dl), mean±SD	0.54±0.19	0.53±0.18	0.567
AST (IU/l), median (IQR) [min-max]	29.5 (20.9) [11.8-127.6]	28.1 (13.5) [10.7-180.7]	0.602
ALT (U/ml), median (IQR) [min-max]	14.1 (12.3) [5.6-85.2]	14.1 (8.6) [4.6-117.9]	0.933
Phosphorus (mg/dl), mean±SD	4.70±1.08	4.51±0.96	0.188
Lactate (mg/dl), mean±SD	1.69±0.67	3.12±1.28	**0.025**
LDH (U/l), mean±SD	257.68±78.39	265.13±62.57	0.674
Procalcitonin, median (IQR) [min-max]	0.07 (0.31) [0.03-4.67]	0.27 (0.26) [0.02-20.77]	0.233
ESR (mm/h), median (IQR) [min-max]	16 (19) [8-60]	19 (32) [2-140]	0.472
CK (mg/dl), median (IQR) [min-max]	109 (103) [19-302]	81 (67) [16-299]	0.589
CK-mb (IU/l), median (IQR) [min-max]	22.5 (31.9) [4-58]	29.0 (15.8) [15-74]	0.295
PT (sn), median (IQR) [min-max]	9.71 (3.29) [1.04-13.70]	9.96 (9.89) [1.08-68.60]	0.978
aPTT (sn), mean±SD	28.89±4.75	30.18±5.38	0.418
D-dimer (mcg/ml), median (IQR) [min-max]	0.26 (0.41) [0.02-9.29]	0.33 (0.61) [0.20-3.43]	0.401
Vitamin D (ng/ml), median (IQR) [min-max]	17.71 (15) [7.40-50.35]	22.43 (13.15) [5.61-53.40]	0.160

WBC: white blood cell, RBC: red blood cell, RDW: red cell distribution width, NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, CRP: C-reactive protein, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ESR: erythrocyte sedimentation rate, CK: creatine kinase, PT: prothrombin time, aPTT: activated partial thromboplastin time, SD: standard deviation, IQR: interquartile range

Table 3. Demographic and clinical characteristics of the PCR-positive patients according to the comorbidity

Comorbidity	Yes (n=19)	No (n=114)	p
Age (years), mean±SD	12.00±5.22	8.11±6.17	**0.010**
Gender, n (%)			
Male	8 (42.1)	57 (50.0)	0.524
Female	11 (57.9)	57 (50.0)	
History of patient contact, n (%)	7 (36.8)	71 (62.3)	**0.037**
Hospitalization rate, n (%)	1 (5.3)	3 (2.6)	0.464
Tachypnea, n (%)	4 (21.1)	2 (1.8)	**0.004**
Normal CT findings, n (%)	17 (89.5)	114 (100)	**0.019**

SD: standard deviation, CT: computed tomography

The reason COVID-19 is less severe in children than in adult patients has not yet been fully clarified. This may be related to both less viral exposure and host factors. Being in less contact with patients and being in a relatively more isolated environment compared to adults are important factors for the prevention of the disease in children. The risk of transmission is further reduced, especially with isolation measures. Children who have been out of the school environment and have an isolated life at home are less likely to catch the disease. Considering the host effect, factors related to angiotensin-converting enzyme II (ACE2) become prominent. This enzyme has been shown to be a cell receptor for the SARS-CoV (9). There is amino acid homology between 2019-nCoV and SARS-CoV, and ACE2 has been identified as the cell receptor of 2019-nCoV, like SARS-CoV (10). Since the level of ACE2 maturity and function (for example, the ability to bind) may be lower in children than in adults, it is estimated that children are less likely to be infected with 2019-nCoV (11). However, the severity of COVID-19 symptoms may change with age due to differences in ACE2 expression, lymphocyte count, and acquired immunity (12). On the other hand, ACE2 may increase especially in children entering adolescence (13). The lack of difference in age and disease severity between PCR-positive and negative pediatric patients in the present study, unlike adult patients, may be related to the study patient group that included younger patients who had not yet entered adolescence. Another prominent factor is the increased incidence of viral infections in children in winter. Children often have respiratory infections, for example, respiratory syncytial virus (RSV), during the winter and have higher levels of antibodies against viruses than adults do (14). Furthermore, the immune system of children is still developing and therefore their response to pathogens may differ from those of adults.

Studies have revealed that history of contact is a significant risk factor for the COVID-19 outbreak (15). The low incidence of COVID-19 in children can be explained by

their fewer contacts. The more common history of contact in SARS-CoV-2 positive children compared to negative children in the present study suggests that the disease is transmitted by contact in children, like in adults.

Admission to the intensive care unit is considered a direct indicator of a more severe course of the disease. Prior studies with pediatric patients report different results regarding the rate of critically ill patients admitted to the intensive care unit. A previous study observed that 13 of 67 SARS-CoV-2 positive pediatric patients presenting to the emergency department needed intensive care. It was reported that cough and shortness of breath were the major symptoms among these patients, and they were considered severe cases and admitted to the intensive care unit (16). Another study found the rate of SARS-CoV-2 positive pediatric patients admitted to the intensive care unit to be 16% (17). The number of critical cases among the patients included in this study was 3%. None of the PCR-negative patients who were admitted to the hospital due to suspected COVID-19 were indicated for intensive care. Even if the patient is clinically suspected to have COVID-19, the PCR test is considered important data for diagnosing the disease and understanding the severity. In addition, hospital stay was longer in PCR-positive children with COVID-19 than in those who were PCR-negative. When the patients were evaluated considering both the length of hospital stay and indications for intensive care, the disease was found to progress more severely in children with COVID-19 compared to those with a negative PCR test.

Viruses are the most common cause of acute respiratory tract infections in children and the etiological agents differ according to the age and immunity of the patient. Imaging also shows different findings according to the etiological agent. CT can provide valuable information for the diagnosis of respiratory tract infections. The type of viral pathogen, the immune status of the host, and the pathogenicity of the viral agent may alter CT findings. Clinical and CT findings of many respiratory viral pathogens such as influenza, human parainfluenza virus, RSV, rhinovirus, and adenovirus have been described. In general, causative agents of respiratory viral infections lead to lung CT findings such as bronchial wall thickening, multifocal consolidation, or ground-glass opacity. When a bacterial infection develops secondary to viral pneumonia, distinctive findings such as diffuse air-space patterns can be observed (18). In the present study, the lung CT findings did not significantly differ between PCR-negative and positive cases. Although PCR is an important marker for diagnosing SARS-CoV-2, it is controversial that PCR negativity can completely exclude the disease. The CT findings of PCR-negative cases being similar to positive cases increase the importance of the PCR test in diagnosis. However, the rate of COVID-19 but PCR-negative cases can also be quite high. Fang et al. (19) reported that the rate of false-negative PCR could increase up to 30%. Another study indicated that an initially negative PCR test might turn positive in repeated testing (20). The present study could not assess the rate of false negativity because PCR-negative patients among the study patients were not tested again. However, similar CT findings suggest that PCR-negative patients might also have COVID-19. We believe that approaching patients as SARS-CoV-2 positive cases until proven otherwise if there is clinical suspicion would be an approach both to increase the success of treatment and to reduce the spread of the disease. On the other hand, it should be kept in mind that other viral agents may also lead to CT findings similar to COVID-19.

Studies with adults have reported that gender might be a significant risk factor for COVID-19 and might affect the severity of the disease. Expression of ACE2 receptor and transmembrane protease serine 2 (TMPRSS2) are believed to be factors effective in the entry of the virus into the cell. These factors may also cause the disease to present different characteristics by gender. However, Mukherjee et al. (21) reported that individual behavioral differences, habits such as smoking, and comorbidities might also affect gender-related differences. Di Stadio et al. (22) stated that the lower prevalence and milder course of COVID-19 in women might be related to the effect of estrogen. According to the researchers, estrogen stimulates the immune system by modulating the functions of B cells and improving the activity of T-helper-2 cells, this effect occurs especially in the upper respiratory tract mucosa, thereby preventing the virus from entering the body and spreading. However, studies show no gender differences in the prevalence and severity of the disease in children (23). The present study also obtained similar results. Apart from genetic predisposition, the lower prevalence of COVID-19 in children can be explained by habits and comorbidities being less common in children compared to adults. Furthermore, the hormonal effect-related factors do not occur since they have not yet entered puberty. Due to all these factors, gender differences may not be observed in pediatric patients with COVID-19.

Comparison of the study group by hematological parameters revealed that WBC and neutrophil counts were statistically significantly lower in PCR-positive patients, but none of the cases were neutropenic. Neutrophils are the most important cellular defense mechanism against infections, which are the first to respond to viral invasion and limit viral replication and spread. Nevertheless, neutrophils are also known to mediate detrimental effects on the host during viral infection (24). A previous study showed that an elevated neutrophil count was associated with the development of acute respiratory distress syndrome (ARDS) and an increased risk of mortality in adults with COVID-19 (25). Accordingly, it can be predicted that patients without neutrophilia would have a milder course of the disease. In the present study, the neutrophil count of the patients did not increase, and most of the cases survived the disease with a mild course. On the other hand, the immune response to a viral infection is primarily mediated by lymphocytes. It is hypothesized that the decreased lymphocyte count may be due to increased lymphocyte consumption, destruction of lymphatic tissues, and cytokine-related T cell apoptosis in COVID-19 patients (26). It has been shown that 2019-nCoV binds to the ACE2 receptor on the lymphocyte surface, infiltrating the lymphocyte and causing lymphopenia (27). Thus, the lymphocyte count decreases with the increasing severity of the disease. While lymphopenia is considered an important prognostic criterion in adult patients, it is a controversial issue in pediatric patients. Some papers have reported a relationship between lymphopenia and disease severity, while others could not demonstrate such a

relationship (28,29). The less severe course of the disease in pediatric patients unlike in adults can be explained by the less severe inflammation, the lower levels of cytokine activation, and the non-development of lymphopenia due to the immature immune system. It was not possible to associate the changes in leukocyte and lymphocyte counts with the severity of the disease because only two patients had a severe course in the study group. In addition, there were no significant changes in lymphocyte and leukocyte counts of these two patients. On the other hand, studies have reported that an increase in the neutrophil-to-lymphocyte ratio is a negative prognostic indicator for hospitalized patients (30). The lack of any difference in this respect in the patient group can be explained by the mild course in most cases.

Although the platelet count was statistically significantly lower in PCR-positive cases than in negative cases, platelet counts were within normal limits in both groups. Changes in platelet count and activity are closely associated with various diseases (31). Platelets not only contribute to hemostasis but are also involved in inflammation and host defense. Decreased production and increased consumption of platelets due to diffuse alveolar damage are believed to cause thrombocytopenia in COVID-19 patients (23). However, this may occur in patients with a severe course and high mortality.

The present study found a higher lactate level in PCR-negative patients than in positive patients; however, there was no clinical difference in disease severity between the groups. Lactate measurement is used in the assessment of critically ill patients as an indicator of both disease severity and mortality. Lactate accumulates in a state of anaerobic metabolism and reflects the degree of tissue hypoxia due to poor perfusion (32). Hyperlactatemia occurs in trauma, hypoxemia, severe anemia, and septic shock (33). In critically ill children with sepsis, hyperlactatemia on admission is associated with high mortality (32). However, research has not yet clarified the clinical impact of changes in serum lactate levels in patients with COVID-19. It is believed that the present study could not obtain any significant result regarding lactate levels due to the low number of severe patients.

Severe rhabdomyolysis cases associated with COVID-19 have been reported in the literature as case reports (23,34). Some studies from China reported patients with elevated levels of CK without developing rhabdomyolysis. A study of 95 adult patients established various levels of CK elevation in 28 patients (35). Another study found high CK levels in 10% of adult patients (36). In children, CK elevation associated with COVID-19 is a rare finding. A study on CK levels in this age group reported that there was only one patient with elevated CK and none of the patients developed rhabdomyolysis (37). In general, viral rhabdomyolysis occurs due to direct viral invasion of the muscle, cytokine storm resulting in muscle damage, and muscle injury caused by circulating viral toxins (34). Chen et al. (38) have suggested that rhabdomyolysis associated with COVID-19 is secondary to cytokine storm due to the presence of elevated inflammatory markers and the absence of viral particles in muscle biopsies. The present study detected a moderate level of CK elevation in eight of the males and only one of the females in the PCR-positive patient group. None of these patients were seriously ill and indicated for intensive care. Cytokine storm is an important complication in COVID-19 that aggravates the clinical picture. However, the disease does not usually progress severely in these patients, suggesting that CK elevation may be due to reasons other than cytokine storm. There is not enough information about this subject in the literature. It is believed that the higher incidence of CK elevation in the males in the study was a coincidental finding rather than sex-related differences. Nevertheless, the CK levels of the patients under follow-up did not increase very much and returned to normal levels in a short time, indicating the clinical insignificance of this elevation.

This study had some limitations. The study only included patients presenting to a healthcare facility, which is a limitation. The patients were not re-evaluated for clinical and laboratory findings after discharge, and no comparison could be made with the disease findings. The third limitation was that the suspected cases were more serious and critical than patients with confirmed COVID-19. This suggests that some of the PCR-negative patients might also have COVID-19. However, other viral serological studies could not be performed for PCR-negative patients. Therefore, the presence of an infection other than COVID-19 could also not be demonstrated in these patients.

CONCLUSION

Early detection and isolation of children with symptoms suggestive of COVID-19 are important to limit the spread of the disease. Although the PCR test is the best diagnostic tool, it could not provide clear information to diagnose the disease. Low viral load, inappropriate specimen type, suboptimal specimen collection, and low analytic sensitivity may be related to false negative PCR test. Considering the prevalence, severity, and complications of the outbreak, it would be a proper approach to initially evaluate suspected patients as COVID-19 patients even if the PCR is negative. As the number of cases increases, more detailed and clear information about COVID-19 will be available. There is a need for studies with broad participation and post-recovery assessment, especially to explain the different courses of the disease between children and adults.

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REFERENCES

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382(13):1199-207.
2. Tan W, Zhao X, Ma X, Wang W, Niu P, Xu W, et al. A novel coronavirus genome identified in a cluster of pneumonia cases - Wuhan, China 2019-2020. China CDC Wkly. 2020;24;2(4):61-2.
3. who.int [Internet]. World Health Organization. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations: scientific brief. [Cited: 2022 March 20]. Available from: https://apps.who.int/iris/handle/10665/331601
4. saglik.gov.tr [Internet]. Republic of Türkiye Ministry of Health. COVID-19 Information Platform. [Cited: 2022 March 20]. Available from: https://covid19.saglik.gov.tr/
5. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;15;395(10223):514-23.
6. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42.
7. CDC COVID-19 Response Team. Coronavirus disease 2019 in children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(14):422-6.
8. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al.; Chinese Pediatric Novel Coronavirus Study Team. SARS-CoV-2 Infection in children. N Engl J Med. 2020;382(17):1663-5.
9. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426(6965):450-4.
10. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.
11. Fang F, Luo XP. [Facing the pandemic of 2019 novel coronavirus infections: the pediatric perspectives]. Zhonghua Er Ke Za Zhi. 2020;58(2):81-5. Chinese
12. Cristiani L, Mancino E, Matera L, Nenna R, Pierangeli A, Scagnolari C, et al. Will children reveal their secret? The coronavirus dilemma. Eur Respir J. 2020;55(4):2000749.
13. Liu J, Ji H, Zheng W, Wu X, Zhu JJ, Arnold AP, et al. Sex differences in renal angiotensin converting enzyme 2 (ACE2) activity are 17β-oestradiol-dependent and sex chromosome-independent. Biol Sex Differ. 2010;1(1):6.
14. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145(6):e20200702.
15. Phan LT, Nguyen TV, Luong QC, Nguyen TV, Nguyen HT, Le HQ, et al. Importation and human-to-human transmission of a novel coronavirus in Vietnam. N Engl J Med. 2020;382(9):872-4.
16. Chao JY, Derespina KR, Herold BC, Goldman DL, Aldrich M, Weingarten J, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 at a tertiary care medical center in New York City. J Pediatr. 2020;223:14-9.e2.
17. Tagarro A, Epalza C, Santos M, Sanz-Santaeufemia FJ, Otheo E, Moraleda C, et al Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. JAMA Pediatr. 2020:e201346.
18. Koo HJ, Lim S, Choe J, Choi SH, Sung H, Do KH. Radiographic and CT features of viral pneumonia. Radiographics. 2018;38(3):719-39.
19. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. Radiology. 2020;296(2):E115-7.
20. Harwood R, Sinha I. Diagnosis of COVID-19 in children: the story evolves. BMC Med. 2020;18(1):158.
21. Mukherjee S, Pahan K. Is COVID-19 gender-sensitive? J Neuroimmune Pharmacol. 2021;16(1):38-47.
22. Di Stadio A, Della Volpe A, Ralli M, Ricci G. Gender differences in COVID-19 infection. The estrogen effect on upper and lower airways. Can it help to figure out a treatment? Eur Rev Med Pharmacol Sci. 2020;24(10):5195-6.
23. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al; China Medical Treatment Expert Group for COVID-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.
24. Naumenko V, Turk M, Jenne CN, Kim SJ. Neutrophils in viral infection. Cell Tissue Res. 2018;371(3):505-16.
25. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-43.
26. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529-39.
27. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020;24;12(1):8.
28. Meena J, Yadav J, Saini L, Yadav A, Kumar J. Clinical features and outcome of SARS-CoV-2 infection in children: A systematic review and meta-analysis. Indian Pediatr. 2020;57(9):820-6.
29. Ma X, Liu S, Chen L, Zhuang L, Zhang J, Xin Y. The clinical characteristics of pediatric inpatients with SARS-CoV-2 infection: A meta-analysis and systematic review. J Med Virol. 2021;93(1):234-40.
30. Allahverdiyev S, Quisi A, Harbalıoğlu H, Alıcı G, Genç Ö, Yıldırım A, et al. The neutrophil to lymphocyte ratio and in-hospital all-cause mortality in patients with COVID-19. Eur J Ther. 2020;26(3):251-6.
31. Zarychanski R, Houston DS. Assessing thrombocytopenia in the intensive care unit: the past, present, and future. Hematology Am Soc Hematol Educ Program. 2017;2017(1):660-6.

32. Hatherill M, McIntyre AG, Wattie M, Murdoch IA. Early hyperlactataemia in critically ill children. Intensive Care Med. 2000;26(3):314-8.
33. Batra P, Dwivedi AK, Thakur N. Bedside ABG, electrolytes, lactate and procalcitonin in emergency pediatrics. Int J Crit Illn Inj Sci. 2014;4(3):247-52.
34. Gefen AM, Palumbo N, Nathan SK, Singer PS, Castellanos-Reyes LJ, Sethna CB. Pediatric COVID-19-associated rhabdomyolysis: a case report. Pediatr Nephrol. 2020;35(8):1517-20.
35. Zhang G, Zhang J, Wang B, Zhu X, Wang Q, Qiu S. Analysis of clinical characteristics and laboratory findings of 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a retrospective analysis. Respir Res. 2020;21(1):74.
36. Zheng F, Tang W, Li H, Huang YX, Xie YL, Zhou ZG. Clinical characteristics of 161 cases of coronavirus disease 2019 (COVID-19) in Changsha. Eur Rev Med Pharmacol Sci. 2020;24(6):3404-10.
37. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis. 2020;20(6):689-96.
38. Chen LL, Hsu CW, Tian YC, Fang JT. Rhabdomyolysis associated with acute renal failure in patients with severe acute respiratory syndrome. Int J Clin Pract. 2005;59(10):1162-6.

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Prognostic Value of Chest CT in the Elderly Patients Admitted with COVID-19 Pneumonia

COVID-19 Pnömonisi ile Başvuran Yaşlı Hastalarda Göğüs BT Prognostik Değeri

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ABSTRACT

Aim: The late elderly, are the leading group of non-survivors infected with the coronavirus disease 2019 (COVID-19). Computed tomography (CT) imaging has been recognized as an important diagnostic method for COVID-19. This study aimed to determine the prognostic performance of CT imaging in patients above 75 years old.

Material and Methods: After meeting the inclusion and exclusion criteria 56 elderly patients, 28 male, and 28 female were included in the study. Two radiologists interpreted CT imaging and a third experienced radiologist was in charge of reviewing the data and imaging findings in the controversial and disagreement cases. The lung score was determined for each patient, and radiologic signs were also examined.

Results: The mean age of the patients was 81.4±5.0 years. Thirty-six patients survived, and 20 did not. 28 (50.0%) patients had central involvement, while 25 (44.6%) patients had diffuse involvement. Radiologic signs such as consolidation and air bronchogram were more common among non-survivors than survivors (both p=0.001). The mean lung score for the survivors was 8.75±6.21 and 13.45±6.41 for non-survivors, and the difference between the two groups was statistically significant (p=0.010). The area under the receiver operating characteristic curve for a cut-off score of 12 was 0.714 (95% CI, 0.577 to 0.827, p=0.003).

Conclusion: It seems that using lung scores can play a very important role in predicting the condition of hospitalized patients over 75 years old.

Keywords: Elderly; geriatrics; COVID-19; computed tomography; imaging; radiology.

ÖZ

Amaç: İleri yaşlılar, koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) ile enfekte olan ve hayatta kalamayanların önde gelen grubudur. Bilgisayarlı tomografi (BT) görüntüleme COVID-19 için önemli bir tanı yöntemi olarak kabul edilmiştir. Bu çalışmanın amacı 75 yaş üstü hastalarda BT görüntülemenin prognostik performansını belirlemektir.

Gereç ve Yöntemler: Dahil etme ve hariç tutma kriterleri karşılandıktan sonra 28 erkek 28 kadın olmak üzere 56 yaşlı hasta çalışmaya dahil edildi. İki radyolog BT görüntülerini yorumladı ve üçüncü bir deneyimli radyolog, tartışmalı ve anlaşmazlık vakalarında verileri ve görüntüleme bulgularını gözden geçirmekten sorumluydu. Her bir hasta için akciğer skoru belirlendi ve radyolojik bulgular incelendi.

Bulgular: Hastaların yaş ortalaması 81,4±5,0 yıl idi. Otuz altı hasta hayatta kaldı ve 20 hasta hayatta kalamadı. 28 (%50,0) hastada merkezi tutulum varken 25 (%44,6) hastada ise yaygın tutulum vardı. Konsolidasyon ve hava bronkogramı gibi radyolojik bulgular hayatta kalamayanlar arasında hayatta kalanlardan daha yaygındı (her iki p=0,001). Hayatta kalanlar için ortalama akciğer skoru 8,75±6,21 ve hayatta kalamayanlar için 13,45±6,41 idi ve iki grup arasındaki farklılık istatistiksel olarak anlamlıydı (p=0.010). Alıcı işlem karakteristiği eğrisi altında kalan alan 12 kesim değeri için 0,714 (%95 GA, 0,577 ile 0,827, p=0,003) idi.

Sonuç: Akciğer skorlarının kullanılmasının hastanede yatan 75 yaş üstü hastaların durumunu tahmin etmede çok önemli bir rol oynayabileceği görülmektedir.

Anahtar kelimeler: Yaşlı; geriatri; COVID-19; bilgisayarlı tomografi; görüntüleme; radyoloji.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is characterized by viral pneumonia accompanied by clinical symptoms such as dyspnea, cough, and fever. COVID-19 is usually associated with a mild clinical course in healthy adults with no pre-existing conditions. Still, it has shown to be associated with acute severe respiratory distress syndrome and a grim clinical outcome in the elderly and those with pre-existing conditions. A retrospective study comparing the elderly with other age groups has shown that the elderly are at higher risk of being hospitalized in the intensive care unit (ICU) and dying from the disease. They also have a significantly higher pneumonia severity index (PSI) score (1). Clinicians speculate that para-clinical findings may be significantly altered in the elderly compared to others, such as laboratory test results and imaging findings observed in chest X-rays and computed tomography (CT). CT imaging has been used extensively in the diagnosis of COVID-19, and studies have proven it to be more sensitive than molecular assays in diagnosing the disease (2,3). CT imaging is also possibly associated with disease severity and can be used in the evaluation of prognosis. Bilateral multifocal involvement is associated with more severe clinical signs and symptoms, increased mortality rate, and specific imaging findings such as airspace consolidations are seen in specific periods of the disease (4).

Furthermore, it has been suggested CT imaging may have distinct characteristics in pediatric patients, with more uncommon radiologic signs observed, such as a tree in bud formation, collapse, nodular opacities, and predominance of central lesions, in contrast to peripheral lesions (5). In contrast to pediatric patients, a rather small number of studies have focused on CT imaging in older adults, especially the late elderly (those who are older than 65 years old), who are at an increased risk of severe complications. Most studies are composed of cases in their 40s and 50s (6). Particular attention should be given to CT imaging in the late elderly, as it may act as a prognostic marker to provide early provision, and prompt early provision of more serious medical interventions, such as hospitalization in ICU wards, early intubation, early initiation of anti-viral medication, etc. (7). This is of clinical significance as the already existing evidence may not be entirely generalizable for the elderly population as a limited number of studies include large groups of the elderly (8). In the current study, we aimed to evaluate the diagnostic and prognostic value of CT imaging on admission for late elderly (aging more than 75) patients.

MATERIAL AND METHODS

The present retrospective study was conducted on late elderly patients admitted to medical, and educational centers at Urmia University of Medical Sciences between February 1st and July 10th, 2020. All of the included patients were initially managed by attending specialist physicians and then had CT imaging. Age and other demographic information of the patients were collected via the health information system of the institutions and electronic medical records of individuals. In cases of disagreement between the information, patients or their representatives were contacted for more information. All patients included in the study were followed until a definite clinical outcome. Inclusion criteria of patients consisted of those ages above 75 years old, who were diagnosed with COVID-19. Exclusion criteria consisted of those individuals with concomitant infections, heart failure on presentation, patients with pre-existing lung disease such as tuberculosis and idiopathic fibrosis, those individuals who had a CT scan performed on late days of admission, or those with CT images not taken in our centers.

Molecular Assay

Polymerase chain reaction (PCR) was performed to detect if patients were indeed infected with the virus. Specimens obtained from the nasopharynx and oropharynx, based on guidelines by the World Health Organization (WHO), were used to detect the virus. Taqman® Premix TAKARA diagnostic kits (TaKaRa, Dalian, China) were used. All patients underwent molecular assay on the first day of admission, and if needed, secondary molecular assay tests were performed if necessary. All of the patients included had positive PCR results.

CT Imaging Protocol

Patients underwent an imaging protocol based on the WHO guidelines and recommendations provided by the Ministry of Health and Education of the country where the study was performed (9). CT imaging was done with (multi-slice and multi-detector), 256-slice Siemens SOMATOM (Hannover, Germany) and (multi-slice and multi-detector), 256-slice Toshiba Alexion (Tokyo, Japan) machines based on the following technical specifications: low dose mode, automatic tube current modulation with a voltage of 120 kVp, axial and sagittal images, matrix size of 512×512, increment and thickness of 1.5 mm.

Interpretation of Imaging Findings

Interpretation of imaging findings was done separately by two board-certified radiologists with 12 and 2 years of experience in cardiothoracic imaging. The radiologists were not aware of the clinical diagnosis or outcome of the patients. In cases of disagreement, a third experienced radiologist was in charge of reviewing the data and imaging findings. A checklist was provided based on the recommendations by the Radiological Society of North America (RSNA), and Kanne et al (10,11). Lung score was defined and estimated based on the article by Francone et al. (4,10-12). As mentioned in the previous publications, lung score was determined based on the following: 0: no involvement seen, 1: less than 5% involvement in the affected lobe, 2: 6-25% involvement in the affected lobe, 3: 26-50% involvement in the affected lobe, 4: 51-75% involvement in the affected lobe, and 5: involvement more than 75% of the affected lobe. Based on the same publications, two cut-off (8 and 12) scores were determined to categorize the patients (13). These cut-offs are based on the anatomic properties of the human lung, and the fact that involvement equal to two or three complete lobes (hence the cut-off of 8 or 12, respectively) is considered as moderate to severe involvement (14).

Statistical Analysis

Statistical analysis was done by SPSS v.23.0 (IBM Inc. Chicago, USA) and MedCalc v.19.3.0 (MedCalc Software Ltd, Ostend, Belgium). The normality assumption was determined using the Kolmogorov-Smirnov test. Categorical variables were presented as numbers and percentages. Mean±standard deviation was used to present

numeric data. Independent samples t, chi-square, and Fisher's exact tests were used to compare findings between the groups. The receiver operating characteristic (ROC) curve was drawn, and the area under the curve (AUC) was determined. An AUC of 1 to 0.9 was considered to have an excellent predictive value, 0.9 to 0.8 to have a good value, and 0.8 to 0.7 was considered to have a fair diagnostic value. The sensitivity and specificity were determined for each lung score cut-off, and the Youden index was calculated based on these cut-offs.

Ethical Considerations

This study was approved by the local ethics committee of the Urmia University of Medical Sciences in which it was performed (IR.UMSU.REC.1399.029). All COVID-19 patients were asked to sign a written informed consent note before hospitalization, and patients were selected from among these cases. The study complied with the latest update of the Helsinki declaration.

RESULTS

A total of 56 patients were included in the study, of which 36 survived the disease, and 20 died. The mean age of the patients included in the study was 81.4±5.0 years. Of all of the patients, 28 (50%) were male, and the rest were female. The mean age of the groups of patients dying from the condition was 83.4±4.8 and was 80.6±4.9 in those surviving the condition. The difference was statistically significant (p=0.045). There were 20 (55.6%) females and 16 (44.4%) male patients in the surviving group, and 8 (40%) females and 12 (60%) males in the other. The difference between the two groups was not statistically significant (p=0.265). The median time between imaging and onset of symptoms was 3 (range, 1-5) days in the surviving group and 3 (range, 1-5) days in non-survivors with the difference being non-significant (p=0.800). The median period of hospitalization was 7 (range, 4-11) days for survivors and 7.3 days (range, 4-13) for non-survivors with the difference not being significant (p=0.203).

The clinical signs and symptoms of patients being included in the study are summarized in Table 1. The pre-existing conditions of the patients are summarized in Table 2.

Most patients had involvement in the upper and lower lobes of the lungs, with every patient except one having peripheral involvement. Figure 1 demonstrates some of the imaging findings. 28 (50.0%) patients had central involvement, while 25 (44.6%) patients had diffuse involvement. Imaging findings are presented in Table 3.

The lung score was calculated for both groups of patients. In patients dying from COVID-19, the mean lung score was 8.75±6.21 for whom survived and 13.45±6.41 for non-survivors. The difference between the two groups was significant (p=0.010). The odds ratio of not surviving COVID-19 in patients whose lung score was more than 8 in comparison to those whose lung score was equal to or

Table 1. Clinical signs and symptoms of the patients

Symptom	n (%)
Fever	12 (21.4%)
Cough	28 (50.0%)
Dyspnea	40 (71.4%)
Malaise	1 (1.8%)
Irritability	3 (5.4%)
Myalgia	4 (7.1%)
Soar trough	4 (7.1%)
Diarrhea	2 (3.6%)
Nausea	7 (12.5%)
Headache	2 (3.6%)
Chest pain	4 (7.1%)
Cyanosis	1 (1.8%)

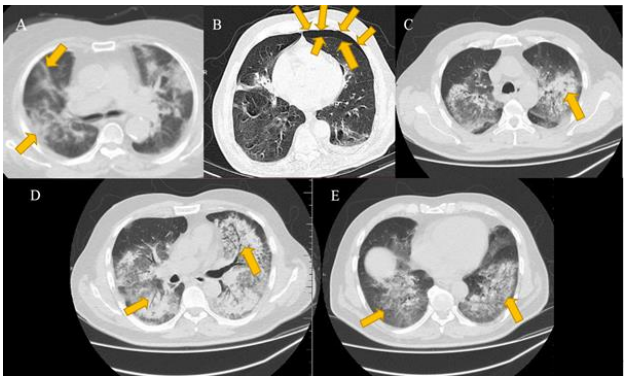

Figure 1. A) Axial HRCT of a 76 years old woman with a lung score of 12 revealed patchy ground-glass opacities in the right upper and right middle lobes (Yellow arrows denote the lesions). Ground glass lesions are also seen in the contralateral lobe. **B)** Axial HRCT of a 56 years old male with a lung score of 13 shows a pleural edge line due to pneumothorax in the left hemithorax (Yellow arrows delineate the contour of the line). **C)** HRCT of an 80 years old man, lung score of 18 with bilateral ground-glass opacities and left upper lobe alveolar consolidation. **D)** HRCT of an 82-year-old man, lung score of 23 with bilateral right and left ground-glass opacities, and alveolar consolidation with air-bronchogram. **E)** HRCT of a 78 years old man, lung score of 18 with bilateral right and left lower lobe ground-glass opacities.

Table 2. Past medical history of the patients

Pre-existing condition	Survivors (n=36)	Non-survivors (n=20)	p	Total (n=56)
Coronary artery disease	13 (36.1%)	6 (30%)	0.644	19 (33.9%)
Diabetes	7 (19.4%)	5 (25%)	0.737	12 (21.4%)
Hypertension	6 (16.7%)	3 (15%)	1.000	9 (16.1%)
Cerebrovascular disease	4 (11.1%)	2 (10%)	1.000	6 (10.7%)
Chronic obstructive pulmonary disease	3 (8.3%)	3 (15%)	0.655	6 (10.7%)
Chronic renal disease	2 (5.6%)	2 (10%)	0.611	4 (7.1%)
Splenectomy	1 (2.8%)	1 (5%)	1.000	2 (3.6%)
Malignancy	1 (2.8%)	0 (0%)	1.000	1 (1.8%)

Table 3. Radiological signs of the patients

	Survivors (n=36)	Non-survivors (n=20)	p	Total (n=56)
Location, n (%)				
Bilateral	29 (80.6%)	18 (90%)	0.466	47 (83.9%)
Unilateral	7 (19.4%)	2 (10%)		9 (16.1%)
Lesion type, n (%)				
Diffuse	13 (36.1%)	12 (60%)		25 (44.6%)
Multiple	17 (47.2%)	6 (30%)	0.226	23 (41.1%)
Single	6 (16.7%)	2 (10%)		8 (14.3%)
Distribution, n (%)				
Peripheral	23 (63.9%)	5 (25%)		28 (50.0%)
Central	0 (0.0%)	1 (5%)	**0.007**	1 (1.8%)
Peripheral and central	13 (36.1%)	14 (70%)		27 (48.2%)
Ground glass opacities, n (%)	35 (97.2%)	19 (95%)	1.000	54 (96.4%)
Reticular lesions, n (%)	0 (0.0%)	1 (5%)	0.357	1 (1.8%)
Consolidation, n (%)	10 (27.8%)	15 (75%)	**0.001**	25 (44.6%)
Air bronchogram, n (%)	7 (19.4%)	13 (65%)	**0.001**	20 (35.7%)
Cavity, n (%)	0 (0.0%)	1 (5%)	0.357	1 (1.8%)
Cystic lesions, n (%)	1 (2.8%)	0 (0%)	1.000	1 (1.8%)
Crazy-paving, n (%)	7 (19.4%)	3 (15%)	1.000	10 (17.9%)
Pleural effusion, n (%)	4 (11.1%)	5 (25%)	0.256	9 (16.1%)

less than 8 was 4.200 (95% CI, 1.253-14.081, p=0.020). The same was 4.278 (95% CI, 1.314-13.928, p=0.015) for a lung score of more than 12 compared to a score of 12 or less. The sensitivity and specificity of a lung score of more than 8 were 75.0%, and 58.3% respectively in the prediction of death probability (positive predictive value of 50.0% and a negative predictive value of 80.8%), and on the other hand sensitivity and specificity of lung score equal to 12 were 55.0%, and 77.8% respectively (positive predictive value equaled 57.9% and negative predictive value equaled 75.7%). The Youden index was 0.3611 and it was associated with the criterion of lung scores which were more than 8. ROC curve was drawn for the sensitivity and specificity of lung score in the prediction of death probability by COVID-19. The area under the curve was 0.714 (95% CI, 0.577 to 0.827, p=0.003), showing a fair predictive value for lung CT score (Figure 2).

Of the survivors, 26 received hydroxychloroquine, 5 received oseltamivir, 9 received Lopinavir/Ritonavir, and 26 received antibiotics. In non-survivors, 14 received hydroxychloroquine, 2 received oseltamivir, 9 received Lopinavir/Ritonavir, and 13 received antibiotics.

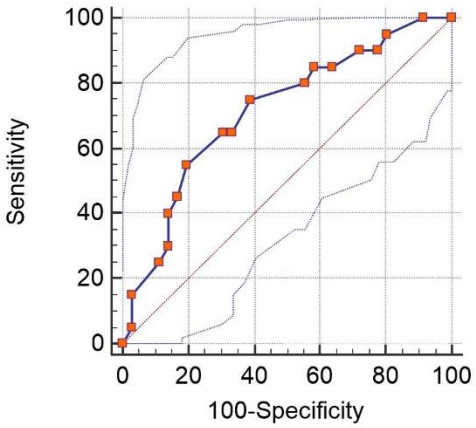

Figure 2. ROC curve for the lung score

DISCUSSION

COVID-19 presents as a viral pneumonia, compromising the ability of the respiratory system to oxygenate the blood. It also initiates an exaggerated inflammatory response, which with the medium of cytokines and interleukins, further interrupts physiologic functions of the body. Retrospective clinical studies have shown that individuals with respiratory and cardiovascular disease are in increased danger of mortality because of COVID-19, such as the elderly. A series of biomechanical changes in cells and tissues renders their functional capacities to a steep decline in instances of pathologic stress (15).

Multiple research initiatives have aimed to establish criteria to classify patients based on their probability of having severe symptoms associated with COVID-19. These criteria have consisted of past medical history, laboratory results, and imaging findings. Retrospective cohorts have shown that pre-existing conditions such as pulmonary, cardiovascular, and immune diseases increase the risk for severe disease and that in specific populations, up to almost a quarter of the population have pre-existing conditions, putting them at an increased risk of COVID-19 related complications (16). A retrospective clinical study from China enrolled 186 elderly patients with a mean age of 70.4±7.1 years and compared characteristics among the survivors and non-survivors. Non-survivors were shown to significantly have a higher rate of smoking, higher serum levels of LDH, ferritin, blood urea nitrogen, and D-dimer. The authors also studied imaging results in these groups of patients and found that non-survivors had a significantly higher rate of diffuse distribution of lesions (17).

A recent retrospective analysis performed on 63 COVID-19 patients with a mean age of 24.45±3.43 years found that patients with severe disease (defined as severe symptoms and need for hospitalization in ICUs) were associated with elevated liver enzymes, acute phase reactants, and IL-6 levels, and decreased levels of eosinophils, CD4+, CD8+, CD19+ and total lymphocyte counts (18).

All of the above studies point out significant differences among the survivors and non-survivors, but the result has

limitations in generalization to a late elderly population. Most studies have a rather small number of late elderly patients included, and even those focusing on the elderly do not include a significant number of late elderly patients. These studies also underline differences between the two groups but do not provide any means of clinical decision making based on these prognostic factors. The utilization of chest CT imaging alone or in combination with any of the following mentioned clinical criteria might be useful in detecting patients with a grim outcome.

Although evidence in this regard is scarce, this issue has significant clinical importance, as studies show mortality of up to 30 percent in patients above 70 years (19,20). Multiple descriptive studies with the mean age of the patients being included ranging between 30-50 years have shown that founding such as ground-glass opacities and consolidations being the most common lesions, with other signs such as halo sign, cavities, bronchiectasis, nodular lesions, and broncho-vascular thickening being less common (21,22). Noteworthy, none of these studies compares survivors and non-survivors, and they do not include a significant number of cases from two crucial demographic groups, the elderly and pediatric patients, who both show an increased rate of atypical findings (23). Our study faced some limitations, including the fact that we had a limited number of subjects. Furthermore, our results may not be generalizable to specific populations with a high rate of pre-existing conditions in their elderly. All of our patients had CT imaging performed before or on the first day of hospitalization. Thus CT imaging taken further in the course of the disease may not be similar in prognostic value. We also did not include asymptomatic patients, and the elderly who were not hospitalized, as diagnosing asymptomatic patients was impossible in our setting and based on institutional guidelines, all late elderly patients were hospitalized.

CONCLUSION

It seems that using lung scores can play a very important role in predicting the condition of hospitalized patients over 75 years old. However, due to the limited number of participants included in this study, designing similar studies in the future with a larger number of participants will be very helpful for the ultimate assessment.

Ethics Committee Approval: The study was approved by the Ethics Committee of Urmia University of Medical Sciences (22.04.2020, 029).

Conflict of Interest: None declared by the authors.

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Author Contributions: Idea/Concept: MMAA; Design: AM, RR; Data Collection/Processing: EF, SAMA, MK; Analysis/Interpretation: AA, AM; Literature Review: EF, SAMA, MK; Drafting/Writing: MMAA, EF, SAMA, MK; Critical Review: AM, RR.

REFERENCES

1. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect. 2020;80(6):e14-8.
2. Lithander FE, Neumann S, Tenison E, Lloyd K, Welsh TJ, Rodrigues JCL, et al. COVID-19 in older people: a rapid clinical review. Age Ageing. 2020;49(4):501-15.
3. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of chest CT for COVID-19: Comparison to RT-PCR. Radiology. 2020;296(2):E115-7.
4. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res. 2020;7(1):4.
5. Chen A, Huang JX, Liao Y, Liu Z, Chen D, Yang C, et al. Differences in clinical and imaging presentation of pediatric patients with COVID-19 in comparison with adults. Radiol Cardiothorac Imaging. 2020;2(2):e200117.
6. Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus disease 2019 (COVID-19): A systematic review of imaging findings in 919 patients. AJR Am J Roentgenol. 2020;215(1):87-93.
7. Chua F, Armstrong-James D, Desai SR, Barnett J, Kouranos V, Kon OM, et al. The role of CT in case ascertainment and management of COVID-19 pneumonia in the UK: insights from high-incidence regions. Lancet Respir Med. 2020;8(5):438-40.
8. Ng MY, Lee EYP, Yang J, Yang F, Li X, Wang H, et al. Imaging profile of the COVID-19 infection: radiologic findings and literature review. Radiol Cardiothorac Imaging. 2020;2(1):e200034.
9. who.int [Internet]. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance. [Cited: 2022 March 13]. Available from: https://apps.who.int/iris/handle/10665/331446
10. Kanne JP. Chest CT findings in 2019 novel coronavirus (2019-nCoV) infections from Wuhan, China: Key points for the radiologist. Radiology. 2020;295(1):16-7.
11. Kanne JP, Little BP, Chung JH, Elicker BM, Ketai LH. Essentials for radiologists on COVID-19: An update-radiology scientific expert panel. Radiology. 2020;296(2):E113-4.
12. Francone M, Iafrate F, Masci GM, Coco S, Cilia F, Manganaro L, et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. Eur Radiol. 2020;30(12):6808-17.
13. Mirza-Aghazadeh-Attari M, Zarrintan A, Nezami N, Mohammadi A, Zarrintan A, Mohebbi I, et al. Predictors of coronavirus disease 19 (COVID-19) pneumonitis outcome based on computed tomography (CT) imaging obtained prior to hospitalization: a retrospective study. Emerg Radiol. 2020;27(6):653-61.
14. Grodecki K, Lin A, Cadet S, McElhinney PA, Razipour A, Chan C, et al. Quantitative burden of COVID-19 pneumonia on chest CT predicts adverse outcomes: A post-hoc analysis of a prospective international registry. Radiology Cardiothoracic Imaging. 2020;2(5):e200389.
15. Mohammadzadeh A, Mirza-Aghazadeh-Attari M, Hallaj S, Saei AA, Alivand MR, Valizadeh A, et al. Crosstalk between P53 and DNA damage response in ageing. DNA Repair (Amst). 2019;80:8-15.

16. Gémes K, Talbäck M, Modig K, Ahlbom A, Berglund A, Feychting M, et al. Burden and prevalence of prognostic factors for severe COVID-19 in Sweden. Eur J Epidemiol. 2020;35(5):401-9.
17. Liao Y, Feng Y, Wang B, Wang H, Huang J, Wu Y, et al. Clinical characteristics and prognostic factors of COVID-19 patients progression to severe: a retrospective, observational study. Aging (Albany NY). 2020;12(19):18853-65.
18. Sun Y, Dong Y, Wang L, Xie H, Li B, Chang C, et al. Characteristics and prognostic factors of disease severity in patients with COVID-19: The Beijing experience. J Autoimmun. 2020;112:102473.
19. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146(1):110-8.
20. Kang YJ. Mortality rate of infection with COVID-19 in Korea from the perspective of underlying disease. Disaster Med Public Health Prep. 2020;14(3):384-6.
21. Caruso D, Zerunian M, Polici M, Pucciarelli F, Polidori T, Rucci C, et al. Chest CT features of COVID-19 in Rome, Italy. Radiology. 2020;296(2):E79-85.
22. Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: A multicenter study. AJR Am J Roentgenol. 2020;214(5):1072-7.
23. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatr Pulmonol. 2020;55(5):1169-74.

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The Value of Fibrinogen/Albumin Ratio on Prognosis of COVID-19 Patients

Fibrinojen/Albümin Oranının COVID-19 Hastalarının Prognozundaki Değeri

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ABSTRACT

Aim: Fibrinogen and albumin are proteins that play a role in inflammation. In this study, it was aimed to investigate the role of fibrinogen, albumin, and fibrinogen/albumin ratio (FAR) levels as markers of disease severity and prognosis in coronavirus disease 2019 (COVID-19) patients.

Material and Methods: Seventy-one patients aged between 19 and 84 years diagnosed with COVID-19 who were hospitalized in Sakarya University Training and Research Hospital, Neurology Department between March and May 2020 were analyzed retrospectively. Fibrinogen, albumin, FAR, D-dimer, platelet, and C-reactive protein (CRP) levels of the patients were compared according to the length of hospitalization duration, survival, and clinical severity of COVID-19.

Results: Twenty-eight (%39.4) of the patients were male and 43 (%60.6) were female, and the mean age was 55.7±20.7 years. There was a significant difference between the groups of COVID-19 clinical severity in terms of age, fibrinogen, albumin, FAR, D-dimer, and CRP values (all p values were <0.001). Also, significantly higher fibrinogen, FAR, D-dimer, and CRP values were found in patients hospitalized longer, while the albumin level was lower in these patients (all p values were <0.001). FAR values were higher and albumin values were lower in non-surviving patients compared to surviving patients (p=0.025 and p<0.001, respectively).

Conclusion: FAR levels may be useful in predicting mortality risk in COVID-19 patients. In addition, it may be helpful and useful in determining the prognosis since it has higher levels as the severity of the disease and the length of hospital stay increase.

Keywords: Fibrinogen; albumin; fibrinogen/albumin ratio; COVID-19.

ÖZ

Amaç: Fibrinojen ve albümin inflamasyonda rol oynayabilen proteinlerdendir. Bu çalışmada, koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) hastalarında fibrinojen, albümin ve fibrinojen/albümin oranı (FAR) düzeylerinin hastalık şiddeti ve prognoz belirteçleri olarak rolünün araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmada Mart ve Mayıs 2020 tarihleri arasında COVID-19 tanısı ile Sakarya Eğitim ve Araştırma Hastanesi Nöroloji Kliniği'ne yatırılan 19 ve 84 yaş arasındaki 71 hasta geriye dönük olarak analiz edildi. Hastaların fibrinojen, albümin, FAR, D-dimer, trombosit ve C-reaktif protein (CRP) düzeyleri, hastanede kalış süresinin uzunluğu, hayatta kalma ve COVID-19 klinik şiddetine göre karşılaştırıldı.

Bulgular: Hastaların 28'i (%39,4) erkek ve 43'ü (%60,6) kadın olup yaş ortalaması 55,7±20,7 yıl idi. COVID-19 klinik şiddetine göre ayrılmış olan gruplar arasında yaş, fibrinojen, albümin, FAR, D-dimer ve CRP değerleri açısından anlamlı bir farklılık vardı (tüm p değerleri <0,001). Ayrıca, hastanede daha uzun süre yatan hastalarda fibrinojen, FAR, D-dimer ve CRP değerleri anlamlı olarak daha yüksek bulunurken, bu hastalarda albümin düzeyleri daha düşüktü (tüm p değerleri <0,001). Hayatta kalamayan hastalarda yaşayan hastalara göre FAR değerleri daha yüksek ve albümin değerleri daha düşüktü (sırasıyla, p=0.025 ve p<0.001).

Sonuç: FAR seviyeleri, COVID-19 hastalarında ölüm riskini tahmin etmede faydalı olabilir. Ayrıca hastalığın şiddeti ve hastanede kalış süresi arttıkça daha yüksek seviyelere sahip olduğu için prognozu belirlemede de yardımcı ve faydalı olabilir.

Anahtar kelimeler: Fibrinojen; albümin; fibrinojen/albümin oranı; COVID-19.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak was categorized as a pandemic by the World Health Organization (WHO) on March 11, 2020. Since then, COVID-19 has caused ~6.4 M deaths worldwide. Among the clinical conditions caused by COVID-19, respiratory disorders and sepsis are the main ones responsible for the severity of COVID-19 (1,2).

COVID-19 patients may progress to the pro-inflammatory process. This pro-inflammatory condition has been related to coagulopathy (3). The causes of organ failures in patients with severe COVID-19 have been investigated before, where previous studies focused on systemic vasculitis and cytokine-mediated coagulation disorders (4). COVID-19 patients show elevated fibrinogen and D-dimer levels as a result of hypercoagulation. This coagulation disorder is usually detected in COVID-19 patients who require hospitalization. Therefore, disease severity is highly related to hypercoagulation (5).

D-dimer, a soluble degradation product of fibrin, results from the systematic degradation of vascular thrombus through the fibrinolytic mechanism. Mortality of COVID-19 highly correlates with the increase in the D-dimer value (3,5,6). On the other hand, fibrinogen, the substrate of thrombin in the coagulation cascade, is an acute phase reactant that increases in the inflammatory process (7). Albumin is a negative acute-phase reactant, and its levels decrease in acute infection. Decreased albumin levels have been related to high mortality in hospitalized COVID-19 patients (8). In addition, the fibrinogen to albumin ratio (FAR) was found to be more sensitive and specific as a predictor of progression of hypercoagulation compared to fibrinogen levels alone (9). COVID-19 patients are difficult to manage due to their rapid deterioration and high mortality rate. Furthermore, prolonged symptoms after COVID-19 infection negatively affect patients' quality of life. Thus, there is a critical need for useful test parameters that can predict clinical prognosis in these patients. Having early information about the prognosis of patients can be a guide for patient management and the selection of adjunctive treatments.

In this study, we aimed to investigate the role of FAR as a predictive mediator on the prognosis of COVID-19 patients. In addition, we examined the D-dimer, platelet, and C-reactive protein (CRP) values of COVID-19 patients.

MATERIAL AND METHODS

A hundred and twenty COVID-19 patients hospitalized for isolation in Sakarya University Training and Research Hospital, Neurology Department between March and May 2020 were evaluated in the study. 71 patients aged between 19 and 84 years who met the criteria were included. The information of the patients recorded in the electronic system of our hospital was reviewed retrospectively.

Forty-nine patients who were transferred to another center, or who did not have serum fibrinogen and albumin levels in the file were excluded from the study. Other exclusion criteria were cancer, severe kidney or renal failure, hematological diseases, and use of drugs such as antiaggregant, oral contraceptives, steroids before admission, and human albumin therapy treatments that may cause hematological side effects.

Gender, age, symptoms of COVID-19, examination findings, serum fibrinogen, albumin, D-dimer, platelet, and CRP levels were measured at the time of their first hospitalization, and imaging findings were recorded in the patients' forms. Blood tests were taken within the first 24 hours after the patients were admitted to the hospital.

Patients were divided into four subgroups according to Chinese management guidelines for COVID-19 (version 6.0): 1-Mild: Patients with mild symptoms and have no pneumonia; 2-Typical: Fever or respiratory symptoms and patients have pneumonia on imaging; 3-Severe: Having one of the three conditions: respiratory distress, respiratory rate ≥30 beats/min; oxygen saturation ≤%93 at rest; arterial blood oxygen partial pressure/oxygen concentration ≤300 mm Hg; 4-Critical: Having one of the three conditions: respiratory failure, shock incidence and requiring mechanical ventilation; admission to intensive care unit (ICU) with other organ function failure (5,10).

Each group was compared in terms of fibrinogen, albumin, FAR, D-dimer, platelet, CRP values, and clinical severity of COVID-19.

Statistical Analysis

IBM SPSS v.23 statistical software program was used for statistical analysis. Compliance of the data with normality and variance homogeneity was examined with the Kolmogorov-Smirnov and Levene tests. The student's t and One-Way ANOVA (post hoc LSD) tests were used for data that meet the criteria of normality and homogeneity, while Mann-Whitney U and Kruskal-Wallis (post hoc Dunn) tests were used for the data which not meet. The mean and standard deviation values or median, interquartile range, and minimum-maximum values were used for numerical data, as appropriate. Chi-square or Fisher's exact test was used to compare categorical data. All reported statistical tests were two-sided, and the level of statistical significance was considered as $p<0.05$.

RESULTS

A total of 71 patients, 28 (%39.4) male, and 43 (%60.6) female were included in the study. The mean age of the patients was 55.7±20.7 years. The mean ages of males and females were 56.1±21.2 years and 55.4±20.7 years, respectively. There was no significant difference between the genders (p=0.883). 38 (%53.5) of the patients had at least one chronic disease. Hypertension (HT) was the most common chronic disease in the patient group (Table 1).

The median hospitalization duration of all patients was 6 (range, 1-28) days. 36 (%50.7) patients' hospitalization duration was less than a week (15 male, 21 female), while 35 (%49.3) patients' hospitalization duration was more than a week (13 male, 22 female). There was no significant difference between the genders in terms of hospitalization for less or more than one week (p=0.697).

Fibrinogen, FAR, D-dimer, and CRP values were significantly higher in patients with hospitalization duration >1 week than in those hospitalized for a short period (less than a week), and albumin values were significantly lower (all p values were <0.001, Table 2).

We found that patients with chronic disease had higher fibrinogen, FAR, D-dimer, and CRP values, and significantly lower albumin values than patients without the chronic disease (all p values were <0.001, Table 3).

Of the 71 patients, 66 (93%) were surviving, and 5 (7%) died. FAR (p=0.025) and D-dimer (p<0.001) values were higher while albumin (p<0.001) and platelet (p=0.035) values were lower in non-surviving patients compared to surviving patients (Table 4).

Patients were divided into 4 groups according to the clinical severity of the COVID-19. Groups were compared in terms of age, fibrinogen, albumin, FAR, D-dimer, platelet, and CRP values (Table 5). There was a significant difference between the groups in terms of age (p<0.001). According to the post hoc test results severe and critical patients were significantly older than mild (both p values were <0.001) and typical (p=0.013 and p=0.006, respectively) patients. Also, the typical group was older than the mild group (p<0.001), while there was no significant difference between the severe and critical groups (p=0.392).

Fibrinogen values were significantly different between the groups (p<0.001). Post hoc test results revealed that fibrinogen values were higher in severe and critical groups than in mild (p<0.001 and p=0.004, respectively) and typical (p=0.002 and p=0.038, respectively) groups. There was no significant difference between the mild and typical (p=0.111), and also severe and critical (p=0.734) groups.

Albumin values were significantly different between the groups (p<0.001). According to the post hoc test results albumin values were significantly lower in critical patients than in all other severe (p=0.024), typical (p=0.002), and mild (p<0.001) groups. While no statistically significant difference was found between the severe and typical groups (p=0.154), albumin values in both of these groups were found as statistically significantly lower than in the mild group (p<0.001 and p=0.001, respectively).

Table 1. Chronic diseases of patients by gender, n (%)

Chronic diseases	Male (n=28)	Female (n=43)	p	Total (n=71)
Hypertension	10 (35.7)	17 (39.5)	0.746	27 (38.0)
Diabetes mellitus	6 (21.4)	4 (9.3)	0.177	10 (14.1)
Coroner artery disease	1 (3.6)	1 (2.3)	0.999	2 (2.8)
Asthma	0 (0.0)	3 (7.0)	0.273	3 (4.2)
Cerebrovascular diseases	1 (3.6)	3 (7.0)	0.649	4 (5.6)

Table 2. Comparison of the patients with hospitalization duration <1 and >1 week

	<1 week (n=36)	>1 week (n=35)	p
Fibrinogen (mg/dL)	316 (78) [180-647]	368 (80) [109-819]	**<0.001**
Albumin (g/L)	41.2 (4.7) [30.0-47.0]	32.3 (12.6) [19.9-46.7]	**<0.001**
FAR	7.42 (2.81) [3.83-20.47]	11.20 (4.04) [4.88-29.15]	**<0.001**
D-dimer (µg FEU/L)	352 (479) [34-6300]	1790 (2909) [124-29400]	**<0.001**
Platelet (K/uL)	218 (76) [124-389]	206 (104) [53-471]	0.084
CRP (mg/L)	3 (2) [3-176]	15.7 (71.7) [1.4-459]	**<0.001**

FAR: fibrinogen/albumin ratio, CRP: C-reactive protein

Table 3. Comparison of the patients with and without chronic disease

	Chronic Disease (+) (n=38)	Chronic disease (-) (n=33)	p
Fibrinogen (mg/dL)	364 (93) [109-819]	308 (89) [180-483]	**<0.001**
Albumin (g/L)	31.8 (11.4) [19.9-43.8]	42.5 (3.7) [25.4-47.0]	**<0.001**
FAR	10.88 (4.33) [5.45-29.15]	7.33 (2.55) [3.83-19.02]	**<0.001**
D-dimer (µg FEU/L)	1515 (1927) [73-29400]	340 (529) [34-12200]	**<0.001**
Platelet (K/uL)	223 (104) [53-471]	206 (87) [124-335]	0.699
CRP (mg/L)	11.3 (42.1) [1.4-459]	3 (2) [3-196]	**<0.001**

FAR: fibrinogen/albumin ratio, CRP: C-reactive protein

Table 4. Comparison of the surviving and non-surviving patients

	Surviving (n=66)	Non-surviving (n=5)	p
Fibrinogen (mg/dL)	329 (74) [180-647]	483 (477) [109-819]	0.086
Albumin (g/L)	40.6 (10.4) [19.9-47.0]	25.4 (6.5) [20.0-28.3]	**<0.001**
FAR	8.75 (3.92) [3.83-20.47]	19.02 (18.40) [5.45-29.15]	**0.025**
D-dimer (µg FEU/L)	573 (1384) [34-29400]	5670 (8420) [2020-12200]	**<0.001**
Platelet (K/uL)	217 (87) [107-471]	159 (154) [53-279]	**0.035**
CRP (mg/L)	3.5 (12.8) [3-288]	74.7 (269.9) [1.4-459]	0.082

FAR: fibrinogen/albumin ratio, CRP: C-reactive protein

Table 5. Comparison of the patients in terms of COVID-19 clinical severity

	Mild (n=11)	Typical (n=32)	Severe (n=23)	Critical (n=5)	p
Age (years)	27.0±5.5[a]	53.9±18.9[b]	66.9±13.3[c]	78.8±3.9[c]	**<0.001**
Fibrinogen (mg/dL)	289 (83) [180-348][a]	318 (69) [207-647][a]	373 (80) [185-472][b]	483 (477) [109-819][b]	**<0.001**
Albumin (g/L)	43.8 (2.1) [41.0-47.0][a]	40.4 (7.7) [19.9-46.1][b]	35.8 (10.0) [23.3-46.7][b]	25.4 (6.5) [20.0-28.3][c]	**<0.001**
FAR	6.39 (2.01) [3.83-7.98][a]	8.27 (2.69) [4.88-20.47][b]	11.20 (3.69) [4.63-17.59][c]	19.02 (18.40) [5.45-29.15][c]	**<0.001**
D-dimer (μg FEU/L)	93 (43) [34-6300][a]	537 (866) [73-4140][b]	1530 (1583) [92-29400][c]	5670 (8420) [2020-12200][c]	**<0.001**
Platelet (K/uL)	214 (64) [156-302]	207 (90) [107-389]	230 (96) [125-471]	159 (154) [53-279]	0.098
CRP (mg/L)	3 (0) [3-29.7][a]	3.1 (4.9) [3-231][b]	13.7 (48.4) [3-288][c]	74.7 (269.9) [1.4-459][c]	**0.001**

FAR: fibrinogen/albumin ratio, CRP: C-reactive protein, [a,b,c]: different superscript letters denote significant differences between groups

There was a significant difference between the groups in terms of FAR (p<0.001). According to the post hoc test results FAR in severe and critical patients were higher than in mild (both p values were <0.001) and typical (p=0.005 and p=0.017, respectively) patients. Also, the typical group had higher values than the mild group (p=0.015), while there was no significant difference between the severe and critical groups (p=0.445).

D-dimer values were statistically significantly different between the groups (p<0.001). Post hoc test results revealed that D-dimer values in severe and critical patients were significantly higher than in mild (both p values were <0.001) and typical (p=0.018 and p=0.001, respectively) patients. Also, the D-dimer values in the typical group were significantly higher than in the mild group (p=0.012), while there was no statistically significant difference between the severe and critical groups (p=0.065) although the critical group had a very high level of D-dimer.

No significant difference was found between the groups according to the clinical severity of the COVID-19 in terms of platelet values (p=0.098).

CRP values were significantly different between the groups (p=0.001). According to the post hoc test results severe and critical groups had significantly higher CRP values than mild (p<0.001 and p=0.002, respectively) and typical (p=0.017 and p=0.049, respectively) patients. Also, CRP values in the typical group were higher than in the mild group (p=0.048). While CRP values in the critical group were higher than in the severe group, there was no significant difference between the groups (p=0.547).

DISCUSSION

When the four groups formed according to the clinical severity of the COVID-19 infection were compared significant differences were found in terms of age, fibrinogen, albumin, FAR, D-dimer, and CRP values. Disease severity and fibrinogen, FAR, D-dimer, and CRP values were positively correlated, while albumin values were negatively correlated. Inflammatory markers checked at the first presentation of the patient were valuable in terms of providing early information about the severity and prognosis of the disease.

Fibrinogen, FAR, D-dimer, and CRP values were higher and album values were lower in patients with a hospital stay longer than 1 week and in patients with chronic disease. These results may be because patients with chronic diseases have a more severe COVID-19 infection clinic and are hospitalized for longer periods.

Several studies have examined the relationship between D-dimer levels and the clinical severity of COVID-19. Many studies have shown the relationship between the disease severity and D-dimer, and it has been stated that D-dimer monitoring will be a very important approach in the clinical practice of COVID-19 infection (11-13). Most studies have shown that high CRP levels are associated with disease severity and mortality in COVID-19, and our results are consistent with this (14,15). In previous studies, when the patients who experienced long-term symptoms after COVID-19 infection were examined, it was reported that these patients had high pro-inflammatory markers such as CRP and D-dimer. Based on this, we can say that patients with high D-dimer and CRP should be followed more closely in terms of prolonged symptoms after COVID-19 infection (16). Reduced protein synthesis, including albumin, is strongly associated with the poor prognoses of these patients (17). It could be useful to control albumin values and replace them when necessary, during hospitalization in COVID-19 patients.

In some previous studies on COVID-19, thrombocytopenia was associated with poor prognosis and mortality (14,18,19). Although, some studies did not find a significant relationship between prognosis and platelet levels (20-23). In this study, when the platelet values were examined according to the hospitalization period of the patients, the clinical severity of the COVID-19 disease, whether they had a chronic disease, and whether they survived/non-survived, no significant relationship was found in terms of these parameters and platelet values.

In this study, FAR values were higher and albumin values were lower in non-surviving patients compared to the surviving patients. This difference was statistically significant. Previous studies have also shown that low albumin levels are associated with mortality (8,24-26).

Although Kucukceran et al. (1) found that D-dimer, fibrinogen, albumin, D-dimer/albumin ratio (DAR), and FAR parameters were significant as predictors of hospital mortality in COVID-19 patients; they said that FAR is a more valuable predictor compared to fibrinogen. In this study, fibrinogen values were not significantly different between surviving and non-surviving groups. FAR value was found more significant than fibrinogen in terms of mortality. FAR may be a more valuable parameter than fibrinogen to predict mortality risk in patients hospitalized for COVID-19. However, low albumin was found to be more significant in non-surviving patients compared to high FAR. There is a need for studies with larger patient series on this subject.

This is a single-center study that included a small number of patients. Patients transferred to the ICU after clinical worsening was not included in the study. Also, various COVID-19 treatment protocols were not included. These can be pointed out as the limitations of the study.

CONCLUSION

In conclusion, FAR levels were found significantly better predicted the mortality risk in COVID-19 patients than fibrinogen levels alone. In addition, looking at the FAR levels could help determine the prognosis as they increase with the severity of the disease and the length of hospital stay.

Ethics Committee Approval: The study was approved by the Ethics Committee of Sakarya University Faculty of Medicine (01.08.2021, 404).

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REFERENCES

1. Küçükceran K, Ayranci MK, Girişgin AS, Koçak S. Predictive value of D-dimer/albumin ratio and fibrinogen/albumin ratio for in-hospital mortality in patients with COVID-19. Int J Clin Pract. 2021;75(7):e14263.
2. Karabela ŞN, Kart Yaşar K. Laboratory tests in the diagnosis of COVID-19. Duzce Med J. 2020;22(S1):5-9.
3. Wool GD, Miller JL. The impact of COVID-19 disease on platelets and coagulation. Pathobiology. 2021;88(1):15-27.
4. Gerotziafas GT, Catalano M, Colgan MP, Pecsvarady Z, Wautrecht JC, Fazeli B, et al. Guidance for the management of patients with vascular disease or cardiovascular risk factors and COVID-19: position paper from VAS-European Independent Foundation in Angiology/Vascular Medicine. Thromb Haemost. 2020;120(12):1597-628.
5. Zakai NA, McClure LA, Judd SE, Kissela B, Howard G, Safford M, et al. D-dimer and the risk of stroke and coronary heart disease. The reasons for geographic and racial differences in stroke (REgARDS) study. Thromb Haemost. 2017;117(3):618-24.
6. Kotan D, Taydaş O, Ateş ÖF, Öztürk MH. Investigating the frequency of stroke in SARS-CoV-2 cases in Sakarya City, Turkey. Duzce Med J. 2020;22(S1):51-5.
7. Akirov A, Masri-Iraqi H, Atamna A, Shimon I. Low albumin levels are associated with mortality risk in hospitalized patients. Am J Med. 2017;130(12):1465.e11-9.
8. Karahan O, Yavuz C, Kankilic N, Demirtas S, Tezcan O, Caliskan A, et al. Simple blood tests as predictive markers of disease severity and clinical condition in patients with venous insufficiency. Blood Coagul Fibrinolysis. 2016;27(6):684-90.
9. Xin H, Jiang F, Xue A, Liang J, Zhang J, Yang F, et all. Risk factors associated with occurrence of COVID-19 among household persons exposed to patients with confirmed COVID-19 in Qingdao Municipal, China. Transbound Emerg Dis. 2021;68(2):782-8.
10. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert Rev Hematol. 2020;13(11):1265-75.
11. Creel-Bulos C, Liu M, Auld SC, Gaddh M, Kempton CL, Sharifpour M, et al. Trends and diagnostic value of D-dimer levels in patients hospitalized with coronavirus disease 2019. Medicine (Baltimore). 2020;99(46):e23186.
12. He X, Yao F, Chen J, Wang Y, Fang X, Lin X, et al. The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients. Sci Rep. 2021;11(1):1830.
13. Huang W, Li C, Wang Z, Wang H, Zhou N, Jiang J, et al. Decreased serum albumin level indicates poor prognosis of COVID-19 patients: hepatic injury analysis from 2,623 hospitalized cases. Sci China Life Sci. 2020;63(11):1678-87.
14. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-8.
15. Velavan TP, Meyer CG. Mild versus severe COVID-19: Laboratory markers. Int J Infect Dis. 2020;95:304-7.
16. Liu Y, Sun W, Guo Y, Chen L, Zhang L, Zhao S, et al. Association between platelet parameters and mortality in coronavirus disease 2019: retrospective cohort study. Platelets. 2020;31(4):490-6.
17. Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. J Thromb Haemost. 2020;18(6):1469-72.
18. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.
19. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol. 2020;95(6):E131-4.
20. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic features, and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA. 2020;323(15):1488-94.
21. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-43.
22. Mani Mishra P, Uversky VN, Nandi CK. Serum albumin-mediated strategy for the effective targeting of SARS-CoV-2. Med Hypotheses. 2020;140:109790.
23. Chojkier M. Inhibition of albumin synthesis in chronic diseases: molecular mechanisms. J Clin Gastroenterol. 2005;39(4 Suppl 2):S143-6.

24. Koh YW, Lee HW. Prognostic impact of C-reactive protein/albumin ratio on the overall survival of patients with advanced nonsmall cell lung cancers receiving palliative chemotherapy. Medicine (Baltimore). 2017;96(19):e6848.
25. Tang N, Li DJ, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-7.
26. Liu F, Xu A, Zhang Y, Xuan W, Yan T, Pan K, et al. Patients of COVID-19 may benefit from sustained Lopinavir-combined regimen and the increase of Eosinophil may predict the outcome of COVID-19 progression. Int J Infect Dis. 2020;95:183-91.

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Morphologic Evaluation of the Glenoid Cavity on Dry Scapula

Cavitas Glenoidalis Morfolojisinin Kuru Kemikler Üzerinde İncelenmesi

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ABSTRACT

Aim: The aim of this study was to determine the notch and shape variations of the glenoid cavity (GC), to emphasize its clinical importance, and compare it with the previous studies.
Material and Methods: This study was performed with 157 (78 right sides, 79 left sides) adult Anatolian dry scapulae. The GCs were typed as oval, pear, and inverted comma shaped and noted the number of GC notch.
Results: The most common GC shape was found as the pear shaped with 63 (80.8%) at the right side, 49 (62%) at the left side, and 112 (71.4%) in total. The second most common GC shape was found as oval shaped with 13 (16.6%) at the right side, 28 (35.5%) at the left side, and 41 (26.1%) in total. The glenoid notch was found at the right side, left side, and totally; 28 (35.9%), 19 (24.1%), and 47 (29.9%), respectively. All of the inverted comma shaped GCs had distinct glenoid notch, while the oval shaped GCs not. The pear shaped GCs had indistinct glenoid notch or no glenoid notch. The glenoid notch was found at the right side, left side, and totally on the pear shaped GC; 26 (41.3%), 17 (34.7%), and 43 (38.4%), respectively.
Conclusion: Pear shaped GC was found as the most (71.4%) common shape in this study. Forty-seven (29.9%) of the scapulae had a glenoid notch. The notch and shape variations of the GC are important and this study will contribute to anatomists, orthopedists, and radiologists from this perspective.
Keywords: Scapula; glenoid cavity; notch; shape.

ÖZ

Amaç: Bu çalışmanın amacı, cavitas glenoidalis (CG) çentik ve şekil varyasyonlarını ortaya koymak, klinik önemini vurgulamak ve daha önceki çalışmalarla karşılaştırmaktır.
Gereç ve Yöntemler: Bu çalışma, erişkin Anadolu popülasyonuna ait 157 (78 sağ taraf, 79 sol taraf) kuru scapula ile yapıldı. CG'ler oval, armut ve ters virgül şeklinde tiplendirildi ve CG çentik sayısı not edildi.
Bulgular: En sık görülen CG şekli, sağ tarafta 63 (%80,8), sol tarafta 49 (%62) ve toplamda 112 (%71,4) ile armut şeklinde CG olarak bulundu. İkinci sıklıktaki CG şekli ise sağ tarafta 13 (%16,6), sol tarafta 28 (%35,5) ve toplamda 41 (%26,1) ile oval şekilli CG olarak bulundu. Glenoid çentik sağ taraf, sol taraf ve toplamda sırası ile 28 (%35,9), 19 (%24,1) ve 47 (%29,9) olarak tespit edildi. Ters virgül şekilli CG'lerin tamamında belirgin glenoid çentik varken oval şekilli CG'lerde ise yoktu. Armut şekilli CG'lerde belli belirsiz glenoid çentik vardı veya hiç glenoid çentik yoktu. Armut şekilli CG'de glenoid çentik sağ taraf, sol taraf ve toplamda sırası ile 26 (%41,3), 17 (%34,7) ve 43 (%38,4) olarak tespit edildi.
Sonuç: Bu çalışmada en sık (%71,4) armut şekilli CG bulunmuştur. Scapulaların 47 (%29,9) tanesinde glenoid çentik vardı. CG'nin çentik ve şekil varyasyonları önemlidir ve bu çalışmanın anatomistler, ortopedistler ve radyologlara bu açıdan katkıda bulunacağı düşünülmektedir.
Anahtar kelimeler: Scapula; cavitas glenoidalis; çentik; şekil.

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INTRODUCTION

The scapula is a flat, triangular bone located between the 2nd to 7th ribs at the posterolateral to the thorax wall. The glenoid cavity (GC), which is the upper end of the lateral border of the scapula, articulates with the head of the humerus (1). The articular surface of the GC is covered with hyaline cartilage and the borders of the joint surface are the attachment points for the glenoid labrum (2). The glenoid labrum is a fibrocartilaginous structure and increases the depth of the articular surface (3). GC has a notch at the anterosuperior border of the articular surface and this notch affects the shape of the GC (4). If the notch is distinct, it is classified as inverted comma shaped, otherwise it is oval shaped, if it is indistinct, it is classified as pear shaped GC (3,4). GC shape differences may also differ between populations and studies performed within the same population (5).

The aim of this study was to determine the notch and shape variations in the Turkish population and compare them with the previous studies.

MATERIAL AND METHODS

This study was performed at the Department of Anatomy, Faculty of Medicine, Hacettepe University, and Department of Anatomy, Faculty of Medicine, Ankara University with 157 adult Anatolian dry scapulae (78 right sides, 79 left sides). The scapula with trauma, pathological condition, and osteoporotic appearance were not included in the study. The ages and genders of scapula were unknown. The GCs were typed as oval, pear, and inverted comma shaped and noted the number of GC notch. These morphologic features were evaluated by three anatomists and the glenoid cavity shape and notch variations were decided together according to studies by Singh R., and Saha and Vasudeva (6,7). If the notch is distinct or pronounced, GC was classified as an inverted comma, otherwise, it was oval, if it is indistinct, it is classified as pear shaped. Ethics approval was taken from the Hacettepe University ethics committee (Date: 15/03/2022, number: 2022/05-44).

Statistical Analysis

Statistical analyzes were performed using SPSS version 23. Qualitative results were expressed as numbers (%). Side and notch, side and shape of GC were given using crosstabs. The chi-square test was used to determine whether there was a statistical difference between the right and left sides. In cases where the chi-square test assumptions could not be met, it was compared with Fisher's exact test. A p value below 0.05 was considered statistically significant.

Figure 1. Oval shaped glenoid cavity

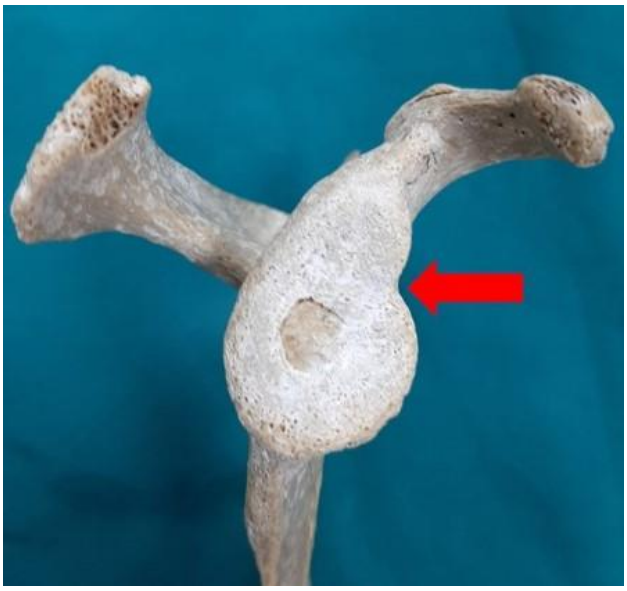

Figure 2. Inverted comma shaped glenoid cavity, the red arrow indicates the notch

RESULTS

The most common GC shape was found as the pear shaped with 63 (80.8%) at the right side, 49 (62%) at the left side, and 112 (71.4%) in total. The second most common GC shape was found as oval shaped with 13 (16.6%) at the right side, 28 (35.5%) at the left side, and 41 (26.1%) in total (Figure 1). The least common GC shape was found as inverted comma shaped with 2 (2.6%) at the right side, 2 (2.5%) at the left side, and 4 (2.5%) in total (Figure 2). There was a statistically significant difference between the sides in terms of the shape of the GC (p=0.023). Post-hoc procedures and Bonferroni correction for the significance limit were applied to determine which group caused this difference (0.05/3=0.017). The chi-square test was applied separately and it was determined that the difference was caused by oval shaped and pear shaped GC (p=0.007 and p=0.009, respectively). The glenoid notch was found at the right side, left side, and totally; 28 (35.9%), 19 (24.1%), and 47 (29.9%), respectively. No glenoid notch was found at the right side, left side, and totally; 50 (64.1%), 60 (75.9%), and 110 (70.1%), respectively. There was no statistical difference between the side and the presence of a notch (p=0.105).

All of the inverted comma shaped GC had a distinct glenoid notch. All of the oval shaped GC had no glenoid notch. The glenoid notch was found at the right side, left side, and all of the pear-shaped GC; 26 (41.3%), 17 (34.7%), and 43 (38.4%), respectively (Figure 3). No glenoid notch was found at the right side, left side, and all of the pear-shaped GC; 37 (58.7%), 32 (65.3%), and 69 (61.6%), respectively (Figure 4). No significant difference was found between the right and left sides for the notch formation of pear shaped GCs (p=0.478). The shape and notch morphology of the GC were summarized in Table 1 and Table 2.

Figure 3. Pear shaped glenoid cavity with a notch, the red arrow indicates the indistinct notch

Figure 4. Pear shaped glenoid cavity with no notch

Table 1. Shape and notch variations of glenoid cavity

	Right (n=78)	Left (n=79)	p	Total (n=157)
Shape, n (%)				
Oval	13 (16.6)	28 (35.5)		41 (26.1)
Pear	63 (80.8)	49 (62.0)	**0.023**	112 (71.4)
Inverted comma	2 (2.6)	2 (2.5)		4 (2.5)
Notch, n (%)				
Yes	28 (35.9)	19 (24.1)	0.105	47 (29.9)
No	50 (64.1)	60 (75.9)		110 (70.1)

Table 2. Notch variations at pear shaped glenoid cavity

	Right (n=63)	Left (n=49)	p	Total (n=112)
Notch, n (%)				
Yes	26 (41.3)	17 (34.7)	0.478	43 (38.4)
No	37 (58.7)	32 (65.3)		69 (61.6)

DISCUSSION

The morphology of the glenoid cavity may differ depending on the populations living in different geographies. In the studies of Prescher and Klumpen (3), and Coskun et al. (8), the glenoid notch was found on 129 (54.7%) and 26 (28.9%) of the scapula, respectively, and they classified them as pear shaped GC. The glenoid notch was not found and they classified them as oval shaped GC. In this study, while 4 (2.5%) of GCs were inverted comma shaped and all of them had distinct glenoid notch; 41 (26.1%) of GCs had no glenoid notch and they were classified as oval shaped. Unlike the studies by Prescher and Klumpken (3), and Coskun et al. (8), in this study, pear shaped GCs were classified as two types according to notch formation and 43 (38.4%) of them had an indistinct glenoid notch, 69 (61.6%) of them had no glenoid notch.

In accordance with the study of Yadav et al. (9), no statistically significant difference was found between notch formation and side in this study.

In studies in which the shape of the GC was typed in populations living in different geographies, Prescher and Klumpen (3), Rajendra et al. (5), Singh R. (6), Saha and Vasudeva (7), Chaijaroonkhanarak et al. (10), Mamatha et al. (11), Akhtar et al. (12), Dhindsa and Singh (13), and this study, pear shaped GC was found the most common shape at the right and left sides. In contrast to these studies, side difference was found in the study of Yadav et al. (9), and the most inverted comma shaped GC was found at the right side and the most pear shaped GC at the left side. While no significant difference was found between the side for the shape of GC in the studies of Dhindsa and Singh (13), and Saha and Vasudeva (7), a significant difference was found between the right and left sides for oval shaped and pear shaped GC in this study.

Considering the studies performed on the Turkish population, while the most oval shaped GC was detected by Coskun et al. (8), in this study, the pear shaped GC was found the most. In the study of Cirpan and Güvençer (14), notch variation of the GC was evaluated in detail and they classified notch variation into 5 types (type 0, type 1a, type 1b, type 2a, and type 2b).

The notch in shallow concave form (type 1a) was found at 24 (38.1) of 63 scapulae, mostly. In this study, notch formation was evaluated as more superficial, distinct, indistinct, or absent compared to the study of Cirpan and Güvençer (14). The studies performed for GC shape and notch variations were summarized in Table 3.

The scapula with distinct glenoid notches, the labrum often does not attach to the glenoidal joint border at the part where the notch is, making the glenohumeral joint more prone to dislocations (3). The adhesions of the labrum in the notch are important for the normal function of the glenohumeral joint. In the inverted comma shaped GC, the labrum does not adhere firmly to the joint face, this arrangement simulates the complex of labral tear, sublabral foramen, and Bufford complex at arthroscopy (15). Frazer reports that the position of the notch shows the junction line of the scapular part of the GC and coracoid process (16). The tendon of the subscapularis muscle crosses the joint at the level of the notch, it is thought that the tendon causes bone atrophy at the anterior border of the joint and causes notch formation (3). Knowledge of the normal anatomy and variations of the joint shape is important for understanding the mechanics of the shoulder joint. This information is important for orthopedic surgeons in shoulder arthroplasty, glenohumeral joint instability, and rotator cuff tear management (13).

CONCLUSION

The pear-shaped GC was found as the most (71.4%) common shape in this study. Forty-seven (29.9%) of the scapula had a distinct glenoid notch. Knowledge of the notch and shape variations of the GC is important and this study will contribute to anatomists, orthopedists, and radiologists from this perspective.

Table 3. Studies on the shape and notch variations at glenoid cavity in the literature

Study	Population	Sample size	Side	Oval	Pear	Inverted comma	Notch (+)
Prescher and Klumpen (3)	Germany	236 (118 M, 118 F)	-	107 (45.3)	129 (54.7)	-	129 (54.7)
Rajendra et al. (5)	India	123 (64 R, 59 L)	-	8 (6.5)	69 (56.1)	43 (35.0)	69 (56.1)
Singh R. (6)	India	172 (91 R, 81 L)	R L	26 (28.6) 25 (30.9)	45 (49.4) 41 (50.6)	20 (22.0) 15 (18.5)	-
Saha and Vasudeva (7)	India	260 (127 R, 133 L)	R L	42 (33.1) 34 (25.6)	51 (40.2) 62 (46.6)	34 (26.8) 37 (27.8)	187 (71.9)
Coskun et al. (8)	Turkey	90 (44 R, 46 L)	-	64 (71.1)	26 (28.9)	-	26 (28.9)
Yadav et al. (9)	India	66 (30 R, 36 L)	R L	4 (13.3) 6 (16.7)	6 (20.0) 16 (44.4)	20 (66.7) 14 (38.9)	-
Chaijaroonkhanarak et al. (10)	Thailand	264 (166 M, 98 F)	-	18 (6.8)	184 (69.7)	62 (23.5)	-
Mamatha et al. (11)	India	202 (98 R, 104 L)	R L	20 (20.4) 25 (24.0)	45 (45.9) 45 (43.3)	33 (33.7) 34 (32.7)	-
Akhtar et al. (12)	India	228 (126 R, 102 L)	R L	17 (13.5) 14 (13.7)	65 (51.6) 50 (49.0)	44 (34.9) 38 (37.3)	-
Dhindsa and Singh (13)	India	80 (41 R, 39 L)	R L	9 (21.9) 7 (17.9)	20 (48.8) 18 (46.2)	12 (29.3) 14 (35.9)	-
This study	Turkey	157 (78 R, 79 L)	R L	13 (16.6) 28 (35.5)	63 (80.8) 49 (62.0)	2 (2.6) 2 (2.5)	47 (29.9)

M: male, F: female, R: right, L: left

Ethics Committee Approval: The study was approved by the Ethics Committee of Hacettepe University Faculty of Medicine (15.03.2022, 05-44).

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REFERENCES

1. Standring S. Gray's anatomy: the anatomical basis of clinical practice. 41st ed. Edinburgh: Elsevier; 2015.
2. Vaishnani H, Jethva K, Rathwa A, Sharma P. Morphometry and morphology of glenoid cavity of scapula. Int J Anat Res. 2018;6(1.1):4798-802.
3. Prescher A, Klumpen T. The glenoid notch and its relation to the shape of the glenoid cavity of the scapula. J Anat. 1997;190(Pt 3):457-60.
4. Churchill RS, Brems JJ, Kotschi H. Glenoid size, inclination, and version: an anatomic study. J Shoulder Elbow Surg. 2001;10(4):327-32.
5. Rajendra GK, Ubbaida SA, Kumar VV. The glenoid cavity: its morphology and clinical significance. Int J Biol Med Res. 2016;7(2):5552-5.

6. Singh R. Surgical anatomy of the glenoid cavity and its use in shoulder arthroplasty among the north Indian population. Cureus. 2020;12(12):e11940.
7. Saha S, Vasudeva N. Morphological variations of glenoid cavity of human scapulae: an anatomical study with clinical relevance. Int J Anat Res. 2020;8(1.2):7288-93.
8. Coskun N, Karaali K, Cevikol C, Demirel BM, Sindel M. Anatomical basics and variations of the scapula in Turkish adults. Saudi Med J. 2006;27(9):1320-5.
9. Yadav Y, Potdar P, Dhakar J. Morphometric study of glenoid cavity of scapulae in north Indian population with clinical significance. Santosh Univ J Health Sci. 2019;5(2):78-81.
10. Chaijaroonkhanarak W, Amarttayakong P, Ratanasuwan S, Kirirat P, Pannangrong W, Welbat JU, et al. Predetermining glenoid dimensions using the scapular dimensions. Eur J Orthop Surg Traumatol. 2019;29(3):559-65.
11. Mamatha T, Pai SR, Murlimanju BV, Kalthur SG, Pai MM, Kumar B. Morphometry of glenoid cavity. Online J Health Allied Scs. 2011;10(3):7.
12. Akhtar MJ, Kumar B, Fatima N, Kumar V. Morphometric analysis of glenoid cavity of dry scapulae and its role in shoulder prosthesis. Int J Res Med Sci. 2016;4(7):2770-6.
13. Dhindsa GS, Singh Z. A study of morphology of the glenoid cavity. J Evol Med Dent Sci. 2014;3(25):7036-43.
14. Cirpan S, Güvençer M. The notch types of the glenoid cavity in adult dry human scapulae. J Basic Clin Health Sci. 2019;3(2):46-50.
15. Tuite MJ, Blankenbaker DG, Seifert M, Ziegert AJ, Orwin JF. Sublabral foramen and buford complex: inferior extent of the unattached or absent labrum in 50 patients. Radiology. 2002;223(1):137-42.
16. Hamilton W. Frazer's anatomy of the human skeleton. Br Med J. 1965;2(5477):1536.

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The Effect of Antibiotic Resistance and Inappropriate Empirical Antibiotic Therapy on 3-Day and 28-Day Mortality in Bacteremic Patients in the Intensive Care Unit: 5-Year Retrospective Analysis

Yoğun Bakım Ünitesindeki Bakteriyemik Hastalarda Antibiyotik Direncinin ve Uygunsuz Ampirik Antibiyotik Tedavisinin 3 Günlük ve 28 Günlük Mortalite Üzerine Etkisi: 5 Yıllık Retrospektif Analiz

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ABSTRACT

Aim: The aim of this study was to examine the effects of antibiotic resistance, empirical antibiotic therapy, and comorbid diseases on 3-day and 28-day mortality in patients with bloodstream infections.

Material and Methods: Files of the patients with positive blood cultures results, between January 1st, 2015, and January 1st, 2020 were analyzed retrospectively. The primary outcome was 3-day mortality and the secondary outcome was 28-day mortality.

Results: A total of 515 patients, 208 (40.4%) female and 307 (59.6%) male, were included in the study. The median age of the patients was 73 (range, 18-95) years. Vancomycin resistance was detected in 8 (3.4%) of 233 gram-positive bacteria. Third-generation cephalosporin, meropenem, and colistin resistance rates of the 282 gram-negative bacteria were found to be 72.7% (n=205), 53.2% (n=150), and 9.9% (n=28), respectively. The 3-day and 28-day mortality rates were 14.4% (n=74) and 64.3% (n=331), respectively. Charlson comorbidity index score (CCIS) (p=0.001) and acute physiology and chronic health evaluation (APACHE) II score (p=0.019) were found to be risk factors for 3-day mortality. Risk factors for 28-day mortality were; age (p<0.001), CCIS (p<0.001), APACHE II score (p=0.001), chronic obstructive pulmonary disease (p=0.007), hospital-acquired infection (p=0.033), and inappropriate antibiotic therapy (p<0.001).

Conclusion: There was no association between antibiotic resistance and mortality, but inappropriate antibiotic treatment was found to increase the risk of 28-day mortality. In addition, since high CCIS and APACHE II scores increase the risk of both 3-day and 28-day mortality, we think that considering these scoring systems will reduce the risk of mortality.

Keywords: Mortality; sepsis; critical care; bacteremia; antibiotic; resistance.

ÖZ

Amaç: Bu çalışmanın amacı, kan dolaşımı enfeksiyonu tanılı hastalarda antibiyotik dirençi, ampirik antibiyotik tedavisi ve komorbid hastalıkların 3 günlük ve 28 günlük mortalite üzerine etkisinin incelenmesidir.

Gereç ve Yöntemler: 1 Ocak 2015 ile 1 Ocak 2020 tarihleri arasında pozitif kan kültürü sonucu olan hastaların dosyaları geriye dönük olarak analiz edildi. Birincil sonlanım noktası 3 günlük mortalite ve ikincil sonlanım noktası 28 günlük mortalite idi.

Bulgular: Çalışmaya, 208 (%40,4) kadın ve 307 (%59,6) erkek, toplam 515 hasta dahil edildi. Hastaların ortanca yaşı 73 (aralık, 18-95) yıl idi. 233 gram pozitif bakterinin 8'inde (%3,4) vankomisin direnci saptandı. 282 gram negatif bakterinin üçüncü kuşak sefalosporin, meropenem ve kolistin direnç oranları sırasıyla %72,7 (n=205), %53,2 (n=150) ve %9,9 (n=28) bulundu. 3 günlük ve 28 günlük mortalite oranları sırasıyla %14,4 (n=74) ve %64,3 (n=331) idi. Charlson komorbidite indeks skoru (Charlson comorbidity index score, CCIS) (p=0.001) ve akut fizyoloji ve kronik sağlık değerlendirmesi (acute physiology and chronic health evaluation, APACHE) skoru (p=0,019) 3 günlük mortalite için risk faktörleri olarak saptandı. 28 günlük mortalite için yaş (p<0,001), CCIS (p<0,001), APACHE II skoru (p=0,001), kronik obstrüktif akciğer hastalığı (p=0,007), hastane kaynaklı enfeksiyon (p=0,033) ve uygunsuz antibiyotik tedavisi (p<0,001) risk faktörleri idi.

Sonuç: Antibiyotik direnci ile mortalite arasında bir ilişki yoktu, ancak uygunsuz antibiyotik tedavisinin 28 günlük mortalite riskini artırdığı saptandı. Ayrıca yüksek CCIS ve APACHE II skorları hem 3 günlük hem de 28 günlük mortalite riskini arttırdığı için, bu skorlama sistemlerinin dikkate alınmasının mortalite riskini azaltacağını düşünüyoruz.

Anahtar kelimeler: Mortalite; sepsis; yoğun bakım; bakteriyemi; antibiyotik; direnç.

INTRODUCTION

Bloodstream infection (BSI) is a serious problem that causes an estimated five million deaths per year worldwide (1). Comorbid disease, antibiotic-resistant microorganisms, and inappropriate antibiotic therapy are thought to be risk factors for mortality in BSI (2-5). Infections due to bacterial resistance to antibiotics are a growing global problem. Unfortunately, our country has the greatest antibiotic use and antibiotic resistance (6,7). Increasing antibiotic resistance negatively affects the success of empirical antibiotic therapy. As a general opinion, it is thought that appropriate empirical therapy reduces mortality rates in patients with bacteremia (5,8). The majority of studies supporting this view were conducted on 28, 30, or 60-day mortality (3,5,9). Studies in England and Japan determined that a significant portion of mortality (6.7-11%) due to BSI occurred in the first 7 days (2,3). The clinical condition of patients who are admitted to the intensive care unit (ICU) with a pre-diagnosis of BSI or patients who develop BSI while being monitored in the ICU rapidly worsens within 3 days and results in mortality. The fact that the risk factors of 3-day mortality have not been investigated until now gives rise to a serious lack of information in the literature. Physicians need new strategies to identify risk factors affecting 3-day mortality from BSI to decrease mortality.

We aimed to examine the effects of antibiotic resistance, empirical antibiotic therapy, and comorbid diseases on 3-day and 28-day mortality in patients with BSI.

MATERIAL AND METHODS

This single-center case-control study was conducted at Niğde Ömer Halisdemir University Training and Research Hospital, a tertiary health care center with 47 beds in the ICU. Data were collected through the hospital's electronic system. Samples for blood cultures were obtained when patients had a body temperature of ≥38.3℃ or when a diagnosis of sepsis was made. Cultures with positive results were examined. Data belonging to the day when the patient's positive blood culture was taken were included in the study. Patients with bacteremia aged 18 years and over who were in the ICU between January 1st, 2015, and January 1st, 2020, were included in the study (Figure 1).

Exclusion criteria:

1. Single blood cultures positive for coagulase-negative staphylococci, *Corynebacterium* spp., *Bacillus* spp., and other potential skin contaminants,
2. Repeated positive culture results with the same bacteria after a first positive blood culture,
3. Two or more different bacteria are identified in the same blood culture.

The primary endpoint was mortality within the first 3 days of admission, while the secondary endpoint was mortality in 28 days. The study was approved by the Niğde Ömer Halisdemir University ethics committee (Date: 04.10.2019, no: 2019/36). The study was performed in accordance with the ethical standards of the 1975 Declaration of Helsinki.

Inappropriate antibiotic therapy was defined as the microorganism being resistant to the antimicrobial agent used. Intermediate susceptibility was classified as resistant. Combination therapy was considered to be appropriate if it contained at least one appropriate antibiotic. Patients who did not take antibiotics on the day of blood culture were considered as having inappropriate antimicrobial therapy. After culture and antibiotic resistance results were obtained, antibiotic therapy was adjusted according to the sensitivity pattern of the microorganism (de-escalation or escalation).

3-day mortality was defined as mortality that occurred within the first 72 hours after a blood culture sample was taken. 28-day mortality was defined as mortality that occurred within the first 28 days after a blood culture sample was taken. Hospital-acquired infection (HAI) was defined as infections that developed 48 hours or more after admission and did not appear to be incubating at the time of admission. The diagnoses of sepsis and septic shock were based on sepsis-1 criteria (10). In determining the sources of bacteremia, the physician's diagnosis in the patient records was taken into consideration. For mortality risk assessment, leukocyte count above 12 000 /mm^3, age of 75 years and over, C-reactive protein (CRP) above 100 mg/L, Charlson comorbidity index score (CCIS) of 4 points and above, and acute physiology and chronic health evaluation (APACHE) II score of 20 points and above were accepted as cut-off value. A white blood cell count (WBC) of 4000 to 10000 cells/mm^3 was considered normal and a CRP level between 0 and 5 mg/L was considered normal.

Bacterial identification and susceptibility were assessed using the VITEK 2 system (bioMérieux, France). Antibiotic susceptibility results were interpreted according to the European committee on antimicrobial susceptibility testing (EUCAST) criteria (11).

Statistical Analysis

All statistical analyses were performed using the IBM SPSS v.23. Normality assumption was assessed through the Kolmogorov-Smirnov test. Categorical variables were summarized as numbers and percentages, and continuous variables as median (interquartile range) [min-max]. The Pearson chi-square test or Fisher's exact test were used for comparisons of categorical variables. For the comparison of continuous measurements between the groups, the Mann-Whitney U test was used. All binary categorical and

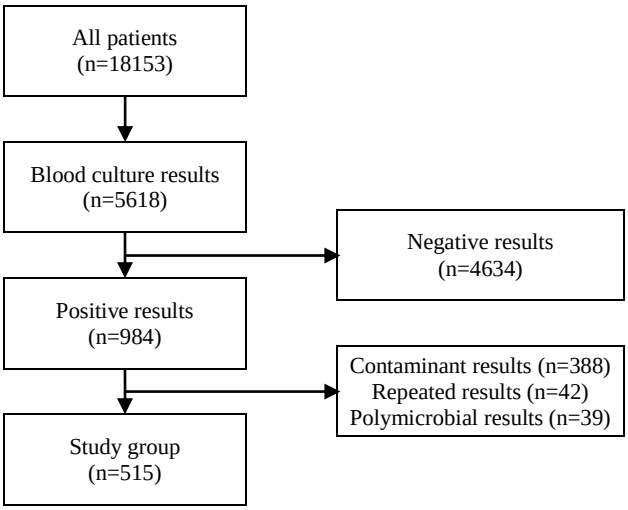

Figure 1. Flowchart of the study

continuous variables were compared to the variable patient survival using univariate binary logistic regression analysis. Variables found to be associated with mortality in univariate analyzes were included in the multivariate binary logistic regression (Backward: Wald method) model used to build a prediction model for BSI mortality. Variables found associated with BSI mortality were expressed with odds ratio (OR) and 95% confidence interval (CI). In all tests, $p<0.05$ was considered statistically significant.

RESULTS

After examining the files of 18 153 patients according to the inclusion and exclusion criteria, a total of 515 patients, of whom 208 (40.4%) were female and 307 (59.6%) were male, were included in the study. The median age of the patients was 73 (range, 18-95) years. The 3-day mortality rate was 14.4% (n=74), while the 28-day mortality rate was 64.3% (n=331). 414 (80.4%) patients had HAI. Of the 74 patients with 3-day mortality, 14 (18.9%) had HAI and of the 331 patients with 28-day mortality, 41 (12.4%) had HAI. 146 (28.3%) patients were in septic shock. Of those with 3-day mortality, 31 (41.9%) were in septic shock, and 104 (31.4%) of those with 28-day mortality were in septic shock. The baseline characteristics of the study group and the comparison of baseline characteristics for 3-day and 28-day mortality were shown in Table 1.

Antibiotic treatment of 332 (64.5%) patients was not found appropriate. While 49 (66.2%) patients in the 3-day mortality group were receiving inappropriate antibiotic treatment, 230 (69.5%) patients in the 28-day mortality group were receiving inappropriate antibiotic treatment. In the 3-day mortality group, empirical antibiotics were not started in 5 (6.8%) patients in the first 24 hours, 47 (63.5%) had monotherapy and 22 (29.7%) had combined empirical antibiotic therapy. Of the patients with 28-day mortality, empirical antibiotics were not started in 23 (6.9%) patients in the first 24 hours, 227 (68.6%) had monotherapy and 81 (24.5%) had combined empirical antibiotic therapy. We found no significant difference in 3-day mortality between those whose empirical antibiotics were not started in the first 24 hours, and those who started monotherapy and combined empirical antibiotic therapy (p=0.148). The most common bacteria was *Acinetobacter baumannii* (Table 2).

In the univariate analyses, CCIS (p<0.001), APACHE II score (p=0.007), septic shock (p=0.005), diabetes mellitus (DM) (p=0.020), malignancy (p=0.029), and *A. baumannii* bacteremia (p=0.030) were found to be risk factors for 3-day mortality. Age (p<0.001), CCIS (p<0.001), APACHE II score (p<0.001), prolonged ICU stay (p=0.004), septic shock (p=0.038), HAI (p<0.001), DM (p=0.032), chronic obstructive pulmonary disease (COPD) (p=0.021), mechanical ventilation (MV) (p<0.001), central venous catheter (p=0.010), history of antibiotic use (p=0.001), source of lung infection (p=0.016), urinary tract infection (UTI) (p=0.031), *A. baumannii* bacteremia (p=0.027), *E. coli* bacteremia (p=0.002), combined empirical antibiotic therapy (p=0.048), and inappropriate empirical antibiotic therapy (p=0.002) were found to be risk factors for 28-day mortality.

Risk factors for 3-day mortality in multivariate analysis were CCIS (p=0.001) and APACHE II score (p=0.019). Age (p<0.001), CCIS (p<0.001), APACHE II score (p=0.001), COPD (p=0.007), HAI (p=0.033), and inappropriate antibiotic therapy (p<0.001) were found to be risk factors for 28-day mortality (Table 3).

Table 1. Baseline characteristics of the 3-day and 28-day survivors and non-survivors

	3-day Mortality			28-day Mortality			Total (n=515)
	Non-Survivors (n=74)	Survivors (n=441)	p	Non-Survivors (n=331)	Survivors (n=184)	p	
Age (years)*	73 (19) [26-95]	73 (20) [18-95]	0.979	75 (19) [22-95]	68 (24) [18-95]	**<0.001**	73 (20) [18-95]
Age ≥75 years, n (%)	32 (43.2)	213 (48.3)	0.420	177 (53.5)	68 (37)	**<0.001**	245 (47.6)
Female, n (%)	35 (47.3)	173 (39.2)	0.191	140 (42.3)	68 (37.0)	0.237	208 (40.4)
DM, n (%)	28 (37.8)	110 (24.9)	**0.020**	99 (29.9)	39 (21.2)	**0.032**	138 (26.8)
COPD, n (%)	21 (28.4)	155 (35.1)	0.256	125 (37.8)	51 (27.7)	**0.021**	176 (34.2)
Malignancy, n (%)	10 (13.5)	28 (6.3)	**0.029**	28 (8.5)	10 (5.4)	0.208	38 (7.4)
MV, n (%)	47 (63.5)	266 (60.3)	0.602	232 (70.1)	81 (44.0)	**<0.001**	313 (60.8)
CVC, n (%)	17 (23.0)	109 (24.7)	0.747	93 (28.1)	33 (17.9)	**0.010**	126 (24.5)
Antibiotic used, n (%)	35 (47.3)	196 (44.4)	0.648	167 (50.5)	64 (34.8)	**0.001**	231 (44.9)
Lung infection, n (%)	28 (37.8)	123 (27.9)	0.082	109 (32.9)	42 (22.8)	**0.016**	151 (29.3)
UTI, n (%)	18 (24.3)	100 (22.7)	0.755	66 (19.9)	52 (28.3)	**0.031**	118 (22.9)
CCIS ≥4, n (%)	38 (51.4)	143 (32.4)	**0.002**	146 (44.1)	35 (19)	**<0.001**	181 (35.1)
CCIS*	4 (3) [0-11]	2 (3) [0-10]	**<0.001**	3 (2) [0-11]	2 (2) [0-9]	**<0.001**	2 (3) [0-11]
APACHE II ≥20, n (%)	34 (45.9)	225 (51.0)	0.240	188 (56.8)	71 (38.6)	**<0.001**	259 (50.3)
APACHE II*	26 (10) [14-36]	23 (10) [6-38]	**0.007**	25 (9) [7-38]	21 (11) [6-34]	**<0.001**	24 (10) [6-38]
DBA-BC*	9 (15) [1-85]	10 (20) [1-170]	0.293	12 (19) [1-170]	5 (14) [1-104]	**0.004**	10 (20) [1-170]
WBC (/mm^3)*	12 (10) [1-30]	12 (8) [1-125]	0.843	12 (9) [1-48]	12 (8) [1-125]	0.370	12 (8) [1-125]
CRP (mg/L)*	152 (146) [24-554]	155 (127) [8-547]	0.225	155 (136) [11-554]	155 (139) [8-470]	0.504	155 (133) [8-554]

DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, MV: mechanical ventilation, CVC: central venous catheter, UTI: urinary tract infection, CCIS: Charlson comorbidity index score, APACHE: acute physiology and chronic health evaluation, DBA-BC: days between admission to blood culture, WBC: white blood cell count, CRP: C-reactive protein, *: median (interquartile range) [minimum-maximum]

Table 2. Distribution of microorganisms, and antibiotics resistance in 3-day and 28-day mortality groups

	3-day Mortality			28-day Mortality			Total (n=515)
	Non-Survivors (n=74)	Survivors (n=441)	p	Non-Survivors (n=331)	Survivors (n=184)	p	
Empirical antibiotic							
3. gen. CPH	16 (21.6)	87 (19.7)	0.706	62 (18.7)	41 (22.3)	0.334	103 (20.0)
PIP-TAZO	17 (23.0)	109 (24.7)	0.747	72 (21.8)	54 (29.3)	0.055	126 (24.5)
Carbapenem	29 (39.2)	169 (38.3)	0.887	135 (40.8)	63 (34.2)	0.143	198 (38.4)
Aminoglycoside	2 (2.7)	8 (1.8)	0.642	8 (2.4)	2 (1.1)	0.507	10 (1.9)
Glycopeptide	11 (14.9)	44 (10.0)	0.208	38 (11.5)	17 (9.2)	0.430	55 (10.7)
Colistin	11 (14.9)	36 (8.2)	0.064	33 (10.0)	14 (7.6)	0.373	47 (9.1)
Quinolones	9 (12.2)	35 (7.9)	0.229	34 (10.3)	10 (5.4)	0.060	44 (8.5)
GNB	45 (60.8)	237 (53.7)	0.258	181 (54.7)	101 (54.9)	0.964	282 (54.8)
A. baumannii	20 (27.0)	73 (16.6)	**0.030**	69 (20.8)	24 (13.0)	**0.027**	93 (18.1)
Klebsiella spp.	11 (14.9)	64 (14.5)	0.937	48 (14.5)	27 (14.7)	0.958	75 (14.6)
E. coli	6 (8.1)	54 (12.2)	0.305	28 (8.5)	32 (17.4)	0.002	60 (11.7)
P. aeruginosa	6 (8.1)	34 (7.7)	0.906	27 (8.2)	13 (7.1)	0.657	40 (7.8)
Others	2 (2.7)	12 (2.7)	1.000	9 (2.7)	5 (2.7)	0.999	14 (2.7)
Antibiotic resistance for GNB (n=282)							
Ampicillin	42 (93.3)	222 (93.7)	1.000	168 (92.8)	96 (95.0)	0.462	264 (93.6)
3. gen. CPH	32 (71.1)	173 (73.0)	0.795	135 (74.6)	70 (69.3)	0.340	205 (72.7)
PIP-TAZO	26 (57.8)	146 (61.6)	0.630	109 (60.2)	63 (62.4)	0.722	172 (61.0)
Meropenem	24 (53.3)	126 (53.2)	0.983	94 (51.6)	56 (55.4)	0.571	150 (53.2)
Colistin	6 (13.3)	22 (9.3)	0.416	20 (11.0)	8 (7.9)	0.400	28 (9.9)
Ciprofloxacin	32 (71.1)	165 (69.6)	0.842	127 (70.2)	70 (69.3)	0.880	197 (69.9)
Gentamycin	24 (53.3)	117 (49.4)	0.626	93 (51.4)	48 (47.5)	0.535	141 (50.0)
GPB	29 (39.2)	204 (46.3)	0.258	150 (45.3)	83 (45.1)	0.964	233 (45.2)
CoNS	9 (12.2)	97 (22)	0.053	65 (19.6)	41 (22.3)	0.477	106 (20.5)
E. faecalis	7 (9.5)	44 (10.0)	0.890	35 (10.6)	16 (8.7)	0.494	51 (9.9)
S. aureus	9 (12.2)	36 (8.1)	0.260	26 (7.8)	19 (10.3)	0.341	45 (8.7)
E. faecium	4 (5.4)	23 (5.2)	1.000	22 (6.6)	5 (2.7)	0.055	27 (5.2)
Streptococcus spp.	0 (0)	4 (0.9)	1.000	2 (0.6)	2 (1.1)	0.620	4 (0.7)
Antibiotic resistance for GPB (n=233)							
Ampicillin	14 (48.3)	128 (62.7)	0.135	91 (60.7)	51 (61.4)	0.907	142 (60.9)
Clindamycin	16 (55.2)	144 (70.6)	0.094	106 (70.7)	54 (65.1)	0.377	160 (68.7)
Ciprofloxacin	17 (58.6)	131 (64.2)	0.558	102 (68.0)	46 (55.4)	0.056	148 (63.5)
Vancomycin	0 (0)	8 (3.9)	0.600	6 (4.0)	2 (2.4)	0.715	8 (3.4)

CPH: cephalosporin, PIP-TAZO: piperacillin-tazobactam, GNB: gram-negative bacteria, GPB: gram-positive bacteria, CoNS: coagulase-negative Staphylococci

DISCUSSION

The mortality of BSI in ICU patients is high worldwide. Many variables such as the patient's underlying diseases, the genus of bacteria, antibiotic resistance, and appropriate treatment are effective on mortality. In the current study, factors affecting the risk of early and late mortality in BSI were examined. Malignancy, DM, chronic renal failure, heart disease, and age were reported as risk factors for mortality (8,12-14). In this study, COPD, DM, and age were associated with increased 28-day mortality risk. We think that the reason why COPD significantly increased the mortality risk in this study was that the source of infection was the lung, the percentage of patients on MV was high, and the frequency of *A. baumannii* was higher. Dysfunction in adaptive and innate immune responses due

Table 3. Multivariate analysis of risk factors for mortality

	B	OR (95% Cl)	p
3-day mortality			
CCIS	0.227	1.255 (1.095-1.438)	**0.001**
APACHE II	0.063	1.065 (1.010-1.122)	**0.019**
28-day mortality			
Age	0.028	1.028 (1.012-1.044)	**<0.001**
CCIS	0.301	1.351 (1.170-1.559)	**<0.001**
APACHE II	0.066	1.068 (1.025-1.112)	**0.001**
COPD	0.811	2.250 (1.242-4.077)	**0.007**
HAI	0.811	2.249 (1.066-4.745)	**0.033**
IAT	0.998	2.712 (1.599-4.599)	**<0.001**

HAI: Hospital-acquired infections, IAT: Inappropriate antimicrobial therapy

to DM reduces survival in sepsis. DM was the only chronic disease affecting both 3-day and 28-day mortality in univariate analysis. We anticipate that the mortality rate in patients with diabetes will decrease with the changes we plan to make in routine practice by monitoring blood glucose levels hourly in critically ill patients, and with early surgical intervention in diabetic foot infections.

It has been stated in many publications that CCIS and APACHE II scores were useful in 28-day mortality estimations in BSI (3,8,9,12,15,16). We found that both high APACHE II scores and CCIS were risk factors for 3-day and 28-day mortality. This was a new result for the literature and was important in the sense that it demonstrated benefits in predicting mortality in both 3-day and 28-day periods in both scoring systems.

Bloodstream infections caused by UTIs have a lower risk of mortality (3,12). In this study, mortality was lower in UTIs, which is consistent with the literature. It is noteworthy that we determined that lung-borne BSI increased 28-day mortality. The first reason why this result was not found in other studies may be the lower rates of MV use and the second reason may be the low prevalence of *A. baumannii* pneumonia (4,12). In this study, the source of infection was not a risk factor for 3-day mortality. According to this result, it can be interpreted that in the treatment of infections caused by the lung or urinary system, similar benefits are provided in the first 3 days, but it is more difficult to control pneumonia in 28 days; UTIs are more easily controlled in the following days. Lower respiratory tract infection frequency can be reduced by following infection control measures, shortening the duration of intubation, and head-of-bed elevation, thus reducing mortality. In studies conducted in Japan, England, and Switzerland, *E. coli* and *S. aureus* were the most frequently detected pathogens in BSI (3,5,12,17). In the study of Ergönül et al. (15) covering gram-negative bacteria, the most frequently seen were *A. baumannii* and *K. pneumoniae*, and in the study of Delle Rose et al. (13) and in this study, the most frequently observed pathogens were *A. baumannii*, *Klebsiella* spp., and coagulase-negative staphylococci. In these studies, where the frequency of *A. baumannii* and *Klebsiella* spp. was high, it is striking that the mortality rate and history of antibiotic use were higher than in other studies. The history of antibiotic use is an important risk factor for the emergence of such resistant microorganisms. We believe that mortality can be reduced by increasing compliance with antibiotic management programs, avoiding prolonged MV, and paying attention to isolation measures and hand hygiene.

In the treatment of BSI, it is essential to start antibiotic therapy quickly, at the right dose, and in accordance with epidemiological data. Inappropriate empirical antibiotic therapy is thought to increase mortality in BSI (5,8,9,12,18). We found that inappropriate antibiotic treatment increased 28-day mortality 2.7 times. However, Lim et al. (4) and Schuttevaer et al. (19) concluded that appropriate empirical antibiotic therapy did not reduce mortality. We think the fact that Lim et al. (4) only included ICU-acquired infections in their study and the frequency of *A. baumannii* was low caused them to reach this conclusion. The difference in patient selection criteria and methodology in the study of Schuttevaer et al. (19) may have led to this result. We believe that regulating empirical antibiotic therapy, taking into account risk factors such as colonization with resistant microorganisms, antibiotic use, and local antibiotic resistance will reduce inappropriate antibiotic use and 28-day mortality.

The irrational use of antibiotics is a serious problem in Türkiye, and the Republic of Türkiye Ministry of Health published a national action plan in 2014 (20). In the article published by Ergönül et al. (15) before this plan, it was determined that 68% of patients with BSI who died had used antibiotics before admission to the hospital. This study was conducted in Türkiye and antibiotic resistance rates of third-generation cephalosporin, quinolone, and carbapenem for gram-negative bacteria were found as 89%, 78%, and 62%, respectively (15). Antibiotic resistance of Türkiye is still higher than that of Japan and Switzerland (3,12). However, the decrease in antibiotic resistance and antibiotic use before hospitalization seen in this study, which was conducted 4 years after the study of Ergönül et al. (15), is promising. It can be predicted that methods to reduce unnecessary antibiotic use, such as the implementation of rational antibiotic management programs and national planning to restrict antibiotic use, will contribute to decreasing antibiotic resistance and the reduction of the mortality rates of BSI in the ICU in the future.

The 28-day mortality rate in this study was consistent with other studies (2-4,9,16,17). No studies in the literature show the 3-day mortality rate, but Evans et al. (2), and Hattori et al. (3) reported 7-day mortality rates of 6.7% and 11%, respectively. It is striking that we had a higher mortality rate in a shorter period. This result can be explained by the high frequency of HAI, the *A. baumannii* rate being much higher than in other studies, and the high rate of inappropriate antibiotic therapy.

The limitations of this study are that because it is a retrospective study, there may be minor errors in the patient records. Other limitations are the absence of Pitt bacteremia scores, sequential organ failure assessment scores, ceftazidime-avibactam treatment results, and intravenous fosfomycin treatment results. The study may be insufficient to reflect global practice because it is a single-center study.

CONCLUSION

In conclusion, the relationship between mortality and empirical antibiotic treatment, bacterial species, antibiotic resistance, CCIS, APACHE II score, and comorbid diseases in BSI were examined. This study indicated that both a high CCIS and a high APACHE II score were associated with increased 3-day and 28-day mortality. In addition, a correlation between 28-day mortality and advanced age, COPD, HAI, and inappropriate antibiotic therapy were found. Reducing HAI by following infection control measures, correct management of comorbid diseases, and appropriate empirical antibiotic use may be beneficial in reducing mortality. We think that this study will contribute to the literature in terms of showing that high APACHE II score and CCIS are important risk factors for both 3-day and 28-day mortality.

Ethics Committee Approval: The study was approved by the Ethics Committee of Niğde Ömer Halisdemir University (04.10.2019, 36).

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REFERENCES

1. Fleischmann C, Scherag A, Adhikari NKJ, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of global incidence and mortality of hospital-treated sepsis current estimates and limitations. Am J Respir Crit Care Med. 2016;193(3):259-72.
2. Evans RN, Pike K, Rogers CA, Reynolds R, Stoddart M, Howe R, et al. Modifiable healthcare factors affecting 28-day survival in bloodstream infection: A prospective cohort study. BMC Infect Dis. 2020;20(1):545.
3. Hattori H, Maeda M, Nagatomo Y, Takuma T, Niki Y, Naito Y, et al. Epidemiology and risk factors for mortality in bloodstream infections: A single-center retrospective study in Japan. Am J Infect Control. 2018;46(12):e75-9.
4. Lim SJ, Choi JY, Lee SJ, Cho YJ, Jeong YY, Kim HC, et al. Intensive care unit-acquired blood stream infections: a 5-year retrospective analysis of a single tertiary care hospital in Korea. Infection. 2014;42(5):875-81.
5. Yamaga S, Shime N. Association between appropriate empiric antimicrobial therapy and mortality from bloodstream infections in the intensive care unit. J Infect Chemother. 2018;24(4):267-71.
6. The Organisation for Economic Co-operation and Development. Stemming the superbug tide: just a few dollars more, OECD health policy studies. Paris: OECD Publishing; 2018. doi: 10.1787/9789264307599-en.
7. Versporten A, Bolokhovets G, Ghazaryan L, Abilova V, Pyshnik G, Spasojevic T, et al. Antibiotic use in Eastern Europe: A cross-national database study in coordination with the WHO Regional Office for Europe. Lancet Infect Dis. 2014;14(5):381-7.
8. Wang W, Jiang T, Zhang W, Li C, Chen J, Xiang D, et al. Predictors of mortality in bloodstream infections caused by multidrug-resistant gram-negative bacteria: 4 years of collection. Am J Infect Control. 2017;45(1):59-64.
9. Brooks D, Polubothu P, Young D, Booth MG, Smith A. Sepsis caused by bloodstream infection in patients in the intensive care unit: the impact of inactive empiric antimicrobial therapy on outcome. J Hosp Infect. 2018;98(4):369-74.
10. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;101(6):864-74.
11. eucast.org [Internet]. European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0, 2019. [Cited: 2022 July 26]. Available from: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_9.0_Breakpoint_Tables.pdf.
12. Papadimitriou-Olivgeris M, Psychogiou R, Garessus J, Camaret A, Fourre N, Kanagaratnam S, et al. Predictors of mortality of bloodstream infections among internal medicine patients in a Swiss Hospital: Role of quick Sequential Organ Failure Assessment. Eur J Intern Med. 2019;65:86-92.
13. Delle Rose D, Sordillo P, Gini S, Cerva C, Boros S, Rezza G, et al. Microbiologic characteristics and predictors of mortality in bloodstream infections in intensive care unit patients: A 1-year, large, prospective surveillance study in 5 Italian hospitals. Am J Infect Control. 2015;43(11):1178-83.
14. Capsoni N, Bellone P, Aliberti S, Sotgiu G, Pavanello D, Visintin B, et al. Prevalence, risk factors and outcomes of patients coming from the community with sepsis due to multidrug-resistant bacteria. Multidiscip Respir Med. 2019;14:23.
15. Ergönül, Aydin M, Azap A, Başaran S, Tekin S, Kaya Ş, et al. Healthcare-associated gram-negative bloodstream infections: antibiotic resistance and predictors of mortality. J Hosp Infect. 2016;94(4):381-5.
16. Mitsuboshi S, Tsuruma N, Watanabe K, Takahashi S, Ito A, Nakashita M, et al. Advanced age is not a risk factor for mortality in patients with bacteremia caused by extended-spectrum β-lactamase-producing organisms: a multicenter cohort study. Jpn J Infect Dis. 2020;73(4):288-92.
17. Gerver SM, Mihalkova M, Bion JF, Wilson APR, Chudasama D, Johnson AP, et al. Surveillance of bloodstream infections in intensive care units in England, May 2016-April 2017: epidemiology and ecology. J Hosp Infect. 2020;106(1):1-9.
18. Vucelić V, Klobučar I, Đuras-Cuculić B, Gverić Grginić A, Prohaska-Potočnik C, Jajić I, et al. Sepsis and septic shock - an observational study of the incidence, management, and mortality predictors in a medical intensive care unit. Croat Med J. 2020;61(5):429-39.
19. Schuttevaer R, Alsma J, Brink A, van Dijk W, de Steenwinkel JEM, Lingsma HF, et al. Appropriate empirical antibiotic therapy and mortality: Conflicting data explained by residual confounding. PLoS One. 2019;14(11):e0225478.
20. akilciilac.gov.tr [Internet]. Republic of Türkiye Ministry of Health. Akılcı ilaç kullanımı ulusal eylem planı 2014-2017. [Cited: 2022 July 26]. Available from: http://www.akilciilac.gov.tr/wp-content/uploads/2014/11/aik-ulusal-eylem-plani.pdf.

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Comparison of the Effect of Board Game and Tobacco Cessation Education on Nicotine Addiction in Adolescent Smokers

Sigara İçen Ergenlerde Masa Oyunu ve Tütün Bırakma Eğitiminin Nikotin Bağımlılığı Üzerine Etkisinin Karşılaştırılması

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ABSTRACT

Aim: The aim of this study was to compare the effect of a board game and tobacco cessation education on nicotine addiction in adolescent smokers.
Material and Methods: This randomized controlled study included 103 adolescents who declared to smoke at least one cigarette per day. For data collection, sociodemographic data form, Fagerstrom test for nicotine dependence, and stages of change scale were used. The study groups consisted of three intervention groups; board game, tobacco cessation education, and the combined use of these two interventions, and a control group. All interventions were compared with the control group. Follow-ups were conducted at baseline, 8th, and 12th week.
Results: While 38.8% (n=40) of all participants were addicted to nicotine at a very low level, 6.8% (n=7) were very high. 37.9% (n=39) of the participants reported smoking the first cigarette of the day within the first 5 minutes. Groups had an effect on the nicotine addiction level of adolescents (p=0.031), while there was no significant difference for the period, and period*group interaction (p=0.472 and p=0.339, respectively). The difference was due to the board game group. In the post evaluation, three of the adolescents who played board games and two of the adolescents who received tobacco cessation training were in the action phase.
Conclusion: The results showed that the board game group participants had a decrease in the level of nicotine addiction. Our suggestion is to use and disseminate games as an alternative method that will attract the attention of adolescents in tobacco cessation education.
Keywords: Adolescent; addiction; board game; change of stage; gamification; tobacco.

ÖZ

Amaç: Bu çalışmanın amacı, sigara içen ergenlerde masa oyunu ve tütün bırakma eğitiminin nikotin bağımlılığı üzerindeki etkisinin karşılaştırılmasıdır.
Gereç ve Yöntemler: Bu randomize kontrollü çalışmaya her gün en az bir adet sigara içtiğini beyan eden 103 adölesan dahil edildi. Veri toplamak için sosyodemografik veri formu, nikotin bağımlılığı için Fagerstom testi ve değişim aşamaları ölçeği kullanıldı. Çalışma grupları masa oyunu, tütün bırakma eğitimi ve bu iki müdahalenin birlikte kullanımını içeren girişimlerden oluşan üç adet müdahale grubu ve bir de kontrol grubundan oluşmaktaydı. Tüm müdahale grupları kontrol grubu ile karşılaştırıldı. Takipler başlangıçta, 8. haftada ve 12. haftada yapıldı.
Bulgular: Tüm katılımcıların %38,8'i (n=40) çok düşük bir düzeyde nikotin bağımlısı iken %6,8'i (n=7) ise yüksek düzeyde nikotin bağımlısı idi. Katılımcıların %37,9'u (n=39) günün ilk sigarasını ilk 5 dakika içinde içtiğini beyan etti. Grupların, ergenlerin nikotin bağımlılık düzeyine anlamlı bir etkisi varken (p=0,031), periyot ve periyot*grup etkileşimi için ise anlamlı bir farklılık yoktu (sırasıyla p=0,472 ve p=0,339). Bu farklılık masa oyunu grubundan kaynaklanmakta idi. Son değerlendirmede, masa oyunu oynayan ergenlerden üçü ve tütün bırakma eğitimi alan ergenlerden ikisi hareket aşamasında idi.
Sonuç: Sonuçlar masa oyunu grubu katılımcılarının nikotin bağımlılığı düzeyinde bir azalma olduğunu göstermiştir. Önerimiz tütün bırakma eğitiminde ergenlerin ilgisini çekecek olan alternatif bir yöntem olarak oyunların kullanılması ve yaygınlaştırılmasıdır.
Anahtar kelimeler: Bağımlılık; ergen; evre değişikliği; masa oyunu; oyunlaştırma; tütün.

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INTRODUCTION

Tobacco use is one of the leading preventable causes of death. The reason for the long-term use of tobacco and the difficulty in quitting is the addictive feature of nicotine in tobacco. Tobacco use is a major risk factor for cardiovascular and respiratory diseases, more than 20 different types or subtypes of cancer, as well as many other debilitating medical conditions (1). In addition; it is possible that the consumption of tobacco products at an early age has a longer duration of tobacco use than those who start at a later age (2). In a study investigating the prevalence of tobacco use among adolescents in 143 countries, the prevalence of any tobacco use for at least 1 day in the last 30 days was reported as 17.9% in boys and 11.5% in girls. It was also reported that the prevalence of smoking at least 1 day in the last 30 days decreased in 80 (57.1%) of 140 countries, remained unchanged in 39 (27.9%), and increased in 21 (15.0%). However, in 81 (59.1%) of 137 countries, it was reported that the prevalence of using tobacco products other than cigarettes did not change or increase (3). Studies conducted in Turkey have reported a smoking prevalence ranging from 15.8 to 36.1% in young groups (4,5). Adolescents are at high risk for tobacco use due to factors such as impulsivity, poor perception, desire to prove themselves, and insufficient neurological development (6). The Centers for Disease Control and Prevention stated that if smoking continues at the current rate among young people, individuals younger than 18 will die prematurely from a smoking-related disease (7).

There are many methods for smoking cessation such as pharmacotherapy, nicotine replacement therapy, and cognitive-behavioral therapies. One of them is the education aiming at intentional behavior change according to the transtheoretical model (TTM). The main goal of the model is to overcome addiction with the use of the stages of change without any medical support. Because the TTM is a model that advocates conscious behavior change. TTM of behavior change is a process of making initiatives in accordance with the change stage of the individual to facilitate the change, otherwise, resistance to behavior change is developed. TTM is a proven model for smoking cessation when used according to the change stages (8). However, these techniques have been reported to have limited success in quitting smoking (9). This has led to the use of different techniques. One of these techniques is games. Gaming is a conscious activity carried out in a certain time period to socialize without any specific financial gain/profit benefit, making the gamer feel like living an extraordinary life and realizing a special purpose according to binding rules (10). As it is very easy to access information thanks to technology in our age, traditional teaching methods are boring and cannot provide motivation (11,12). Therefore, games can create learning environments that make education fun. While the use of games in health education exposes individuals to subjects, it aims to create an internal motivation, targeting the protection and improvement of health (13). Board games are a type of game used to reduce or cease nicotine addiction associated with tobacco use. One of these board games is "Pick-Klop". The aim of "Pick-Klop" is to inform smokers about smoking and/or quitting smoking in a way that does not make them feel guilty about smoking, to increase their self-efficacy regarding smoking cessation skills, change their attitudes toward tobacco addiction, and assist tobacco addiction treatments and gain quitting behavior (14).

The aim of this study was to evaluate the effect of a board game and smoking cessation education on nicotine addiction in adolescents.

MATERIAL AND METHODS

Study Design

This study was designed as a single-blind randomized controlled trial to evaluate the effects of the different interventions on smoking cessation. The study was approved by the Ethics Committee of Eskişehir Osmangazi University (21.11.2017, 09) and the Ministry of National Education (16.02.2018, 3401438). The study adhered to the CONSORT guidelines and used a CONSORT-EHEALTH checklist.

Sample Size

The sample size of the study was calculated by the G*Power v.3.1.9 and estimated using Cohen's effect size. Repeated measures: within-between interactions: ANOVA approach was used to calculate effect size (15). For sample size calculation the doctoral thesis carried out by the authors of this study was used. Considering that the number of groups was 4, the number of measurements was 3, the effect size was 0.76, the type I error was 0.05, and the power of the study was 0.80, it was determined that at least 24 participants should be selected for each group.

Participants

Participants consisted of students studying at Eskişehir Mustafa Kemal Atatürk Vocational and Technical High School in Turkey. In order to form the intervention groups, permission was obtained from the school principal and teacher of each class, and the students were informed about the purpose of the study and the participation criteria. Participant recruitment began in October 2018 and end in January 2019. The inclusion criteria were studying at Eskişehir Mustafa Kemal Atatürk Vocational and Technical High School, smoking at least one cigarette a day, and volunteering to participate in the study. There were 103 students who volunteered to participate in the study and declared that they smoked at least one cigarette per day. All students were included in the study.

Randomization

After baseline assessment, eligible students were given an automated number using the Java built-in random number generator and were randomly assigned to four groups; board game (BG), tobacco cessation education (TCE), combined intervention (CI), and the control groups. Randomization was done by a person who was blinded to the study in Excel. Research personnel were blinded to allocation at initial randomization but were briefed after assigning participants to the groups. Participants were informed about the group they were allocated to.

Interventions

Board Game

The Pick-Klop game is a board game played with cards that allows interaction between players. The game aims to help smokers to change their attitudes and cognitions about nicotine/cigarette/tobacco addiction. The goals of the game are to inform smokers about tobacco smoking and quitting in a way that does not make them feel guilty, to increase their level of self-confidence in their ability to

cessate smoking, to change attitudes toward tobacco addiction (perceived advantages and disadvantages), and to help them through the cessation process. The cards of the game consist of three categories: question card, advantage-disadvantage card, and stimulus-punishment card (16). Question cards are cards that include questions about tobacco use, its harms, ways to cessation, problems experienced during cessation, and ways to cope with these problems. If the player gives correct answers in the question category, s/he gets points the same as the number on the dice. Points gained are used in the stimulus-punishment category. Surprise cards are cards that add fun to the game, allowing them to get gifts or hidden cards, and help or hinder another player during the game. Stimulus-punishment cards are cards that vary depending on the player's approach, which can either cause a return to the starting line of the game or prevent a return to the beginning by offering alternative behaviors to tobacco smoking behavior.

The game is played with a minimum of two and a maximum of six people. The player with the highest roll is the player who goes first. The game is managed by a moderator who knows the game. The dice are rolled a second time. The pawn is moved by the number on the rolled dice. Whichever category of the card is in the box, the player draws a card from that category. If the box is in the category of questions, the player who rolls the dice draws a card and gives it to the moderator. The moderator reads the question. If the player answers the question correctly, s/he gets points. If the player comes to the surprise card category with the dice roll, s/he chooses from the surprise cards. The player who rolls the dice and falls into the stimulus-punishment card category chooses a card. In the situation indicated on the card, the player either says "I smoke" or chooses the strategy to prevent smoking. If the player did not answer the question on the question card correctly or did not choose the anti-smoking strategy on the stimulus-punishment card, s/he loses points. If the player does not have enough points, he or she turns to one of three different levels on the game board. The winner is the player who is first to reach the final game box. The duration of each game varies between 15-45 minutes, depending on the speed of the player's response and reaching the final game box (16).

Tobacco Cessation Education Program According to the Transtheoretical Model

TTM was developed by Prochaska and DiClemente in 1982, which is defined as a five-stage process of change, including precontemplation, contemplation, preparation, action, and maintenance, which enables individuals to adapt and determine their readiness for smoking cessation treatment (17). The model's definition of behavior change as a gradual, continuous, and dynamic structure is the most basic feature that distinguishes it from other traditional behavioral approaches that evaluate behavior change as a sharp and direct result. This model, which was first used in smoking cessation programs, includes sensitive tools to measure the individual's cognitive and behavioral processes, self-confidence about change, perception of decision making, and factors that make change difficult. With this feature, it allows for identifying individuals in different stages of behavior change, planning individual-specific interventions, evaluating the effectiveness of implemented interventions, and planning new initiatives (17,18).

The training, which is organized according to the stages of the change model, which includes the stages of pre-thinking, contemplation, preparation, action, and care, was designed by the researchers in the light of the Ministry of Health's Tobacco Cessation Guide. In this study, goals and appropriate initiatives were determined in accordance with the stages of precontemplation, contemplation, preparation, action, and maintenance in the stages of the change model.

Precontemplation: The goal of this step is to make those with tobacco addiction consider quitting tobacco use. For this purpose, group members were asked to explain the reasons why they smoke tobacco/cigarettes, discuss the perceived benefits and harms of tobacco addiction, and the negative effects of tobacco addiction on their health. The most important output targeted at the end of the education is to state that tobacco addiction is a harmful habit. During the interviews, the group participants were led to feel confident about a change.

Contemplation: The aim of this stage is that the participants can evaluate themselves, determine their personal motivation points, and summarize their coping skills with stress. Participants were informed about coping with nicotine withdrawal symptoms, ways to get away from nicotine addiction, methods of coping with obstacles to getting away from tobacco addiction, coping with stress, and relaxation exercises.

Preparation: This stage aims to create an action plan for the tobacco addiction behavior of the participants who have recognized their own resources and motivation points. This stage emphasized the importance of recording and controlling stimuli promoting tobacco addiction, examination, the things to be done before getting rid of tobacco addiction, and the importance of avoiding reminders. They were asked to write down their reasons for quitting smoking. The aim was to enable them to see their reasons for quitting smoking concretely. The importance of determining the quit date was mentioned. Alternative behaviors to be developed when tobacco use is discontinued were discussed. The importance of receiving social support systems was explained.

Action: The purpose of this stage is the prevention of reverts to tobacco addiction behavior, development of individual strength, and making a plan to manage possible risky situations. In order to achieve this goal, the importance of self-rewarding, methods of coping with nicotine withdrawal symptoms, and nicotine deficiency were discussed with participants. In addition, how to avoid situations that encourage nicotine consumption behavior, the importance of saying no, the importance of environmental change, and the importance of avoiding relapse were discussed.

Maintenance: Because of the study design and the lack of participants in the maintenance step, interventions specific to this stage were not planned in this study.

Combined Intervention

The combined intervention included the board game together with tobacco cessation education.

Control Group

The scales were applied to the control group at baseline, at the end of the eighth, and twelfth weeks.

Application

The BG and TCE that would play the game were divided into nine groups, with five or six participants in each group. Each group received intervention every two weeks.

Stages of change scale (SCS) was administered after each interview. The groups were rearranged before each intervention and divided into TCE 1 (Precontemplation), TCE 2 (Contemplation), and TCE 3 (Preparation), according to the thinking skills scale. Before interventions, to communicate with the participants on the phone, message groups were created. The purpose of creating these message groups was to announce the classroom and time of each intervention. The interventions were carried out in different classrooms and at different times by the researcher only in order to ensure an atmosphere of trust and full benefit from the interventions.

Measurements

Sociodemographic Data Form

The sociodemographic data form prepared by the researcher consists of questions about age, gender, class, place of residence, daily cigarette consumption, age at onset of smoking, smoking status of parents, and the reason for starting smoking.

Fagerstrom Test for Nicotine Dependence (FTND)

FTND was developed by Heatherton et al. (19) in 1991. The Turkish validity and reliability study of the scale was performed by Uysal et al. (20) in 2003 with a Cronbach's alpha coefficient of 0.56. In scoring the FTND, yes/no items are scored from 0 to 1 and multiple-choice items are scored from 0 to 3. The items are summed to yield a total score of 0-10. The higher the total Fagerstrom score, the more intense the patient's physical dependence on nicotine. Addiction classification is calculated as 0-2 points very low, 3-4 points low, 5 points medium, 6-7 points high, and 8-10 points very high (19).

The reliability analysis results of the FTND administered to the participants in this study were 0.726 in the pre-test, 0.715 in the mid-test, and 0.700 in the post-test.

Stages of Change Scale (SCS)

The SCS scale was developed by Prochaska and DiClemente (17) in 1982. SCC shows the stages of change individuals go through when they are trying to change their problematic behaviors. The scale does not have scoring. The stage of change is determined according to the answers given by the individual to the question. When asked "Have you stopped smoking?, the response of the individual "I don't plan to quit in the next 6 months" indicates the precontemplation stage, "I intend to quit within 6 months" contemplation stage, "I intend to quit within 30 days" preparation stage, "I quit less than 6 months ago" action stage, and "I quit a while ago" maintenance stage (17).

Outcome Measures

The sociodemographic data form was used at the beginning of the study to determine the characteristics of the participants. According to the Russell standard definition, prolonged abstinence was defined as not having smoked more than 5 cigarettes in the past 8 weeks during a 3-month follow-up (21). Based on these criteria, the FTND scale was used at the beginning of the study, at the eighth, and twelfth weeks. The SCS was used at the beginning of the study and after each intervention (every two weeks) to determine the individual's thinking stage.

Statistical Analysis

Data analysis was performed with IBM SPSS v.26. The distribution of the data was examined by the Shapiro-Wilk test, and skewness and kurtosis values were also considered. Nicotine dependence levels according to groups and tests are given as mean and standard deviation. Categorical variables were summarized as numbers and percentages. Pearson chi-square, Fisher's exact, and continuity correction tests were used to compare the demographic and smoking-related characteristics of the groups. Two-Way ANOVA for repeated measures was used to examine the effect of period*group interaction on nicotine addiction levels of adolescents. LSD post hoc tests were used to test the difference between the groups. The significance level was considered the value of 0.05.

RESULTS

The age of the participants ranged from 14-18 with a mean age of 16.2±0.9 years. Of the participants, 54.4% (n=56) were female students. It was found that 46.6% (n=48) of the participants were studying at 12nd class. Of all participants, 84.5% (n=87) were living in a nuclear family. 69.9% (n=72) of the participants' mothers and 43.7% (n=45) of participants' fathers had an educational level of primary school and below. 22.3% (n=23) of the participants' mothers and 88.3% (n=91) of the participants' fathers were employed. While 91.3% (n=94) of the participants were living with their families, 8.7% (n=9) of the participants were living in a non-family household. The distribution of adolescents' intervention groups by some sociodemographic characteristics was given in Table 1. The distributions of age, gender, class, family type, place of residence, education levels of mother and father, and employment status of mother and father were homogeneous and did not differ according to the groups.

The results of the study showed that 38.8% (n=40) of the participants were very light smokers, and 6.8% (n=7) were very heavy smokers. In the study group, 37.9% (n=39) of the participants smoked the first cigarette of the day within the first 5 minutes. Of the participants, 51.5% (n=53) stated that they experience difficulty when they do not smoke in places where smoking is prohibited. Moreover, 57.3% (n=59) of the participants reported that the cigarette which was most difficult to give up was the cigarette smoked during the day. Of the participants, 52.4% (n=54) stated that they smoked ten or fewer cigarettes per day. The mean number of cigarettes smoked daily by adolescents was found to be 10.5±9.0 (range, 1-50). 53.4% (n=55) of the participants reported that they smoked even when they had a disease that would require hospitalization. The distribution of adolescents' intervention groups by the FTND scale was given in Table 2.

Of the participants, 92.2% (n=95) reported that they had smokers in their close environment, and 74.8% (n=77) reported that their parents smoked. 62.1% (n=64) of the participants reported that smoking for 2 years or less. Of the adolescents, 34.0% (n=35) reported that they started smoking at the age of fourteen. 53.4% (n=55) of the study group stated that they started smoking due to stress. Of the participants, 71.8% (n=74) reported that attempted to quit smoking. The distribution of adolescents' intervention groups by smoking-related characteristics was given in Table 3. According to the groups, the distribution of smoking status in the close environment and family, years of smoking, age of onset of smoking, reason for smoking and attempt to quit smoking were homogeneous and did not differ.

When the nicotine addiction levels of adolescents were compared between the groups by measurement periods, the period*group interaction effect was not found significant (p=0.339). Also, it was determined that there was no significant difference in the nicotine addiction levels of the adolescents participating in the study according to the measure periods (p=0.472). However, a statistically significant difference was found in the nicotine addiction levels between the groups (p=0.031). According to the post hoc test results, it was seen that the nicotine addiction levels of the adolescents in the BG and TCE groups were significantly lower than the nicotine addiction levels of the adolescents in the control group in the post-test (Table 4, Figure 1).

Table 1. Comparison of sociodemographic characteristics of the participants, n (%)

	BG (n=25)	TCE (n=26)	CI (n=26)	Control (n=26)	p	Total (n=103)
Age						
14 years	1 (4.0)	0 (0.0)	2 (7.7)	2 (7.7)		5 (4.9)
15 years	2 (8.0)	9 (34.6)	3 (11.5)	3 (11.5)		17 (16.5)
16 years	9 (36.0)	6 (23.1)	10 (38.5)	3 (11.5)	0.064	28 (27.2)
17 years	13 (52.0)	9 (34.6)	10 (38.5)	17 (65.4)		49 (47.6)
18 years	0 (0.0)	2 (7.7)	1 (3.8)	1 (3.8)		4 (3.9)
Gender						
Female	14 (56.0)	10 (38.5)	14 (53.8)	18 (69.2)	0.183	56 (54.4)
Male	11 (44.0)	16 (61.5)	12 (46.2)	8 (30.8)		47 (45.6)
Class						
9	1 (4.0)	0 (0.0)	2 (7.7)	2 (7.7)		5 (4.9)
10	2 (8.0)	9 (34.6)	3 (11.5)	3 (11.5)	0.054	17 (16.5)
11	9 (36.0)	6 (23.1)	13 (50.0)	5 (19.2)		33 (32.0)
12	13 (52.0)	11 (42.3)	8 (30.8)	16 (61.5)		48 (46.6)
Family type						
Nuclear	21 (84.0)	23 (88.5)	23 (88.5)	20 (76.9)		87 (84.5)
Extended	1 (4.0)	1 (3.8)	1 (3.8)	3 (11.5)	0.900	6 (5.8)
Divorced	3 (12.0)	2 (7.7)	2 (7.7)	3 (11.5)		10 (9.7)
Mother's education						
Primary school and below	18 (72.0)	18 (69.2)	15 (57.7)	21 (80.8)		72 (69.9)
High school	5 (20.0)	5 (19.2)	8 (30.8)	4 (15.4)	0.693	22 (21.4)
University and above	2 (8.0)	3 (11.5)	3 (11.5)	1 (3.8)		9 (8.7)
Father's education						
Primary school and below	9 (36.0)	12 (46.2)	9 (34.6)	15 (57.7)		45 (43.7)
High school	13 (52.0)	10 (38.5)	9 (34.6)	8 (30.8)	0.333	40 (38.8)
University and above	3 (12.0)	4 (15.4)	8 (30.8)	3 (11.5)		18 (17.5)
Mother's work	4 (16.0)	10 (38.5)	6 (23.1)	3 (11.5)	0.101	23 (22.3)
Father's work	21 (84.0)	24 (92.3)	24 (92.3)	22 (84.6)	0.703	91 (88.3)
Living with family	23 (92.0)	26 (100)	21 (80.8)	24 (92.3)	0.119	94 (91.3)

BG: board game, TCE: tobacco cessation education, CI: combined intervention

Table 2. Comparison of Fagerstrom test for nicotine dependence, n (%)

	BG (n=25)	TCE (n=26)	CI (n=26)	Control (n=26)	p	Total (n=103)
Nicotine dependence						
Very light	13 (52.0)	9 (34.6)	10 (38.5)	8 (30.8)		40 (38.8)
Light	7 (28.0)	6 (23.1)	8 (30.8)	7 (26.9)		28 (27.2)
Moderate	3 (12.0)	5 (19.2)	6 (23.1)	5 (19.2)	0.669	19 (18.4)
High	1 (4.0)	3 (11.5)	2 (7.7)	3 (11.5)		9 (8.7)
Very high	1 (4.0)	3 (11.5)	0 (0.0)	3 (11.5)		7 (6.8)
First cigarette after waking up						
<5 minutes	13 (52.0)	10 (38.5)	10 (38.5)	6 (23.1)		39 (37.9)
5-30 minutes	5 (20.0)	5 (19.2)	7 (26.9)	10 (38.5)	0.074	27 (26.2)
31-60 minutes	4 (16.0)	5 (19.2)	9 (34.6)	7 (26.9)		25 (24.3)
>60 minutes	3 (12.0)	6 (23.1)	0 (0.0)	3 (11.5)		12 (11.7)
Number of cigarettes per day						
≤10	14 (56.0)	12 (46.2)	15 (57.7)	13 (50.0)		54 (52.4)
11-20	11 (44.0)	12 (46.2)	11 (42.3)	10 (38.5)	0.264	44 (42.7)
≥21	0 (0.0)	2 (7.7)	0 (0.0)	3 (11.5)		5 (4.9)
Most hated cigarettes to quit						
First one of the morning	15 (60.0)	9 (34.6)	11 (42.3)	9 (34.6)	0.217	44 (42.7)
Any other	10 (40.0)	17 (65.4)	15 (57.7)	17 (65.4)		59 (57.3)
Difficulty in forbidden places	17 (68.0)	10 (38.5)	15 (57.7)	11 (42.3)	0.123	53 (51.5)
Smoking more in the first hours	5 (20.0)	9 (34.6)	4 (15.4)	6 (23.1)	0.403	24 (23.3)
Smoking when so ill	10 (40.0)	14 (53.8)	15 (57.7)	16 (61.5)	0.442	55 (53.4)

BG: board game, TCE: tobacco cessation education, CI: combined intervention

Table 3. Comparison of groups by smoking-related characteristics, n (%)

	BG (n=25)	TCE (n=26)	CI (n=26)	Control (n=26)	p	Total (n=103)
Smoking in close environment	22 (88.0)	23 (88.5)	25 (96.2)	25 (96.2)	0.569	95 (92.2)
Smoking in family						
Parents	17 (68.0)	18 (69.2)	22 (84.6)	20 (76.9)		77 (74.8)
Siblings	5 (20.0)	5 (19.2)	3 (11.5)	5 (19.2)	0.737	18 (17.5)
Other	3 (12.0)	3 (11.5)	1 (3.8)	1 (3.8)		8 (7.8)
Smoking year						
≤2 years	15 (60.0)	15 (57.7)	22 (84.6)	12 (46.2)		64 (62.1)
3-4 years	8 (32.0)	7 (26.9)	4 (15.4)	11 (42.3)	0.082	30 (29.1)
≥5 years	2 (8.0)	4 (15.4)	0 (0.0)	3 (11.5)		9 (8.7)
Age to start smoking						
≤12 years	1 (4.0)	4 (15.4)	1 (3.8)	4 (15.4)		10 (9.7)
13 years	6 (24.0)	6 (23.1)	2 (7.7)	6 (23.1)		20 (19.4)
14 years	11 (44.0)	7 (26.9)	8 (30.8)	9 (34.6)	0.256	35 (34.0)
15 years	3 (12.0)	7 (26.9)	10 (38.5)	6 (23.1)		26 (25.2)
16 years	4 (16.0)	1 (3.8)	4 (15.4)	1 (3.8)		10 (9.7)
17 years	0 (0.0)	1 (3.8)	1 (3.8)	0 (0.0)		2 (1.9)
Reason for smoking						
Curiosity	15 (60.0)	15 (57.7)	8 (30.8)	10 (38.5)	0.094	48 (46.6)
Stress	10 (40.0)	11 (42.3)	18 (69.2)	16 (61.5)		55 (53.4)
Attempt to quit smoking	17 (68.0)	17 (65.4)	18 (69.2)	22 (84.6)	0.407	74 (71.8)

BG: board game, TCE: tobacco cessation education, CI: combined intervention

Table 4. Comparison of nicotine addiction levels by period and groups

Period	BG (n=25)	TCE (n=26)	CI (n=26)	Control (n=26)	Total (n=103)
Pre-test	2.64±2.51	4.04±2.57	3.11±1.90	3.96±2.59	3.44±2.44
Intermediate	2.96±2.05	4.46±2.56	3.81±2.05	3.53±3.03	3.69±2.48
Post-test	2.52±2.40	3.57±2.38	2.92±1.88	4.34±2.34	3.35±2.33

BG: board game, TCE: tobacco cessation education, CI: combined intervention, F and p values for the period, group, and period*group were 0.878 and 0.472, 3.089 and 0.031, 1.145 and 0.339, respectively, according to the post hoc LSD test results, in the post-test, nicotine addiction levels of the adolescents in the BG and TCE were lower than in the control group

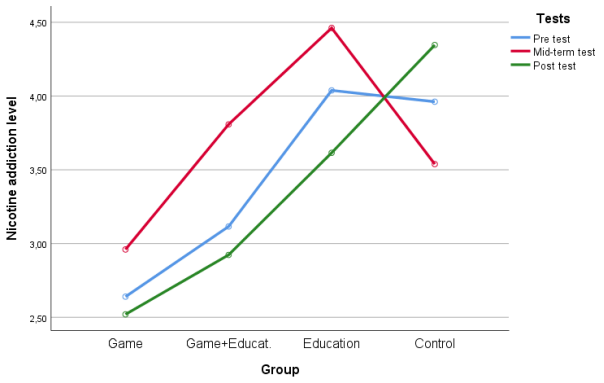

Figure 1. Nicotine addiction levels by period and groups

DISCUSSION

There is no safe level of nicotine, which is an addictive substance. For this reason, all levels of nicotine addiction starting in the adolescence period are important. This study demonstrated that 38.8% of the adolescents were very light smokers, 8.7% were heavy smokers, and 6.8% were very heavy smokers. Studies have reported a very low level of nicotine addiction in 32.6-68.2% (22,23), a moderate level of nicotine addiction in 45.7% (24), a high level of nicotine addiction in 23.9-31.8% (22,25), and a very high level of nicotine addiction in 5.5% of adolescents (22). Studies in the literature and this study show that nicotine addiction remains an important health issue all over the world.

One of the most important determinants of the level of nicotine addiction is the time of the first cigarette smoked in the morning (26). This study showed that 37.9% of the adolescents, almost four out of ten, smoked their first cigarette within the first five minutes after waking up. The study by Petrelli et al. (23) reported this rate as 6.6%.

It is an expected situation for adolescents to smoke even in the school environment due to the "willingness to do what is prohibited". The results of this study revealed that 51.5% of the adolescents had difficulty in stopping smoking in places where smoking was prohibited. Studies on adolescents have reported the rates of having difficulty in staying away from smoking as 59.3% in Türkiye (26) and 85.5% in Romania (23). Considering these results, we can state that the rate of difficulty in staying away from smoking was lower in this study compared to the study conducted by Petrelli et al. (23).

One of the indicators of addiction is an excessive desire for the substance anywhere (25). In this study, 57.3% of the adolescents stated that it was difficult to give up smoking at other times of the day (except in the morning). In the study by Petrelli et al. (23), 73.3% of the adolescents reported that it was difficult to give up smoking at other times of the day. Moreover, the results of this study showed that 76.7% of the adolescents mostly smoked at other times of the day rather than during morning hours. In other words, the results of the difficulty in stopping smoking and/or indispensable smoking time can be explained by the fact that adolescents regard smoking as a means of socializing due to reasons such as acceptance and proof among their peers (27).

The number of cigarettes smoked daily is one of the most important determinants of the level of addiction (26). This study revealed that 52.4% of the adolescents smoked less than 10 cigarettes a day, while 4.9% of them smoked 21 cigarettes and more a day. The study by Petrelli et al. (23) reported that 54.1% of the adolescents smoked less than 10 cigarettes and 6.2% smoked 21 cigarettes and more. However, it should be kept in mind that regular consumption of nicotine, which does not have a safe dose, is sufficient for addiction, even though the number of cigarettes smoked is small.

It is known that adolescents have low awareness of the negative effects of smoking on health and the relationship between disease and smoking (28). In this study, 53.4% of the adolescents reported that they smoked even if they had a disease that would require hospitalization. This result shows that one of two adolescents continues the negative behavior that will cause the disease process to prolong. The study by Petrelli et al. (23) reported this rate as 24.5%. The presence of a smoker in the environment is important in the development of smoking behavior (22,28). In this study, 92.2% of the adolescents were found to have a smoker in their close environment. Most of the mothers and fathers smoked in the adolescents' families (74.8%). A study conducted by Sezer et al. (22) with high school students reported that 55.5% of fathers and 36.0% of mothers smoked cigarettes. Another study conducted in Northern Ireland found that 48% of family members smoked (29). These rates are quite high. Considering that parents are one of the important role models in shaping their children's lives, it can be stated that one of the groups who should be motivated to quit smoking is family members.

It is known that adolescents start smoking because of many factors such as difficulties, fear, curiosity, and stress (30). In this study, 53.4% of the students reported that they smoked due to stress. In the study by Sezer et al. (22), 46% of the adolescents stated that they smoked due to stress, while this rate was found to be 37.3% in the study by Gungormus and Erci (18).

It is known that starting smoking at an early age is a risk factor for a high level of addiction that may occur in older ages and that decreases the quality of life (27,30). The results of our study showed that adolescents started smoking at an average age of thirteen years. In addition, it was found that 40% of adolescents started smoking under the age of thirteen. In the literature, adolescents have been reported to start smoking at similar ages, while some studies have reported the age at onset of smoking as sixteen and above (18,22). Results of this study and other studies in the literature reveal the necessity of giving information about the effects of cigarette addiction on the quality of life at an early age and the risks that smoking will pose in older ages, starting from primary school years the adolescence period.

Social influences and pressures, such as appearing "cool" during adolescence, can lead to the initiation of tobacco use (31). It is difficult to solve the nicotine addiction in the adolescent group who always say no. Games have been used increasingly to prevent smoking among adolescents or to motivate and support them to quit smoking (32). In this study, the post-test score of nicotine addiction was found to be lower in the adolescents in the BG and TCE groups compared to the control group. This result suggests that a learning technique such as play, in which adolescents can be active in quitting their nicotine addiction may be effective. In the literature, we have not yet encountered an intervention study for nicotine addiction of adolescents using the game method. Comparing the effectiveness of play and psychoeducation in individuals over the age of 18, Khazall et al. (14) stated that games and psychoeducation had a similar effect on nicotine addiction. This result can be attributed to the fact that the intervention was limited to twelve weeks and adolescents are a difficult group to create behavioral changes due to their developmental characteristics. However, what was pleasing that the SCS post-test evaluation, it was determined that three adolescents from the BG group and two adolescents from the TCE group were in the action stage. In addition, when Figure 1 is examined, it can be said that the addiction levels of the adolescents in the control group were higher than the addiction levels of the BG, TCE, and CI groups.

The most important limitation of this study was that the time to evaluate smoking cessation was limited to three months. It is recommended for future studies to keep the study period longer in order to make sure that the behavior of smoking cessation has become definite.

CONCLUSION

In conclusion, this study demonstrated that the BG provided a more decrease in the FTND score. In line with the results of this study, the BG is recommended to be used in smoking cessation programs and in smoking cessation and/or nicotine addiction studies designed according to the stages of behavior changes as this game has been designed for the stages of behavior changes.

Ethics Committee Approval: The study was approved by the Non-Interventional Ethics Committee of Eskişehir Osmangazi University (21.11.2017, 09).

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REFERENCES

1. Badrooh A, Mozaffari N, Barikani A, Dadkhah B. The effect of individual and group education done by nurses on smoking dependency and smoking cessation motivation in patients with coronary artery disease. Addict Health. 2020;12(4):269-77.
2. Drope J, Schluger N, Cahn Z, Drope J, Hamill S, Islami F, et al. The Tobacco Atlas. 6th ed. Atlanta, GA, USA: American Cancer Society and Vital Strategies; 2018.
3. Ma C, Xi B, Li Z, Wu H, Zhao M, Liang Y, et al. Prevalence and trends in tobacco use among adolescents

aged 13-15 years in 143 countries, 1999-2018: findings from the Global Youth Tobacco Surveys. Lancet Child Adolesc Health. 2021;5(4):245-55.
4. Oztekin C, Batra M, Abdelsalam S, Sengezer T, Ozkara A, Erbas B. Impact of individual, familial and parental factors on adolescent smoking in Turkey. Int J Environ Res Public Health. 2021;18(7):3740.
5. Fırat M, Demir Gökmen B, Özcan M. The effect of social appearance anxiety on smoking in high school students: Agri example. Turkish J Sci Health. 2021;2(1):104-12.
6. Mahajan SD, Homish GG, Quisenberry A. Multifactorial etiology of adolescent nicotine addiction: a review of the neurobiology of nicotine addiction and its implications for smoking cessation pharmacotherapy. Front Public Health. 2021;9:664748.
7. Singh T, Arrazola RA, Corey CG, Husten CG, Neff LJ, Homa DM, et al. Tobacco use among middle and high school students--United States, 2011-2015. MMWR Morb Mortal Wkly Rep. 2016;65(14):361-7.
8. Prochaska JO. Decision making in the transtheoretical model of behavior change. Med Decis Making. 2008;28(6):845-9.
9. Martinez U, Simmons VN, Sutton SK, Drobes DJ, Meltzer LR, Brandon KO, et al. Targeted smoking cessation for dual users of combustible and electronic cigarettes: a randomised controlled trial. Lancet Public Health. 2021;6(7):e500-9.
10. Sezgin S, Bozkurt A, Yılmaz EA, van der Linden N. Gamification, education and theoretical approaches: motivation, dedication and sustainability in learning processes. Mehmet Akif Ersoy University Journal of Education Faculty. 2018;2018(45):169-89. Turkish.
11. Şenocak D, Bozkurt A. Gamification, player types and gamification design frameworks. Açıköğretim Uygulamaları ve Araştırmaları Dergisi. 2020;6(1):78-96. Turkish.
12. Arabacı İB, Polat M. Digital natives, digital immigrants and classroom management. Electronic Journal of Social Sciences. 2013;12(47):11-20. Turkish.
13. Pimentel J, Cockcroft A, Andersson N. Impact of co-designed game learning on cultural safety in colombian medical education: protocol for a randomized controlled trial. JMIR Res Protoc. 2020;9(8):e17297.
14. Khazaal Y, Chatton A, Prezzemolo R, Zebouni F, Edel Y, Jacquet J, et al. Impact of a board-game approach on current smokers: a randomized controlled trial. Subst Abuse Treat Prev Policy. 2013;8:3.
15. Serdar CC, Cihan M, Yücel D, Serdar MA. Sample size, power and effect size revisited: simplified and practical approaches in pre-clinical, clinical and laboratory studies. Biochem Med (Zagreb). 2021;31(1):010502.
16. Khazaal Y, Chatton A, Prezzemolo R, Hoch A, Cornuz J, Zullino D. A game for smokers: a preliminary naturalistic trial in a psychiatric hospital. Patient Educ Couns. 2008;70(2):205-8.
17. Prochaska JO, DiClemente CC. Transtheoretical therapy: toward a more integrative model of change. Psychotherapy: Theory, Research & Practice. 1982;19(3);276-88.
18. Gungormus Z, Erci B. Transtheorethical model-based education given for smoking cessation in higher school students. Southeast Asian J Trop Med Public Health. 2012;43(6):1548-59.
19. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: A revision of the Fagerström Tolerance Questionnaire. Br J Addict. 1991;86(9):1119-27.
20. Uysal MA, Kadakal F, Karşidağ C, Bayram NG, Uysal O, Yilmaz V. Fagerstrom test for nicotine dependence: reliability in a Turkish sample and factor analysis. Tuberk Toraks. 2004;52(2):115-21.
21. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction. 2005;100(3):299-303.
22. Erol S, Balci AS, Sisman FN. Effect of transtheoretical model based smoking cessation program on high school students. J Nutr Health Sci. 2018;5(3):301.
23. Petrelli F, Scuri S, Tanzi E, Nguyễn TTC, Grappasonni I. Lifestyles and discomfort in a sample of young Romanian students. J Prev Med Hyg. 2018;59(3):E230-5.
24. Johnson JM, Muilenburg JL, Rathbun SL, Yu X, Naeher LP, Wang JS. Elevated nicotine dependence scores among electronic cigarette users at an electronic cigarette convention. J Community Health. 2018;43(1):164-74.
25. Islam K, Datta AK, Seth S, Roy A, Das R. A study on the prevalence and correlates of nicotine dependence among adolescents of Burdwan Town, West Bengal. Indian J Psychiatry. 2019;61(1):89-93.
26. Bozkurt N, Bozkurt Aİ. Assessment of the Fagerström test for nicotine dependence (FTND) used in the determination of nicotine dependence and developing a new test for the nicotine dependence. Pam Med J. 2016;9(1):45-51. Turkish.
27. Gumus Dogan D, Ulukol B. Factors contributing to smoking and efficiency of two different education models among adolescents. Ann Med Res. 2010;17(3):179-85. Turkish.
28. Bilgiç N, Günay TA. A method for supporting smoking cessation in adolescents: peer education. Turk Thorac J. 2014;15(3):102-5. Turkish.
29. Badham J, McAneney H, Dunne L, Kee F, Thurston A, Hunter RF. The importance of social environment in preventing smoking: an analysis of the Dead Cool intervention. BMC Public Health. 2019;19(1):1182.
30. Kim DJ, Kim SJ. Impact of nearby smoking on adolescent smoking behavior in Korea. Medicine (Baltimore). 2018;97(45):e13125.
31. Bernat D, Gasquet N, Wilson KO, Porter L, Choi K. Electronic cigarette harm and benefit perceptions and use among youth. Am J Prev Med. 2018;55(3):361-7.
32. Derksen ME, van Strijp S, Kunst AE, Daams JG, Jaspers MWM, Fransen MP. Serious games for smoking prevention and cessation: A systematic review of game elements and game effects. J Am Med Inform Assoc. 2020;27(5): 818-33.

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STAT3 Expression and Correlation Between Ki-67 and PHH3 in Meningiomas: Is it Possible to Predict Recurrence?

Meningiomlarda STAT3 Ekspresyonu ve Ki-67 ile PHH3 Arasındaki Korelasyon: Rekürrensi Öngörmek Mümkün mü?

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ABSTRACT

Aim: The aim of this study was to investigate the correlation between PHH3 and ki-67 labeling index, and the association of STAT3 expression with mitotic index, grade by World Health Organization 2016 classification, and clinicopathological features of meningioma cases.
Material and Methods: A total of 25 meningioma cases from the archives of the Department of Pathology, Düzce University School of Medicine, diagnosed between 2012 and 2021 were included in the study. The mitotic count from the ten fields with the highest number of mitotic figures was determined. Immunohistochemistry was performed on the formalin-fixed, paraffin-embedded tissue blocks to determine STAT3, ki-67, and PHH3 expression. STAT3 was scored between 0 and 3 points according to staining intensity. Staining percentages for STAT3 were determined using a manual count of stained cells and the total number of tumor cells. The ki-67 labeling index was determined as a percentage by a manual count. For PHH3, the total number of immunostained mitotic figures per 10 high-power fields were evaluated in each case.
Results: A statistically significant difference was found in terms of the percentage of STAT3 staining between the tumor grades (p=0.047). STAT3 expression was significantly higher in cases with high tumor grades. A moderate positive correlation was found between ki-67 and PHH3 when calculated as a percentage in the area with the highest mitotic index by manual counting (r=0.621, p=0.001).
Conclusion: A combination of ki-67, PHH3, and STAT3 will be useful in the grading of meningiomas and predict the recurrence.
Keywords: Meningioma; tumor grade; STAT3; PHH3; ki-67.

ÖZ

Amaç: Bu çalışmanın amacı meningiom vakalarında PHH3 ile ki-67 proliferasyon indeksi arasındaki korelasyonu incelemek ve STAT3 ekspresyonunun mitotik aktivite, Dünya Sağlık Örgütü 2016 sınıflandırmasına göre derece ve klinikopatolojik özellikler ile ilişkisini değerlendirmektir.
Gereç ve Yöntemler: Düzce Üniversitesi Tıp Fakültesi Patoloji Anabilim Dalı arşivlerinden 2012 ve 2021 yılları arasında tanı alan toplam 25 meningiom olgusu çalışmaya dahil edildi. Mitotik figür sayısının en fazla olduğu on büyük büyütme alanından mitotik sayı belirlendi. STAT3, ki-67 ve PHH3 ekspresyonunu belirlemek için formalinle sabitlenmiş, parafine gömülü doku blokları üzerinde immünohistokimyasal çalışma yapıldı. STAT3, boyama yoğunluğuna göre 0 ile 3 puan arasında puanlandı. STAT3 için boyama yüzdeleri, boyanmış hücrelerin manuel sayımı ve toplam tümör hücresi sayısı ile belirlendi. Ki-67 proliferasyon indeksi, manuel sayımla yüzde olarak belirlendi. PHH3 için her bir vakada, 10 büyük büyütme alanından immün boyanmış mitotik figürlerin toplam sayısı değerlendirildi.
Bulgular: STAT3 boyama yüzdesi bakımından tümör dereceleri arasında istatistiksel olarak anlamlı bir farklılık bulundu (p=0,047). Tümör derecesi yüksek olgularda STAT3 ekspresyonu anlamlı olarak daha yüksek idi. Manuel sayım ile en yüksek mitotik indekse sahip olan alanda yüzde olarak hesaplandığında PHH3 ve ki-67 arasında orta derecede pozitif bir korelasyon olduğu bulundu (r=0,621; p=0,001).
Sonuç: Ki-67, PHH3 ve STAT3'ün kombinasyon olarak kullanılması, meningiomların histopatolojik derecelendirilmesinde ve rekürrensi öngörmede faydalı bir yöntem olacaktır.
Anahtar kelimeler: Meningiom; tümör derecesi; STAT3; PHH3; Ki-67.

The results of this study has been presented partially as an oral presentation at the 3rd International TURAZ Academy Forensic Sciences, Forensic Medicine, and Pathology Congress (September 8-12, 2021; Baku, Azerbaijan).

INTRODUCTION

Meningiomas are the most frequent primary tumors of the central nervous system, consisting of 36% of all brain tumors (1). They are mostly benign, slow-growing, low-grade tumors (1). In 2016, the World Health Organization (WHO), defined a grading system to predict the risk of recurrence; benign, atypical, and anaplastic with the recurrence rates of 7-25%, 29-52%, and 50-94%, respectively (1). Mitotic activity is the most dependable prognostic factor for defining the grade in meningiomas. On hematoxylin and eosin (H&E) stained slides, mitotic figure counts per 10 high-power microscope fields (HPFs) (0.16 mm^2) are essential, but additional immunohistochemical staining with proliferation markers may be helpful (2,3).

The ki-67 labeling index (LI) is widely used worldwide, allowing analysis of the ki-67 antigen immunohistochemically, a non-histone cell cycle protein (4,5). Phosphorylated histone H3 (PHH3) is a phosphorylated histone protein that targets serine 10 of histone H3 (6,7). This marker helps to make the differentiation between mitosis and apoptotic nuclei, to define histopathological grade correctly (8,9). Signal transducer and transcription activator 3 (STAT3) is a pro-oncogenic transcription factor and, STAT3 plays an important role in many biological processes like cell life and proliferation, chronic inflammation, the acute phase response, autoimmunity, and cancer progression (10-12). STAT3 activation is increased more in grade I and II meningiomas than in normal dural tissue, and STAT3 expression is enhanced with increasing tumor grade (13).

In this study, we aimed to evaluate the correlation between PHH3 and ki-67 LI and the association of STAT3 expression with mitotic index, WHO classification grades, and clinicopathological features of meningioma cases.

MATERIAL AND METHODS

The study was compatible with the tenets of the Helsinki Declaration and has been approved by the local ethics committee of Düzce University (protocol number 187 of September 6, 2021). A total of 25 meningioma cases diagnosed between 2012 and 2021 were included in the study. The inclusion criteria were i) histopathologic diagnosis of meningioma, ii) clinically sufficient history, and iii) sufficiency of pathologic material for histological and immunohistochemical analysis. The exclusion criteria were i) insufficient tumor tissue for immunohistochemistry, and ii) the patients without clinical follow-up. All of the cases were recruited from the archives of the Pathology Department of Düzce University School of Medicine. Demographic data (gender, age, and recurrence status after diagnosis) were obtained from the patient files and archived reports. The mitotic count from 10 HPFs with the highest number of mitotic figures was determined. The tumor location, histological subtype, and grade due to WHO 2016 (1), local invasion, presence of psammoma bodies, and tumor size were evaluated.

On the formalin-fixed, paraffin-embedded tissue blocks, immunohistochemistry was performed to determine STAT3, ki-67, and PHH3 expression. The pathological material was examined by a pathologist to make sure every paraffin-embedded tissue block has sufficient tumor content for immunohistochemical analysis. Immunohistochemical staining with a fully automated assay was performed on 3-4 μm-thick slices based on manufacturer's instructions. Phospho-STAT3 (Tyr705) [RM261] Conc. 0.1mL (1:1000-10000), rabbit monoclonal anti-Ki67 (Thermo #RM-9106-R7), and rabbit polyclonal pHH3 (Thermo #RB-9425-R7) antibodies were used on the Ventana® Benchmark XT (Ventana-Roche Diagnostics, Meylan, France).

All the slides were examined by a pathologist. STAT3 expression was scored between 0 and 3 points due to staining intensity. No staining was considered as 0, light staining as 1, moderate staining as 2, and strong staining as 3 points. Staining percentage points were determined using a manual count of stained cells and the total number of tumor cells. After the hotspot was identified under low magnification, the ki-67 LI was determined as percentage by a manual count. For PHH3, for which the highest number of mitotic figures were identified, the total number of immunostained mitotic figures per 10 HPFs was evaluated in each case.

Statistical Analysis

The distribution of the data was examined using the Shapiro-Wilk test, and comparisons of the groups were made using the Mann-Whitney U test. The correlation between numerical variables was analyzed using Spearman correlation analysis. Descriptive statistics were given as mean±standard deviation, or median, and minimum-maximum values for numerical variables, and numbers and percentages for categorical variables. Statistical analyses were made with the IBM SPSS v.22 program and the significance level was taken as 0.05.

RESULTS

Ten (40%) of the cases were male and 15 (60%) were female. The age range was 37-82 years, with a mean age of 62.4±11.8 years. The most common site of meningiomas was the brain (88%, n=22), followed by the spinal cord (8%, n=2), and the sphenoid wing (4%, n=1). Eighteen (72%) of the cases were WHO grade I and the other 7 (28%) cases were grade II. Transitional was the most common histological subtype (44%, n=11), followed by atypical (24%, n=6), meningothelial (20%, n=5), fibrous (4%, n=1), angiomatous (4%, n=1), and chordoid (4%, n=1). Tumor size ranged from 2-11 cm and the mean tumor size was 5.0±2.5 cm. Psammoma bodies were seen in 13 (52%) cases. The dural invasion was present in 8 (32%) cases. In cases with dural invasion, six cases were accompanied by bone invasion (Figure 1). Only one of the tumors with dural invasion was grade II, the others were grade I. Brain invasion was detected in 1 (4%) patient with an atypical meningioma.

The percentage of STAT3 staining ranged from 2 to 25%, with no staining in five (20%) cases, focal positivity below 5% in 10 (40%), 10% in five (20%), 15% in four (16%), and 25% in one (4%), respectively (Figure 2). Staining intensity was moderate (score 2) in all cases with immunoexpression. All cases that did not show staining with STAT3 were grade I tumors. The percentage of STAT3 staining was statistically significantly different between tumor grades (p=0.047). STAT3 expression was not related to recurrence rate and other clinicopathologic parameters such as tumor size, dura, and bone invasion.

The ki-67 LI was between 1 and 5%. Mitotic count per 10 HPFs was between 1 and 5. A moderate positive correlation was found between PHH3 and ki-67 when calculated as a percentage in the area with the highest mitotic index by manual counting (r=0.621; p=0.001). There was also a moderate positive correlation between the mitotic count and PHH3 of 10 HPFs (r=0.576; p=0.003). Recurrence developed in two cases in the 2nd and 3rd years of follow-up, and both were grade I tumors. The relevant data are shown in Table 1.

DISCUSSION

Although meningiomas are mostly slow-growing, benign tumors, it is important to diagnose the high-grade variants because of the risk of recurrence and different therapy approaches (14,15). Meningiomas may recur, at a rate of up to 25% even in grade I tumors, and high recurrence rates remain a challenge in clinical management (1). Being able to predict early recurrence in meningiomas will be beneficial in providing sufficient postoperative treatment (16). The benefits of post-operative radiation, extending the resection area, and drug therapies in high-grade meningiomas are

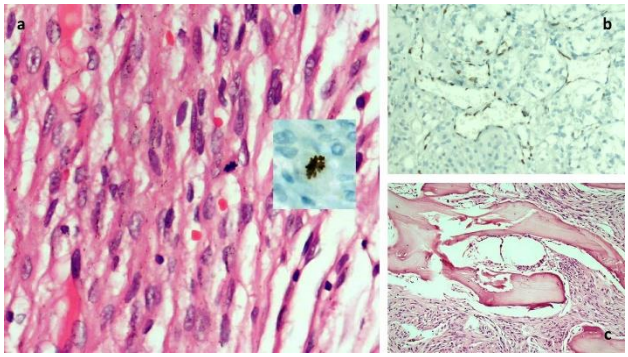

Figure 1. a) Mitotic figure in H&E slide (x40) and the same mitotic figure stained with PHH3 (x40, insert photo), **b)** endothelial staining with PHH3 (x40), **c)** bone invasion in H&E slide (x20)

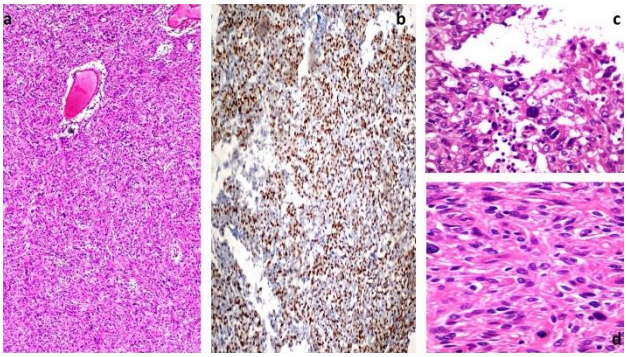

Figure 2. a) Atypical meningioma shows a highly cellular patternless growth pattern (H&E, x4), **b)** STAT3 staining pattern of a hot spot (x10), **c, d)** atypical cells with high nuclear/cytoplasmic ratio (H&E x40)

Table 1. Clinicopathological features of meningiomas

Case	Age	Gender	Localization	Tumor size (cm)	Histological subtype	Grade	STAT3 %	STAT3 score	Ki-67 (%)	Mitotic count (/10 HPF)	PHH3 (/10 HPF)	Bone invasion	Dura invasion	Brain invasion	Recurrence
1	37	M	Left parietal	3	Meningothelial	I	0	0	2	1	4	Yes	Yes	No	No
2	82	F	Right frontal	6	Transitional	I	0	0	1	1	1	No	Yes	No	No
3	56	M	Left frontal	2	Transitional	I	10	2	1	1	6	No	No	No	No
4	75	M	Right frontal	5	Transitional	I	0	0	5	2	6	No	No	No	No
5	59	F	Left frontal	6	Transitional	I	0	0	1	1	3	No	No	No	No
6	66	F	L1	3	Meningothelial	I	0	0	1	1	1	No	No	No	No
7	65	F	Foramen magnum	4	Transitional	I	2	2	1	1	1	No	No	No	No
8	64	F	Left frontal	4	Transitional	I	2	2	2	1	2	No	No	No	No
9	66	M	Right frontoparietal	5	Transitional	I	3	2	1	1	2	Yes	Yes	No	2 years
10	73	M	Left frontal	2	Meningothelial	I	3	2	1	1	1	Yes	Yes	No	No
11	46	M	Right slyvian	5	Angiomatous	I	3	2	2	1	2	No	No	No	No
12	73	F	Right frontoparietal	3	Transitional	I	5	2	2	1	2	No	No	No	No
13	58	M	Left frontal	11	Fibrous	I	5	2	1	1	6	Yes	Yes	No	No
14	59	F	Left slyvian	4	Meningothelial	I	5	2	2	1	4	Yes	Yes	No	No
15	37	F	Right frontal	4.5	Transitional	I	10	2	2	1	5	No	No	No	No
16	56	F	Frontal	2	Transitional	I	10	2	1	1	6	No	No	No	3 years
17	74	M	Right parietal	2	Meningothelial	I	15	2	3	2	30	No	No	No	No
18	79	F	Left frontotemporal	8	Transitional	I	25	2	2	1	5	No	Yes	No	No
19	56	F	Left frontal	4.5	Chordoid	II	10	2	2	1	1	No	No	No	No
20	56	F	T11-12	3.5	Atypical	II	3	2	3	4	12	No	No	No	No
21	66	M	Right frontotemporal	8	Atypical	II	3	2	1	5	7	No	No	No	No
22	50	M	Right parietal	8	Atypical	II	10	2	5	3	8	No	No	No	No
23	66	M	Right sphenoid	10	Atypical	II	15	2	1	1	2	Yes	Yes	No	No
24	69	F	Left frontoparietal	8	Atypical	II	15	2	2	3	3	No	No	Yes	No
25	73	F	Left frontoparietal	4	Atypical	II	15	2	3	2	21	No	No	No	No

STAT3: signal transducer and transcription activator 3, PHH3: phosphorylated histone H3, HPF: high power field, M: male, F: female

controversial (17). Advances in molecular and histopathological studies and advanced imaging techniques are currently promising for meningioma patients with diagnostic challenges (18). Finding new biomarkers and advanced targeted therapies requires a better understanding of meningioma oncogenesis, as predicting the aggressiveness of meningiomas based on histological and genetic criteria is not efficient (15,19).

Histomorphological features, STAT3 activation, NF-2 gene mutation, inactivation of DAL-1, and loss of inhibition of TGFβ may all play a role in recurrence, but it remains unclear which specific changes contribute to the pathway (20).

STAT3 plays a role in the control of mitochondrial function and tumor progression by regulating pro-inflammatory genes and cell survival (21). STAT3 is mutated in numerous human cancers, playing an important role in tumor processes as a critical molecular abnormality (22). Previous studies suggested that elevated STAT3 expression is related to better prognosis in breast cancer; however, carcinomas of the lung, stomach, liver, prostate, pancreas, and osteosarcomas and gliomas show poorer prognosis as STAT3 protein expression levels increase (23).

Johnson et al. (24) suggested that the JAK-STAT3, PI3K-Akt-mTOR, and MEK-1-MAPK pathways are activated in WHO grade II meningiomas, and inhibition of STAT3 activation may be effective in next-generation chemotherapies for high-grade meningiomas. They found significantly higher STAT3 activation in grade II meningiomas than in grade I, but no difference between meningioma subtypes, similarly to our results.

Magrassi et al. (13) suggested that various elements of the STAT family show higher immunoreactivity in meningiomas compared to normal dural tissue. In our study, according to the immunohistochemical results, difference between the percentage of STAT3 staining and tumor grade was statistically significant and, STAT3 expression was significantly higher in cases with high tumor grades. On the contrary, Johnson et al. (16) reported no significant difference in STAT3 immunohistochemical staining between grade I and grade II tumors. Johnson et al. (16) also suggested that the expression of STAT3 is not a sensitive predictor of recurrence in meningiomas. In our study, STAT3 expression was not related to recurrence rate; however, only two patients had a recurrent tumor, so this data is not sufficient to suggest that STAT3 does not impact recurrence.

While evaluating tumor grade, the most important parameter is mitotic count (1). Recognizing the mitoses morphologically is essential to define mitotic count (25). The conventional method used to determine the extent of proliferation of the tumor may not be objective, as finding the area with the highest mitotic activity and mitotic figures may be difficult (25). Distinguishing mitotic figures and other chromatin changes such as apoptotic figures, pyknotic nuclei, and artifacts secondary to crush, may vary with experience. Areas of different cellular densities within the tumor may make it difficult to evaluate these features per area (4). PHH3 is helpful to differentiate apoptosis and mitosis, as there is a direct relationship between H3 phosphorylation and mitotic chromosome condensation that begins during the early prophase, whereas phosphorylation of histone H3 is not observed in apoptosis (26). It is important to decide whether to use a "hotspot" or "mean" counting method because the mitotic activity may show variation in different regions of the tumor (25).

The ki-67 proliferation index helps to identify the most active site and predict recurrence (27). While both the mitotic index and ki-67 can be used to quantify cell proliferation, it should be considered that ki-67 stains positive nuclei in the G1, G2, or S phases, which are generally more variable and longer than the M phase (25). The ki-67 LI is a quantitative indicator used to define proliferation activity, which is the percentage of tumor cell nuclei positively stained for ki-67 (26). In the literature, a ki-67 LI above 4% has been defined as a high-risk factor for recurrence, but there is still no definite cut-off value. Various studies have suggested different values, ranging from 1-10% (27,28). This heterogeneity may be due to interlaboratory differences. The ki-67 LI was 1% in two cases with recurrence in our study. To our knowledge, ki-67 does not seem to be a reliable marker for predicting recurrence and prognosis.

PHH3 specifically detects core protein histone H3 when it is phosphorylated at serine 10 (Ser10) or serine 28 (Ser28). Phosphorylation of histone H3 is a process that occurs almost exclusively during mitosis (26). In their series consisting of 48 meningioma cases, Puripat et al. (29) reported that PHH3 is a fast, sensitive, and easy method for determining mitotic activity. Winther et al. (4) stated that the most reliable method for predicting prognosis in a series of 160 cases was the PHH3 proliferation index.

Ozek et al. (3) found a strong correlation between the PHH3 and ki67 proliferation indices in a series of 104 cases; however, there was no significant correlation between PHH3 and tumor recurrence. Elmaci et al. (27) stated in a review that PHH3 is useful, but more studies are needed to replace this method with the mitosis counting method in conventional H&E slides. In our study, we found a moderate positive correlation between mitotic count and PHH3/10 HPF, and a moderate positive correlation between the ki67 proliferation index and PHH3 index.

The background staining of PHH3 in leukocytes and highly vascular areas, and the lack of a definite cut-off value create an obstacle for the use of PHH3 instead of counting mitotic figures. Additionally, staining of any prophase nuclei may create difficulties in evaluating PHH3 (30). Nonetheless, morphologically distinguishing M-phase from prophase nuclei is essential but not very difficult.

CONCLUSION

A combination of ki-67, PHH3, and STAT3 is useful in the grading of meningiomas and prediction of recurrence. The use of these three methods together may contribute to larger studies that will shed light on the prognosis of these tumors.

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REFERENCES

1. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. WHO classification of tumours of the central nervous system. WHO Classification of Tumours. 4th ed. Lyon: IARC Press; 2016.
2. Olar A. Phosphohistone H3: implications for clinical practice and risk assessment in meningioma. Neuro Oncol. 2015;17(5):631-3.
3. Ozek E, Akdag H, Tosuner Z, Abdallah A, Hatiboglu MA. The correlation between phosphorylated histone H3 (PHH3) and p-STAT3 in meningiomas. Clin Neurol Neurosurg. 2019;178:46-50.
4. Winther TL, Arnli MB, Salvesen Ø, Torp SH. Phosphohistone-H3 proliferation index is superior to mitotic index and MIB-1 expression as a predictor of recurrence in human meningiomas. Am J Clin Pathol. 2016;146(4):510-20.
5. Liu, N, Song SY, Jiang JB, Wang TJ, Yan CX. The prognostic role of Ki-67/MIB-1 in meningioma: A systematic review with meta-analysis. Medicine (Baltimore). 2020;99(9):e18644.
6. Jin C, Huang Y, Nasim M, Yang Y, Lee L. Gastrointestinal stromal tumors risk stratification utilizing phospho-histone H3 evaluated by manual counting and computer-assisted image analysis. Int J Surg Pathol. 2019;27(7):706-12.
7. Hao Q, Dai C, Deng Y, Xu P, Tian T, Shuai Lin S, et al. Pooling analysis on prognostic value of PHH3 expression in cancer patients. Cancer Manag Res. 2018;10:2279-88.
8. Hacking SM, Sajjan S, Lee L, Ziemba Y, Angert M, Yang Y, et al. Potential pitfalls in diagnostic digital image analysis: experience with ki-67 and PHH3 in gastrointestinal neuroendocrine tumors. Pathol Res Pract. 2020;216(3):152753.
9. Kim MJ, Kwon MJ, Kang HS, Choi KC, Nam ES, Cho SJ, et al. Identification of phosphohistone H3 cutoff values corresponding to original WHO grades but distinguishable in well-differentiated gastrointestinal neuroendocrine tumors. Biomed Res Int. 2018;2018:1013640.
10. Huynh J, Chand A, Gough D, Ernst M. Therapeutically exploiting STAT3 activity in cancer - using tissue repair as a road map. Nat Rev Cancer. 2019;19(2):82-96.
11. Setsu N, Kohashi K, Endo M, Yamamoto H, Tamiya S, Takahashi Y, et al. Phosphorylation of signal transducer and activator of transcription 3 in soft tissue leiomyosarcoma is associated with a better prognosis. Int J Cancer. 2013;132(1):109-15.
12. Lee I, Fox PS, Ferguson SD, Bassett R, Kong LY, Schacherer CW, et al. The expression of p-STAT3 in stage IV melanoma: risk of CNS metastasis and survival. Oncotarget. 2012;3(3):336-44.
13. Magrassi L, De-Fraja C, Conti L, Butti G, Infuso L, Govoni S, et al. Expression of the JAK and STAT superfamilies in human meningiomas. J Neurosurg. 1999;91(3):440-6.
14. Chohan MO, Ryan CT, Singh R, Lanning RM, Reiner AS, Rosenblum MK, et al. Predictors of treatment response and survival outcomes in meningioma recurrence with atypical or anaplastic histology. Neurosurgery. 2018;82(6):824-32.
15. Delgado-López PD, Cubo-Delgado E, González-Bernal JJ, Martín-Alonso J. A practical overview on the molecular biology of meningioma. Curr Neurol Neurosci Rep. 2020;20(12):62.
16. Johnson M, O'Connell M, Walter K. STAT3 activation and risk of recurrence in meningiomas. Oncol Lett. 2017;13(4):2432-6.
17. Paldor I, Awad M, Sufaro YZ, Kaye AH, Shoshan Y. Review of controversies in management of non-benign meningioma. J Clin Neurosci. 2016;31:37-46.
18. Nowosielski M, Galldiks N, Iglseder S, Kickingereder P, von Deimling A, Bendszus M, et al. Diagnostic challenges in meningioma. Neuro Oncol. 2017;19(12):1588-98.
19. Parada CA, Osbun J, Kaur S, Yakkioui Y, Shi M, Pan C, et al. Kinome and phosphoproteome of high-grade meningiomas reveal AKAP12 as a central regulator of aggressiveness and its possible role in progression. Sci Rep. 2018;8(1):2098.
20. Johnson MD, O'Connell M, Facik M, Maurer P, Jahromi B, Pilcher W. Cerebrospinal fluid stimulates leptomeningeal and meningioma cell proliferation and activation of STAT3. J Neurooncol. 2012;107(1):121-31.
21. Valle-Mendiola A, Soto-Cruz I. Energy metabolism in cancer: the roles of STAT3 and STAT5 in the regulation of metabolism-related genes. Cancers (Basel). 2020;12(1):124.
22. Page BD, Ball DP, Gunning PT. Signal transducer and activator of transcription 3 inhibitors: a patent review. Expert Opin Ther Pat. 2011;21(1):65-83.
23. Igelmann S, Neubauer HA, Ferbeyre G. STAT3 and STAT5 activation in solid cancers. Cancers (Basel). 2019;11(10):1428.
24. Johnson MD, O'Connell M, Vito F, Bakos RS. Increased STAT-3 and synchronous activation of Raf-1-MEK-1-MAPK, and phosphatidylinositol 3-Kinase-Akt-mTOR pathways in atypical and anaplastic meningiomas. J Neurooncol. 2009;92(2):129-36.
25. Cree IA, Tan PH, Travis WD, Wesseling P, Yagi Y, White VA, et al. Counting mitoses: SI(ze) matters! Mod Pathol. 2021;34(9):1651-7.
26. Kim YJ, Ketter R, Steudel WI, Feiden W. Prognostic significance of the mitotic index using the mitosis marker anti-phosphohistone H3 in meningiomas. Am J Clin Pathol. 2007;128(1):118-25.
27. Elmaci I, Altinoz MA, Sari R, Bolukbasi FH. Phosphorylated histone H3 (PHH3) as a novel cell proliferation marker and prognosticator for meningeal

tumors: A short review. Appl Immunohistochem Mol Morphol. 2018;26(9):627-31.
28. Nagahama A, Yashiro M, Kawashima T, Nakajo K, Morisako H, Uda T, et al. Combination of p53 and Ki67 as a promising predictor of postoperative recurrence of meningioma. Anticancer Res. 2021;41(1):203-10.
29. Puripat N, Loharamtaweethong K. Phosphohistone H3 (PHH3) as a surrogate of mitotic figure count for grading in meningiomas: a comparison of PHH3 (S10) versus PHH3 (S28) antibodies. Virchows Arch. 2019;474(1):87-96.
30. Fukushima S, Terasaki M, Sakata K, Miyagi N, Kato S, Sugita Y, et al. Sensitivity and usefulness of anti-phosphohistone-H3 antibody immunostaining for counting mitotic figures in meningioma cases. Brain Tumor Pathol. 2009;26(2):51-7.

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Comparison of Intraoperative and Postoperative Outcomes of Proximal Femoral Nailing and Bipolar Hemiarthroplasty Techniques in Intertrochanteric Femur Fracture Treatment

İntertrokanterik Femur Kırığı Tedavisinde Proksimal Femoral Çivileme ve Bipolar Hemiartroplasti Tekniklerinin İntraoperatif ve Postoperatif Sonuçlarının Karşılaştırılması

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ABSTRACT

Aim: This study was undertaken with the purpose of comparing the short and long term surgical, clinical, and functional results between bipolar hemiarthroplasty and proximal femoral nailing in the same cohort of patients.

Material and Methods: The retrospective scanning of two-year data of a tertiary care hospital has been carried out for patients with hip fractures undergoing proximal femoral nailing and bipolar hemiarthroplasty. 67 patients underwent proximal femoral nailing and 74 patients underwent bipolar hemiarthroplasty were included in the study. Each patient's short and long term outcomes were documented as well as their preoperative, intraoperative, and postoperative features.

Results: There were no significant differences in the demographic features of both groups. The median intraoperative blood loss was significantly higher in the group who underwent bipolar hemiarthroplasty compared to the group who underwent proximal femoral nailing (450 cc vs 300 cc, respectively, $p<0.001$). It was found that the bipolar hemiarthroplasty procedure was associated with a greater need for intraoperative transfusion than the proximal femoral nailing procedure ($p=0.007$). Intraoperative complications were reported only in patients who underwent bipolar hemiarthroplasty. The need for intensive care unit was significantly higher in the bipolar hemiarthroplasty group than in the proximal femoral nailing group, with the rate of 86.5% (n=64) and 68.7% (n=46), respectively ($p=0.011$).

Conclusion: According to the results of this study, the proximal femoral nailing procedure appears to be a more reliable surgical technique in patients with hip fractures in terms of both intraoperative complications and the postoperative need for an intensive care unit.

Keywords: Elderly; hemiarthroplasty; intertrochanteric fracture; proximal femur nailing; surgery outcomes.

ÖZ

Amaç: Bu çalışma, benzer özelliklere sahip hasta grubunda bipolar hemiartroplasti ile proksimal femoral çivileme arasında kısa ve uzun dönem cerrahi, klinik ve fonksiyonel sonuçları karşılaştırmak amacıyla yapılmıştır.

Gereç ve Yöntemler: Proksimal femur çivileme ve bipolar hemiartroplasti uygulanan kalça kırığı olan hastalar için, üçüncü basamak bir hastanenin iki yıllık verilerinin geriye dönük taraması yapıldı. 67 proksimal femoral çivileme uygulanan hasta ve 74 bipolar hemiartroplasti uygulanan hasta çalışmaya dahil edildi. Her bir hastanın kısa ve uzun vadeli sonuçları ile ameliyat öncesi, ameliyat sırasındaki ve ameliyat sonrası özellikleri kayda alındı.

Bulgular: Her iki grubun demografik özelliklerinde istatistiksel olarak anlamlı bir farklılık yoktu. Bipolar hemiartroplasti uygulanan grupta ameliyat sırasındaki ortanca kan kayıp miktarı proksimal femoral çivileme uygulanan gruba göre anlamlı derecede daha yüksekti (sırasıyla 450 cc'ye karşı 350 cc; $p<0,001$). Bipolar hemiartroplasti prosedürünün, proksimal femoral çivileme prosedüründen daha fazla ameliyat sırasında transfüzyon ihtiyacı ile ilişkili olduğu saptandı ($p=0,007$). Sadece bipolar hemiartroplasti yapılan hastalarda ameliyat sırasında komplikasyon varlığı rapor edilmiştir. Yoğun bakım ihtiyacı bipolar hemiartroplasti grubunda, proksimal femoral çivileme grubuna göre, sırasıyla %86,5 (n=64) ve %68,7 (n=46) oranları ile anlamlı derecede daha yüksekti ($p=0,011$).

Sonuç: Bu çalışmanın sonuçlarına göre, kalça kırığı olan hastalarda proksimal femoral çivileme prosedürü hem ameliyat sırasındaki komplikasyonlar ve hem de ameliyat sonrası yoğun bakım ihtiyacı açısından daha güvenilir bir cerrahi teknik olarak görünmektedir.

Anahtar kelimeler: Yaşlılar; hemiartroplasti; intertrokanterik kırık; proksimal femur çivileme; cerrahi sonuçlar.

INTRODUCTION

As a consequence of increased life expanse, complications related to aging increase, one of the most common complications of aging is hip fractures. The approximate rate of hip fractures is predicted to reach 4.5 million by 2050 worldwide (1,2). The unstable intertrochanteric fractures can only be treated surgically; therefore, choosing the optimal medical innervation with minimal complications is essential for quality aging. Stabil fixation, early mobilization, and weight-bearing are the expectations from surgical treatment. However, underlying diseases and comorbidities of the patients and the low surgical tolerance of the under-risk population make it hard to achieve the ideal result. Therefore, exhaustive studies and reports on surgical techniques always are required. The most common surgical technics in femur neck and trochanteric fractures are the proximal femoral nailing (PFN) technique, uni and bipolar hemiarthroplasty (BHA), and external fixation. Unfortunately, there is no consensus regarding the most reliable method for elderly patients to avoid complications and gain maximum benefit. This study aimed to compare the complications and the clinical and functional outcomes of patients with intertrochanteric fractures of the femur treated with PFN and BHA.

MATERIAL AND METHODS

Study Design

This is a retrospective study analyzing patients admitted to the orthopedic clinics of Ahi Evran University Faculty of Medicine with unstable trochanteric fractures and treated with PFN or BHA from January 2018 to December 2020. The medical records were collected from the hospital database. Ethical approval was obtained for the study from the Ethics Committee of Ahi Evran University Faculty of Medicine numbered 2021-03/30, date 09/02/2021. The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed. The authors have provided contributions to data collection, manuscript preparation, and literature review.

Patients and Data

The patients admitted with unstable intertrochanteric fractures according to Evans's classification were studied. The patients were included if the fracture occurred after low or minor energy trauma and if they were followed up at least two years after the surgery. The patients were excluded if the fracture occurred after multi-trauma, on pathologic or malignant baseline, and stable fractures, patients with previous immobility, patients with a preexisting femoral implant, and severe infection or sepsis were also excluded.

A total of 213 cases of unstable femur fractures were accepted into our clinic between January 2018 and December 2020. Among them, a total of 72 cases were excluded from the study because they did not meet the study criteria, were multi-trauma cases or emergency cases, or had insufficient follow-up data.

Patients' demographic and clinical information such as age, gender, concomitant comorbid disease status, and the American Society of Anesthesiologists (ASA) score were recorded. Information regarding trauma, such as side and etiology of injury, preoperative Arbeitsgemeinschaft für Osteosynthesefragen (AO) evaluation of fracture, was also noted. The preoperative and postoperative information of the patients such as the length and type of surgery, the length of hospital stay, the intensity and duration of intensive care, the length of fat storage, the need for intraoperative blood supplementation, and any intra- and postoperative complications were collected.

Treatment and Follow-up

All the patients were operated on by a surgeon with at least a 5-year of experience. In addition, all the patients included were evaluated with the ASA classification for the preoperative health status, and the fractures were classified using the AO classification. All the patients were followed up at least one year after the operation; the short-term (the first-month follow-up) and the long-term (the 12 months follow-up) complications were recorded. Intraoperative blood loss, duration of the procedure, and complications were recorded. In addition, the postoperative mobilization, complication, and mortality status were detected.

Surgical Technique

After supine positioning on the orthopedic table, the surgical area was prepared following the closed reduction, and an appropriate incision was made to reach the trochanter major. Using the trochanteric reamer over the K-wire after being seen on both planes on the scopy, the proximal femur was reamed. Nails of appropriate diameter and length were placed with the placement guide. After the nail was placed over the guide wire, the K-wire was removed. After the nail was sent, the tissue saver system (A-PFN Blade Drill & Prox. Screw K-Wire Guide) was placed to deliver the proximal neck screw and antirotation wedge. A-PFN (Antirot.-Prox. Fem. Nail) model from TST Orthopedic Implants was used for the surgery. Preoperative images of two proximal femur fractures and their postoperative images after placement of PFN were presented in Figure 1. Preoperative images of a femur fracture and the postoperative image after repairing with BHA were presented in Figure 2.

Statistical Analysis

All analyses were performed on SPSS v.21. Normality assumption was examined by the Kolmogorov-Smirnov test, and the Levene test was used to examine the homogeneity of variances. Descriptive statistics were given as mean±standard deviation or median, 25^{th}-75^{th} percentile, and minimum-maximum for continuous variables, as appropriate. Categorical variables were summarized as frequency and percentage. Independent samples t, Welch, or Mann-Whitney U test were used to compare groups if the assumptions were met. The Pearson chi-square or Fisher-Freeman-Halton tests were performed for categorical comparisons. A p value of <0.05 was defined as the significance level for all statistical analyses.

RESULTS

A total of 141 patients, 67 patients who underwent PFN and 74 patients who underwent BHA were included. The general demographic characteristics of the patients were similar and homogenous. The mean age was similar between the groups. The age range of the patients in the PFN group started from 26 years of age. It was the youngest patient in the group; the next patient's age was 54 years. When evaluating the patients according to comorbidities, we found out that another four patients and the present young had no comorbidities, and those

patients' ages ranged from 62-84 years of age. Therefore, we did not exclude the young patient from the study, considering it differed from the study population environment. The side of the fracture (p=0.558), and the median interval between the trauma and surgery (p=0.070) were similar. All patients with existing comorbid diseases were homogenous (p=0.245). The general features of the patients were shown in Table 1.

Pre- and Intraoperative Data Comparison

According to AO classification, the fracture types were similarly proximal and diaphyseal femoral fractures in all the patients. The patients had similar operative risks with similar preoperative ASA scores. There was no significant difference between the groups according to the duration of the procedure; the median duration for both techniques were approximately 60 minutes (p=0.205). However, intraoperative bleeding was significantly higher in the BHA group (p<0.001), and there was a significantly more need for transfusion in the BHA group (p=0.007). The intraoperative complications were reported only in the BHA group (periprosthetic fracture, trochanter major fracture, trochanter minor fracture). The intraoperative data of the PFN and BHA groups were shown in Table 2.

Postoperative Data Comparison

There was no significant difference in hospital stay days between the groups; the patients who underwent PFN were hospitalized for a median of 7 (range, 2-17) days, and the patients who underwent BHA for 6 (range, 3-28) days after the surgery. 68.7% (n=46) of the patients in PFN and 86.5% (n=64) of the patients in the BHA group needed intensive care unit follow-up after the surgery, and the difference was statistically significant (p=0.011). Only two patients in the PFN group and only four patients in the BHA group were unable to mobilize (p=0.683). Both short-term and long-term complications were similar in both groups (p=0.668). The mortality rate was similar between the BHA group and the PFN group (p=0.683). Table 2 presents the postoperative data in detail.

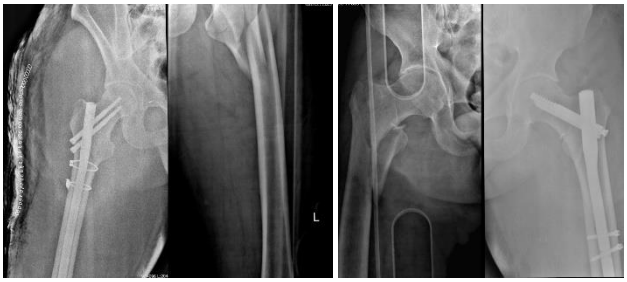

Figure 1. A pre- and post-operative image of proximal femur fractures; the proximal femur nailing

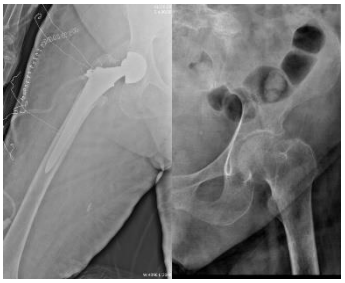

Figure 2. A female patient with a proximal femur fracture was repaired with bipolar hemiarthroplasty

Table 1. Comparison of the baseline features of the patients

	PFN (n=67)	BHA (n=74)	p
Age (years), mean±SD	77.99±12.67	80.12±7.04	0.225
BMI (kg/m^2), mean±SD	27.55±3.25	26.71±4.45	0.197
Gender, n (%)			
Female	36 (53.7)	45 (60.8)	0.396
Male	31 (46.3)	29 (39.2)	
Side, n (%)			
Right	32 (47.8)	39 (52.7)	0.558
Left	35 (52.2)	35 (47.3)	
Comorbidity, n (%)	62 (92.5)	64 (86.5)	0.245
Time before surgery (hours)$^{\#}$	2 (1-3) [1-6]	2 (2-4) [1-8]	0.070

PFN: proximal femoral nailing, BHA: bipolar hemiarthroplasty, SD: standard deviation, $^{\#}$: median (25^{th}-75^{th} percentile) [minimum-maximum]

Table 2. Comparison of pre-, intra-, and postoperative features of the patients

		PFN (n=67)	BHA (n=74)	p
Preoperative features	**AO classification of the fracture**, n (%)			
	A1	37 (55.2)	36 (48.6)	0.592
	A2	27 (40.3)	32 (43.2)	
	A3	3 (4.5)	6 (8.1)	
	ASA score, n (%)			
	1	1 (1.5)	0 (0.0)	0.121
	2	18 (26.9)	29 (39.2)	
	3	47 (70.1)	41 (55.4)	
	4	1 (1.5)	4 (5.4)	
Intraoperative features	**Duration of operation** (minutes)$^{\#}$	60 (55-70) [45-95]	60 (50-65) [40-85]	0.205
	Intraoperative blood loss (cc)$^{\#}$	300 (200-350) [100-600]	450 (385-500) [250-650]	**<0.001**
	Need for transfusion, n (%)	34 (50.7)	54 (73.0)	**0.007**
	Intraoperative complication, n (%)	0 (0.0)	1 (1.4)	1.000
Postoperative features	**Hospitalization time** (days)$^{\#}$	7 (6-9) [2-17]	6 (5-8) [3-28]	0.095
	Need for intensive care unit, n (%)	46 (68.7)	64 (86.5)	**0.011**
	Postoperative complications*, n (%)	4 (6.0)	3 (4.1)	0.708
	Long term complications**, n (%)	3 (4.5)	2 (2.7)	0.668
	Lack of mobilization, n (%)	2 (3.0)	4 (5.4)	0.683
	Mortality, n (%)	2 (3.0)	4 (5.4)	0.683

PFN: proximal femoral nailing, BHA: bipolar hemiarthroplasty, AO: Arbeitsgemeinschaft für Osteosynthesefragen, ASA: American Society of Anesthesiologists, $^{\#}$: median (25^{th}-75^{th} percentile) [minimum-maximum], *: delirium, superficial infection, deep tissue infection, deep vein thrombosis, pulmonary embolism, **: coxarthrosis, revision surgery, devise loosening

DISCUSSION

Hip fractures are a significant cause of morbidity and mortality in the elderly, and surgery is indicated for most cases. Nevertheless, comorbidities, osteoporotic, and poor bone structure of the elderly make it challenging to obtain an ideal treatment for hip fractures. A large number of studies suggested surgical repair. According to study reports performed after 1971, when primary arthroplasty was performed first, most surgical intervention patients were mobilized earlier. Mortality in patients who underwent surgical intervention was reported to be fourfold lower at one year and threefold lower at two-year follow-up compared to those with chose non-operative treatment (3,4). Furthermore, surgical repair provides better pain control and more rapidly improves mobility, even in bed (5).

The baseline composition of patients in this study showed a typical prototype of femoral trochanteric fracture due to minor trauma population: senile, female dominate population with coexisting diseases in leading of the patients. Therefore, the average demographics, fracture types, and preoperative ASA scores were coequal between the groups.

Several studies have evaluated the association of preoperative duration with some postoperative outcomes in the literature (6-8). It was found that delayed operative intervention results in a deferral of full weight-bearing and leads to delayed functional recovery. In addition, operating the hip within 24 hours was found to be associated with reduced pain and a decreased hospitalization stay compared with delayed (>24 hours) surgery (9). Consequently, surgical intervention is recommended within 24 hours in medically stable patients without significant comorbidities. And for all patients, it is recommended to avoid delaying surgery beyond 72 hours. In this study, the median trauma to surgery time was 2 hours both in PFN and BHA groups. The widely accessible healthcare and experienced consensus of surgeons on early intervention may be the reason for the algorithmic standardization in such early intervention.

Comparing the surgical techniques, we investigated the duration of operation, intraoperative blood loss, need for transfusion, and intraoperative complications. It took a similar time (approximately 60 minutes) to repair the injured hip in both methods. However, the remaining features were privileged to PFN surgery. Intraoperative blood loss, need for transfusion and need for intensive care unit were reported to be significantly higher in BHA. The complications were periprosthetic and trochanteric fractures. Some studies reported either PFN or BHA techniques benefit in either operation time. Ekinci et al. (10) reported that BHA surgery is advantageous in terms of operating time, allowing early weight bearing, on the contrary, Özkayın et al. (11) have reported a shorter time for the PFN method, or intraoperative bleeding amount. Several studies report that both methods as equally safe for the patients (12). There is no single ideal method according to operative outcomes.

Interestingly, this study found that more patients who underwent BHA needed intensive care unit hospitalization after the surgery. It may be a consequence of BHA intraoperative disadvantages. Again, there were many mortalities and especially long-term mortality after the BHA surgery. So, we may say that the BHA method is a disadvantageous technique for hip fracture repair in general. Tan et al. (13) have also reported significantly high postoperative complication and mortality rates in patients who underwent BHA and therefore suggested not to select BHA as a primary option in trochanteric fractures in the elderly. In their systematic review, Kumar et al. (14) also suggested the PFN method in elderly patients as a safer surgical technique.

Literature reports that mortality of hip fracture surgery range from approximately 1 to 10 percent, depending on patient characteristics (15,16). The mortality rate arises over time, one-year mortality rates have ranged from 12 to 37 percent (17). The mortality rate in this study was approximately 3.0% for PFN and 5.4% for the BHA group. Like as LeBlanc et al. (17) reported no increased risk of mortality after the first-year follow-up in their large prospective case-control study, we found out that long-term mortality is similar between the groups.

Considering that many studies comparing the PFN and BHA techniques have been performed, and the data reported still gives no consensus on the ideal approach, as a suggestion for further studies, we would offer to collect all the previous reports in a single detailed meta-analysis.

As a limitation of the study, it is a single-center study with a comparatively low number of patients. Nevertheless, the clear and close follow-up data of the patients increases the value of the study.

CONCLUSION

Intraoperative and some long term postoperative outcomes of BHA treated to give a negative impression on this technique. Patients with hip fractures treated with BHA have more intraoperative blood loss, have more need for transfusion during the surgery, have more intraoperative complications, and have a higher rate of need for intensive care unit. Therefore, PFN techniques seem to be a safer surgery method for patients with hip fractures.

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REFERENCES

1. Gashi YN, Elhadi AS, Elbushra IM. The outcome of primary cemented bipolar hemiarthroplasty compared with dynamic hip screw in elderly patients with unstable intertrochanteric fracture. Malays Orthop J. 2018;12(1):36-41.

2. Kannus P, Parkkari J, Sievänen H, Heinonen A, Vuori I, Järvinen M. Epidemiology of hip fractures. Bone. 1996;18(1 Suppl):57s-63s.
3. Jolly A, Bansal R, More AR, Pagadala MB. Comparison of complications and functional results of unstable intertrochanteric fractures of femur treated with proximal femur nails and cemented hemiarthroplasty. J Clin Orthop Trauma. 2019;10(2):296-301.
4. Tay E. Hip fractures in the elderly: operative versus nonoperative management. Singapore Med J. 2016;57(4):178-81.
5. Bhandari M, Swiontkowski M. Management of acute hip fracture. N Engl J Med. 2017;377(21):2053-62.
6. Bottle A, Aylin P. Mortality associated with delay in operation after hip fracture: observational study. BMJ. 2006;332(7547):947-51.
7. Lieten S, Herrtwich A, Bravenboer B, Scheerlinck T, Van Laere S, Vanlauwe J. Analysis of the effects of a delay of surgery in patients with hip fractures: outcome and causes. Osteoporos Int. 2021;32(11):2235-45.
8. Vidán MT, Sánchez E, Gracia Y, Marañón E, Vaquero J, Serra JA. Causes and effects of surgical delay in patients with hip fracture: a cohort study. Ann Intern Med. 2011;155(4):226-33.
9. Orosz GM, Magaziner J, Hannan EL, Morrison RS, Koval K, Gilbert M, et al. Association of timing of surgery for hip fracture and patient outcomes. JAMA. 2004;291(14):1738-43.
10. Ekinci Y, Gürbüz K, Batın S, Kahraman M, Doğar F, Kaya Erten Z. A multicenter intertrochanteric fracture study in the elderly: Hemiarthroplasty versus proximal femoral nailing. Jt Dis Relat Surg. 2020;31(2):209-17.
11. Özkayın N, Okçu G, Aktuğlu K. Intertrochanteric femur fractures in the elderly treated with either proximal femur nailing or hemiarthroplasty: a prospective randomised clinical study. Injury. 2015;46(Suppl 2):S3-8.
12. Zhou S, Liu J, Zhen P, Shen W, Chang Y, Zhang H, et al. Proximal femoral nail anti-rotation versus cementless bipolar hemiarthroplasty for unstable femoral intertrochanteric fracture in the elderly: a retrospective study. BMC Musculoskelet Disord. 2019;20(1):500.
13. Tan WL, Shi YX, Zhang JY, Tang CR, Guan QB, Tan JJ. Bipolar hemiarthroplasty should not be selected as the primary option for intertrochanteric fractures in elderly patients aged 85 years or more. Medicine (Baltimore). 2020;99(37):e21862.
14. Kumar P, Rajnish RK, Sharma S, Dhillon MS. Proximal femoral nailing is superior to hemiarthroplasty in AO/OTA A2 and A3 intertrochanteric femur fractures in the elderly: a systematic literature review and meta-analysis. Int Orthop. 2020;44(4):623-33.
15. Yong EL, Ganesan G, Kramer MS, Howe TS, Koh JSB, Thu WP, et al. Risk factors and trends associated with mortality among adults with hip fracture in Singapore. JAMA Netw Open. 2020;3(2):e1919706.
16. Frost SA, Nguyen ND, Black DA, Eisman JA, Nguyen TV. Risk factors for in-hospital post-hip fracture mortality. Bone. 2011;49(3):553-8.
17. LeBlanc ES, Hillier TA, Pedula KL, Rizzo JH, Cawthon PM, Fink HA, et al. Hip fracture and increased short-term but not long-term mortality in healthy older women. Arch Intern Med. 2011;171(20):1831-7.

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17-year-old Selective Mutism Case without Treatment for A Long Time

Uzun Süredir Tedavisiz Kalan 17 Yaşındaki Selektif Mutizm Olgusu

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ABSTRACT

Selective mutism is a rare childhood anxiety disorder characterized by the inability to speak in certain social situations in which speech is expected, despite speaking fluently in other situations. The average age of onset for selective mutism is 2 to 5 years old, but symptoms may not be noticed until starting school. The cause is still not known and the prevalence varies between 0.03% and 1%. Psychopharmacology and psychotherapeutic approaches are recommended in the treatment. Although the treatment is difficult, early diagnosis is one of the good prognostic factors. In this case report, we aimed to discuss the psychiatric and sociocultural functionality of a 17-year-old adolescent with selective mutism. Our case is remarkable as she has not been treated for many years. Her treatment continues with psychopharmacological and psychotherapeutic interventions. Recognition of selective mutism and getting support on this issue will help to solve the problem.
Keywords: Selective mutism; treatment; adolescent.

ÖZ

Selektif mutizm, başka durumlarda akıcı konuşmaya rağmen, konuşmanın beklendiği belirli sosyal durumlarda konuşamama ile karakterize, nadir görülen bir çocukluk çağı anksiyete bozukluğudur. Selektif mutizm için ortalama başlangıç yaşı 2 ila 5 yaş arasındadır, ancak çocuklar okula başlayana kadar semptomlar fark edilmeyebilir. Nedeni tam olarak bilinmemektedir; yaygınlığı %0,03 ile %1 arasında değişmektedir. Tedavisinde psikofarmakoloji ve psikoterapötik yaklaşımlar önerilmektedir. Tedavisi güç olmakla birlikte erken tanı iyi prognostik faktörlerden biridir. Bu olgu sunumunda, selektif mutizmli 17 yaşındaki bir ergenin psikiyatrik ve sosyokültürel işlevselliğini tartışmayı amaçladık. Olgumuz uzun yıllar tedavi edilmediği için dikkat çeken bir vaka olma özelliğine sahiptir. Tedavisi psikofarmakolojik ve psikoterapötik girişimlerle devam etmektedir. Selektif mutizmin fark edilmesi ve bu konuyla ilgili destek alınması sorunun çözümüne fayda sağlayacaktır.
Anahtar kelimeler: Selektif mutizm; tedavi; ergen.

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INTRODUCTION

Selective mutism is a rare childhood anxiety disorder characterized by the inability to speak in certain social situations in which speech is expected, despite speaking fluently in other situations (1). The average age of onset for selective mutism is 2 to 5 years old, but symptoms may not be noticed until starting school. In general, selective mutism improves with age, while other mental disorders can be seen later (2). Social phobia and depression are common comorbidities. Traumatic events were suspected in the etiology in the past, while today genetic, psychological, and language-related factors have been assumed (3).

Its prevalence varies between 0.03% and 1% in various clinical and school samples (4). Selective mutism is 1.2 to 2 times more common in girls (5). In treatment, psychotherapies, psychosocial interventions, and selective serotonin reuptake inhibitors (SSRIs) are used (6).
In this case, we aimed to discuss the psychiatric and sociocultural functionality of an adolescent with selective mutism, who did not be treated for 12 years.

CASE REPORT

A 17-year-old female patient in her 2nd year of high school applied to our polyclinic with her father voluntarily because of "not talking to foreigners".
At the age of 5, the patient started not to talk to anyone except her parents. According to the family, she did not have any problems in speech-related developmental stages and she had no problem talking to strangers before the age of 5. No significant stressor was described. Despite all the efforts of her parents, the patient continued to suffer from this condition.
When she started primary school, she applied to child psychiatry twice with this complaint, and fluoxetine solution, an SSRI, was started. The dose of fluoxetine could not be learned. The drug was discontinued because the family thought it was ineffective. She has not received any psychotherapeutic support.
She could not go to primary school in her first year as she could not stay at school and run away. After that year, she was able to adapt to school. However, since then, she has been communicating with her teacher and friends with gestures and facial expressions or just nodding her head. Her academic performance was good.
Her family stated that she was a worried child, and her anxiety increased in the mornings of school days. It was learned that she checked her bag and receipts frequently, though it did not take most of her time during the day. According to her family, she is a curious child who is quick to learn. Her family does not think she is shy.
During the clinical examination, she was making effective eye contact and communicating by nodding. Her intelligence seemed to be normal. She had no problems with sleeping and appetite.
According to the mother, the prenatal and postnatal period was normal. She was delivered vaginally at 38 gestational weeks. Her first words were at the age of 9 months, she started to walk when she was 12 months, and completed toilet training when she was 2.5 years old. Her mother was the primary caregiver during her childhood. She always lives with her family and no traumatic experiences have been described. There was not any pathology in her medical and neurological examinations. There was no psychiatric disorder or speech-related disorder in her family history.
Our case cannot speak in social areas (eg. school), although she speaks in other situations (eg. at home with family). This impairs social communication, the duration lasts longer than one month, and the state of being unable to speak is not related to not knowing the language of the society or not being able to speak that language comfortably. She met the diagnostic criteria for selective mutism according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), Fifth Edition (DSM-5), as she did not have a condition that was explained by autism spectrum disorder, communication disorder, or any psychotic disorders.
In the treatment, sertraline 50 mg/day and lorazepam 1 mg/day were started. She was seen biweekly. After one month, her anxiety decreased and she started going out with her friends, but there was no improvement in her verbal communication. At the end of the first month, lorazepam treatment was stopped and psychotherapy was recommended. It was observed that the patient started to talk to the teacher and close friends in the second month after the beginning of the treatment, although it was observed that there was an increase in her functionality, the expected recovery has not been fully achieved yet. The patient's follow-up continues.

DISCUSSION

Selective mutism was first defined in 1877 as "aphasia voluntaria" and was named "elective mutism" in the DSM. Its name was changed to "selective mutism" in 1990 (7). The clinical course of selective mutism is very variable, it may regress suddenly and completely, or it may show a slow regression. Continuation into adulthood is less common (3). While this diagnosis was under the title of "Other Disorders of Infancy, Childhood or Adolescence" in DSM-4-TR, it was included under the title of "Anxiety Disorders" of DSM-5 and entered the focus of adult psychiatry.
Selective mutism is a rare psychiatric disorder and it's difficult to treat. A multidisciplinary treatment approach is required. Today, cognitive behavioral therapies (8,9) and psychopharmacological agents are used (6,10).
In this case, selective mutism symptoms started at the age of 5 and continued till 17 years old. This is due to the lack of regular visits to a child psychiatrist, and so lack of regular follow-up and treatment.
Selective mutism impairs psychosocial and academic functioning (11), but in this case, the impairment seemed not to be important. This may be due to the low socioeconomic level and cultural structure of the family. Also, the reason for ignoring the deterioration in social functioning at school may be because of good academic achievement.
Studies have shown that 80% of cases with selective mutism are frequently accompanied by an additional diagnosis of anxiety disorder, especially social phobia (69%) (12,13). Untreated selective mutism can lead to impaired functioning and increase the risk of other psychiatric disorders (7).
The timely diagnosis and treatment of selective mutism with psychotherapeutic and psychopharmacological approaches can prevent comorbid conditions and deterioration in functionality.

CONCLUSION

Shy behaviors and limited speech, especially in girls, may be considered as appropriate and respectful behavior culturally and it may be difficult to treat the situation as a disorder. As a result of delays in diagnosis and treatment, it is inevitable for the disorder to become chronic. Although selective mutism is seen rarely with age, physicians other than psychiatrists are needed to be more aware and should refer the patients to psychiatry when suspected.

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REFERENCES

1. Steains SY, Malouff JM, Schutte NS. Efficacy of psychological interventions for selective mutism in children: A meta-analysis of randomized controlled trials. Child Care Health Dev. 2021;47(6):771-81.
2. Hua A, Major N. Selective mutism. Curr Opin Pediatr. 2016;28(1):114-20.
3. Rogoll J, Petzold M, Ströhle A. [Selective mutism]. Nervenarzt. 2018;89(5):591-602. German.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. American Psychiatric Publishing; 2013.
5. Driessen J, Blom JD, Muris P, Blashfield RK, Molendijk ML. Anxiety in children with selective mutism: a meta-analysis. Child Psychiatry Hum Dev. 2020;51(2):330-41.
6. Manassis K, Oerbeck B, Overgaard KR. The use of medication in selective mutism: a systematic review. Eur Child Adolesc Psychiatry. 2016;25(6):571-8.
7. Smith-Schrandt HL, Ellington E. Unable to speak: selective mutism in youth. J Psychosoc Nurs Ment Health Serv. 2018;56(2):14-8.
8. Lang C, Nir Z, Gothelf A, Domachevsky S, Ginton L, Kushnir J, et al. The outcome of children with selective mutism following cognitive behavioral intervention: a follow-up study. Eur J Pediatr. 2016;175(4):481-7.
9. Oerbeck B, Overgaard KR, Stein MB, Pripp AH, Kristensen H. Treatment of selective mutism: a 5-year follow-up study. Eur Child Adolesc Psychiatry. 2018;27(8):997-1009.
10. Percinel İ, Yazici KU. [Fluoxetine treatment in preschool cases with selective mutism: Discussion through two cases]. Turk J Child Adolesc Ment Health. 2014;21(2):123-30. Turkish.
11. Rodrigues Pereira C, Ensink JBM, Güldner MG, Lindauer RJL, De Jonge MV, Utens EMWJ. Diagnosing selective mutism: a critical review of measures for clinical practice and research. Eur Child Adolesc Psychiatry. 2021;[Epub ahead of print]. doi: 10.1007/s00787-021-01907-2.
12. Driessen J, Blom JD, Muris P, Blashfield RK, Molendijk ML. Anxiety in children with selective mutism: A meta-analysis. Child Psychiatry Hum Dev. 2020;51(2):330-41.
13. Steinhausen HC, Wachter M, Laimböck K, Metzke CW. A long-term outcome study of selective mutism in childhood. J Child Psychol Psychiatry. 2006;47(7):751-6.

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- Sorumlu yazar, tüm yazarlar adına makalenin son halinin sorumluluğunu taşır.

ETİK SORUMLULUK

- "İnsan" öğesini içeren tüm çalışmalarda Helsinki Deklerasyonu Prensipleri'ne (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) uygunluk aranır. Bu tip çalışmalarda yazarların, GEREÇ VE YÖNTEMLER bölümünde çalışmayı bu prensiplere uygun olarak yaptıklarını, kurumlarının etik kurullarından onay ve çalışmaya katılmış insanlardan "bilgilendirilmiş olur" (informed consent) aldıklarını belirtmeleri gerekmektedir.
- Çalışmada "Hayvan" öğesi kullanılmış ise yazarların, GEREÇ VE YÖNTEMLER bölümünde Guide for the Care and Use of Laboratory Animals (https://grants.nih.gov/grants/olaw/guide-for-the-care-and-use-of-laboratory-animals.pdf) prensipleri doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmeleri gerekmektedir.
- Olgu sunumlarında hastalardan "bilgilendirilmiş olur" (informed consent) alınmalıdır.
- Etik kurul onay bilgisi GEREÇ ve YÖNTEMLER bölümünde kurul adı, onay tarihi ve sayısı ile birlikte belirtilmelidir.
- Eğer çalışmada direkt-indirekt ticari bağlantı veya maddi destek veren kurum mevcut ise yazarlar; kullanılan ticari ürün, ilaç, firma vb. ile ticari hiçbir ilişkisinin olmadığını veya varsa nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar), editöre sunum sayfasında belirtmelidirler.
- Yazarlar çalışma ile ilgili kişisel ve finansal tüm ilişkilerin bildirilmesinden sorumludur. Makalenin başvurusu ve/veya değerlendirmesi ile ilişkili herhangi bir çıkar çatışması olup olmadığının açıkça beyan edilmesi gerekmektedir.
- Makalelerin bilimsel ve etik kurallara uygunluğu yazarların sorumluluğundadır.

BAŞVURU DOSYALARI

Makaleler aşağıda belirtilen şekilde ayrı dosyalar halinde sisteme yüklenmelidir.

Telif Hakkı Devir Formu: Başvuru sırasında sistemden alınacak Telif Hakkı Devir Formu tüm yazarlar tarafından makaledeki yazar sıralamasına uygun şekilde imzalanmış olmalıdır.

Başvuru Mektubu: Makalenin türü, daha önce hiç bir yerde yayınlanmamış ve/veya yayınlanmak üzere değerlendirme sürecinde olmadığı, varsa çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve bu kuruluşların yazarlarla olan ilişkileri (yoksa olmadığı) belirtilmelidir. Makalenin konusuyla ilgili olarak önerilen, yazarlarla ve kurumlarıyla ilgisi olmayan en az iki hakemin adları, akademik unvanları, kurumları, iletişim bilgileri ve e-posta adresleri yazılmalıdır. Editörlerin hakemleri seçme hakkı saklıdır.

Başlık Sayfası: Makalenin başlığını (İngilizce ve Türkçe), 40 karakteri geçmeyen kısa başlık, tüm yazarların adlarını, akademik unvanlarını, ORCID® numaralarını, kurumlarını, e-posta adreslerini ve ayrıca sorumlu yazarın adını, yazışma adresini, telefon numarasını, e-posta adresini içermelidir. Makale daha önce bilimsel bir toplantıda sunulmuş ise toplantı adı, tarihi ve yeri (yoksa sunulmadığı) belirtilmelidir.

Ana Metin: Makalenin başlığı (İngilizce ve Türkçe), 40 karakteri geçmeyen kısa başlık, Öz (İngilizce ve Türkçe), Anahtar kelimeler (İngilizce ve Türkçe), Ana Metin (gönderilen makalenin türüne uygun olarak bölümlere ayrılmış), Kaynaklar, Tablolar ve Şekil açıklamaları yer almalıdır.

Etik Kurul Onay Belgesi: Tüm araştırma makaleleri için Etik Kurul Onay Belgesi ayrı bir dosya olarak yüklenmelidir.

Not: Makalede şekil, resim veya fotoğraf varsa bunların da her biri ayrı birer dosya olarak yüklenmelidir.

MAKALE TÜRÜNE GÖRE KULLANILMASI GEREKEN BÖLÜMLER

Araştırma Makalesi

BAŞLIK (İngilizce ve Türkçe), KISA BAŞLIK, ÖZ (İngilizce ve Türkçe), Anahtar kelimeler (İngilizce ve Türkçe), GİRİŞ, GEREÇ VE YÖNTEMLER, BULGULAR, TARTIŞMA, SONUÇ, KAYNAKLAR

ÖZ ve ABSTRACT çeviri açısından uyumlu olmalı ve her biri kendi içinde 200-250 kelime arasında olmalıdır.

ABSTRACT, "Aim, Material and Methods, Results, Conclusion" şeklinde yapılandırılmalıdır.

ÖZ, "Amaç, Gereç ve Yöntemler, Bulgular, Sonuç" şeklinde yapılandırılmalıdır.

Derleme (Sadece Davetli)

BAŞLIK (İngilizce ve Türkçe), KISA BAŞLIK, ÖZ (İngilizce ve Türkçe), Anahtar kelimeler (İngilizce ve Türkçe), GİRİŞ, Konu ile İlgili Alt Başlıklar, SONUÇ, KAYNAKLAR

ÖZ ve ABSTRACT çeviri açısından uyumlu olmalı ve her biri kendi içinde 150-200 kelime arasında olmalıdır.

Olgu Sunumu

BAŞLIK (İngilizce ve Türkçe), KISA BAŞLIK, ÖZ (İngilizce ve Türkçe), Anahtar kelimeler (İngilizce ve Türkçe), GİRİŞ, OLGU SUNUMU, TARTIŞMA, KAYNAKLAR

ÖZ ve ABSTRACT çeviri açısından uyumlu olmalı ve her biri kendi içinde 100-150 kelime arasında olmalıdır.

Diğer

Bu üç temel makale türü dışındaki (editöre mektup, editöryel yorum/tartışma vb.) yazıların hazırlanmasında da genel yazım kuralları geçerlidir. Bu tür yazılarda başlık ve öz bölümleri yoktur. Kaynak sayısı 5 ile sınırlıdır. İthaf olunan makale sayı ve tarih verilerek belirtilmelidir. Yazının sonunda yazarın ismi, kurumu ve adresi yer almalıdır. Mektuba cevap, editör veya makalenin yazarları tarafından, yine dergide yayınlanarak verilir.

YAZARLARA BİLGİLENDİRME

YAZIM KURALLARI
- Makaleler Microsoft Word® belgesi olarak hazırlanmalıdır.
- Sayfa kenarlarında 2,5 cm boşluk bırakılmalıdır.
- Sayfa numaraları sayfanın sağ alt köşesine yerleştirilmelidir.
- Tüm metinler 12 punto Times New Roman karakteri kullanılarak çift satır aralığı ile sola hizalanmış olarak yazılmalıdır.

ANAHTAR KELİMELER
- Anahtar kelime sayısı en az 2 olmalı, kelimeler birbirlerinden noktalı virgül (;) ile ayrılmalıdır.
- Türkçe anahtar kelimeler Türkiye Bilim Terimleri (TBT)'ne (http://www.bilimterimleri.com), İngilizce anahtar kelimeler Medical Subject Headings (MESH)'e (http://www.nlm.nih.gov/mesh/MBrowser.html) uygun olarak verilmelidir.

İSTATİSTİKSEL YÖNTEMLER
- Tüm araştırma makaleleri biyoistatistik açıdan değerlendirilmeli ve uygun plan, analiz ve raporlama ile belirtilmelidir. Bu makalelerde, GEREÇ VE YÖNTEMLER bölümünün son alt başlığı "İstatistiksel Analiz" olmalıdır.
- Bu bölümde çalışmada kullanılan istatistiksel yöntemler ne amaçla kullanıldığı belirtilerek yazılmalı, istatistiksel analiz için kullanılan paket programlar ve sürümleri belirtilmelidir.
- p değerleri ondalık üç basamaklı (p=0,038; p=0,810 vb.) olarak verilmelidir.
- Makalelerin biyoistatistik açıdan uygunluğunun kontrolü için ek bilgi www.icmje.org adresinden temin edilebilir.

KISALTMALAR
- Terim ilk kullanıldığında parantez içinde kısaltmayla birlikte açık olarak yazılmalı ve tüm metin boyunca aynı kısaltma kullanılmalıdır.
- Uluslararası kullanılan kısaltmalar Bilimsel Yazım Kurallarına uygun şekilde kullanılmalıdır.

TABLOLAR VE ŞEKİLLER
- Metinde ilgili cümlenin sonunda (Tablo 1) ve/veya (Şekil 1) şeklinde belirtilmelidir.
- Tablolar (başlıklarıyla birlikte) ve şekiller (açıklamalarıyla birlikte) kaynaklardan sonra ve her biri ayrı bir sayfada olacak şekilde metnin sonuna eklenmelidir.
- Tablo başlıkları tablo üstünde (Tablo 1. Tablo başlığı), şekil açıklamaları ise şeklin altında (Şekil 1. Şekil açıklaması), ilk harfleri büyük olacak şekilde yazılmalıdır.
- Tablolarda ve şekillerde kısaltma veya sembol kullanılmış ise altında dipnot olarak açıklanmalıdır.
- Şekiller ve fotoğraflar, .png, .jpg vb. formatta ve en az 300 dpi çözünürlükte ayrı dosyalar halinde yüklenmelidir.
- Şekil ve fotoğraf alt yazıları, son tablonun olduğu sayfadan sonra, ayrı bir sayfada sırasıyla verilmelidir.
- Daha önce basılmış şekil, resim, tablo, grafik vb. kullanılmış ise yazılı izin alınmalı ve açıklama olarak belirtilmelidir. Bu konudaki hukuki sorumluluk yazarlara aittir.

TEŞEKKÜR
- Eğer çıkar çatışması/çakışması, finansal destek, bağış ve diğer bütün editöryel (İngilizce/Türkçe değerlendirme) ve/veya teknik yardım varsa, bu bölümde, KAYNAKLAR bölümünden önce belirtilmelidir.

KAYNAKLAR
- Kaynaklar, kullanım sırasına göre numaralandırılmalı ve metin içinde ilgili cümlenin sonunda parantez içinde numaralarla (1) veya (1,2) veya (3-5) şeklinde verilmelidir.
- Kaynaklar dizini, metin içinde kaynakların kullanıldığı sıraya göre oluşturulmalıdır.
- Yazar sayısı 6 veya daha az ise tüm yazarlar belirtilmeli, 7 veya daha fazla ise ilk 6 yazar belirtildikten sonra "et al." eklenmelidir.
- Kongre bildirileri, kişisel deneyimler, basılmamış yayınlar, tezler ve internet adresleri kaynak olarak gösterilmemelidir.
- DOI tek kabul edilebilir online referanstır.

Makale:

Al-Habian A, Harikumar PE, Stocker CJ, Langlands K, Selway JL. Histochemical and immunohistochemical evaluation of mouse skin histology: comparison of fixation with neutral buffered formalin and alcoholic formalin. J Histotechnol. 2014;37(4):115-24.

Aho M, Irshad B, Ackerman SJ, Lewis M, Leddy R, Pope T, et al. Correlation of sonographic features of invasive ductal mammary carcinoma with age, tumor grade, and hormone-receptor status. J Clin Ultrasound. 2013;41(1):10-7.

Kitap:

Buckingham L. Molecular diagnostics: fundamentals, methods and clinical applications. 2nd ed. Philadelphia: F.A. Davis; 2012.

Kitap Bölümü:

Altobelli N. Airway management. In: Kacmarek R, Stoller JK, Heuer AJ, editors. Egan's fundamentals of respiratory care. 10th ed. St. Louis: Saunders Mosby; 2013. p.732-86.


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