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EDITORIAL

Our dear readers,

We are proud to publish the 4th issue of our journal for 2020 with 28 articles. In this issue, there are 20 research articles and 8 case reports. We strive to increase the scientific quality of our journal, which addresses all areas of health sciences and is followed by a wider audience over time. With the first issue of 2021, all articles accepted to our journal will be published in English. Thus, we want to contribute to international literature at an increasing level and to increase the success bar of our journal by entering indexes such as PubMed, SCI and SCI-E. I would like to thank all authors for submitting articles contributing to both domestic and international literature with their comprehensive scientific content for publication in our journal. Our goal is to improve our publication quality day by day with the support of all our writers and readers. We hope that this issue will be useful to our readers.

Sincerely yours.

Assoc. Prof. Dr. Alpaslan TANOGLU
Editor-in-Chief

EDİTÖRDEN

Çok değerli okuyucularımız,

Dergimizin 2020 yılına ait 4. sayısını 28 makale ile çıkartmanın gururunu yaşıyoruz. Bu sayımızda sayısında 20 araştırma makalesi, 8 olgu sunumu var. Sağlık bilimlerinin her alanına hitap eden ve zamanla daha geniş okuyucu kitlesince takip edilen dergimizin bilimsel kalitesini artırmak için yoğun çaba sarf etmekteyiz. 2021 yılının ilk sayısı ile birlikte dergimize kabul edilen tüm makaleler İngilizce yayımlanacaktır. Böylece hem uluslararası literature artan seviyede katkıda bulunmak hem de PubMed, SCI ve SCI-E gibi indekslere girerek dergimizin başarı çıtasını daha da artırmak istiyoruz. Kapsamlı bilimsel içerikleri ile hem yerli hem de uluslararası literatüre katkısı olan makaleleri dergimizde yayımlanmak üzere gönderdikleri için tüm yazarlara teşekkürlerimizi sunuyorum. Hedefimiz tüm yazar ve okuyucularımızın desteği ile yayın kalitemizi her geçen gün daha iyi noktalara taşıyabilmektir. Yayımlanan bu sayımızın okuyucularımıza faydalı olması ümidiyle, esen kalın.

Saygılarımla.

Doç. Dr. Alpaslan TANOĞLU
Baş Editör

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Original Article / Özgün Makale

HEALTH SCIENCES
MEDICINE

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Comparison of the hemostatic suture with non-suture cold-knife conization methods for cervical surgery

Servikal ameliyatlarda hemostatik sütürlü ve sütürsüz soğuk konizasyon yöntemlerinin karşılaştırması

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ABSTRACT

Aim: The primary purpose of this study is to compare the suture with non-suture cold-knife after conization methods.

Material and Method: The study included 172 women who underwent the cold-knife conization. In the first group, patients underwent cold-knife conization without sutures, and in the second group, patients underwent cold-knife conization with suture. This study's essential variables include blood loss, duration of operation, number of pregnancies, type of labor, and age of the patient. The results are calculated based on t-test, Fisher exact test, chi-square, and nonparametric Mann-Whitney tests.

Result: There was no significant difference between the variables studied, including blood loss (p-value=0.185). The only significant difference was in the duration of operation (p-value=0.000).

Conclusion: Our findings showed no significant difference in the amount of blood loss between the sutured and non-sutured groups. These results also showed that the operation duration was significantly reduced. This result was excepted since there was no need for suturing, and the other stages of the procedure were the same throughout the cold knife conization in both groups. Due to the shorter operation duration, no difference in the amount of postoperative bleeding, and the specific risks of suture, it is suggested to use a non-suture technique for cold-knife conization.

Keywords: Cervical intraepithelial neoplasia, CIN, cold-knife conization, cervical surgery

ÖZ

Amaç: Bu çalışmanın amacı soğuk konizasyon sonrası hemostatik suture atılan ve atılmayan yöntemleri karşılaştırmaktır.

Gereç ve Yöntem: Bu çalışma soğuk konizasyon geçiren 172 kadını kapsamaktadır. İlk gruptaki hastalar dikişsiz soğuk konizasyonu, ikinci gruptaki hastalar ise dikişli soğuk konizasyonu geçirmiştir. Bu çalışmadaki temel değişkenler kan kaybı, ameliyat süresi, gebelik sayısı, çocuk doğurma tipi ve hastaların yaşını kapsar. Sonuçlar t-testi, Fisher kesin testi, ki-kare ve parameter dışı Mann-Whitney testlerine göre hesaplanmıştır.

Bulgular: Kan kaybı (p-değeri=0,815) gibi çalışılan değerler arasında anlamlı fark gözlemlenmemiştir. Tek anlamlı fark ameliyat süresinde olmuştur (p-değeri=0,000).

Sonuç: Sütürlü ve sütürsüz konizasyon geçiren olguşlar arasında kan kayıpları arasında anlamlı bir fark yoktur. Ayrıca sonuçlar ameliyat süresinin anlamlı ölçüde kısaldığını göstermiştir. Bu sonuç hemostatik suture hiçbir gerek olmadığını ve her iki grupta da prosedürün diğer aşamaları soğuk konizasyon boyunca aynı olduğu için beklenen bir sonuçtu. Ameliyat süresinin kısa olması ve post-operatif kanama miktarında değişim ya da suture özgü riskler gözlemlenmemesi sebebiyle soğuk konizasyonunda sütürsüz yöntem önerilmektedir.

Anahtar Kelimeler: Servikal intraepitelyal neoplazi, CIN, soğuk konizasyon, servikal cerrahi

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INTRODUCTION

Pathologically, cervical intraepithelial neoplasia (CIN) is a change in the cervical squamous cell that is confined to the basal layer of the epithelium (1). If left untreated, they can progress to malignancy and become cervical cancer (2). Cervical cancer is the most common cancer in women in developing countries (3). In cases where there is a need for treatment of the lesion, the affected area can be removed by conization (1,3). Studies have shown that cervical conization is as effective as hysterectomies in preventing the spread of Carcinoma in Situ (CIS) (4) and in 90% of cases improve high-grade CIN (5,6). Cervical conization has long been an accepted method of diagnosing and treating CIN, and despite the development of new methods, classical conization indications are still in place (7). This procedure is performed by various techniques such as the Loop Electrosurgical Excision Procedure (LEEP) or Cold-Knife Cone (CKC) method. Cutting a cone with cold-knife and hemostasis through the suture is one of the most common methods of doing cervical conization (8).

Cold-knife conization is often used for lesions that do not have invasive cancer or are not satisfactory for colposcopy, and most of the disease has spread to the endocervical canal (8,9). In general, cold-knife conization indications include the inability to observe the entire T-Zone, the mismatch between colposcopy and Pap smear, the suspicion of invasive colonoscopic cancer, and the Adenocarcinoma in situ (AIS). The inability to observe the entire T-zone has been the most important indication of cold-knife conization in various studies. The criticism of the cold-knife conization is based on the need for general anesthesia and the risk of complications (10,11). However, numerous reports have shown that the procedure can be performed with minimal complications (12-14).

Cervical conization plays an essential role in dealing with patients with CIN (2,4). The operation of a cone with the cold-knife method is both a diagnostic and a therapeutic approach (5), and its advantage is to provide a tissue specimen to the pathologist for further examination (14). The sample should include all affected areas, including exocervix and endocervix (15). Because all treatments for CIN have a 10% chance of recurrence, they should be examined by cytology at 6-month intervals and followed by colposcopy if anything abnormal is observed (16).

In the mid-20th century, the hemostatic sutures were added to the cold-knife conization technique to minimize blood loss (17). Since then, using these sutures and their effectiveness has been discussed by many authors (18-22). This study compares the effect of these sutures on patients undergoing cold-knife conization.

MATERIAL AND METHOD

In August 2016-September 2019, a retrospective study was conducted at Gynecology and Obstetrics Department. The procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association. The study was carried out with the permission of Research Ethics Committee of Beykoz University (Permission granted/CAAE number: 2020/26.2, Decision no: 1). All the patients were given signed informed consent. All patients in this experiment underwent cold knife conization. The study included 172 women who were randomly divided into non-suture and suture groups. In the first group, which was the non-suture group, there were 63 participants, and in the second group, which was the suture group, there were 109 participants.

In the first group (with sutures), a lateral suture was applied on each side of the cervix, and after cutting the sample cone with blade No.11, the raw surface of the cone bed was closed with two figure-of-eights and Sturmdorf sutures. In the second group (without sutures), a cone-shaped sample was taken from the cervix with blade No. 11, and the inner and outer flaps were held with two Allis tissue forceps. Meanwhile, a 2 cm wide-gauze roll soaked in Monsel's solution was pressed onto the conical bed. Monsel's solution was used only for the conical bed. Excessive Monsel's solution was swabbed out, and the gas roll was packed in the upper vagina to prevent the conical bed pack from loosening. The operation was performed for both groups under general anesthesia.

The variables measured in each patient were: age, number of pregnancies, number of labor, type of labor (vaginal, cesarean, or both), prolonged labor, smoking, duration of operation, and blood loss through measuring preoperative hemoglobin (Hb), postoperative Hb, and pathology.

The inclusion criteria for this study were undergoing cold knife conization. The excluding criteria were to use other techniques than cold-knife for conization, undergoing conization in the past by other methods than cold-knife or unwillingness of the patient to participate in the study. After explaining the experiment and describing the procedure, informed consent was obtained from all participants.

Statistical Analysis

SPSS statistical package program for Windows (Statistical Package for Social Sciences, version 16.0, SPSS Inc. Chicago, Illinois, USA) was used to evaluate the study results. Percent and average calculations in descriptive statistics, chi-square analysis of the relationship between dependent and independent variables, Student t and Mann-Whitney U test analysis methods were used. A value of $p<0.05$ was considered statistically significant.

RESULTS

In **Table 1**, the first two columns are the descriptive statistics. The median and interval between the first and third quartiles were reported for the variables that were not normal. For example, for the non-normal age variable, the mean of this variable is 43, the first quartile is 38, and the third quartile is 49 in the non-suture group. We also report these values for the suture group. For a normal variable, its ± mean, standard deviation, and range of numbers ranging from lowest to highest are reported.

Table 1. Descriptive statistics for quantitative variables

Variables		Non-suture group (n= 63)	Suture group (n= 109)	P-value
Age	Median (Interval)	43 (38-49)	42 (37-49.5)	0.650
Number of pregnancies	Median (Interval)	3 (2-4)	3 (2-5)	0.736
Number of labor	Median (Interval)	2 (2-3)	2 (1-3)	0.347
Duration of operation	Median (Interval)	25 (25-30)	30 (27.5-35)	0.000
Blood loss	Median (Interval)	0.90 (0.60-1.40)	1 (0.75-1.30)	0.185

The normality test was first performed for the quantitative variables reported in **Table 1**. If the variables are normal in each group, we use an independent T-test to investigate the difference between the suture and non-suture groups. That is, the variable in question should be normal in both the suture and non-suture groups at the same time, and if not in one or both groups, we should use a nonparametric alternative Mann-Whitney test.

After the normalization test, we found that the age, number of pregnancies, number of labor, duration of operation, and blood loss variables are not normal, so we use the Mann-Whitney test for them.

After performing the Mann-Whitney tests, it was found that the variables age, number of pregnancies, number of labor, and blood loss were not significant because their p-value was higher than 0.05. So for these variables, there is no difference between the suture and non-suture groups.

However, the duration of the operation variable is significant because its P-Value is less than 0.05. So, for this variable, there is a difference between the suture and non-suture groups.

The four qualitative variables of type of labor, smoking, pathology, and prolonged labor, are reported in **Table 2.** For these variables, the chi-square test was used to investigate the difference between non-suture and suture groups. If more than 20% of the chi-square test cells have a value of less than 5, then we use Fisher's exact test.

Table 2. Descriptive statistics for qualitative variables

Variables	Non-suture group (n = 63)	Suture group (n = 109)	P-Value
Type of labor			
NSD (Normal Spontaneous Delivery)	73 (46)	75 (68.8)	0.315
CS (Caesarean Section)	6 (9.5)	17 (15.6)	
NSD & CS	6 (9.5)	5 (6.4)	
NOT giving birth	4 (6.3)	12 (11)	
Smoking			
No-Smoker	43 (68.3)	73 (67)	0.868
Smoker	20 (31.7)	(33)36	
Pathology			
Benign	23 (36.5)	33 (30.3)	0.062
LSIL (Low Grade Squamous Intraepithelial Lesion)	1 (1.6)	9 (8.3)	
HSIL (High Grade Squamous Intraepithelial Lesion)	26 (41.3)	56 (51.4)	
Carcinoma in situ	7 (11.1)	2 (1.8)	
SCC (Squamous cell carcinoma)	3 (4.8)	5 (4.6)	
Adenocarcinoma in situ	2 (3.2)	3 (2.8)	
Adenocarcinoma	1 (1.6)	1 (0.9)	
Prolonged labor			
Normal time	60 (95.2)	104 (95.4)	1
Extended labor time	3 (4.8)	5 (4.6)	

According to the P-values of the Chi-square and Fisher's tests, none of these variables were significant because their P-values were higher than 0.05. So, in these four variables, there is no difference between non-suture and suture groups.

For the pathology and prolonged labor variables, since more than 20% of their table cells had a value higher than 5, then we report the P-Value of the Fisher test.

The second and third column in **Table 2** also reports the values of descriptive statistics, in which the first number is the number of people in that class in each group (suture and non-suture). The number in parentheses represents the percentage of people in that group. For example, for the type of labor variable, the value of NSD is in 46 participants in the non-suture group, with 73% of the group, and it is in 75 participants in the suture group, with 68.8% of the group.

We did not use the preop Hb and postop Hb variables, indicating pre- and postoperative Hb levels in analyses. Instead, we used the blood loss variable, which was the difference between the two variables, since they are pre and post Hb, and their differences show the amount of blood loss in the patient.

The results showed that the only variable that had a significant difference between the sutured and non-sutured groups was the operation duration variable. This means that there was a significant difference between the duration of operation in the sutured and non-sutured groups. It was also shown that among other factors, such as the amount of blood loss or pathology, there were no significant differences between the sutured and non-sutured groups.

DISCUSSION

Our study results showed that in the non-suture group, the duration of operation was significantly reduced compared to the suture used group. There were no significant differences between the two groups for other variables, such as blood loss. Our results showed that the operative time was shorter in patients without sutures. This result was expected because the suture stage had not been performed for the non-suture group. All other conization procedures were similar in both groups, and there was no significant difference between them. There was no difference between the qualifications of surgeons, postoperative interventions, and the amount of bleeding.

Many studies have explored different methods and techniques for reducing cold-knife conization complications. The reduction of operation duration for patients treated with non-suture techniques has also been reported in some studies (18-22).

The results of our findings were consistent with those of Tangtrakul et al. (18). In this study, the authors studied 112 patients undergoing cold knife colonization in two groups without sutures (using Monsel's solution) and with sutures. Their findings showed that there was no significant difference in the amount of blood loss between the two groups. They also reported shorter operative times in the non-suture group (18).

In a similar study, the authors compared the use of sutures and Monsel's solution by testing two groups of patients with cone biopsy. Their results showed a lower operative time in the group using the Monsel's solution (19). In another study of 191 participants who underwent conization procedure with cold-knife technique, two methods of cauterization and suture were compared. Their results showed that in patients who used cauterization, there was less bleeding and surgery time than the suture group (20). The results obtained from the amount of blood loss in our study were consistent with those obtained in (19, 20). In our study, smoking and non-smoking were not significantly different for either group. These results were consistent with those in (20).

In our study, no differences were found between postoperative complications such as bleeding in the sutured and non-sutured groups. These results were consistent with (19,20). However, these results were inconsistent with the findings of Dane et al. (21) in which the cerclage group was more likely to have late bleeding.

Consistent with our results, another study by Letícia Rossi Bueno et al. (22) investigated the cold-knife conization with and without sutures and found similar results. The authors found no difference in bleeding between the two groups of with and without sutures. They also reported shorter operation times in the non-suture group. Because of no difference is found in the bloodloss of the two groups, the reduction in operation time and the different risks of suture (5,10,18), it is recommended to use a non-suture technique.

CONCLUSION

In this study, we investigated the difference between non-suture and suture groups in patients undergoing cold-knife conization. In our findings, the operative time was shorter in the non-suture group. This reduction was only due to the reduction in suture time, and other procedures, such as anesthesia or hemostasis, were similar in both groups and had no effect on the results. We observed no difference in blood loss and the need for postoperative interventions between the two non-suture and suture groups. Therefore, due to the findings of our study, such as no difference in postoperative bleeding and the reduction in operation time, it is recommended to use a non-suture technique.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Research Ethics Committee of Beykoz University (Permission granted /CAAE number: 2020/26.2, Decision no: 1).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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REFERENCES

1. Mathevet P, Dargent D, Roy M, Beau G. A randomized prospective study comparing three techniques of conization: cold knife, laser, and LEEP. Gynecol Oncol 1994; 54: 175-9.
2. Larsson GÖ, Gullberg B, Grundsell HA. A comparison of complications of laser and cold knife conization. Obstetr Gynecol 1983; 62: 213-7.
3. Mathevet P, Chemali E, Roy M, Dargent D. Long-term outcome of a randomized study comparing three techniques of conization: cold knife, laser, and LEEP. Eur J Obstetr Gynecol Reproduct Biol 2003; 106: 214-8.
4. Duggan BD, Felix JC, Muderspach LI, et al. Cold-knife conization versus conization by the loop electrosurgical excision procedure: a randomized, prospective study. Am J Obstetr Gynecol 1999; 180: 276-82.
5. Reich O, Lahousen M, Pickel H, Tamussino K, Winter R. Cervical intraepithelial neoplasia III: long-term follow-up after cold-knife conization with involved margins. Obstetr Gynecol 2002; 99: 193-6.
6. Reich O, Pickel H, Lahousen M, Tamussino K, Winter R. Cervical intraepithelial neoplasia III: long-term outcome after cold-knife conization with clear margins. Obstetr Gynecol 2001; 97: 428-30.
7. Larsson G, Alm P, Grundsell H. Laser conization versus cold knife conization. Surg Gynecol Obstetr 1982; 154: 59-61.
8. Huang LW, Hwang JL. A comparison between loop electrosurgical excision procedure and cold knife conization for treatment of cervical dysplasia: residual disease in a subsequent hysterectomy specimen. Gynecol Oncol 1999; 73: 12-5.
9. Naumann RW, Bell MC, Alvarez RD, et al. LLETZ is an acceptable alternative to diagnostic cold-knife conization. Gynecol Oncol 1994; 55: 224-8.
10. Giacalone PL, Laffargue F, Aligier N, Roger P, Combecal J, Daures JP. Randomized study comparing two techniques of conization: cold knife versus loop excision. Gynecol Oncol 1999; 75: 356-60.
11. Girardi F, Heydarfadai M, Koroschetz F, Pickel H, Winter R. Cold-knife conization versus loop excision: histopathologic and clinical results of a randomized trial. Gynecol Oncol 1994; 55: 368-70.
12. Oyesanya OA, Amerasinghe C, Manning ED. A comparison between loop diathermy conization and cold-knife conization for management of cervical dysplasia associated with unsatisfactory colposcopy. Gynecol Oncol 1993; 50: 84-8.
13. Klaritsch P, Reich O, Giuliani A, Tamussino K, Haas J, Winter R. Delivery outcome after cold-knife conization of the uterine cervix. Gynecol Oncol 2006; 103: 604-7.
14. Saidi MH, Setzler Jr FD, Sadler RK, Farhart SA, Akright BD. Comparison of office loop electrosurgical conization and cold knife conization. J Am Assoc Gynecol Laparoscopists 1994; 1: 135-9.
15. Mohamed-Noor K, Quinn MA, Tan J. Outcomes after cervical cold knife conization with complete and incomplete excision of abnormal epithelium: a review of 699 cases. Gynecol Oncol 1997; 67: 34-8.
16. Demeter A, Sziller I, Csapo Z, Szánthó A, Papp Z. Outcome of pregnancies after cold-knife conization of the uterine cervix during pregnancy. Eur J Gynecol Oncol 2002; 23: 207-10.
17. Hillemanns P, Kimmig R, Dannecker C, et al. LEEP versus cold knife conization for treatment of cervical intraepithelial neoplasias. Zentralblatt fur Gynakologie 2000; 122: 35-42.
18. Tangtrakul S, Srisupundit S, Linasmita V, et al. A randomized study comparing suture with non-suture cold-knife conization. J Obstetr Gynaecol 1995; 21: 587-91.
19. Gilbert L, Saunders NJ, Stringer R, Sharp F. Hemostasis and cold knife cone biopsy: a prospective randomized trial comparing a suture versus non-suture technique. Obstetr Gynecol 1989;74: 640-3.
20. Kamat AA, Kramer P, Soisson AP. Superiority of electrocautery over the suture method for achieving cervical cone bed hemostasis. Obstetr Gynecol 2003; 102: 726-30.
21. Dane C, Dane B, Cetin A, Erginbas M. Haemostasis after cold-knife conisation: a randomised prospective trial comparing cerclage suture versus electro-cauterisation. Australian and New Zealand J Obstetr Gynaecol 2008; 48: 343-7.
22. Bueno LR, Binda M, Monego H, et al. Randomized clinical trial comparing cold knife conization of the cervix with and without lateral hemostatic sutures. Int J Surg 2015; 18: 224-9.

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Knowledge, attitude and practices about pharmacovigilance and adverse drug reactions among dental research assistants in a Turkish hospital: a cross-sectional study

Bir Türk hastanesindeki diş araştırma asistanları arasında farmakovijilans ve advers ilaç reaksiyonları hakkında bilgi, tutum ve uygulamalar: kesitsel bir çalışma

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ABSTRACT

Aim: This study was aimed to assess pharmacovigilance and adverse drug reactions knowledge, attitudes and practices of dental research assistants.

Material and Method: A cross-sectional survey was conducted in a teaching hospital at Cukurova University, Adana, Turkey, for one month. All the registered dental research assistants were invited to participate in the study. Data collection was carried out through the self-administered and validated questionnaire. The final data was analyzed by using SPSS version 21.0 (IBM, Armonk, NY, USA). Descriptive statistics such as frequencies and percentages have been determined.

Results: The questionnaire was completed by invited participants with a response rate of 92.5%. Male (n=30, 60%) was more than female (n=20, 40%) with an average age of 27.44 (SD±2.32) years. None of the participants received pharmacovigilance training in the last 1 year. The majority of participants (60%) were unable to define pharmacovigilance and only 20% (n=10) of the dentists have correctly defined ADRs. The Most of respondents (90%) recognize ADR reporting as a professional obligation and sixty percent (n=30) perceived that the reporting of serious and unexpected ADRs are mandatory. The participants perceived that difficulties during filling of ADR forms, loss of timing and lack of information on pharmacovigilance are the main reason for the under-reporting of ADRs. Moreover, all dentists reported that they did not observe serious/severe ADRs, and 40% (n=20) reported not asking about ADR history while interacting with a patient for the first time during their practice. The participants had poor knowledge attitude and practice towards the pharmacovigilance and adverse drug reactions (P value<0.05).

Conclusion: The current study demonstrated a lack of awareness and knowledge of pharmacovigilance and ADR among dental research assistants. The inclusion of pharmacovigilance literature in the education program is mandatory and pre-and post-graduate training should be provided to dentists for rational practices.

Keywords: Pharmacovigilance, adverse drug reactions, dentists, knowledge, Turkey, hospital

ÖZ

Amaç: Bu çalışma, dental araştırma görevlilerinin farmakovijilans ve advers ilaç reaksiyonları (ADR) bilgilerini, tutumlarını ve uygulamalarını değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Bir ay süreyle Adana, Çukurova Üniversitesi'nde bir eğitim hastanesinde kesitsel araştırma yapıldı. Kayıtlı tüm diş hekimliği araştırma görevlileri çalışmaya katılmaya davet edildi. Veri toplama, kendi kendine yönetilen ve doğrulanan anket aracılığıyla gerçekleştirildi. Nihai veriler, SPSS sürüm 21.0 (IBM, Armonk, NY, ABD) kullanılarak analiz edildi. Frekanslar ve yüzdeler gibi tanımlayıcı istatistikler belirlendi.

Bulgular: Anket, davet edilen katılımcılar tarafından% 92,5 yanıt oranıyla dolduruldu. Erkeklerin (n=30, %60) yaş ortalaması kadınların (n=20, %40) yaş ortalamasından 27,44 (SS ±2,32) fazlaydı. Son 1 yılda katılımcıların hiçbiri farmakovijilans eğitimi almamıştı. Katılımcıların çoğu (% 60) farmakovijilansı tanımlayamadı ve diş hekimlerinin yalnızca %20'si (n=10) ADR'leri doğru şekilde tanımladı. Ankete katılanların çoğu (% 90) ADR raporlamasını profesyonel bir zorunluluk olarak kabul ediyor ve yüzde altmışı (n=30) ciddi ve beklenmedik ADR'lerin bildirilmesinin zorunlu olduğunu algıladı. Katılımcılar, ADR formlarının eksik raporlanmasının ana nedeninin ADR formlarının doldurulması sırasında yaşanan zorluklar, zamanlama kaybı ve farmakovijilans konusunda bilgi eksikliğinden kaynaklandığını fark ettiler. Ayrıca tüm diş hekimleri muayenehaneleri sırasında ciddi/şiddetli ADR gözlemlemediklerini belirtti ve % 40'ı (n=20) bir hastayla ilk kez iletişimde bulunurken ADR öyküsü sormadığını bildirdi. Katılımcıların farmakovijilans ve advers ilaç reaksiyonlarına karşı zayıf bilgi tutumu ve uygulaması vardı (p değeri <0,05).

Sonuç: Bu çalışma, diş hekimliği araştırma asistanları arasında farmakovijilans ve ADR konusunda farkındalık ve bilgi eksikliği olduğunu göstermiştir. Eğitim programına farmakovijilans literatürünün dahil edilmesi zorunludur ve akılcı uygulamalar için diş hekimlerine mezuniyet öncesi ve sonrası eğitim verilmelidir.

Anahtar Kelimeler: Farmakovijilans, advers ilaç reaksiyonları, diş hekimleri, bilgi, Türkiye, hastane

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INTRODUCTION

The World Health Organization (WHO) define an adverse drug reaction (ADR) as "a hazardous and unintended effect occurs at normal doses used for prophylaxis, diagnosis or treatment in humans for the modification of physiological function" (1) adverse drug reactions are among the main causes of illness, death and higher economic burden in health systems worldwide (2). ADRs are estimated to cause 3% of all deaths in the general population and up to 5% of all deaths in hospitalized patients (3). Despite all the benefits of pharmacotherapy, ADRs are known to pose a risk to drug therapy. In preclinical studies, the substance was found to be positive in terms of efficacy and safety in humans placed on the market after the new drug application process. Although these drugs are questioned for ADRs during clinical drug research and some ADRs are identified in the short product information for any drug. However, these data may not be sufficient and, for this reason, safety data must be collected in real life after the drug has been released. Knowledge of pharmacovigilance is crucial for the timely identification of ADRs. According to WHO, pharmacovigilance consists of activities to identify, evaluate, understand and prevent ADRs and other drug-related problems (1).

The Uppsala Monitoring Center (UMC), a WHO collaborating center, was founded in 1978 and continuously monitors ADRs reported from collaborative countries and plays a vital role in decision-making for national pharmacovigilance authorities. Turkey started the pharmacovigilance program under the name of the "Turkish Pharmacovigilance Center" (TUFAM) in 2005. ADR reports may be forwarded by health care professionals (HCPs) to TUFAM either directly or through the pharmacovigilance contact person (PCP) (2,4). Spontaneous reporting plays an important role in the detection of unsuspected, serious and unusual ADRs previously undetected during different phases of the clinical trial. However, reporting remains a major challenge and highlighted in the previously published studies (2, 4-6).

Prescriber is a core member of the healthcare team, supplying information relevant to suspicious ADRs is the prescriber's moral obligation and an essential component of pharmacovigilance and improved patient care practices (4). Many factors related to knowledge, attitudes, and practices are responsible for under-reporting of ADRs by prescribers and relate to ignorance, lack of awareness, training, supporting staff and time (2,4,6). Various studies have been conducted to assess knowledge and attitudes towards pharmacovigilance and ADR reporting among medical professionals (4-9). However, there are limited data available, particularly among dental professionals in Turkey, and no studies conducted previously in our setting. Dental doctors are also involved in the prescription of many therapeutic interventions, including allopathic medicines such as local anesthetics, antibiotics, analgesics and anti-inflammatory drugs (6,10). Antibiotics and analgesics are among the major causes of ADRs (6,11).

Consequently, the possibility of ADRs in dentistry cannot be overlooked and it is important to consider the experience and attitude of a very particular group of prescribers. The aim of this study was therefore to assess pharmacovigilance and adverse drug reactions knowledge, attitudes and practices of research assistants working at the public sector university dental hospital in Turkey and, if possible, to suggest ways to enhance good pharmacovigilance activities based on findings.

MATERIAL AND METHOD

A cross-sectional survey was conducted in a teaching hospital at Cukurova University, Adana, Turkey, for one month. All the registered dental research assistants were invited to participate in the study. This study was approved by the university /local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was carried out with the permission of Çukurova University's Institutional Review Boards and Çukurova University School of Medicine Non-Interventional Clinical Research Ethics Committee (Meeting number: 86, Decision number: 114, Date of approval: 08 March 2019).

The dental research assistant is a person who assists the dentist in the entire treatment process, including operations. Informed written consent was also obtained from the study participants. Pharmacists, nurses, and paramedics working in dental hospital were under exclusion criteria. A pre-validated survey questionnaire was design for this study. Several strategies concerning the professional appearance of the questionnaire, the easy language, the conciseness, the good balance between content and length, and prescribers had dedicated time to read and complete the questionnaire were adopted to improve the response rate. The available literature has been systematically reviewed by investigators. Relevant published studies (4-6,12,13) were evaluated for the design of a questionnaire. Content and face validity of the questionnaire have been carried out. Two academic experts evaluated the contents of the questionnaire for validation purposes. The final recommended amendments have been included in the questionnaire. The final questionnaire consisted of four parts; first, covering basic demographic characteristics of the participants such as age, gender, work experience, and pharmacovigilance training in the last one year. Second, the assessment of participants 'knowledge included seven questions (three open-ended and four closed-ended questions). Third, evaluate the attitude of

the respondents to close-ended questions. The fourth part included questions to evaluate their practices.

Statistics

The final data was analyzed by using SPSS version 21.0 (IBM, Armonk, NY, USA). Descriptive statistics such as frequencies and percentages have been determined. Chi-Square tests were applied to determine the nature of correlation among knowledge, attitude, and practice sections. A p-value of less than 0.05 was considered as a level of significance.

RESULTS

A total of 54 research assistants are enrolled and worked in a selected setting according to the data given by the teaching hospital. The questionnaire was completed by 50 participants with a response rate of 92.5%. Male (n=30, 60%) was more than female (n=20, 40%). The average age of respondents was 27.44 (standard deviation of ±2.32) years. The participants were found to be a dentist for an average of 4.5 years. In the last year, none of the participants received pharmacovigilance training. The results obtained on the question of the definition of pharmacovigilance show that the majority of participants (60%) were unable to define pharmacovigilance. Only 20% (n=10) of the dentists have correctly defined ADRs. Moreover, no one could answer the question "Can you write the TUFAM expansion?" (Table). Approximately 40% of the respondents reported that they had encountered with ADR. Surprisingly, however, all participants have poor knowledge and have also not previously learned about filling out the ADR notification form. All respondents expect that herbal medicines are also responsible to cause ADRs. The majority of respondents (90%) recognize ADR reporting as a professional obligation. Sixty percent (n=30) of the participants felt that the reporting of serious and unexpected ADRs are mandatory. All respondents (n=50) also reported that ADRs can be a responsible cause of death and proper reporting of ADRs is crucial to improved patient safety. Half of the participants (n=25) believe that filling of ADR notification forms causes difficulties and loss of time in the working environment. All dentists perceived the lack of information on pharmacovigilance as the main reason for under-reporting of ADRs and the availability of ADR forms in an accessible collection box in all clinical departments would be helpful for better practices. On the other hand, the result shows that all dentists reported that they did not observe serious/severe ADRs, nor did they witness ADRs due to herbal products during their practice. Questioning about the past and current history of the drug is an important part of the medical treatment process. However, 40% (n=20) of dentists reported not asking about drug history while interacting with a patient for the first time. The participants had poor knowledge attitude and practice towards the pharmacovigilance and adverse drug reactions (P value<0.05) (**Table**).

Table. Knowledge, attitudes, and practices of dental research assistants on pharmacovigilance and ADR reporting

Variables	Response n (%)	Response n (%)	Chi-square test
Knowledge questions (open-ended)	Correct	Wrong	P-Value*
1. Can you please describe the pharmacovigilance?	20 (40)	30 (60)	<0.05
2. Can you define an adverse drug reaction?	10 (20)	40 (80)	<0.05
3. Can you write the extension of the TUFAM?	0 (0)	50 (100)	<0.05
Knowledge questions (close-ended)	Yes	No	
4. Have you ever had encountered any adverse drug reactions?	20 40)	30 (60)	<0.05
5. Do you know how to fill out the notification form for an adverse drug reaction?	0 (0)	50 (100)	<0.05
6. Have you learned to fill out an adverse drug notification form before that?	0 (0)	50 (100)	<0.05
7. Can we expect adverse reactions to herbal medicines?	50 (100)	0 (0)	<0.05
Attitude questions (closed-ended)	Yes	No	
8. Is there a professional obligation to report an adverse drug reaction?	45 (90)	5 (10)	<0.05
9. Should it be reported when there are serious adverse reactions or unexpected adverse reactions?	30 (60)	20 (40)	<0.05
10. Do you think that adverse drug reactions can lead to death?	50 (100)	0 (0)	<0.05
11. Do you think that the safety of the patient will be improved by filling out the adverse reaction reporting forms?	50 (100)	0 (0)	<0.05
12. Do you think that filling out the adverse reaction notification forms will cause difficulties and loss of time in the working environment?	25 (50)	25 (50)	1.000
13. Do you think that the lack of information on pharmacovigilance is the main reason behind the under-reporting of ADRs	50 (100)	0 (0)	<0.05
14. Does it help that the adverse reaction reporting forms are in an accessible collection box in all clinical departments?	50 (100)	0 (0)	<0.05
Practice questions (closed-ended)	Yes	No	
15. Have you ever had an encounter with serious/severe adverse drug reactions during practice?	0 (0)	50 (100)	<0.05
16. If you have ever had an adverse drug reaction, have you reported it?	0 (0)	50 (100)	<0.05
17. Have you ever seen an adverse reaction to herbal products?	0 (0)	50 (100)	<0.05
18. When taking a medical history, do you ask about an adverse drug reaction while interacting with a patient for the first time?	30 (60)	20 (40)	<0.05

DISCUSSION

ADRs are among the common causes of morbidity and mortality and impose a higher financial burden on health care systems. Awareness of pharmacovigilance and ADRs among health professionals can minimize the factors that contribute to ADR reporting. Knowledge is a very important factor that influences attitudes and practices. In the current study, the knowledge of the majority of participants was poor and the terms pharmacovigilance and ADRs were incorrectly defined. Similar findings have also been reported in previously published studies (4-6). This finding urges the need for continuing education and training (4). Establishing national pharmacovigilance centers and drug information points in all hospitals for patients and dentists is compulsory for continuous education and training.

Of all the respondents, about 40% had encountered with ADR. Surprisingly, however, all participants (100%) stated that they did not know how to fill out the ADR reporting form and had not even learned about the procedure before. The studies conducted in the United Kingdom (74.6%) (12) and India (27.5%) (6) reported increased awareness about the ADRs reporting system among dental practitioners as compared to our study. Low awareness and malpractice related to pharmacovigilance in the current setting may be attributed to the poor TUFAM education campaigns (4). Therefore, increased awareness among dental practitioners about the reporting system of ADR is required through effective campaigning by health care authorities (6).

Most of the respondents (90%) perceived ADR reporting as a professional obligation. These findings have been supported by a study in Malaysia (13). However, the study carried out in India (6) reported that more than 50% of the respondents did not realize ADR reporting as a professional obligation. Personal discussions and awareness-raising programs to change the attitudes of the dentist may be helpful to dispel misconceptions (6,13).

Half (50%) of the participants believed that filling of ADR form caused difficulties and time loss in the work environment. Additionally, the respondents also stated that the lack of information and training on pharmacovigilance are the main reasons for the under-reporting of ADR. A similar finding has also been reported in previous studies (6,13). Each year, TUFAM organizes one or two training sessions for PCPs and HCPs, including dentists, and also monitors their work in each health care institution. However, as stated by a previous study (4), the TUFAM did not systematically follow up on these activities.

All of the participants reported that they had not experienced a serious/severe ADR, had not reported it and nor witnessed an ADR due to herbal products in their practice. Moreover, about 40% (40%) of the dentist indicated that they did not ask about ADRs while taking a patient's medical history for the first time. Such findings are troubling and need immediate attention. Therefore, to enhance patient health care, continuous training modules on the subject of pharmacovigilance and activities such as highlighting the purpose and value of ADR reports are important (15).

According to the TUFAM Regulation, it is compulsory to include the literature on pharmacovigilance in the curricula of the educational program. Since there is no relevant global standard for teaching and training related to pharmacovigilance at the university level for medical, pharmacy, nursing and other paramedical undergraduate students in Turkey (4,14,15). The recommendations suggested by the recently published study, which highlighted the program that focused on deliberate discussions on pharmaceutical care activities, including appropriate pre-and post-treatment counseling, periodic drug use and error prevention audits, drug discharge reviews, and ADR reporting, should be implemented in Turkey for better health outcomes (16).

There are some strengths and limitations to this study. No significant effort has been made to the best of our knowledge, focusing mainly on the assessment of knowledge attitude and practice among dental research assistants. Socio-cultural factors also have a significant impact that varies from country to country. First, it is not a representative sample of general practitioners, as we reported cross-sectional data from only one hospital. Second, the potential for bias on the part of respondents, such as any survey, where respondents choose to have a socially favorable opinion instead of real answers. Despite these limitations, our findings indicate significant implications and highlight sizeable pharmacovigilance activities in Turkey.

CONCLUSION

This study concluded that there was a lack of awareness and knowledge of pharmacovigilance and ADR among dental research assistants. The majority of the participants had poor knowledge attitude and practice towards the pharmacovigilance and adverse drug reactions. The participant perceived that a lack of information and training on pharmacovigilance are the main reasons for under-reporting ADRs. The inclusion of pharmacovigilance literature in the education program is mandatory and pre-and post-graduate training should be provided to dentists for better practices. Additionally,

the close follow-up of pharmacovigilance activities and prescribing practices, the incorporation of the ADR reporting system into the electronic prescribing system and the timely feedback of TUFAM to dentists are effective interventions for improved knowledge, reporting rates and better pharmacovigilance system.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Çukurova University's Institutional Review Boards and Çukurova University School of Medicine Non-Interventional Clinical Research Ethics Committee (Meeting number: 86, Decision number: 114, Date of approval: 08 March 2019).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. International society of pharmacovigilance. 18th ISoP Annual Meeting "Pharmacovigilance without borders" Geneva, Switzerland, 11–14 November, 2018. Drug Safety 2018; 41: 1103-273.
2. Özcan G, Aykaç E, Kasap Y, Nemutlu NT, Sen E, Aydınkarahaliloğlu ND. Adverse drug reaction reporting pattern in Turkey: analysis of the national database in the context of the first pharmacovigilance legislation. Drugs-real world outcomes 2016; 3: 33-43.
3. Ithnin M, Rani MDM, Latif ZA, et al. Mobile app design, development and publication for adverse drug reaction assessments of causality, severity and preventability. JMIR Mhealth Uhealth 2017; 5: e78.
4. Güner MD, Ekmekci PE. Healthcare professionals' pharmacovigilance knowledge and adverse drug reaction reporting behavior and factors determining the reporting rates. J Drug Assess 2019; 8: 13-20.
5. Alshakka M, Bahattab OA, Ali H, et al. Comparison of the knowledge and perception of pharmacovigilance among pharmacy, dental and medical students in Aden-Yemen. J Pharm Pract Community Med 2017; 3: 254-61.
6. Khan SA, Goyal C, Tonpay SD. A study of knowledge, attitudes, and practice of dental doctors about adverse drug reaction reporting in a teaching hospital in India. Perspect Clin Res 2015; 6: 144-9.
7. Sivadasan S, Sellappan M. A study on the awareness and attitude towards pharmacovigilance and adverse drug reaction reporting among nursing students in a private university, Malaysia. Int J Current Pharm Res 2015; 7: 84-9.
8. Farha RA, Alsous M, Elayeh E, Hattab D. A cross-sectional study on knowledge and perceptions of pharmacovigilance among pharmacy students of selected tertiary institutions in Jordan. Trop J Pharm Res 2015; 14: 1899-905.
9. Khan MU, Ahmad A, Ejaz A, et al. Comparison of the knowledge, attitudes, and perception of barriers regarding adverse drug reaction reporting between pharmacy and medical students in Pakistan. J Educ Eval Health Prof 2015; 12: 28.
10. Howard RL, Avery AJ, Slavenburg S, et al. Which drugs cause preventable admissions to hospital? A systematic review. Br J Clin Pharmacol 2007; 63: 136-47.
11. Mersha AG. Attitude and perception of medical interns about antimicrobial resistance: a multi-center cross-sectional study in Ethiopia. Antimicrob Resist Infect Control 2018; 7: 149.
12. Yip J, Radford DR, Brown D. How do UK dentists deal with adverse drug reaction reporting? Br Dent J 2013; 214: e22.
13. Shalini S, Mohan S. Knowledge and attitude towards pharmacovigilance and adverse drug reaction reporting among dental students in a private university, Malaysia. J Young Pharm 2015; 7: 118-25.
14. Ergün Y, Ergün TB, Toker E, Ünal E, Akben M. Knowledge attitude and practice of Turkish health professionals towards pharmacovigilance in a university hospital. Int Health 2019; 11: 177-84. doi:10.1093/inthealth/ihy073.
15. Karataş Y, Pelit A. Yeni çıkan ilaçların güvenlik (farmakovijilans) açısından izlenmesinin önemi [Translate: Importance of monitoring new drugs in terms of security (pharmacovigilance)]. Arşiv Kaynak Tarama Derg 2018; 27: 500-6.
16. Sharma S, Khanal T, Shrestha S, Adhikari B. A celebration of world pharmacist day 2018 focusing to strengthen the pharmacy services at an oncology-based hospital in Nepal: Inspiration for others in developing countries. Res Social Adm Pharm 2019; 15: 117–8.

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Seroprevalence of *Toxoplasma gondii* in HIV-infected patients admitted to a university hospital

Bir üniversite hastanesine başvuran HIV ile enfekte hastalarda Toxoplasma gondii seroprevalansı

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ABSTRACT

Objective: *Toxoplasma gondii* may lead to opportunistic infections that threaten life in patients infected with HIV as opposed to the case of healthy individuals. It was aimed to investigate the seroprevalence of *Toxoplasma gondii* in HIV-infected patients admitted to our clinic.

Material and Method: The files of HIV-infected patients who were admitted to our polyclinic in the period of January 1995-December 2019 were examined. From the files, information was recorded on demographic characteristics, first diagnosis date, CD4+ T lymphocyte counts at first admission, HIV RNA, *T. gondii* IgG/M values and whether or not they received antibiotic prophylaxis.

Findings: Although the files of 804 HIV-infected patients were examined, data on *T. gondii* antibodies could be accessed only in the files of 685 patients. The median values of the ages and disease durations of the patients were respectively 33 (range: 17-83) and 4 (range 0-27) years. Among the patients, 88.5% (n: 606) were male. While no patients showed *T. gondii* IgM antibody positivity, 41.6% (n:285) had *T. gondii* IgG positivity. The CD4+ T lymphocyte count was under 100 in 10.0% (n: 68/678) of the patients, and among 36.8% (n: 25/68) of these patients, *T. gondii* IgG was positive. While *T. gondii* IgG positivity was significant in the patients over the age of 40 and those who were diagnosed before 2010, no significant relationship was found between sex, being men who have sex with men or not, CD4+ T lymphocyte counts and HIV-RNA values.

Conclusion: In patients with *T. gondii* IgG positivity, the risk of toxoplasmosis reactivation increases especially when the CD4+ T lymphocyte counts fall below 200. For this reason, investigating the seroprevalence of *T. gondii* in patients of all ages is important to be able to assess the risks that may develop, and it should be kept in mind that seropositivity may increase by advanced age.

Keywords: Toxoplasmosis, HIV, seroprevalence

ÖZ

Amaç: *Toxoplasma gondii*, sağlıklı bireylerin aksine HIV ile enfekte hastalarda hayatı tehdit eden fırsatçı enfeksiyonlara neden olabilmektedir. Kliniğimize başvuran HIV ile enfekte hastalarda *Toxoplasma gondii* seroprevalans araştırılması amaçlandı.

Gereç ve Yöntem: Ocak 1995-Aralık 2019 tarihleri arasında polikliniğimize başvuran, HIV ile enfekte hastaların dosyaları incelendi. Dosyalardan demografik bilgiler, ilk tanı tarihi, ilk başvurduklarında ölçülen CD4+ T lenfosit sayısı, HIV RNA, *T. gondii* IgG/M değerleri ve antibiyotik profilaksisi alıp almadıkları kayıt edildi.

Bulgular: HIV ile enfekte 804 hasta dosyası incelenmesine rağmen, sadece 685 hasta dosyasında *T. gondii* antikor verilerine ulaşılabildi. Hastaların yaş ve hastalık sürelerinin ortanca değerleri sırasıyla 33 (yaş aralığı: 17-83) ve 4 (yıl aralığı 0-27) yıldı. Çalışmaya katılanların %88,5' i (n:606) erkek hasta idi. Hastaların hiçbirinde *T. gondii* IgM antikor pozitifliği saptanmazken %41,6 (n: 285) 'da *T. gondii* IgG pozitifliği saptandı. Hastaların %10,0'unda (n: 68/678) CD4+ T lenfosit sayısı 100 altındaydı ve bunların %36,8 'inde (n: 25/68) *T. gondii* IgG pozitifti. *T. gondii* IgG pozitifliği istatistiksel olarak 40 yaş üzeri ve 2010 yılından önce tanı alan hastalarda anlamlı bulunurken cinsiyet, erkeklerle seks yapan erkek olup olmama, CD4+ T lenfosit sayısı ve HIV RNA değerleri ile arasında istatistiksel olarak ilişki saptanmadı.

Sonuç: *T. gondii* IgG pozitif olan hastalarda özellikle CD4+ T lenfosit sayısı 200'ün altına düştüğünde toksoplazmoz reaktivasyonu gelişme riski artmaktadır. Bu nedenle her yaştaki hastada *T. gondii* seroprevalansının araştırılması gelişebilecek riskleri değerlendirebilmek için önemli olup, ilerleyen yaşla birlikte seropozitifliğin artabileceği unutulmamalıdır.

Anahtar kelimeler: Toksoplazmoz, HIV, seroprevalans

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INTRODUCTION

Toxoplasmosis is a zoonotic infection caused by *Toxoplasma gondii*, which is an obligate intracellular parasite. While the disease may develop as a result of contact with cat excrements or raw or undercooked consumption of foods contaminated with excrements, it may also be transmitted through the vertical path from the mother to the fetus in pregnancy. It was also reported to develop in the form of organ transplantation and laboratory accidents (1-3).

It is estimated that a third of the world's population are infected with toxoplasma (4). Although the disease usually progresses asymptomatically in adults and healthy children, it may lead to life-threatening conditions in immunosuppressed individuals.

In patients whose immune system is suppressed by the human immunodeficiency virus (HIV), toxoplasmosis may appear as an opportunistic infection According to the 2018 data of the World Health Organization (WHO), 37.9 million HIV-infected individuals are living in the world, and 23.3 million individuals received antiretroviral treatment by the end of 2018 (5). While the risk of encountering opportunistic infections is reduced by highly active antiretroviral therapy (HAART), toxoplasmosis continues to be a significant problem for HIV/ AIDS (Acquired Immune Deficiency Syndrome) patients (4, 6). One of the risk factors for development of toxoplasmic encephalitis is a CD4+ T lymphocyte count of under 100/mm3 (7).

There are few studies in Turkey which investigated the seroprevalence of toxoplasmosis in HIV-infected patients. In this study, our purpose is to determine the toxoplasma seroprevalences of patients with a diagnosis of HIV/ AIDS who were admitted to our polyclinic at their first admission and to closely monitor patients in terms of latent infection reactivation and primary toxoplasmosis that may develop especially in patients with low CD4+ T lymphocyte counts.

MATERIAL AND METHOD

This study was approved by the university/local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was carried out with the permission of Medeniyet University Göztepe Education and Research Hospital Ethics Committee. (Permission granted 20.11.2019, Decision No. 2019/0466).

The files of patients who were admitted to our polyclinic for the first time in the period of January 1995-December 2019 whose HIV positivity was confirmed by Western Blot test were examined. From the patient files, information was retrospectively collected on demographic characteristics, date of first diagnosis, CD4+ T lymphocyte count measured at first admission to the polyclinic, HIV RNA viral load, *T. gondii* IgG and IgM values and whether or not they received trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis.

T. gondii IgG and M studied with the ELISA method, CD4+ T lymphocyte counts studied with the flow cytometric method and HIV RNA values measured by the PCR method were determined and recorded. The files of 804 HIV-infected patients could be accessed, but 119 patients whose *T. gondii* data could not be reached were removed from the study, and only 685 patients were included in the analysis. The relationship between patients age, sex, period when HIV was diagnosed, being men who have sex with men (MSM) or not, CD4+ T lymphocyte counts and HIV RNA values during first application, and *T. gondii* seroprevalence was evaluated statistically.

Statistical analyses were carried out using the SPSS IBM 22,0 (SPSS Inc, Chicago II) software. The descriptive results of the categorical variables are shown as frequency distributions and percentages. The data not conforming to normal distribution are expressed as median (minimum-maximum). While the categorical variables were analyzed, chi-squared or Fisher's exact test was used.

RESULTS

In the study, the data of 685 patients, including 606 (88.5%) male and 79 (11.5%) female patients, were analyzed. Among the male patients, 57.6% (n: 349) were MSM (men who have sex with men). The median values of the ages and disease durations of the patients were respectively 33 (range: 17-83) and 4 (range: 0-27) years. The demographic data and *T. gondii* IgG antibodies of the patients are shown in **Table 1**. 285 (41.6%) of the patients showed *T. gondii* IgG seropositivity. 68 (10.0%) patients had CD4+ T lymphocyte counts of lower than 100 cells/ mm^3, while 25 (36.8%) of these patients were positive for *T. gondii* IgG. Median value of CD4 + T lymphocyte counts was 371 (range: 0-1860), median value of HIV RNA was 205.387 IU/ml (range: 2 -198.700.180). **Table 2** shows the Toxoplasma antibody distribution by CD4 + T lymphocyte counts and HIV RNA levels.

The earliest diagnosis of the disease was made in 1992, and the toxoplasma antibody distribution in the infected patients based on years is shown in **Figure 1**.

Table 1. Distribution of patients according to demographic features

	T. gondii IgG positive n (%)	*T. gondii* IgG negative n (%)	Total n
Gender			
Woman	37 (46.8)	42 (53.2)	79
Male	248 (40.9)	358 (59.1)	606
Age			
18-40	179 (36.2)	315 (63.8)	494
41-60	85 (54.5)	71 (45.5)	156
61 and above	21 (61.8)	13 (38.2)	34
Education Level (n:351)			
University	85 (36.6)	147 (63.4)	232
Below university level	46 (38.7)	73 (61.3)	119
Contamination path			
Heterosexual relationship	126 (46.0)	148 (54.0)	274
Homosexual relationship	127 (36.4)	222 (63.6)	349
Unknown	32 (51.6)	30 (48.4)	62
Diagnostic History			
1992- 2000	10 (58.8)	7 (41.2)	17
2001-2009	42 (58.3)	30 (41.7)	72
2010-2019	233 (39.1)	363 (60.9)	596

Table 2. Toxoplasma antibody distribution by CD4 + T lymphocyte counts and HIV RNA levels

	T. gondii Ig G positive n (%)	*T. gondii* Ig G negative n (%)
CD4 + T Lymphocyte Counts (n:678)		
<100 (n: 68)	25 (36.8)	43 (63.2)
100-200 (n: 79)	29 (36.7)	50 (63.3)
201-500 (n: 334)	151 (45.2)	183 (54.8)
500 üzeri (n: 197)	76 (38.6)	121(61.4)
HIV RNA levels (n: 613)		
<10.000 (n:55)	25 (45.5)	30 (54.5)
10.000-100.000 (n:166)	58 (34.9)	108 (65.1)
100.001-1000000 (n:281)	119 (42.3)	162 (57.7)
>1.000.000 (n:111)	43 (38.7)	68 (61.3)

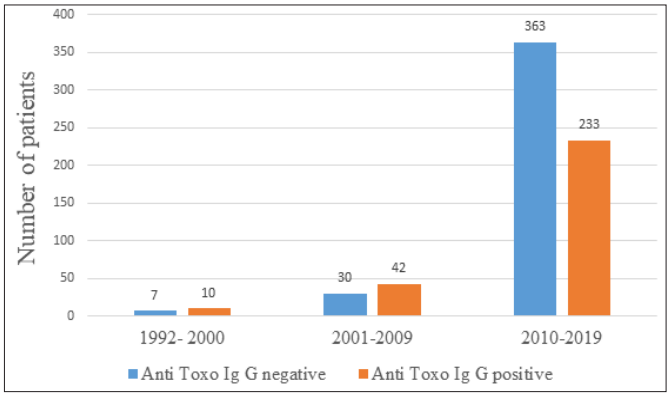

Figure 1. Toxoplasma antibody distribution in infected patients by years

T. gondii IgG positivity was significant in the patients over the age of 40 (p<0.001), while there was no significant relationship between sex (p=0.316) and CD4+ T lymphocyte counts (p=0.177), being MSM or not (p= 0.034) , HIV RNA values (p= 0.366). T.gondii IgG positivity within patients who diagnosed before 2010 and T.gondii IgG negativity within patients who diagnosed after 2010 were significantly higher. (p=0.003)

DISCUSSION

In the diagnosis of toxoplasmosis, investigation of IgG-type antibodies is a commonly used method. It is used in following immunosuppressive patients such as a HIV/AIDS and pregnant women (4). In two different studies investigating the seroprevalence of *T. gondii* IgG in HIV-infected patients in Turkey, respectively 614 and 164 patients were examined, and the rates were reported respectively as 43.5% and 52% (8, 9). In studies conducted in other countries, *T. gondii* IgG rates were determined as 21.1% in Iran, 9.7% in China, 13.6% in the USA, 57.6% in Ghana, 36.3% in Thailand and 80% in Brazil (10-15). In the meta-analysis conducted by Safarpour et al. (16) including 37 countries, 111 studies and 66,139 serum samples, the seroprevalence of *T. gondii* IgG was found as 44.22%. The *T. gondii* IgG positivity in our study was detected as 41.6%, which was similar to the results of previous studies in Turkey and the meta-analysis of Safarpour et al. (16). Seroprevalence rates may vary from country to country and based on ethnic and cultural structure, nutritional habits, education levels and socioeconomic levels.

In our study, the IgG positivity within patients older than 40 and patients who diagnosed before 2010 was found significantly higher. The reason why IgG positivity is seen more in patients older than 40 is attributed to the increasing risk of exposure to infectious agents as age increases. It is thought that seronegativity is increased with increase in drinking safe water, increase in public awareness of the risks of eating raw meat and the infections that may develop with it and change in our feeding habits. The meaningful increase in seronegativity in patients who diagnosed after 2010 brings risk of development of acute infections in patients. It is important to prevent the reactivation of latent infection in seropositive patients, as well as to take the necessary precautions to prevent the disease in seronegative patients.

In our study, unlike the study made by Şenoğlu and their friends in 2018, we didn't find any meaningful difference in IgG positivity within patients who are MSM. (8) Also there wasn't any significant difference between men and women as well as between HIV RNA levels and CD4+ lymphocyte levels.

In HIV-infected individuals, *T. gondii* most typically and prevalently involves the central nervous system and causes toxoplasmic encephalitis, while it may also lead to chorioretinitis, pneumonia, myocarditis, hepatitis, pancreatitis and septic shock-like clinical pictures. Toxoplasmic encephalitis, which emerges as the reactivation of latent infection, may progress fatally in HIV-infected patients (4, 17, 18). None of these presentations have been encountered in patients who have been followed in our clinic since 1995.

In HIV/AIDS-diagnosed patients with a CD4+ T lymphocyte count of under 200 cells/mm³, accompanying history of cancer chemotherapy and those who have been using rituximab-like biological agents or long-term steroid treatments, it is recommended to provide prophylactic antibiotics therapy to prevent opportunistic infections (16,19).

Primary antibiotic prophylaxis is used to protect patients with both negative and positive *T. gondii* serology. In the application of prophylaxis, TMP-SMX is the firstly preferred agent (20). As an alternative treatment to TMP-SMX, dapsone or pyrimethamine in *T. gondii* IgG negative patients and atovaquone, dapsone + pyrimethamine + folinic acid or atovaquone + pyrimethamine + folinic acid in positive patients are recommended (19,20). Prophylactic antibiotics usage may be stopped in patients with CD4+ T lymphocyte counts of higher than 100 cells/mm³ for at least three months and undetectable HIV RNA levels (19). With the start of HAART usage, a reduction was observed in opportunistic infections like toxoplasmic encephalitis by the decrease in the HIV viral load and the increase in the CD4+ lymphocyte counts. A randomized controlled study showed that there was no increase in the risk of toxoplasmic encephalitis development despite stopping prophylaxis (21). In a study in Denmark including 6325 HIV-infected patients in the pre-HAART (1995-1996) and HAART (1997-2014) periods, it was reported that, despite the start of HAART usage, toxoplasmic encephalitis may still be a cause of mortality and morbidity, but neurological sequalae and mortality considerably decrease by treatment (22).

In this study, 160/800mg TMP-SMX per day treatment was started in all patients with CD4+ T lymphocyte counts lower than 200 cells/mm³. Latent toxoplasma reactivation or toxoplasmic encephalitis cases were not observed during the follow up of the patients.

CONCLUSION

HIV-infected patients with *T. gondii* IgG negativity should be provided information regarding protection from consumption of infected meats and contaminated foods and contact with infected animal excrements, prophylactic antibiotics should be applied on all patients with CD4+ T lymphocyte counts of lower than 200 cells/mm³, and antibody screening should be performed to assess the risk of toxoplasmosis that usually emerges as the reactivation of latent infection.

ETHICAL CONSIDERATIONS

Ethics Committee Approval: The study was carried out with the permission of Medeniyet University Göztepe Education and Research Hospital Ethics Committee. (Permission granted 20.11.2019, Decision No. 2019/0466).

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

Status of Peer-review: Externally peer-reviewed.

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

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

REFERENCES

1. Kochanowsky JA, Koshy AA. Toxoplasmagondii. CurrBiol 2018; 28: 770-1.
2. Sukthana Y. Toxoplasmosis: beyond animals to humans. Trends Parasitol 2006; 22: 246.
3. Nissapatorn V. *Toxoplasma gondii* and HIV: a never-ending story. Lancet HIV 2017; 4: 146-7.
4. Montoya JG, Liesenfeld O. Toxoplasmosis. Lancet 2004; 363: 1965-76.
5. WHO. HIV/AIDS Data and statistics. (https: //www.who.int/hiv/data/en/) Erişim Tarihi 08.01.2020
6. Saadatnia G, Golkar M. A review on human toxoplasmosis. Scand J Infect Dis 2012; 44: 805-14.
7. Nissapatorn V, Lee C, Quek KF, Leong CL, Mahmud R, Abdullah KA. Toxoplasmosis in HIV/AIDS patients: a current situation. Jpn J Infect Dis 2004; 57: 160-5.
8. Şenoğlu S, Yeşilbağ Z, Altuntaş Aydın Ö, Kumbasar Karaosmanoğlu H, Kart Yaşar K. *Toxoplasma gondii* IgG Seroprevalence in Patients with HIV/AIDS. Turkiye Parazitol Derg 2018; 42: 175-9.
9. Aydın OA, Karaosmanoğlu HK, Korkusuz R, Nazlıcan O. *Toxoplasma gondii* IgG seroprevalence in HIV/AIDS patients Turkiye Parazitol Derg 2011; 35: 65-7
10. Rezanezhad H, Sayadi F, Shadmand E, et al. Seroprevalence of *Toxoplasma gondii* among HIV Patients in Jahrom, Southern Iran. Korean J Parasitol 2017; 55: 99-103.
11. Shen G, Wang X, Sun H, Gao Y. Seroprevalence of *Toxoplasma gondii* Infection among HIV/AIDS Patients in Eastern China. Korean J Parasitol 2016; 54: 93-6

12. O'Bryan TA, Okulicz JF, Bradley WP, Ganesan A, Merritt SE, Agan BK. *Toxoplasma gondii* seroprevalence: 30-year trend in an HIV-infected US military cohort. Diagn Microbiol Infect Dis 2016; 84: 34-5.

13. Ayi I, Sowah AO, Blay EA, Suzuki T, Ohta N, Ayeh-Kumi PF. *Toxoplasma gondii* infections among pregnant women, children and HIV-seropositive persons in Accra, Ghana. Trop Med Health 2016; 44: 17.

14. Chemoh W, Sawangjaroen N, Siripaitoon P, et al. *Toxoplasma gondii*-prevalence and risk factors in HIV-infected patients from songklanagarind Hospital, Southern Thailand. Front Microbiol 2015; 6: 1304.

15. Xavier GA, Cademartori BG, Cunha Filho NA, Farias NA. Evaluation of seroepidemiological toxoplasmosis in HIV/AIDS patients in the south of Brazil. Rev Inst Med Trop Sao Paulo 2013; 55: 25-30

16. Safarpour H, Cevik M, Zarean M, et al. Global status of *Toxoplasma gondii* infection and associated risk factors in people living with HIV. AIDS 2020; 34: 469-74. doi: 10.1097/QAD.0000000000002424. [Epub ahead of print].

17. Wang ZD, Wang SC, Liu HH, et al. Prevalence and burden of *Toxoplasma gondii* infection in HIV-infected people: a systematic review and meta-analysis. Lancet HIV 2017; 4: 177-88

18. Barratt JL, Harkness J, Marriott D, Ellis JT, Stark D. Importance of nonenteric protozoan infections in immunocompromised people. Clin Microbiol Rev 2010; 23: 795-836.

19. EACS European AIDS Clinical Society Guidelines 10.0, PART VI 105, 2019.

20. (https://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html) Access date: 25.11.2019.

21. Guidelines for the prevention and treatment of opportunistic ınfections in adults and adolescents with HIV. (https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/322/*toxoplasma-gondii*) Access date: 01.10.2020.

22. Pozio E. Highly Active AntiRetroviral Therapy and opportunistic protozoan infections Parassitologia. 2004 ;46: 89-93.

23. Martin-Iguacel R, Ahlström MG, Touma M, et al. Incidence, presentation and outcome of toxoplasmosis in HIV infected in the combination antiretroviral therapy era. J Infect 2017; 75: 263-73.

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Evaluation of the timing and indications of antenatal corticosteroid administration

Antenatal kortikosteroid uygulama zamanlamasının ve endikasyonlarının değerlendirilmesi

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ABSTRACT

Objective: To investigate the timing of antenatal corticosteroid administration for pregnant women who were anticipated for preterm birth.

Material and Method: This retrospective cohort study was conducted between September 2016 and September 2017 on cases treated with antenatal steroids and then performed birth in our hospital. The first 113 patients with 23-37 weeks of singleton or twin pregnancy, whose birth records could be accessed, were included in the study. Those who gave birth in another hospital, patients with incomplete records, and those carrying more than one of the indication types were excluded from the study.

Results: The median interval between antenatal steroid administration and childbirth was 1.00 (0.02-97.00, IQR: 17.77) days. The interval from the first dose until birth was less than 2 days in 57.5% of cases (n=65), 2-7 days in 11.5% of cases (n=13), and more than 7 days in 31% of cases (n=35). Totally, this period was 7 days or below in 69% of cases (n=78). A significant correlation was found between spontaneous preterm labour as indication of steroid administration and appropriate timing (p=0.001, Odds Ratio:4.62, Confidence Interval: 1.90-11.19).

Conclusion: The number of patients giving birth within optimal 2-7 days following the first dose of antenatal steroid administration, is very low. Attempts to improve timing are needed.

Keywords: Antenatal corticosteroid, preterm birth, indication, optimal timing, administration

ÖZ

Amaç: Preterm doğumu öngörülen gebelere yapılan antenatal kortikosteroid uygulama zamanlamasının incelenmesidir.

Gereç ve Yöntem: Eylül 2016- Eylül 2017 tarihleri arasında, antenatal steroid uygulaması yapılan ve ardından doğumu da hastanemizde gerçekleştiren olgular üzerinde yapılan bir retrospektif kohort çalışmadır. Doğum kaydına ulaşılabilen, tekil ya da çoğul, 23-37 hafta gebeliğe sahip, ilk 113 hasta çalışmaya dahil edildi. Başka bir hastanede doğum yapanlar, kayıtları eksik olan ve endikasyon tiplerinden birden fazlasını taşıyan hastalar çalışma dışı bırakıldı.

Bulgular: Antenatal steroid uygulaması ile doğum arasında ortanca geçen süre 1,00 (0,02-134,00), IQR:17,77 gündü. Olguların %57,5'inde (n=65) ilk doz ile doğuma kadar geçen süre 2 günün altında, %11,5 inde (n=13) süre 2-7 gün arasında, %31'inda (n=35) süre 7 günün üzerinde tespit edildi. Toplamda olguların %69'unda (n=78) bu süre 7 gün ve altındaydı. Steroid yapılma endikasyonlarından spontan preterm eylem ile uygun zamanlama arasında bir ilişki tespit edildi (p=0,001, odds oranı: 4,62, güven aralığı: 1,90-11,19).

Sonuç: Antenatal steroid uygulamasının ilk dozunu takip eden 2-7 gün içinde doğuran hasta sayısı oldukça azdır. Zamanlamanın iyileştirilmesine ait girişimlere ihtiyaç vardır.

Anahtar Kelimeler: Antenatal kortikosteroid, preterm doğum, endikasyon, uygun zamanlama, uygulama,

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INTRODUCTION

Preterm birth is a significant cause of perinatal mortality and morbidity (1-3). Although preventing preterm birth is not always succeeded, it is possible to delay the birth and allow the baby to be better prepared for childbirth (4,5). Administration of antenatal steroids has been shown to reduce perinatal mortality and morbidity (6,7). Administration of antenatal corticosteroids is the best available treatment that improves perinatal outcomes in patients who are anticipated for preterm birth with various indications (8). It is thought that the fetus receives the maximum benefit from the administration of antenatal steroids between 2 and 7 days after the first dose (8,9). Since it is known that antenatal steroid administration is protective against important and common causes of neonatal mortality, such as respiratory distress syndrome, intraventricular bleeding, and necrotizing enterocolitis (6), the aim is to ensure that each preterm fetus benefits from therapy. However, studies have shown that mothers who give preterm birth receive treatment at the optimal time at a lower rate than expected (10,11).

In the present study, we wanted to investigate the timing of antenatal corticosteroid administration in our hospital. Our goal is to determine the rate of patients in our hospital who receive antenatal steroids for preterm delivery at the optimal time and investigate the relationship between optimal application and indications.

MATERIAL AND METHOD

This study was approved by the university /local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics committee approval for the study was received from the institutional review board (Zekai Tahir Burak Women's Health Training and Research Hospital's institutional review board, Admission Date:5th December 2017, decision number:10).

This retrospective cohort study was conducted at Zekai Tahir Burak Women's Health Training and Research Hospital between September 2016 and September 2017 on pregnant women who received antenatal steroid administration for preterm birth. Patients who received antenatal steroids at 23-37 gestational weeks were accessed from the hospital pharmacy database. Among these patients, subjects who had steroid treatment and gave birth at the same hospital were sought. the first 113 patients with accessible birth records, either singleton or twin pregnancy, and with steroid administration at 23-37 weeks of pregnancy were included in the study. Patients who gave birth in another hospital, with missing records, or those carrying more than one of the indication types were excluded from the study.

The period from the initial dose of antenatal steroid administration to birth was calculated in days. For the rescue cure, the interval between the first dose of the rescue cure and birth was calculated. The patients were divided into two groups: those with optimal timing (less than 7 days) and those with suboptimal timing (above 7 days). The demographic characteristics of the groups were obtained from patient files.

Antenatal steroid is applied to pregnant women who are anticipated to give preterm birth with various indications to ensure lung maturation of the fetus, reduce neonatal mortality and morbidity. As standard, 24 mg of betamethasone is administered as twice 12mg doses with an interval of 24 hours. Rescue cure is administered in pregnancies under 34 weeks, 14 days after the first dose. It is known that the fetus receives maximum benefit from the administration of antenatal steroids between 2-7 days after the first dose (8).

There are several indications for the administration of antenatal steroids. In the present study, indications for the administration of antenatal steroids were classified as maternal causes, fetal causes, spontaneous preterm labor, and preterm premature rupture of membranes (PPROM). Maternal indications included maternal conditions such as preeclampsia, gestational hypertension, placental abruption, placenta previa, and other maternal diseases. Fetal indications included conditions related to the fetus such as isolated fetal growth restriction and abnormal Doppler findings, oligohydramnios, and nonreactive nonstress test (NST). Spontaneous preterm labor was defined by the presence of cervical changes accompanying regular painful contractions in the NST, in pregnant women under 37. gestational week. PPROM was defined as membrane rupture before the onset of uterine contractions in pregnant women under 37. gestational week. In case of any of the abovementioned indications, decision for labor was made if the situation threatened the life of the mother or baby.

Statistical Analysis

IBM SPSS statistical 22 program was used for data analysis. Normality of data was examined by Shapiro-Wilk test. The demographic data of groups were presented by mean±standard deviation for numerical variables with normally distribution and median (minimum-maximum) for numerical variables with not-normally distribution. Categorical variables were presented as number and percentage. The difference between groups was evaluated by Student's t test for numerical data with normally distribution, Mann-Whitney U test for numerical data without normally distribution, and Chi-square test for categorical data. Logistic regression analysis was performed to assess whether the groups showed difference according to the indications. Correlation between indications and optimal timing of steroid administration was evaluated by using logistics regression analysis. The data were examined at 95% confidence level and $p< 0.05$ was considered statistically significant in all analyses.

RESULTS

Totally 113 cases who gave birth in our hospital and who were previously administered with antenatal steroids during the same pregnancy were included in the study. The median interval between antenatal steroid administration and childbirth was 1.00 (0.02-97.00) and IQR: 17.77 days. The interval from the first dose until birth was less than 2 days in 57.5% of cases (n=65), 2-7 days in 11.5% of cases (n=13), and more than 7 days in 31.0% of cases (n=35). In total, this period was 7 days and below in 69.0% of cases (n=78). In 47.8% of cases (n=54), the dose of steroids was limited to the initial dose of 12 mg, while in 52.2% (n=59) of the cases, the dose was 24 mg. Rescue cure was administered in 4 (3.5%) cases. All these cases gave birth within 7 days after the administered dose.

Seventy eight cases with optimal timing formed one group and 35 cases with suboptimal timing formed the other group. There was no difference between the two groups in terms of age, gravida, parity, smoking, twin pregnancy and previous cesarean section (p=0.7, p=0.8, p=0.6, p=0.9, p=0.8, p=0.1, respectively). Gestational week at steroid administration was higher in the optimal timing group [34.1 (23.0-37.0) weeks vs. 32.5 (24.3-36.0) weeks, p=0.001]. Birth weight was higher in the suboptimal timing group [2970 (660-4280) grams vs. 2350 (500-3690) grams, p=0.001] (**Table 1**)

According to the indications for steroid administration, 57 cases were listed as spontaneous preterm labor (50.4%), 21 as early membrane rupture (18.6%), 18 as fetal causes (15.9%), and 17 as maternal causes (15.0%). (**Table 2**) A correlation was found between the indications for steroid administration and appropriate timing (p=0.003). When the relationship between the types of indications and optimal timing was evaluated individually, a significant correlation was found only for spontaneous preterm labor. It was found that spontaneous preterm labor status significantly affected the optimal timing group (p=0.001, Odds Ratio: 4.62, Confidence Interval: 1.90-11.19). When the effect of indication types on steroid dose of 12 and 24 mg was examined, it was found that only spontaneous preterm labor significantly affected the dose to remain at 12 mg (p=0.001, Odds ratio: 3.61, Confidence Interval:1,66-7.87).

Table 1. Demographics characteristics of groups

Variables	Optimal timing (≤7 days), N=78, 69%	Suboptimal timing (>7days), N=35, 31%	p
Age (years)	27.3 (±5.6)	27.8 (±7.4)	0.7
Gravidity	2 (1-6)	2 (1-5)	0.8
Parity	2 (0-4)	0 (0-4)	0.6
Smoking	2 (2.6%)	1 (2.9%)	0.9
Previosly cesarian section	25 (32.1%)	7 (20.0%)	0.1
Twin pregnancy	5 (6.4%)	2 (5.7%)	0.8
Additional medical condition	8 (10.3%)	1 (2.9%)	0.2
Gestational age (weeks) at the steroid administration	34.1 (23.0-37.0)	32.5 (24.3-36.0)	0.001
Time between first dose and birth, (days)	0.41 (0.02-6.0)	38.0 (10.0-134.0)	0.000
Time between first dose and birth, (hours)	10.0 (0.5-144.0)	888.0 (240.0-3216.0)	
Dose, mg	12 (12-24)	24 (12-24)	0.000
Birth weight, gr	2350 (500-3690)	2970 (660-4280)	0.001
Rescue cure	4 (3.5%)	0 (0%)	0.2

Table 2. Comparison of indications for antenatal corticosteroids administration between optimal vs suboptimal timing groups

	Optimal timing (≤7 days) N=78. 69%	Suboptimal timing (>7 days) N=35. 31%	p
Maternal indications	11 (14.1%)	6 (17.1%)	
Preeclampsia/gestational hypertension	5 (6.5%)	5(14.3%)	
Abruptia placenta	3 (3.9%)	0 (0%)	
Intrahepatic cholestasis of pregnancy	2 (2.6%)	0 (0%)	
Placenta accreta	0 (0%)	1 (2.9%)	
Fetal indications	8 (10.3%)	10 (28.6%)	0.003
FGR[α] and abnormal doppler findings	5(6.5%)	7 (20.0%)	
Nonreactive NST [€]	1 (1.3%)	1 (2.9%)	
Oligohydramnios	1 (1.3%)	2 (5.7%)	
Spontaneous preterm labor	48 (61.5%)	9 (25.7%)	
PPROM[µ]	11 (14.1%)	10 (28.6%)	

[α]FGR: Fetal growth restriction, [€]NST: nonstress test, [µ]PPROM: premature preterm rupture of membranes

In the present study, the birth of 13 patients took place between 2-7 days after the first dose. Steroid administration was performed for spontaneous preterm labor in 7 (53.8%), for fetal causes in 3 (23.1%), for maternal causes in 2 (15.4%), and for early membrane rupture in 1 (7.7%) of these patients.

DISCUSSION

The present study showed that the targeted 2-7 day period between the first dose of antenatal steroid administration and childbirth was met in 11.5% of the cases, while the timing of less than 7 days was met in 69% of cases. Optimal application was most often achieved when antenatal corticosteroid was performed with the indication of spontaneous preterm labor. In 47.8% of the cases, the doses could not be completed.

Optimal application rate varies in the literature. Vis et al. (5) included 439 patients with spontaneous preterm labor and PPROM in their study, and found that the dose was completed in 79% of cases, 41% of these patients gave birth within 7 days, and median interval was 11 days (12). In the present study, median interval was 1 day. Boesveld et al. (13) included patients with preterm labor, PPROM, maternal and fetal indications, and vaginal bleeding, and found that 45.4% of cases gave birth within 7 days and this rate was 61.5% in patients with maternal indications. In 2015, Adams (10) conducted two studies on this topic. In the first study, Adams examined timing only in patients with spontaneous preterm labor, and found that median interval was 41 (0-119) days and 20% of patients gave birth within 7 days after antenatal steroid administration. In the other study, Adams et al. (14) excluded patients with preterm labor and included maternal and fetal indications, and found that median interval was shorter with 9 (0-83) days and 48% of the patients gave birth within 7 days. Only maternal and fetal indications were included in the recent study of Rottenstreich et al. (15); the ratio of patients receiving optimal application was 32.4%, rescue dose was performed in one third of patients in this study. In the present study, this ratio was 3.5%. In conclusion, the indications of patients included and the rates of achieving optimal timing differ between studies. Various studies have reported that the ideal period of 2-7 days can be achieved in 20-40% of women (12,13). Similarly, another study reported that rate of women receiving steroid administration within the 2-14 day period was 45% (16). In the present study, this rate (11.5%) was considerably lower compared to other studies. This low rate shows the needs for efforts to improve timing of steroid administration.

Factors affecting the rate can be diverse. Conditions before hospitalization which lead late admission and various other factors such as unawareness to disease, uncertainty in diagnosis or unstandardized inpatient application etc. may affect the success of the timing of steroid administration (17). In our study, the gestational week at which steroid administration was performed was lower in the suboptimal timing group. Decision of steroid administration can be made more liberally in cases with small gestational age where the possible effects of prematurity may be more severe. In this study, relation of indications with optimal timing was sought. Only relation was seen with spontaneous preterm labor as indication. Some of maternal or fetal indications such as intrauterine fetal growth restriction or preeclampsia without acute presentation or placenta previa may partially allow optimal timing with respect to labor. Larger studies including subgroups with other indications may reveal various criteria to predict optimal timing accurately. Hence a study suggests use of some criteria such as amount of bleeding, presence of contractions and cervical canal length to predict time of labor in women to whom steroid was administered with the indication of placenta previa (11). It is clear that uncovering the reasons for the various rates obtained in different studies of optimal timing rates will contribute to the improvement of steroid administration timing.

The administration of antenatal corticosteroids is the best available antenatal treatment, which improves neonatal outcomes in patients planned for preterm birth (4). Therefore, the aim is to ensure that all premature infants benefit from this treatment. Patients giving birth before the optimal period benefit less from steroid administration (9). Conversely, in those giving birth after the optimal period both fetus and mother are exposed to the toxic effects of the drug without benefit (18,19). In cases of acute conditions, which may be life threatening for mother or fetus, emergency of labor results in time restrictions, while the insufficiency of tests to accurately predict the timing of birth as in spontaneous preterm labor may lead to prolongation of this interval. In the present study, when the optimal timing was taken as under 7 days, it was found that optimal timing could be achieved 4.6 times more when steroid administration was performed with the indication of spontaneous preterm labor. Full dose could be administered in 52.2% of cases. However, when patients with an interval of less than 24 hours were examined, the effect of spontaneous preterm labor indication was observed with 3.6 times. Additionally, these patients mostly delivered within 2 days. It was observed that spontaneous preterm labor could also lead to extreme shortening of the interval. In addition, 25.7% of patients in the suboptimal timing group also consisted of patients with spontaneous preterm labor indication. Therefore, although the effect of spontaneous preterm labor indication on optimal timing is observed in the present study, the likelihood of planning birth correctly

seems to be low in patients with this indication. Strategies that encourage timely administration of corticosteroids to women at risk of premature birth within 7 days and avoid excessive use of corticosteroids in women with low risk is important. Measures should be taken to monitor the use of prenatal corticosteroids for infants born before the 34th week of gestation, and quality improvement measures should be supported to optimize appropriate and timely corticosteroid administration regarding childbirth.

The strength of the present study is that it demonstrates the antenatal corticosteroid administration tendencies of a tertiary hospital. Relatively small sample size can be considered as one of the limitations of this study. A larger sample would increase the size of subgroups (complete/incomplete dose, optimal application/suboptimal application) and better reveal the affecting factors.

CONCLUSION

The number of patients giving birth within 2-7 days following the first dose of antenatal steroid administration, which is our primary target, is very low. Attempts to improve timing are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval for the study was received from the institutional review board (Zekai Tahir Burak Women's Health Training and Research Hospital's institutional review board, Admission Date:5th December 2017, decision number:10).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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REFERENCES

1. Huddy CL, Johnson A, Hope PL. Educational and behavioural problems in babies of 32-35 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001; 85: 23-8.
2. Wang ML, Dorer DJ, Fleming MP, Catlin EA. Clinical outcomes of near-term infants. Pediatrics 2004; 114: 372-6.
3. Beck S, Wojdyla D, Say L, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ 2010; 88: 31-8.
4. American College of Obstetricians and Gynecologists, Practice Bulletin No. 171: Management of Preterm Labor. Obstet Gynecol 2016; 128: e155-64.
5. Haas DM, Imperiale TF, Kirkpatrick PR, Klein RW, Zollinger TW, Golichowski AM. Tocolytic therapy: a meta-analysis and decision analysis. Obstet gynecol 2009; 113: 585-94.
6. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2017; 3: Cd004454.
7. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972; 50: 515-25.
8. ACOG Committee Opinion No. 475: antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol 2011; 117: 422-4.
9. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006: CD004454.
10. Adams TM, Kinzler WL, Chavez MR, Vintzileos AM. The timing of administration of antenatal corticosteroids in women with indicated preterm birth. Am J Obstet Gynecol 2015; b212: 645.
11. Makhija NK, Tronnes AA, Dunlap BS, Schulkin J, Lannon SM. Antenatal corticosteroid timing: accuracy after the introduction of a rescue course protocol. Am J Obstet Gynecol 2016; 214: 120. e1-120.e1206.
12. Vis JY, Wilms FF, Kuin RA, et al. Time to delivery after the first course of antenatal corticosteroids: a cohort study. Am J Perinatol 2011; 28: 683-8.
13. Boesveld M, Heida KY, Oudijk MA, Brouwers HA, Koenen SV, Kwee A. Evaluation of antenatal corticosteroid prescribing patterns among 984 women at risk for preterm delivery. J Matern Fetal Neonatal Med 2014; 27: 516-9.
14. Boesveld M, Heida KY, Oudijk MA, Brouwers HA, Koenen SV, Kwee A. Evaluation of antenatal corticosteroid prescribing patterns among 984 women at risk for preterm delivery. J Maternal Fetal Neonatal Med 2014; 27: 516-9.
15. Adams TM, Kinzler WL, Chavez MR, Fazzari MJ, Vintzileos AM. Practice patterns in the timing of antenatal corticosteroids for fetal lung maturity. J Maternal Fetal Neonatal Med 2015; 28: 1598-601.
16. Rottenstreich A, Elchalal U, Haj Yahya R, et al. Missed opportunities for optimal antenatal corticosteroid timing in medically indicated preterm births. J Maternal Fetal Neonatal Med 2019; 3: 1-7.
17. Collaborative OPQ, Committee W. 521: A statewide project to promote optimal use of antenatal corticosteroids (ANCS). Am J Obstet Gynecol 2013; 208: S224.
18. Mc Goldrick EL, Crawford T, Brown JA, Groom KM, Crowther CA. Identifying the barriers and enablers in the implementation of the New Zealand and Australian Antenatal Corticosteroid Clinical Practice Guidelines. BMC Health Serv Res 2016; 16: 617-30.
19. Sweet DG, Carnielli V, Greisen G, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome-2019 Update. Neonatology 2019; 115: 432-50.
20. Räikkönen K, Gissler M, Kajantie E. Associations between maternal antenatal corticosteroid treatment and mental and behavioral disorders in Children. JAMA 2020; 323: 1924-33.

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Comparison of Gleason scoring and the new grade-group system in prostate cancers: a 15-year retrospective study

Prostat kanserlerinde Gleason skorlaması ile yeni grade-group sisteminin karşılaştırılması: 15 yıllık retrospektif bir çalışma

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ABSTRACT

Aim: Prostate cancer is the most common malignant tumour in men. The most widely used histological grading scheme for prostate cancer is Gleason scoring. After the original, this system has been modified several times. In this study, we retrospectively investigated the new Grade-group system (GGS).

Material and Method: This study includes 486 cases diagnosed with prostate cancer between 2000 and 2015. All cases were re-grouped for the new Grade-group system and its relationship with prognosis was examined.

Results: Grade-group system subgroups had a statistically significant relationship between prognostic factors and this relationship was more significant between GGS 2 and GGS 3 [tumor status (p<0.001), age (p=0.045), PN invasion (p<0.001), stage (p=0.004), and LN status (p<0.001)]. In univariable survival analysis, there was a significant difference between Grade-group system subgroups (for GGS 2-GGS 3, RFS: p=0.035 and OS: p=0.012; for GGS 4-GGS 5, RFS: p=0.001 and OS: p=0.001). In multivariable survival analysis, GGS subgroups were found to be an independent survival parameter for prostate cancer (for GGS 2-GGS 3, OS: HR=2.56, p=0.012 and RFS: HR=2.69, p=0.038; for GGS 4-GGS 5, OS: HR=2.84, p=0.011 and RFS: HR=2.59, p<0.001).

Conclusions: According to our results, the new Grade-group system performs the prognostic risk grading more accurately than the old classification. Also, the fact that this system contains fewer categories and is simpler has increased the interobserver compatibility.

Keywords: Grade-group system, Gleason scoring, prostate cancer.

ÖZ

Amaç: Prostat kanseri (PK) erkeklerde en sık görülen malign tümördür. PK için en yaygın kullanılan histolojik derecelendirme şeması Gleason skorlamasıdır. Orijinalinden sonra bu sistem birkaç kez değiştirildi. Bu çalışmada, prostat kanseri için tanımlanan yeni Grade-group sistemini (GGS) geriye dönük olarak inceledik.

Gereç ve Yöntem: Bu çalışma 2000-2015 yılları arasında prostat kanseri tanısı konmuş 486 vakayı içermektedir. Tüm olgular yeni Grade-group sistemini için yeniden gruplandırıldı ve prognozla ilişkisi incelendi.

Bulgular: Grade-group sistemini alt gruplarının prognostik faktörler arasında istatistiksel olarak anlamlı bir ilişki vardı ve bu ilişki GGS 2 ve GGS 3 arasında daha anlamlı idi [tümör durumu (p<0,001), yaş (p=0,045), PN invazyonu (p<0,001), evre (p=0,004), ve LN durumu (p<0,001)]. Tek değişkenli sağkalım analizinde Grade-Group sistemini alt grupları arasında anlamlı bir fark vardı (GGS 2-GGS 3, RFS: p=0.035 ve OS: p=0.012; GGS 4-GGS 5, RFS için: p=0,001 ve OS: p=0,001). Çok değişkenli sağkalım analizinde Grade-Group sisteminin alt gruplarının prostat kanseri için bağımsız bir sağkalım parametresi olduğu bulundu (GGS 2-GGS 3, OS: HR=2,56, p=0,012 ve RFS: HR=2,69, p=0,038; GGS 4- için GGS 5, OS: HR=2,84, p=0,011 ve RFS: HR=2,59, p<0,001).

Sonuçlar: Çalışmamıza göre, yeni Grade-group sistemini sistemi prognostik risk sınıflandırmasını eski sınıflandırmadan daha doğru bir şekilde gerçekleştirmektedir. Ayrıca, bu sistemin daha az kategori içermesi ve daha basit olması, gözlemciler arası uyumluluğu artırdı.

Anahtar Kelimeler: Grade-grup sistemi, Gleason skorlaması, prostat kanseri.

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INTRODUCTION

Prostate cancer (PC) is one of the most common cancers worldwide. In 2018, 1,276,106 new PC cases were detected. Mortality rates for PC are reported as 9.3% and its incidence increases with age (1). The most common subtype of PC is acinar adenocarcinoma. PCs are usually multifocal and mostly originate from the peripheral region of the gland. Considering the incidence and heterogeneous clinical behaviour of prostate carcinoma, it is very important to classify patients according to the risk group correctly (1,2). Several clinical and pathological parameters (Gleason score [GS], serum prostate-specific antigen [PSA] level, radiological assessment, the status of surgical margin, regional lymph nodes, tumour stage, etc.) are used to identify risk groups. Among these factors, the GS system is still one of the most important prognostic parameters for the PC today (2,3).

Gleason scoring system was defined by Donald F. Gleason in the 1960s (4). This classification is based on the architectural structure of the glands. Gleason drew a basic diagram for this classification by visualizing five different patterns of the tumour. In this system, the most common first and second patterns of 5 different patterns are summed and the total GS is given. This system is performed by histopathological evaluation of hematoxylin and eosin (H&E) stained sections in x4 and x10 magnification. Modifications were made to this system in 1974 and 2005 (5,6). Lastly, in 2013, the foundation of a Grade-group system (GGS) was laid with a study from Johns Hopkins Hospital. In this study, Epstein et al. (7) proposed dividing GS into prognostic risk categories. Thus, this system groups classic GS cases from 1 to 5. This new rating system, which was later approved by many multicenter studies, was accepted at the 2014 International Society of Urological Pathology (ISUP) conference and entered WHO in 2016 (3).

In this study, we analyzed this new system retrospectively in terms of prognosis prediction, usefulness, and contribution to daily practice.

MATERIAL AND METHOD

Ethical Approval

The study was approved by the Kırıkkale University Health Research Ethics Committee (Permission granted/ date: 2020, decision number: 2020.06.18). In this retrospective study, all procedures and practices are in accordance with the ethical standards of the national/ institutional research committee and the 1964 Helsinki declaration.

Study Design

This study was carried out in Kırıkkale University Faculty of Medicine, Department of Pathology. All patients who underwent biopsy and resection due to PC between 2000 and 2015 were included in this study. Patients with second malignancy synchronized with PC were excluded from the study (n=9). Also, cases with tumour block deficiency (n=10) and insufficient tissue in the block (n=7) were excluded from the study. As a result, four hundred and eighty-six cases were collected. Tumour location and volume, GS, age, lymph node status, perineural and vascular invasion, stage, surgical margin, and survival information were recorded from the archive data.

Processing of Tissues

Necessary formalin-fixed paraffin-embedded tumour samples were collected from the tissue archives of the pathology department for cases deemed necessary (n=98). 4-micron thick sections prepared from paraffin blocks of these tissue samples were stained with H&E.

Assessment of Gleason Grade Group

In this study, archive records, H&E painted sections, conventional light microscope (Nikon Eclipse E600, Nikon AG Instruments, USA), and x4-x10 lenses were used for evaluation. Three experienced pathologists re-evaluated all cases. The scores of the cases varying between 2 and 10 were re-grouped in terms of GGS. GS ≤6 patients were GGS1 group, GS 3+4=7 patients GGS2 group, GS 4+3=7 patients GGS3 group, GS 8 patients GGS4 group and GS 9-10 patients GGS5 group. The relationship between GGS and clinicopathological parameters was evaluated statistically. American Cancer Joint Committee (8^{th}) guidelines were used in evaluations.

Reproducibility of the study

Inter-observer agreement was investigated to assess reproducibility. Three experienced pathologists (MZ, ME and MAA) evaluated all cases without knowing the clinical and pathological information. Kappa test (κ), which is a variance ratio, was used for inter-observer agreement. κ was grouped as weak, medium and perfect for values of 0.41-0.60, 0.61-0.80 and 0.81-1, respectively.

Patients follow-up

The survival data for the outcome measures were obtained from the archive records. The start time was calculated from the day of the primary biopsy. 15 years of follow-up was considered appropriate to make a more reliable decision about the relapse of the disease. Recurrence-free survival (RFS) was defined as the time from primary biopsy day to local/regional recurrence day or death day. Overall survival (OS) was defined as the time from the day of primary biopsy to the day of death. All events after sixty months of follow-up were censored in sixty months.

Statistical Evaluation

Ranges, averages, and standard deviation were used to define continuous data and percentages and frequencies for categorical data. Chi-square test was used to analyze

the relationships between clinicopathological prognostic factors and categorical variables. Significant differences between univariable survival groups were evaluated by the Log-rank test and survival curves were presented by the Kaplan-Meier method. Multivariable survival groups were evaluated by the Cox-regression model with a 95% confidence interval (CI) and a 1.0 hazard ratio (HR). All tests were two-sided and p values less than 0.05 were considered statistically significant. Statistical data were analyzed using SPSS 21.0 (IBM institute, North Castle, USA).

RESULTS

General Features

The mean of age and tumor volume were 65.54±8.77 (range: 50-89) and 4.50 cm±1.50 cm (range: 2 cm-5 cm). 135 (27.7%) of tumors were GGS 1, 120 (24.6%) were GGS 2, 114 (23.4%) were GGS 3, 60 (12.3%) were GS 4, and 57 (11.7%) were GS 5. Tumour was single lobe in 291 (60.0%) cases, and of tumour ratio was <50% in 310 (63.9%) cases.

Evaluation of GGS

Particular attention was paid when reassessing GS 3+4 and 4+3 cases because the GGS scores would be different. In general, our GS scores were compatible with archive records. There was a statistical relationship between GGS subgroups and prognostic factors, and there was more significant relationship, especially between GGS 2 and GGS 3 [tumour status (p<0.001), age (p=0.045), PN invasion (p<0.001), stage (p=0.004), LN status (p<0.001), and surgical margin (p=0.003)]. The statistical relationship between clinicopathological features and GGS is shown in **Table 1**.

Reproducibility of GGS

The inter-observer agreement was generally in the clinically useful range and ranged from moderate to significant (κ=0.51-0.70). We also found that the agreement between observers for GGS is generally higher (κ=0.63-0.70).

Follow-up of Patients

In the follow-up, one hundred and sixty-five cases died (n=25 for GGS1, n=89 for GGS 2 and GGS 3, n=51 for GGS 4 and GGS 5) and two hundred and ninety cases relapsed (n=32 for GGS 1, n=96 for GGS 2 and GGS 3, n=62 for GGS 4 and GGS 5). The 5-year RFS and OS rates were 81% and 83% for GGS 2 and 65% and 66% for GGS 3, respectively. Also, the 5-year RFS and OS rates were 55% and 58% for GGS 4 and 42% and 43% for GGS 5, respectively **(Table 2)**.

Survival Analyses

There was a significant difference in survival in univariate analysis for GGS subgroups (for GGS 2-GGS 3, RFS: p=0.035 and OS: p=0.012; for GGS 4-GGS 5, RFS: p=0.001 and OS: p=0.001) **(Table 2, Figure 2).** Other parameters associated with poor survival were LN status, stage, and surgical margin. GGS subgroups were an independent survival parameter for survival in multivariate analysis (for GGS 2-GGS 3, OS: HR=2.56 [1.81-4.32], p=0.012 and RFS: HR=2.69 [1.49-4.52], p=0.038; for GGS 4-GGS 5, OS: HR=2.84 [1.34-3.49], p=0.011 and RFS: HR=2.59 [1.46-4.19], p<0.001). Other independent parameters associated with poor survival were LN status, stage and surgical margins **(Table 2).**

Table 1. Statistical relationship of GGS subgroups with prognostic factors

		GGS (%)			GGS (%)		
		GGS 2	**GGS 3**	**p-value**	**GGS 4**	**GGS 5**	**p-value**
Tumour status	Single lobe	39 (32.5)	72 (63.1)	<0.001*	22 (36.6)	33 (57.8)	**0.021***
	Both lobes	81 (67.5)	42 (36.9)		38 (63.4)	24 (42.2)	
Age	<65	57 (47.5)	69 (23.4)	**0.045***	27 (45.0)	36 (63.1)	**0.048***
	≥65	63 (52.5)	45 (76.6)		33 (55.0)	21 (36.9)	
AL invasion	No	54 (45.0)	63 (55.2)	0.116	29 (48.3)	30 (52.6)	0.642
	Yes	66 (55.0)	51 (44.8)		31 (51.7)	27 (47.4)	
PN invasion	No	54 (45.0)	78 (68.4)	<0.001*	29 (48.3)	38 (66.6)	**0.045***
	Yes	66 (55.0)	36 (31.6)		31 (51.7)	19 (33.4)	
Tumour volume	<50%	54 (45.0)	63 (55.2)	0.116	24 (40.0)	34 (59.6)	**0.033***
	≥50%	66 (55.0)	51 (44.8)		36 (60.0)	23 (40.4)	
Stage	PT1	48 (40.0)	72 (63.1)	0.004	23 (38.3)	37 (64.9)	0.004*
	PT2	72 (60.0)	52 (36.9)		37 (61.7)	20 (35.1)	
LN status	Negative	52 (35.0)	81 (71.0)	***<0.001****	24 (40.0)	38 (66.6)	0.003*
	Positive	78 (65.0)	33 (29.0)		36 (60.0)	19 (33.4)	
Surgical margin	Negative	52 (35.0)	72 (63.1)	0.003*	22 (36.6)	35 (61.4)	0.007*
	Positive	78 (65.0)	52 (36.9)		38 (63.4)	22 (38.6)	

*. The limit of significance was accepted as 0.05 for the Chi-square test. Statistically significant results were recorded in italics. **Abbreviations:** GGS: Grade-Group system, AN: Angiolymphatic, PN: Perineural, LN: Lymph node

Table 2. Survival curves of GGS

	Univariate survival analysis(%)				Multivariate survival analysis(%)			
	OS		RFS		OS		RFS	
	5-year (%)	p-value	5-year (%)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Tumour status		0.248		0.233		NC		NC
Single lobe	89%		88%		-		-	
Both lobes	78%		77%		-		-	
Age		0.457		0.449		NC		NC
<65	85%		86%		-		-	
≥65	75%		84%		-		-	
AL invasion		0.559		0.489		NC		NC
No	87%		88%		-		-	
Yes	79%		88%		-		-	
PN invasion		0.162		0.168		NC		NC
No	87%		87%		-		-	
Yes	75%		76%		-		-	
Tumour volume		0.667		0.823		NC		NC
<50%	88%		87%		-		-	
≥50%	79%		80%		-		-	
Stage		0.007*		0.009*		0.041*		0.032*
PT1-2	90%		89%		1		1	
PT3-4	73%		73%		1.42 (1.23-4.56)		1.37 (1.33-2.44)	
LN status		0.003*		0.001*		0.021*		0.014*
Negative	79%		78%		1		1	
Positive	63%		60%		1.31 (1.11-4.12)		1.43 (1.52-3.88)	
Surgical margin		0.005*		<0.001*		0.0017*		0.003*
Negative	88%		89%		1		1	
Positive	72%		70%		1.42 (1.28-2.16)		1.54 (1.37-3.62)	
GGS		0.012*		0.003*		0.038*		0.012*
GGS 2	83%		81%		1		1	
GGS 3	66%		65%		2.56 (1.81-4.32)		2.69 (1.49-4.52)	
GGS		0.001*		<0.001*		0.011*		0.001*
GGS 4	58%		55%		1		1	
GGS 5	43%		42%		2.84 (1.34-3.49)		2.59 (1.46-4.19)	

*. The limit of significance was accepted as 0.05 for the Chi-square test. Statistically significant results were recorded in italics. **Abbreviations:** GGS: Grade-Group system, AN: Angiolymphatic, PN: Perineural, LN: Lymph node, OS: Overall survival, RFS: Relapse-free survival, HR: Hazard ratio, NC: Not calculable, CI: Confidence interval

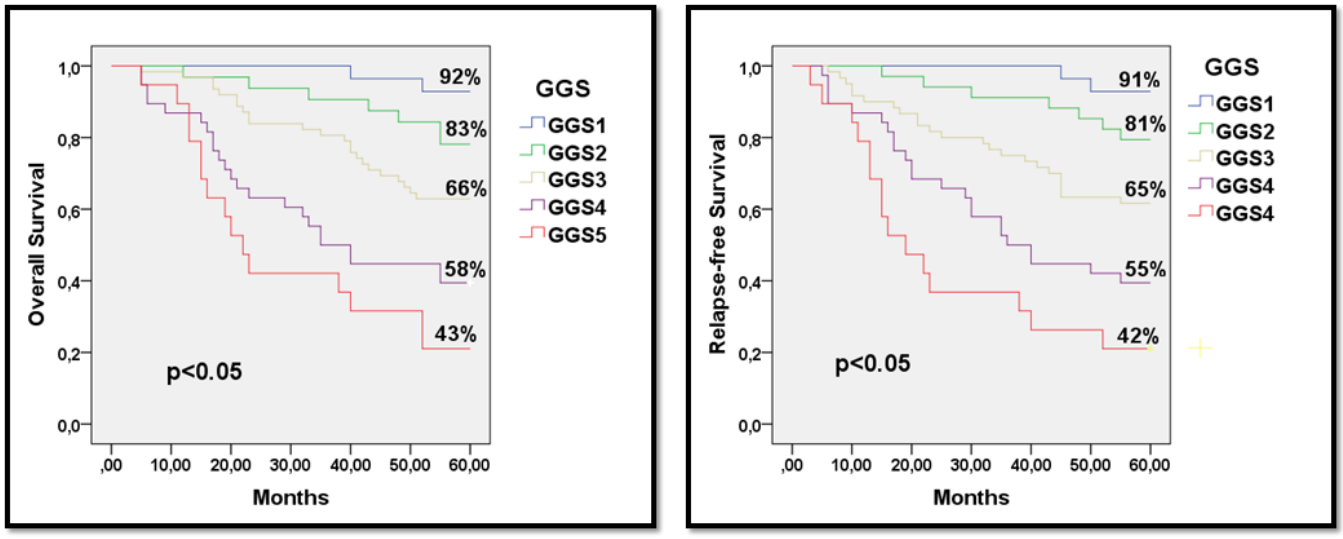

Figure 2: Overall survival and relapse-free survival of Grade-Group system
Survival curves were presented with the Kaplan-Meier curves. The limit of significance was accepted as 0.05 for the Chi-square test.

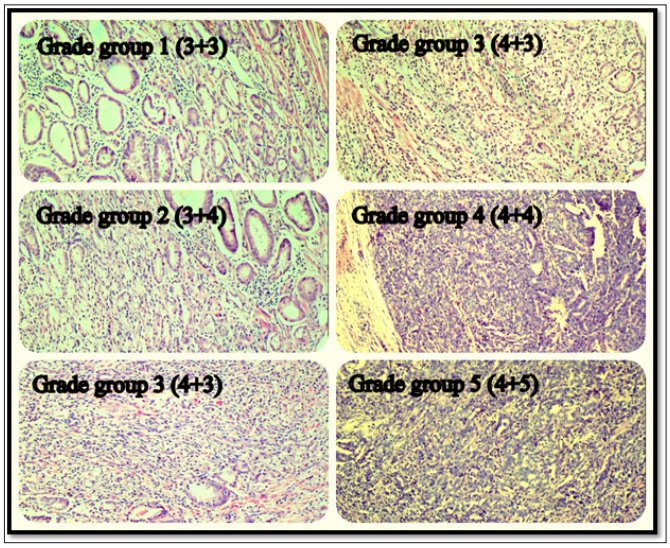

Figure 1. Representative examples of Grade-Group system (GGS) While examining prostate cancers in terms of GGS, x10-x20 lens, hematoxylin and eosin-stained sections, and classical microscope were used.

Table 3. Reproducibility of GGS

N	Kappa values (Weighted)
GGS	0.70 **(A&B)**, 0.62 **(B&C)**, 0.63 **(A&C)**
GS	0.55 **(A&B)**, 0.51 **(B&C)**, 0.53 **(A&C)**

Abbreviations GS: Gleason scoring, GGS: Grade-Group system, A: First observer, B: Second observer, C: Third observer

DISCUSSION

In this study, we compared the new GGS with the old system. According to our findings, this system classified patients more accurately in terms of survival. Also, due to the simplicity of the GGS, this system increased the inter-observer agreement.

Prostate cancer is one of the most common malignant tumours in the world and methods such as serum PSA level, transrectal prostate needle biopsy, and prostate ultrasound are used for its screening and diagnosis. Treatment options for PC are radical prostatectomy, chemotherapy, radiotherapy and hormonotherapy (8). The characteristics of the tumour should be evaluated correctly at the time of diagnosis for the correct treatment selection and correct prognosis estimation (9). While PC patients are divided into risk groups, GS and preoperative PSA level are very important (10,11). Between these two factors, the final GS may change before and after surgery. Therefore, much attention should be paid to the correct evaluation of GS at the time of diagnosis for an appropriate treatment decision (12,13).

Gleason scoringis a rating system developed in the 1960s and remains the strongest prognosis estimator for PC today. GS was first modified from its original definition in 1974 by Gleason and Mellinger (5). In 2005, the 2nd modification was made by the ISUP, thereby achieving a better correlation between the Gleason degree, patient stage, and biochemical PSA values (6). Although these new changes were more complex than before, they showed better relationships with prognostic factors. As an example of the complexities, low-grade cancer, which covers less than 5% in needle biopsy of high-grade cancer, would not be included in GS (14). Also, the highest grade pattern was included in the biopsy score, but not in the resection score. However, many studies reported that GS 6 cases with pattern 4 differ in recurrence.That is, GS 6 cases with a high-grade component had a prognosis between GS 6 and GS 3+4=7 (15,16). In our study, we experienced that the GS system is more complex. Also, the prognosis of the groups containing pattern 4 was worse than pattern 3.

The last modification for the GS was made by ISUP in 2014. Accordingly, considering approximately 20000 radical prostatectomy data collected from different centres, PCs were categorized into 5 histological classes described above. Also, many multicenter studies have confirmed that GGS classifies PC patients more accurately in terms of prognosis (3). In addition, with the new grading system, the score that could have a value between 2-10 was reduced to 5 and a simpler stratification was created. Moreover, it was provided to express low and medium risk groups more easily (10, 13). In our study, it was seen that this system was easy to understand and useful. Also, the agreement between observers was higher. The GS 3+4 and GS 4+3 groups are scored as 7 in the GS system. However, studies have shown that the percentage of pattern 4 adversely affects patient prognosis in GS 7 patients. In the new system, GS 3+4=7 cases are considered as GGS2, and GS 4+3=7 cases are considered as GGS3 (17-19). In our study, we also found that GGS 3 has a worse prognosis than GG2.

In tumours with a GS score of 8 and above, the prognosis is significantly worse, but this is more pronounced at the 9-10 level. GS 8 and above are considered as a single category in most studies, including prediction tables and nomograms (20). This is because the number of patients with GS 9-10 is small and combined with GS 8 for meaningful statistical analysis. For this reason, some urologists consider GS 8 the same as GS 9-10. GS 9-10 patients are rarely seen, but GS 9-10 tumours have a worse prognosis than GS 8. Also, patients with these tumours are mostly not suitable for resection (20,21). In addition, there is a significant decrease in prognosis in the first three years in GS 9-10 patients. For the above reasons, GS 9-10 patients should be evaluated separately from GS8 patients (21,22). In our study, a significant difference was also observed between these two groups in terms of prognosis.

The limitations of our study are as follows. Since our study is retrospective, there are some limitations inherent in retrospective studies. For example, it is not possible to overcome the sampling difference. Also, archive records were used for our study and individual records were not used. In addition, since our patients were treated according to protocols before 2015, there may be differences according to current treatment approaches.

CONCLUSION

According to our results, the new GGS divides patients more accurately into risk groups. Also, this system is very simple and this is an important advantage for daily practice, observers agreement and patient management.

Abbreviations

PC: Prostate cancer, GS:Gleason scoring, GGS:Grade-Group system, HPF: High power field, ISUP: International Society of Urological Pathology, AJCC: American Joint Cancer Committee, κ: Kappa, H&E: Hematoxylin and eosin, SD:Standard deviation, HR: Hazard ratio, OS: Overall survival, RFS: Relapse-free survival

ETHICAL DECLARATIONS

Ethics Committee Approval: Our study was approved by the Kırıkkale University Health Research Ethics Committee (Permission granted/date: 2020, decision number: 2020.06.18). Attention has been paid to ensure that all steps performed during our study comply with the 1964 Helsinki Declaration and national/institutional ethical standards

Informed Consent: Because the study was designed retrospectively, no written informed consentform wasobtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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REFERENCES

1. Siegel RL, Miller KD, Jemal A.Cancer statistics, 2017. CA Cancer J Clin 2017; 67: 7-30.
2. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016; 66: 271-89.
3. Epstein JI, Egevad L, AminMB, et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016; 40: 244-52.
4. Mellinger GT, Gleason D, Bailar J. The histology and prognosis of prostatic cancer. J Urol 1967; 97: 331– 7.
5. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol 1974; 111: 58–64.
6. Epstein JI, Allsbrook WC, Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol 2005; 29: 1228–42.
7. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: Data based on the modified Gleason scoring system. BJU Int 2013; 111: 753–60.
8. Hamdy FC, Donovan JL, Lane JA,et al. ProtecT Study Group. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer.N Engl J Med 2016; 375: 1415-24.
9. Barocas DA, Alvarez J, Resnick MJ, et al. Association between radiation therapy, surgery, or observation for localized prostate cancer and patient-reported outcomes after 3 years. JAMA 2017; 317: 1126-40.
10. Ozok HU, Sagnak L, Tuygun C, et al. Will the modification of the Gleason grading system affect the urology practice? Int J Surg Pathol 2010; 18: 248–54.
11. Alenda O, Ploussard G, Mouracade P, et al. Impact of the primary Gleason pattern on biochemical recurrence-free survival after radical prostatectomy: a single-center cohort of 1.248 patients with Gleason 7 tumors. World J Urol 2010; 29: 671–6.
12. Billis A, Guimaraes MS, Freitas LL, et al. The impact of the 2005 international society of urological pathology consensus conference on standard Gleason grading of prostatic carcinoma in needle biopsies. J Urol 2008; 180: 548–52.
13. Helpap B, Egevad L. The significance of modified Gleason grading of prostatic carcinoma in biopsy and radical prostatectomy specimens. Virchows Arch 2006; 449: 622–7.
14. Tsivian M, Sun L, Mouraviev V, et al. Changes in Gleason score grading and their effect in predicting outcome after radical prostatectomy. Urology2009; 74: 1090–3.
15. Trock BJ, Guo CC, Gonzalgo ML, et al. Tertiary Gleason patterns and biochemical recurrence after prostatectomy: proposal for a modified Gleason scoring system. J Urol 2009; 182: 1364–70.
16. Pan CC, Potter SR, Partin AW, et al. The prognostic significance of tertiary Gleason patterns of higher grade in radical prostatectomy specimens: a proposal to modify the Gleason grading system. Am J Surg Pathol 2000; 24: 563–9.
17. AminA, Partin A, Epstein JI. Gleason score 7 prostate cancer on needle biopsy: relation of primary pattern 3 or 4 to pathological stage and progression after radical prostatectomy. J Urol 2011; 186: 1286–90.
18. Wright JL, Salinas CA, Lin DW, et al. Prostate cancer specific mortality and Gleason 7 disease differences in prostate cancer outcomes between cases with Gleason 4+3 and Gleason 3+4 tumours in a population based cohort. J Urol 2009; 182: 2702–7.

19. Rasiah KK, Stricker PD, Haynes AM, et al. Prognostic significance of Gleason pattern in patients with Gleason score 7 prostate carcinoma. Cancer 2003; 98: 2560–5.
20. Mosse CA, Magi-Galluzzi C, Tsuzuki T, et al. The prognostic significance of tertiary Gleason pattern 5 in radical prostatectomy specimens. Am J Surg Pathol 2004; 28: 394–8.
21. Whittemore DE, Hick EJ, Carter MR, et al. Significance of tertiary Gleason pattern 5 in Gleason score 7 radical prostatectomy specimens. J Urol 2008; 179: 516–22.
22. Sabolch A, Feng FY, Daignault-Newton S, et al. Gleason pattern 5 is the greatest risk factor for clinical failure and death from prostate cancer after dose-escalated radiation therapy and hormonal ablation. Int J Radiat Oncol Biol Phys 2011; 81: 351–60.

Original Article/Özgün Makale

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Predicting vitamin D deficiency through parathormone in the children of a small city located in the warm climate belt of Northern Hemisphere

Kuzey Yarımküre'de ılıman iklim kuşağındaki küçük bir ilde parathormon üzerinden D vitamini eksikliğini öngörme

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ABSTRACT

Aim: The aim of this study is to analyse the serum levels of parathormone (PTH), calcium (Ca), phosphorus (P), vitamin D and define a cut off value for vitamin D deficiency and insufficiency in a sample of healthy children.

Method: A total of 543 healthy children enrolled to this study. The data of parathormone, Ca, P, 25 (OH) D levels, season of blood sample collection, age, sex and health status were collected from the hospital record system retrospectively. The relationships between these variables were defined by statistical analyses and explained in detail in the text.

Results: The inflection point that triggered parathormone rise was 13.6 ng/ml. The optimal level (50p) was 20.3 ng/ml for preadolescent group, 18.3 ng/ml for male adolescents and 18.1 ng/ml for female adolescents. Logistic regression analyses pointed that age, parathormone and seasons contributed to vitamin D status.

Conclusion: The habitat is a significant variable for vitamin D status because altitude and latitude affect solar Zenith angle. Age, gender and seasonal variations must be taken in consideration when recommending supplementation.

Keywords: Vitamin D deficiency, 25 (OH) D, PTH, latitude, child

ÖZ

Amaç: Bu çalışmanın amacı bir grup sağlıklı çocukta parathormon (PTH), kalsiyum (Ca), fosfor (P), D vitamini düzeylerini ortaya koymak ve "D vitamini eksikliği" ile "yetersizliği" tanıları için düzey saptamaktır.

Yöntem: Çalışmaya bilinen kronik sağlık sorunu olmayan 543 çocuk katıldı. Parathormon, Ca, P, 25 (OH) D düzeyleri, kan örneğinin alındığı mevsim, yaş, cinsiyet ve sağlık durumuna ait veriler hastane kayıt sisteminden geriye dönük olarak elde edildi. Değişkenler arasındaki ilişkiler metinde ayrıntılı olarak tanımlanan istatistiksel yöntemlerle değerlendirildi.

Bulgular: Parathormon yükselmesini tetikleyen en düşük parathormon değeri 13,6 ng/ml olarak saptandı. Farklı yaş grupları için 25 (OH) D düzeyi persentil değerleri hesaplandı, buna göre ideal 25 (OH) D düzeyi (50 persentil) ergenlik öncesi grupta 20,3 ng/ml, ergen erkeklerde 18,3 ng/ml, ergen kızlarda 18.1 ng/ml olarak saptandı. Yaş, parathormon ve mevsimin D vitamini düzeylerine katkısı olduğu lojistik regresyon analizleri ile gösterildi.

Sonuç: Yaşanılan yerin rakımı ve enlemi güneşin Zenith açısını etkilediğinden D vitamini durumunda önemli bir değişkendir. Destek ve tedavi yaklaşımında yaş, cinsiyet ve mevsimler dikkate alınmalıdır.

Anahtar Kelimeler: D vitamini eksikliği, 25 (OH) D, PTH, enlem, çocuk

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INTRODUCTION

Vitamin D is a steroid hormone and a fat-soluble vitamin (1). It is synthesized in the skin under direct sunlight. The provitamin form, 7-dehydrocholesterol, is converted to Vitamin D3 upon ultraviolet B rays with the wave band of 290-315 nm (1). The efficiency of cutaneous vitamin D synthesis depends on the intensity of sunlight, surface area of the skin exposed to the direct sunlight, duration of exposure, the zenith angle of the sun, thickness and color of the skin (2,3). Seasons, time of the day, indirect sunlight exposure, sunscreens, clothes preventing sunlight exposure, aging, lived latitude, outdoor activities, physical exercise and obesity affect this transformation rate (1). It is hydroxylated in the liver and kidneys to create the active form: 1, 25 dihydroxy vitamin D. The dietary intake of vitamin D is limited unless fortified food is not consumed. The content of vitamin D in breast milk is poor and oily fish, yolk sac; the richest food sources, contain little amounts (1,4). Also, vitamin D insufficiency (VDI) and VDD may be the result of genetic factors influencing the metabolism of the vitamin (5).

Vitamin D is the key nutrient for healthy skeletal system. Calcium (Ca) and phosphorus (P) absorption is under the control of parathormone (PTH)–vitamin D interaction. The precision balance between these markers provide the homeostasis of bone turnover and healthy growing up (1,6). When serum Ca decreases PTH secretion increases to mobilize Ca from bones. Vitamin D regulates PTH secretion on this basis and increases intestinal Ca absorption (7). The inverse proportion between PTH and vitamin D (the metabolite for laboratory evaluation is 25 (OH) D) is already known, but the inflection point of PTH may vary between populations or geographic areas. Ca and PTH are reliable parameters for laboratory evaluations, but P and ALP may be affected from environmental conditions, especially hemolysis which is common in pediatric blood samples (1,8). The lowest level of 25 (OH) D that triggers PTH secretion is defined as "vitamin D deficiency (VDD)" and this process disrupts bone mineralization whereas sufficient vitamin D levels provide PTH plateau to provide homeostasis (9). In addition, vitamin D has other crucial roles in other tissues where its receptors exist, including cardiovascular, neurologic, gastrointestinal, immune and endocrine systems. Deficiency may result in multisystem health troubles because regulation of approximately 1000 genes and nuclear transcription factors disrupts (5). Immune modulation troubles in case of deficiency leading to autoimmune diseases, recurrent infections, cancers or the rate of exacerbations of chronic illnesses increases (10,11). In critically or chronically ill children, if there is vitamin D deficiency, replacement and supplementation can provide better outcomes (12). Thus, VDD is an important public health problem especially for growing up children (6). However, sufficiency can be evaluated via its relationship with PTH, but this may reflect its only role in Ca-P metabolism. It is unclear whether serum PTH suppression is an appropriate method for determining optimal vitamin D levels in children and adolescents for other metabolic effects.

The optimal vitamin D level providing all metabolic effects has not been clearly defined. Diagnosis of VDD is methodologically challenging because of various measurement techniques (radioimmunoassay, competitive protein binding assays (CPBA), high pressure liquid chromatography (HPLC), and liquid chromatography-tandem mass spectrometry). These methods may yield different results about 10-25% range (13). Available assays can measure 25 (OH) D levels, the product of the reactions in the liver. It is the main indicator of vitamin D status since it has a longer half-life than the active form. Also, there is lack of consensus about "adequate" serum 25 (OH) D levels, considering the skeletal and non- skeletal effects (6). Various cut off points for VDD have been adopted by various organizations and authors (14-16). Differences in the study groups, geographic areas (different altitudes and latitudes) or techniques to determine 25 (OH) D levels lead to conflicts in VDD definition (17).

VDD prevalence is a common public health problem in the pediatric population (18,19). It is observed that children and their mothers spend more time indoors and less for outdoor activities. Consumption of sunscreens has increased recently and clothing habits may prevent direct sunlight exposure (20,21). The aim of this study is to evaluate the serum levels of 25 (OH) D, PTH, Ca, P, alkaline phosphatase (ALP) and to define VDD and VDI in a sample of healthy children in a small city of Turkey, a country located in the warm climate belt of northern hemisphere.

MATERIAL AND METHOD

This retrospective and cross-sectional study was conducted in pediatric outpatient clinics of a secondary health care center in middle northern Turkey within two years. The source of data was the medical records of the participants, investigated through the hospital information system (Sisoft, HBYS ®). Children younger than 1 year old were excluded from the study because they were supposed to be under the cover of national Vitamin D supplementation campaign of

Health Ministry of Turkish Republic. In addition, patients having chronic diseases or weight and height measurements other than 3 to 97 percentiles according to the growth charts based on age and sex for Turkish children, the ones having metabolic defects in Ca and vitamin D metabolism and taking vitamin D or multivitamin preparations were excluded from the study. A total of 543 healthy children aged 1 to 17 years old were enrolled. Weights were measured with a calibrated digital scale and heights with a stadiometer before physical examination. Venous blood samples for laboratory studies were obtained from all participants in the morning, 8.00-12.00 am. Serum levels of 25 (OH)D were measured by electrochemiluminescence immunoassay method (Siemens Advia Centaur XP®, Erlangen Germany). The specificity and sensitivity of the method was 98% and 95% respectively with coefficient of variation value 6.8. PTH levels were analysed by electrochemiluminescence method (Siemens Advia Centaur XP®, Erlangen Germany) and the blood samples for PTH testing were transported to laboratory in cold conditions. ALP, Ca were tested by kinetic color test method and P levels were measured by molybdate UV test method (Beckman Coulter AU 5800®, Brea California, United States). All tests were performed immediately after taking the blood samples. For the evaluation of the results the participants were divided into four age groups: 1-4 years (preschool), 5-8 years (middle childhood), 9-12 years (early adolescence), and 13-17 years (adolescence).

Statistical analyses

Statistical analyses were performed by using SPSS 21.0 for Windows (SPSS, Inc., Chicago, IL, USA). The data were presented as frequencies and percentages for categorical variables and as median, interquartile range (IQR), minimum–maximum, range or mean±SD, percentiles for scale variables by descriptive statistics, when indicated. The distribution patterns of variables were investigated by visual (histograms, probability plots) and analytical (Kolmogorov Simirnov test) methods. As the serum 25 (OH) D, age, PTH, ALP levels were non -normally distributed in the whole group, Kruskall Wallis tests were conducted to compare their levels among seasonal and gender groups. Mann Whitney U test was performed to test the significance of pairwise differences using Bonferroni corrections to adjust for multiple comparisons. Ca and P, normally distributed variables, were analyzed by t-test. In addition, all variables (Ca, P, ALP, PTH, 25 (OH) D) were distributed normally within preadolescent and adolescent age groups so they were analyzed by t-test. The Chi-square test or Fisher's exact tests were also used to compare categorical variables in different groups. The correlation associations were calculated by using Spearman test. The 25 (OH) D level that triggers PTH secretion was analyzed by using Receiver Operating Characteristics (ROC) analyses. The areas under ROC curves were calculated. For some ROC analyses the participants were divided into age groups as "prepubertal" (≤10 years old) and "pubertal" (>10 years old). The variables that contribute 25 (OH) D status were tested via logistic regression analyses to form an equation model. The clearness of the model was tested by Nagelkerke R2 and Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. A 5% type 1 error level was used to infer statistical significance ($p<0.05$).

Ethics

This study was approved by the local committee of non-invasive scientific researches with decision no: 27/02/2020-E.5675.

RESULTS

This study was conducted with 543 children aged 1 to 17 (median: 5; IQR: 8) years old in a small city located in the warm climate belt of the north hemisphere (36°57'06"-36°31'53"eastern meridians and 41°04'54"-40°16'16"northern parallels). The participants consisted of 296 (54.5%) females and 247 (45.5%) males. Approximately 60% of the blood samples were collected in summer and autumn. The median concentrations of 25 (OH) D, PTH, ALP were 18.7 ng/dl (IQR: 15.9), 39 pg/ml (IQR: 24.2), 200 IU/L (IQR: 81.5), mean concentrations of Ca and P were 9,7±0.4 mg/dl; 4.9±0.7 mg/dl respectively. Serum PTH levels were high (>65 pg/ml) in 10.3% (n=56) of the study group.

The median of 25 (OH) D levels in males was 21.4(IQR:16.9) ng/ml and 17.0 (IQR: 14.1) ng/ml in females, the difference was significant statistically ($p<0.0001$). In addition, PTH and P values were also different, but there was no significant difference in Ca, ALP concentrations between sexes. 25 (OH) D, PTH, Ca, P, ALP levels were all statistically different between age groups ($p<0.001$). The median 25 (OH) D concentrations were different in each seasonal group, with higher levels in summer and autumn ($p<0.0001$). Age and 25 (OH) D levels were inversely correlated ($p<0.001$; r=-266) (**Table**). Additionally, 25 (OH) D and PTH levels were inversely correlated ($p<0.001$; r=-272). The correlation was not significant between 25 (OH) D and Ca ($p=0.08$; r=0.077).

Table. 25 (OH) D, PTH, Ca, P, ALP levels according to age, sex, season (Page 7)

	AGE (years) median (IQR)	25 (OH) D (ng/ml) median (IQR)	PTH (pg/ml) median (IQR)	CALCIUM (mg/dl) mean ±SD	PHOSPHORUS (mg/dl) mean ±SD	ALP (IU/ml) median (IQR)
SEX						
Males (n=247)	4.0 (8)	21.40 (16.90)	34.70 (27.35)	9.7±0.4	5.0±0.7	202.0 (78.0)
Females (n=296)	5.0 (8)	17.0 (14.13)	41.10 (22.60)	9.6±0.4	4.8±0.7	197.0 (90.0)
p		<0.001	0.003	0.164	0.026	0.266
SEASON						
Spring	6.0(8)	13.55 (11.0)	40.90 (23.90)	9.7±0.4	4.8±0.7	199.5 (89.7)
Winter	5.0 (9)	11.58 (11.64)	38.10 (27.40)	9.6±0.3	4.7±0.6	191.0 (92.0)
Autumn	4.0 (7)	20.0 (13.90)	36.30 (25.0)	9.7±0.4	5.0±0.7	201.0 (82.0)
Summer	5.0 (8)	25.10 (12.20)	38.70 (23.50)	9.6±0.4	5.0±0.6	203.5 (82.0)
p		<0.001	0.115	0.625	0.002	0.435
AGE						
Pre-adolescent (≤10 years old)	4.1±2.8	21.8±1.0	39.6±2.2	9.7±0.4	5±0.6	217±86.3
Adolescent (>10 years old)	13.7±1.9	15.8±1.0	51.0±2.3	9.5±0.3	4.2±0.7	174.1±98.2
p		<0.0001	<0.0001	0.0002	<0.0001	<0.0001

The ROC analyses for this study group revealed that the inflection point of 25 (OH) D to trigger PTH rise was 13.6 ng/dl and this cut off value had 58.9% sensitivity with 70% specificity for identification of vitamin D deficiency (p<0.0001; area under the curve (AUC): 0.656; 95% confidence interval (CI): 0.61-0.76). Thirty-three percent (n= 179) of the participants had 25(OH) D levels <13.6 ng/dl, referring VDD. The median age of VDD group was 7 (IQR: 9) and the median age of the participants having sufficient 25 (OH) D levels (>13.6ng/ml) was 4 (IQR: 6). Age was a statistically significant variable for 25 (OH) D status. PTH concentrations were significantly higher in deficiency and lower in sufficiency groups with median values 43.8 pg/ml (IQR: 28.2) and 37.3 pg/ml (IQR: 23.5) respectively (p<0.001). Approximately 60% of the participants having high PTH levels (>65pg/ml) had VDD. Mean Ca levels of the deficiency and sufficiency groups were 9,7±0,4 and 9,6±0,4 mg/dl, but the difference was not significant (p= 0.11). Six (1.1%) of the participants had hypocalcemia (serum Ca level<8.8 mg/dl) and 5 of them had VDD. Median ALP and mean P levels revealed statistical significance between two groups (p=0.006; p<0.0001). Hypophosphatemia (serum P level<3.8mg/dl) was detected in 37 (6.8%) of the participants and 67.6% (n=25) of them had VDD which was also a significant finding (p<0.001). ROC analyses were performed for females and males considering age groups as preadolescence (≤10 years old) and adolescence (>10 years old), but cut off values of 25 (OH) D deficiency could not be determined statistically. The results were analyzed to calculate the values of 50p for age groups. The optimal level (50p) was 20.3 ng/ml for preadolescent group, 18.3 ng/ml for male adolescents and 18.1 ng/ml for female adolescents.

Logistic regression analyses pointed that age, PTH and seasons contributed to poor vitamin D status. Each one-year increase in age, increased VDD risk 1.08-fold (p=0.012). Also, one-unit increase in PTH levels increased the risk of low 25 (OH) D status 1.015-fold (p=0.021). The prominent risk factor was seasonal changes as VDD risk increased 16.3 folds in winter (Nagelkerke R2=0.369; Hosmer Lemeshow test p=0,520)

DISCUSSION

In this study 543 healthy children aged between 1to 17 were evaluated for vitamin D status through 25 (OH) D, circulating metabolite of active vitamin D, and its metabolic interactions with Ca, P, ALP and PTH. The study was conducted in a small city of northern Turkey where the estimated maximum monthly average global solar radiation ranged from 20.05 to 23.71 MJ/m^2 (22,23). In this country, children younger than 1 year old are under the cover of national Vitamin D supplementation campaign of Health Ministry of Turkish Republic. Three drops of cholecalciferol solution that contains 133 IU vitamin D3 in each drop is recommended and provided freely to all infants younger than one year old by this campaign (24). 25 (OH) D levels decreased with age and it had higher levels in summer and autumn as a gift of direct sunlight exposure. Females had lower 25 (OH) D levels than males and this became more apparent with increasing age. The inflection point for VDD of this study population was detected to be 13.6 ng/ml. The optimal value (50p) of 25 (OH) D for preadolescent age group (≤10 years old) was 20.3 ng/ml. It was calculated to be 18.3ng/ml for adolescent males and 18.1 ng/ml for adolescent females.

Vitamin D has a crucial role in Ca- P metabolism and healthy growing up of the skeletal system during childhood and adolescence (6). Moreover, multisystem effects of VDD or VDI cause problems in the homeostasis of the whole body. Many studies have proved that VDD or VDI is a global public health problem contributing to disturb skeletal, mental, immunological, metabolic, cardiovascular harmony (25). Physiologically 25 (OH) D and PTH has inverse correlation whereas Ca and P are positively correlated with 25 (OH) D. In this study group 57 participants had hyperparathyroidism and 57.9% (n=33) of them had low 25 (OH) D levels (<13.6 ng/ml). The rate of hyperparathyroidism may be lower than expected because PTH rise becomes apparent within four weeks in case of VDD (26). Additionally, hypocalcaemia and hypophosphatemia rates were higher in VDD group, to be expected. The levels of P are higher and ALP levels are lower than expected in this study which is thought to be a result of hemolysis caused during blood sample punctuation procedure. All variables were statistically different between preadolescents and adolescents ($p<0.0001$).

The efficiency of vitamin D -25 (OH) D can be evaluated via its relationship with PTH and most of the studies have been based on this concept. In 2015, Endocrine Society defined vitamin D status with a consensus statement and the cut off value was determined to be <30 nmol/ml (<12ng/ml; 1 ng/ml=2.5 nmol/l.) to prevent nutritional rickets (14). The American Academy of Pediatrics (AAP) defined deficiency for values <15 ng/ml; insufficiency for values between 15 and 20 ng/ml; sufficiency for values between 20 and 100 ng/ml (15). A study from Korea including 193 children aged between 2 months and 17 years old defined the inflection point of 25 (OH) D due to PTH as 18ng/ml. The health status of the study group was mixed. The data were based on hospital records as in our study (27). Crews et al. (28) defined the lowest 25 (OH) D level as 10ng/ml in child population having no renal insufficiency. Also, Atapattu et al. (9) evaluated 214 children having no conditions related with Ca-P metabolism and concluded that the biochemical abnormalities are demonstrated when 25 (OH) D level was <34 nmol/l (13.6 ng/ml), similar to the results of this study. However, Hill et al. (17) analyzed the levels of PTH and 25 (OH) D in 735 healthy children aged between 7-18 in three different sites having different latitudes in USA and could not define an inflection point. They concluded that their inability to clearly identify an inflection point of serum 25 (OH) D for maximal suppression of serum PTH for healthy children and adolescents was because of fast growing up and bone turnover. Age and sex should be taken in consideration because of differences in growing up patterns (29). In this study, the inflection point of 25 (OH) D was detected as 13.6ng/ml for the whole study group. Our results were compatible with literature supporting Atapattu et al. (9) and Hill et al. (17). We defined the optimal levels (50p) for preadolescent and adolescent age groups as vitamin D has crucial roles not only in skeletal system, but homeostasis as well.

Here, vitamin D status of a healthy child population was presented, but this study has several limitations: It was a retrospective study based on hospital records. The study group had a small size and did not reflect the whole population. Also, the number of participants was not sufficient to determine the inflection point of VDD according to age and gender. Dietary habits, skin colour, sunlight exposure history, clothing habits of the participants were not mentioned. The pubertal stage of the adolescent group, which is important for bone turnover, was not in consideration. There was no data about rickets and radiologic findings to support vitamin D effects at different levels of 25 (OH) D. In addition, the accuracy of 25(OH) D measurement techniques may vary and technical standardization is usually difficult.

CONCLUSION

We recommend that the inflection point of serum 25 (OH) D level that triggers PTH rise is 13.6 ng/ml for our latitude. The habitat may cause variations in optimal 25 (OH) D levels as altitude and latitude affect solar zenith angle which is directly related with sunlight exposure. In addition, seasons and sex must be taken in consideration when recommending supplementation as winter and spring provides poor sunlight which limits skin synthesis and females are more prone to deficiency. Since PTH levels increase apparently four weeks after deficiency onset, we recommend that target levels of 25 (OH) D levels (for the same latitude) should be taken in consideration while deciding supplementation (20.3 ng/ml for preadolescents, 18.3 ng/ml for adolescent males and 18.1 ng/ml for adolescent females). However, high doses of vitamin D can be prescribed when 25 (OH) D is <13.6 ng/dl and PTH levels are increased and/or biochemical and radiologic signs of rickets occur.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the local committee of non-invasive scientific researches with decision no: 27/02/2020-E.5675.

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

REFERENCES

1. Holick MF. Environmental factors that influence the cutaneous production of vitamin D. Am J Clin Nutr 1995; 6: 638–45.
2. Wahl DA, Cooper C, Ebeling PR, et al. A global representation of vitamin D status in healthy populations. Arch Osteoporos 2012; 7: 155–72.
3. Grant WB, Strange RC, Garland CF. Sunshine is good medicine: the health benefits of ultraviolet-B induced vitamin D production. J Cosmet Dermatol 2003; 2: 86–98.
4. Reeve LE, Chesney RW, DeLuca HF. Vitamin D of human milk identification of biologically active form. Am J Clin Nutr 1982; 36: 122-6.
5. Wang TJ, Zhang F, Richards JB, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet 2010; 376: 180–8.
6. Antonucci R, Locci C, Clemente MG, Chicconi E, Antonucci L. Vitamin D deficiency in childhood: old lessons and current challenges. J Pediatr Endocrinol Metab 2018; 31: 247–60.
7. Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G. Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. JAMA 2005; 294: 2336–41.
8. Bikle D. Vitamin D: an ancient hormone. Exp Dermatol 2011; 20: 7-13.
9. Atapattu N, Shaw N, Hogler W. Relationship between serum 25- hydroxyvitamin D and parathyroid hormone in the search for a biochemical definition of vitamin D deficiency in children. Pediatr Res 2013; 74: 552-6.
10. Holick MF. Vitamin D: important for prevention of osteoporosis, cardiovascular heart disease, type 1 diabetes, autoimmune diseases, and some cancers. South Med J 2005; 98: 1024–7.
11. Holick MF. The vitamin D deficiency pandemic and consequences for non-skeletal health: mechanisms of action. Mol Aspects Med 2008; 29: 361–8.
12. Sankar J, Ismail J, Das R, Dev N, Chitkara A, Sankar J. Effect of severe vitamin D deficiency at admission on shock reversal in children with septic shock: A prospective observational study. J Intensive Care Med 2017; 20: 1-7
13. Enko D, Fridrich L, Rezanka E, et al. 25-hydroxy-vitamin D status: limitations in comparison and clinical interpretation of serum-levels across different assay methods. Clin Lab 2014; 60: 1541–50.
14. Munns CF, Shaw N, Kiely M, et al. Global consensus recommendations on prevention and management of nutritional rickets. J Clin Endocrinol Metab 2016; 101: 394–415.
15. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M, Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 2008; 122: 398–417.
16. Braeger C, Campoy C, Colomb V, et al. ESPGHAN Committee on Nutrition. Vitamin D in the healthy European paediatric population. JPGN 2013; 56: 692–701.
17. Hill KM, McCabe GP, McCabe LD, Gordon CM, Abrams SA, Weaver CM. An inflection point of serum 25-hydroxyvitamin D for maximal suppression of parathyroid hormone is not evident from multi-site pooled data in children and adolescents. J Nutr 2010; 140: 1983-8.
18. Akman AO, Tümer L, Hasanoğlu A, İlhan M, Çaycı B. Frequency of vitamin D insufficiency in healthy children between 1 and 16 years of age in Turkey. Pediatr Int 2011; 53: 968–73.
19. Şahin ÖN, Serdar M, Serteser M, Ünsal İ, Özpınar A. Vitamin D levels and parathyroid hormone variations of children living in a subtropical climate: a data mining study. Ital J Pediatr 2018; 44: 40.
20. Erkuran N, Gücük S. Relationship between vitamin D levels and demographic factors and life style characteristics of 18-49 age women. Euras J Fam Med 2017; 6: 35-42.
21. Seo JH, Chung HJ, Kim HJ, et al. Increasing vitamin D deficiency in children from 1995 to 2011.Turk J Pediatr 2016; 58: 616-22.
22. Location. (Amasya Valiliği web site). Available at http://www.amasya.gov.tr/cografi-konum. Accessed in September 2018.
23. Tarhan S, Sarı A. Model selection for global and diffuse radiation over the Central Black Sea (CBS) region of Turkey. Energy Conversion and Management 2005; 46: 605-13.
24. Hatun S, Ozkan B, Bereket A. Vitamin D deficiency and prevention: Turkish experience. Acta Pediatr 2011; 100: 1195-9.
25. Wimalawansa SJ. Non-musculoskeletal benefits of vitamin D. J Steroid Biochem Mol Biol 2018; 175:60-81.
26. Kroll MH, Bi C, Garber CC, et al. Temporal relationship between vitamin D status and parathyroid hormone in the United States. PLoS ONE 2015; 10: e0118108.
27. Kang JI, Lee YS, Han YJ, Kong KA, Kim HS. The serum level of 25-hydroxyvitamin D for maximal suppression of parathyroid hormone in children: the relationship between 25- hydroxyvitamin D and parathyroid hormone. Korean J Pediatr 2017; 60: 45-9.
28. Crews BO, Moore J, Dietzen DJ. Circulating intact parathyroid hormone is suppressed at 25-hydroxyvitamin D concentrations >25 nmol/L in children. J Pediatr Endocrinol Metab 2014; 27: 657-60.
29. Harkness L, Cromer B. Low levels of 25-hydroxy vitamin D are associated with elevated parathyroid hormone in healthy adolescent females. Osteoporos Int 2005; 16: 109-13.

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Anticipated decrease in surgeons: does orthopedic internship affect medical students career choice?

Cerrahlarda beklenen azalma: ortopedi stajı tıp öğrencilerinin kariyer seçimini etkiler mi?

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ABSTRACT

Aim: The aim of this study is to determine medical students' career choices and to identify the effect of both demographic factors and the orthopedics residency education program on medical students' career choices.

Material and Method: This study was performed on a total of 154 medical students (92 females and 62 males; mean age 23.7±2.8) who attended Orthopedic internship program between 2018 and 2019 academic years. The students were subjected to a questionnaire twice on the first and last days of their internship program, which investigated distribution of selection of final year medical students' career choices and factors that may play role on this selection.

Results: Eighty-three (53.9%) students had changed their preferences and 72 (46.8%) had changed the order of preferences after Orthopedic internship program. The increase in the number of students who chose Orthopedics ($p<0.001$) and who placed Orthopedics in first order in their list of preferences ($p=0.039$) was statistically significant after the Orthopedic internship program. There was no significant difference between the female and male students in terms of placing surgical branches first in their list of preferences before ($p=0.955$) and after Orthopedic internship program ($p=0.182$). It was found that male students chose Orthopedics significantly more than females both before ($p<0.001$) and after ($p<0.001$) the internship.

Conclusion: We demonstrated that early and active recruitment in surgery and operating theatre with positive support of faculty, residents and even operating room staff may increase interest in orthopedic surgery both for male and female medical students.

Keywords: Career choice, medical education, undergraduate, orthopedic residency, surgical residency

ÖZ

Amaç: Bu çalışmanın amacı tıp öğrencilerinin kariyer seçimlerini ve demografik faktörlerin ve ortopedi uzmanlık eğitim programının tıp öğrencilerinin kariyer seçimleri üzerindeki etkisini belirlemektir.

Gereç ve Yöntem: Bu çalışma, 2018-2019 akademik yılları arasında Ortopedi stajına katılan toplam 154 tıp öğrencisi (92 kadın ve 62 erkek; ort. yaş 23.7±2.8) üzerinde gerçekleştirildi. Öğrenciler, staj programlarının ilk ve son günlerinde olmak üzere iki kez bir ankete tabi tutuldu ve son sınıf tıp öğrencilerinin kariyer seçimi tercihleri ve bu seçimde rol oynayabilecek faktörler incelenmiştir.

Bulgular: Seksen üç (%53,9) öğrenci Ortopedi stajından sonra tercihini ve 72 öğrenci (%46,8) tercih sırasını değiştirmiştir. Ortopedi stajından sonra ortopedi tercih eden ($p<0.001$) ve ortopedi branşını tercih listesinde birinci sıraya yerleştiren ($p=0.039$) öğrenci sayısındaki artış istatistiksel olarak anlamlı bulunmuştur. Kız ve erkek öğrenciler arasında, ortopedi stajından önce ($p=0.955$) ve sonra ($p=0.182$) cerrahi branşları tercih listesinde ilk sıraya koyma açısından anlamlı bir fark bulunmamıştır. Erkek öğrencilerin ortopedi branşını hem staj öncesi ($p<0.001$) hem de staj sonrasında ($p<0.001$) kız öğrencilerden anlamlı olarak daha fazla tercih ettikleri görülmüştür.

Sonuçlar: Öğretim üyeleri, araştırma görevlileri ve hatta ameliyathane personelinin olumlu desteği ile öğrencilerin ameliyatlara ve ameliyathaneye erken dönemde ve aktif olarak katılımlarının sağlanması hem erkek hem de kız tıp öğrencilerinin ortopedi branşına olan ilgisini artırabilir.

Anahtar Kelimeler: Kariyer seçimi, tıp eğitimi, lisans eğitimi, ortopedi asistanlığı, cerrahi branş asistanlığı

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INTRODUCTION

The number of specialists in each branch of medicine has a direct effect on the running of high-quality public healthcare services as well as on the continuance of medical education. However, some studies have reported a decrease in medical students'interest in surgical specialties (1,2). Various factors have been found to affect medical students' career choices such as the individual characteristics, (3,4) anticipation of a high income, (5) prestige, the education content, (6) and experiences at medical school, (7,8) the desire for a controllable lifestyle, (9,10) flexibility of working management, (5,11) career features, (1) and sex (12). One branch of surgery, namely, Orthopedics and Traumatology (hereafter referred to as orthopedics) has also experienced a decrease in medical students'interest. In contrast, the number of patients seeking medical attention for musculoskeletal disease is high, (13) and has been reported to involve 20% of patients in primary care and emergency presentations (14,15). To address the discrepancy between the need for healthcare and the number of medical professionals in this branch, the number of orthopedic surgeons should be increased to a sustainable level, and factors affecting medical career choices need to be clarified. Understanding the potential effects of the content of education, medical school experience, and other specific factors involved in selecting an orthopedics residency education may help program directors to guide students more effectively in selecting this internship. This study is a pioneering study that investigated the factors affected the specialty choice of medical students and if their preferences changed after the orthopedic internship.

In this study, we aimed to determine medical students career choice and to identify the effect of both demographic factors and the orthopedics education program on medical students' career choices.

MATERIAL AND METHOD

The study was approved by the local Ethics Committee (Date: 11.07.2018, Approval no. 2018.10.16) and performed in the skill practice laboratory of the Department of Orthopedics and Traumatology at Kırıkkale University School of Medicine. All reported research involving "Human beings" conducted in accordance with the principles set forth in the Helsinki Declaration 2008. This cross sectional study involve 154 final 5th-year medical faculty students (women, n=92 [59.7%]; men, n=62 [40.3%]; mean age, 23.7±2.8 [range, 22-53] years) from the 2018-2019 academic year who had undergone an orthopedics internship program (OIP), at a university in Anatolia, Turkey. All the students who attend to OIP and volunteer for completing the questionnaire were included in the study. As a result of a post-hoc power analysis undertaken through, calculating a type 1 (alpha) error level at 0.05, the power of the study was found to be 99% with 154 students. A theoretical and practical OIP is undertaken during the 5th year of medical school over 3 weeks for all students. In the orthopedic internship program, students take active recruitment in an orthopedic outpatient clinic, patients'room, and operation room under faculty, residents, and OR staff support. Students were requested to complete the previously described questionnaire, (16,17) in which the sub-branches of medicine were divided into pre-clinical, non-surgical, and surgical categories to simplify statistical analyses and to accurately evaluate the preferences of specialties in Turkey. The students completed the questionnaire twice, once on the first day and again on the last day of their OIP. We investigated the distribution of final-year medical students' career choices and the factors that may have played a role in their selection process (**Figure 1a, 1b**). Data collected from final-year medical students who completed the questionnaire included demographic characteristics and the students'interest in each of the pre-clinical, non-surgical, and surgical subspecialties during their OIP in 2018-2019 academic year. Students who declined to volunteer for this study and those who did not complete the questionnaire were excluded (all students participated in the study and completed the


A

First name, surname: Date:

Age: Sex:

Marital status: single/married

Father's occupation: Mother's occupation:

Region:

- Central Anatolia
- Black Sea
- Marmara
- Mediterranean
- Aegean
- Southeast
- Eastern Anatolia

Do you have a family member who is a medical specialist? Yes/No

What factor most influenced your choice?

- Internet
- Medical School
- Family
- Friends
- Books
- Others

Was your selection of specialty branch clear prior to starting medical school: Yes/No

Figure 1a. Questionnaire of career choice

Table of preferences B

Pre-clinical	Order	Non-Surgical	Order	Surgical	Order
Anatomy		Emergency medicine		Anesthesiology	
Medical education and informatics		Forensic and legal medicine		Plastic reconstructive and plastic surgery	
Medical biology		Pediatric psychiatry		Pediatric surgery	
Biophysics		Pediatrics		Neurosurgery	
Medical ethics and history		Dermatology		Cardiovascular surgery	
Immunology		Infectious diseases		Thoracic surgery	
Physiology		Chest and pulmonary medicine		Ophthalmology	
Histology and embryology		Physical therapy and rehabilitation		Gynecology and obstetrics	
Microbiology		Public health		Orthopedics and traumatology	
Biochemistry		Internal medicine		Pathology	
Pharmacology		Cardiology		Urology	
		Neurology		General surgery	
		Nuclear medicine		Ear nose and throat	
		Radiation oncology			
		Radiology			
		Psychiatry			

Figure 1b. Questionnaire of career choice

questionnaire).

The Statistical Package for the Social Sciences (SPSS for Windows Release 21.0 Standard Version Copyright SPSS, Illinois, USA) program was used for statistical analysis. Descriptive statistics related to categorical variables are shown as numbers and percentages, and those associated with numerical variables are presented as mean, standard deviation, median, minimum, and maximum values. A McNemar test was used to compare categorical variables in dependent groups. Chi-square and Fisher's exact tests were used to compare categorical variables in independent groups. A significance level of 0.05 was set ($p<0.05$ if there was a significant difference; $p>0.05$ if no significant difference was stated).

RESULTS

In total, 154 medical students completed the questionnaire before and after their OIP. Most students were from Central Anatolia (71.4%), where our university is located, and one student was not from Turkey. Most students were single (95.5%), and only 23 (14.9%) students had other family members who

Table 1. Demographic characteristics of students.

Demographic features (n=154)	Number	Percentage (%)
Sex		
Female	92	59.7%
Male	62	40.3%
Region		
Central Anatolia	110	71.4%
Black sea	12	7.8%
Mediterranean	10	6.5%
Marmara	9	5.85%
Eastern Anatolia	5	3.25%
Southeastern Anatolia	4	2.6%
Aegean	3	1.95%
Abroad	1	0.65%
Marital status		
Single	147	95.5%
Married	7	4.5%
Specialist physician in the family	23	14.9%
No specialist physician in the family	131	85.1%
Mother's occupation* (n=154)		
Housewife	103	66.9%
Teacher	20	13%
Nurse	13	8.45%
Office worker	9	5.85%
Engineer	3	1.95%
Manual worker	3	1.95%
Retired	2	1.3%
Dental technician	1	0.6%
Father's occupation* (n=154)		
Public servant	39	25.3%
Tradesman	25	16.2%
Manual worker	18	11.7%
Teacher	17	11.0%
Soldier	11	7.2%
Engineer	9	5.9%
Physician	7	4.6%
Laboratory technician	5	3.25%
Farmer	5	3.25%
Academic	3	1.95%
Judge	3	1.95%
Police officer	2	1.3%
Office executive	2	1.3%
Health technician	2	1.3%
Imam	2	1.3%
Building contractor	1	0.65%
Manager	1	0.65%
International relations specialist	1	0.65%
Taxi-driver	1	0.65%
Resources in career choice **		
Medical school	93	60.4%
Friends	39	25.3%
Family	37	24.6%
Internet	29	18.8%
Books	9	5.8%
Other	28	18.2%
Decided on a specialty prior to medical school	28	18.2%
Decided on a specialty during medical school	126	81.8%

** Multiple options were marked

were specialist medical doctors. Students demographic characteristics are given in **Table 1**.

Our findings showed that after the OIP 83 (53.9%) students had changed their preferences and 72 (46.8%) had changed their order of preference. In total, 22 (14.3%) students chose orthopedics prior to the internship and 45 (29.2%) chose orthopedics after the OIP. Prior to the OIP, 4 students (2.6%) placed orthopedics as their first order of preference. After the OIP, this number increased to 11 (7.1%). The increase in the numbers of students who preferred orthopedics (p<0.001) and who placed orthopedics as their first order of preference (p=0.039) was statistically significant after the OIP. Prior to the OIP 100 students placed other surgical specialties in their preference list, while 99 students placed other surgical specialties in their preference list after OIP. Prior to the OIP, 65 students (42.2%) marked surgical specialty as their first preference, and this number increased to 67 (43.5%) after the OIP. However, this increase in the number of students marking surgical specialty as their first preference was not statistically significant after the OIP (p=0.832). Details of pre- and post- OIP preferences of students were summarized in **Table 2**.

Table 2. Details of pre- and post-OIP students'preferences (Orthopedic internship program; OIP)

	Pre-OIP n (%)	Post-OIP n (%)	p values
Who chose orthopedics	22 (14.3%)	45 (29.2%)	<0.001
Placed orthopedics in the first row	4 (2.6%)	11 (7.1%)	0.039
Placed surgical specialties in the first row	65 (42.2%)	67 (43.5%)	0.832
Marking surgical branches			
Female	39 (42.4%)	64 (69.5%)	0.549
Male	26 (41.9%)	44 (70.9%)	0.227

Figure 2 shows the distribution of students'pre- and post-OIP non-surgical, surgical, and pre-clinical specialization preferences. In terms of female students'first order of preference prior to the OIP, 51 (55.4%) had chosen a non-surgical preference, 39 (42.4%) had selected a surgical preference, and 2 (2.2%) had marked pre-clinical branches as their first preference; whereas for male students, 35 (56.5%) had selected non-surgical specialties, 26 (41.9%) had selected surgical specialties, and 1 (1.6%) had marked pre-clinical branches as their first preference. There was no significant difference between the female and male students in terms of marking surgical branches in their first order of preference pre (p=0.955) and post OIP (p=0.182). There was also no significant difference between pre- and post-OIP periods among female (p=0.549) and male (p=0.227) students in terms of marking surgical branches in their first order of preference (**Table 3**). The prevalence of placing orthopedics in any order on the preference list was statistically higher after the OIP than after the pre-OIP period in female (3.3-16.3%) and male (30.6-48.4%) students (p<0.001 and p=0.003, respectively). However, the increase in placing orthopedics in any order in the preference list was significantly greater in male students than in female students pre- (p<0.001) and post-OIP (p<0.001). More male students than female students marked orthopedics as their first order of preference both pre- (6.5%-0%) and post-OIP (12.9%-3.3%) (p=0.025 and p=0.029, respectively). None of the female students and 4 (6.5%) of the male students marked orthopedics in first place pre-OIP, whereas 3 (3.3%) female students and 8 (12.9%) male students marked orthopedics in first place post-OIP (**Table 3**). However, this increase was not statistically significant (p=0.219). We found that the order of orthopedics had changed to become the foremost position on 2 female and 3 male students'preference lists in the pre-OIP period. None of the female students removed or downgraded the order of orthopedics in their preference lists. However, post-OIP, 4 male students downgraded the order of orthopedics in their preference list, and 1 student subsequently removed

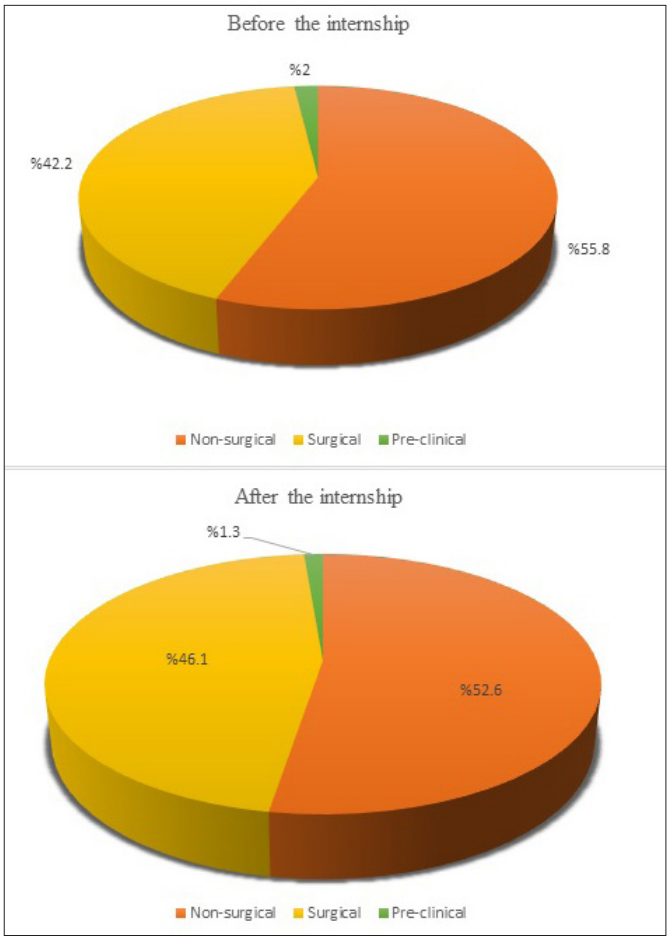

Figure 2. The ratio of students'non-surgical, surgical, and pre-clinical specialization preferences

Table 3. Details of students' preference by pre- and post-OIP according to gender. (Orthopedic internship program; OIP)

	Female n (%)		Male n (%)		p values	
	Pre-OIP	Post-OIP	Pre-OIP	Post-OIP	Pre-OIP	Post-OIP
Placed orthopedics in the first row	0 (0%)	3 (3.3%)	4 (6.5%)	8 (12.9%)	0.025	0.029
Placing orthopedics in any order	3 (3.3%)	19 (30.6%)	15 (16.3%)	30 (48.4%)	<0.001	<0.001
Placed surgical specialties in the first row	39 (42.4%)	36 (39.1%)	26 (41.9%)	31 (50%)	0.955	0.182

it as a preference. The students who changed the order of orthopedics or removed it from the list stated that orthopedics involved a greater workload and had more complicated operations.

Most students'mothers were housewives (66.9%) and most students'fathers were public servants (25.3%). Details of parental occupations are presented in **Table 1**. Twenty-three (14.9%) of the medical students had specialist medical doctors in their families. The distribution of medical students who had a specialist medical doctor in their family was as follows; 6 family medicine, 3 pediatrics, 2 internal medicine, 2 orthopedics, 2 ophthalmology, 2 emergency medicine, 1 physical therapy and rehabilitation, 1 nuclear medicine, 1 public health, 1 pathology, 1 microbiology, 1 psychiatry, 1 general surgery, 1 pediatric surgery, 1 ear nose and throat, and 1 anesthesiology. Of these, 13 students indicated that family-derived information determined their career choice. Two (8.6%) students with specialist doctors in their families chose orthopedics pre-OIP and 6 (26%) students chose orthopedics post-OIP, whereas 20 (15.3%) of the other students chose orthopedics pre-OIP and 39 (29.8%) chose orthopedics post-OIP. Of the medical students who had specialist doctors in their families, 7 (30.4%) marked orthopedics first on their list of preferences pre-OIP and 8 (34.8%) marked orthopedics first on their preference list post-OIP. The frequency of choosing orthopedics as a specialty was significantly higher post-OIP among students with parents in non-medical occupations ($p<0.001$).

Ninety-three (60.4%) students stated that the medical school had influenced their career choice, and most students (81.8%) stated that they had made decisions concerning their career while at medical school. Details of possible factors influencing career choice and decision-making for specialty selection are shown in **Table 1**.

There were 7 (4.5%) married students (3 women, 4 men), none of whom chose orthopedics pre-OIP, whereas one married female and one married male student added orthopedics to their preference list post-OIP. The remaining 6 married students prioritized non-surgical specialties both pre- and post-OIP.

DISCUSSION

This is the first study to determine factors affecting the selection of a medical specialty and choice distribution among 5th-year medical students in Turkey. This pioneering study investigated the factors that affected the specialty choice of medical students and if their preferences changed after the OIP. One of the main study findings was that there were changes in student preferences and preference order after the OIP. However, the number of students who chose surgical specialties did not differ significantly after the OIP. Students undertaking the OIP usually spend their time actively in the outpatient clinic, in patient rooms, in the operating room (OR), and in the orthopedics training laboratory which may explain the increase in the students'choice of orthopedics in their preferences in the early post-OIP period. Therefore, these changes may be temporary, with further changes occurring due to other internship programs. It is possible that the practical aspects of orthopedics, such as casting and splinting, and using plates, screws and hammers might attract certain students more readily than to other surgical branches. On the other hand, this increase in the choice of orthopedics could be a result of the change in the students'perspective regarding surgical branches which may help overcome their reluctance to pick surgical specialties.

A decrease in the selection of surgical specialties among medical students remains a current issue for healthcare services and medical education facilities internationally (18-21). Williams et al. (21) estimated that there would be a deficit of orthopedic surgeons in the United States of America in 2030. Turkey faces a similar situation, where compared with the number of students preferring surgical programs, the number of students preferring both pre-clinical and non-surgical residency programs has increased each year. To address a potential lack of surgeons in the near future, factors affecting career choices in medical education need to be determined.

More than half the students (60.4%) reported their medical school experience and education as the most influential factors in their decision-making. However, there was no significant change in the number of students who chose surgical branches after the 3-week OIP. In contrast, Marshall et al. (22) reported an increased

interest in a surgical career and positive experiences gained within the surgical rotation. Many factors related to career decision-making have been reported to play a significant role in positive experiences. Sedaghat et al. (23) reported that intensive exposure to surgical practice assisted the early student classes with future planning. Cloyd et al. (24) underlined the importance of strong mentorship from the surgical faculty in attracting interest in surgical careers. Active involvement in the OR with exposure to role models (25-27) and supportive relationships with both faculty members and OR staff (27) have been reported to result in positive experiences for medical students, which may influence their choice of a surgical career. In our study, the significant increase in the number of students who added orthopedics to their list of preferences post-OIP may have been related to positive experiences gained during the 3-week OIP. However, there was no increase in preferences for other surgical branches post-OIP. The unchanged status of choosing surgical specialties rather than orthopedics post-OIP may have been due to differences between the OIP content and that of other surgical education programs. The students may have been more actively involved in the OIP with more positive experiences consequently. Moreover, if completion of a program is accepted as a factor affecting career choice in medicine, attendance or nonattendance at other surgical branches at the time of OIP may also have played a role in this result. Wijnen et al. (28) underlined that scientific and empirical-based working methods, knowing their personal limits and possibilities, active professional development, teamwork, and verbal communication with colleagues and supervisors are the most important competences for entrustment decisions of supervisors. The OIP provided certain benefits for the medical students, such as direct and active instructional contact with the orthopedic faculty, find out their personal limits, learning how to be a part of teamwork, including sharing any information about the content, and frankly discussing the positives and negatives of live as an orthopedics resident and life post-residency.

The students'sex may have been a determinant in specialty preference (29). Orthopedic surgery has been reported to be one of the least preferred subspecialties of surgery among female students, (30) despite reports indicating that the total number of female medical students undertaking OIPs has increased (20,30). Our study showed a significant difference between male and female students in selecting orthopedics both pre-OIP (30.6% vs. 3.3%, respectively) and post-OIP (48.4% vs. 16.3%, respectively), although the rates of selecting a surgical specialty were similar. The rates of selecting surgery among female students were similar to those reported in other studies (2,32). Chew et al. (33) stated that female medical students in Malaysia were 1.91 times more likely to choose internal medicine than their male counterparts. In terms of orthopedic surgery, the results in relation to male and female preferences appear more concerning as only 16.3% of female students reported an interest in orthopedic surgery, whereas only 3 students (3.3%) reported placing orthopedics first in their list of preferences post-OIP, and these results are similar to other studies concerning orthopedic residency programs and interest among female students (16,19,31,33). Despite an increase in the number of female medical school students, lower reported rates of interest in surgery and an even lower interest in orthopedics are likely to provide challenges in recruiting high-achieving students into these specialties (31). Failure to attract female students to orthopedics has been reported to be related to factors such as a lack of role models, a perception of physical inadequacy, a mismatch of family life, and the difficulties of orthopedic residency (34,35).

The availability of a non-surgical specialty concerning physical medicine and rehabilitation in treating musculoskeletal system diseases may be another factor contributing to the lack of female orthopedic surgeons. Lambert et al. (36) stated that, popularity of specialties offering a better work/life balance among female students had led to increase in the number of women medical students and to more interest in non-scientific fields than in medicine when compared with previous generations. However, we consider that the reported male dominance in surgery in previous studies cannot simply be associated with the demanding mechanical and technical aspects of the profession as female medical students have been found to be as proficient in terms of surgical and mechanical skills as their male counterparts (35,37). In support of this view, we found that none of the female students removed or downgraded the ranking of orthopedics among their preferences. Baldwin et al. (20) in their retrospective study of factors affecting the interest of female medical students in orthopedics, reported that long working hours, length of residency, and the nature and physical demands of orthopedic procedures were major factors that led to a decreased interest in orthopedics. To increase female students'interest in orthopedics, early exposure to orthopedic education and more practical experience may be effective. Blackmore et al. (31) suggested the creation and implementation of maternity support policies in training programs and in practice to boost female interest in orthopedic surgery.

Of 23 students who had specialist doctors in their family, only 2 students had chosen the same specialization as the family member prior to the OIP, and one student had completely removed orthopedics from their preference list. The remaining 20 students did not choose the same specialization as their family. Baldwin et al. (20) reported

that medical students who had orthopedic surgeons as close friends or family members did not show any significant preference for selecting orthopedic surgery. Similarly, this study found that 2 students who had orthopedic surgeons in their families as well as other students who had specialist doctors in their families did not choose the same specialization as the specialist in their families, although they referred to their family as the most influential factor in their career choice. This finding may be because new-generation medical students tend to be influenced in their career selection primarily role models during their OIP. Johnson et al. (38) found that among 4th-year medical students, the most influential individuals were faculty and resident staff, in terms of affecting residency choice. Blackmore et al. (31) suggested that better representation of orthopedics by both faculty and residents may help students to select orthopedics as a surgical specialty.

This study had several limitations. The questionnaire was conducted pre- and post-OIP. If it had been conducted at the beginning and at the end of the 5th-year of medical school, the final-year students might have provided more informed responses, with more information available concerning all the specialty branches. Changes to specialist preferences may be temporary and student responses may have been affected due to recent exposure to orthopedics. Moreover, each class had completed different internships prior to starting OIP. Therefore, the preferences of students who complete different internships are likely to differ accordingly. In a future study, it is necessary to question the students who have completed 6th year to assess whether the students'interest in surgical branches still continue. Factors such as negative work/life balance, enforced residency, and higher income may have affected students' career choices and these factors were not examined in the study. The questionnaire was not pilot-tested, could have been tested to increase its reliability. Finally, a multicenter study with a greater number of participants, would allow further and more thorough investigation of this topic for gathering both country based, and worldwide data and such a study is recommended in future.

CONCLUSIONS

Non-surgical residency programs are chosen more often than surgical programs in the career choices of medical students, which is likely to lead to a deficit in the number of surgeons in Turkey and countries with similar education programs. Interest in orthopedics among female students is extremely low, mainly due to the lack of role models, the physical demands of the surgical procedures, and a negative work/life balance. A combination of various factors may affect career choice before, during, and after each internship. We demonstrated that early and active recruitment in orthopedics (outpatient clinic and patients'room) and the OR with positive support from faculty, residents, and OR staff may increase interest in orthopedic surgery for both male and female medical students. Therefore, we suggest planning the surgical internship programs by active recruitment of medical students to increase interest in surgical branches.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the local Ethics Committee (Date: 11.07.2018, Approval no. 2018.10.16) and performed in the skill practice laboratory of the Department of Orthopedics and Traumatology at Kırıkkale University School of Medicine.

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

REFERENCES

1. Hauer KE, Durning SJ, Kernan WN, et al. Factors associated with medical students' career choices regarding internal medicine. JAMA 2008; 300: 1154-64.
2. Lefevre JH, Roupret M, Kerneis S, et al. Career choices of medical students: a national survey of 1780 students. Med Educ 2010; 44: 603-12.
3. Wigney T and Parker G. Factors encouraging medical students to a career in psychiatry: qualitative analysis. Aust N Z J Psychiatry 2008; 42: 520-5.
4. Takeda Y, Morio K, Snell L, et al. Characteristic profiles among students and junior doctors with specific career preferences. BMC Med Educ 2013; 13: 125.
5. Newton DA, Grayson MS and Thompson LF. The variable influence of lifestyle and income on medical students' career specialty choices: data from two U.S. medical schools, 1998-2004. Acad Med 2005; 80: 809-14.
6. Gorenflo DW, Ruffin MTt and Sheets KJ. A multivariate model for specialty preference by medical students. J Fam Pract 1994; 39: 570-6.
7. Harris MG, Gavel PH and Young JR. Factors influencing the choice of specialty of Australian medical graduates. Med J Aust 2005; 183: 295-300.
8. Cleland JA, Johnston PW, Anthony M, et al. A survey of factors influencing career preference in new-entrant and exiting medical students from four UK medical schools. BMC Med Educ 2014; 14: 151.
9. Schwartz RW, Jarecky RK, Strodel WE, et al. Controllable

lifestyle: a new factor in career choice by medical students. Acad Med 1989; 64: 606-9.

10. Dorsey ER, Jarjoura D and Rutecki GW. Influence of controllable lifestyle on recent trends in specialty choice by US medical students. JAMA 2003; 290: 1173-8.

11. Saigal P, Takemura Y, Nishiue T, et al. Factors considered by medical students when formulating their specialty preferences in Japan: findings from a qualitative study. BMC Med Educ 2007; 7: 31.

12. Cleland J, Johnston PW, French FH, et al. Associations between medical school and career preferences in Year 1 medical students in Scotland. Med Educ 2012; 46: 473-84.

13. Rosenblatt RA, Cherkin DC, Schneeweiss R, et al. The structure and content of family practice: current status and future trends. J Fam Pract 1982; 15: 681-722.

14. Craton N and Matheson GO. Training and clinical competency in musculoskeletal medicine. Identifying the problem. Sports Med 1993; 15: 328-37.

15. Rekola KE, Keinanen-Kiukaanniemi S and Takala J. Use of primary health services in sparsely populated country districts by patients with musculoskeletal symptoms: consultations with a physician. J Epidemiol Community Health 1993; 47: 153-7.

16. Schroeder JE, Zisk-Rony RY, Liebergall M, et al. Medical students'and interns'interest in orthopedic surgery: the gender factor. J Surg Educ 2014; 71: 198-204.

17. Weissman C, Schroeder J, Elchalal U, et al. Using marketing research concepts to investigate specialty selection by medical students. Med Educ 2012; 46: 974-82.

18. Bath MF, Harries RL and Gokani VJ. Medical Students'and Interns'Interest in Orthopedic Surgery: The Gender Factor. J Surg Educ 2017; 74: 1.

19. Correia Lima de Souza L, Mendonca VR, Garcia GB, et al. Medical Specialty Choice and Related Factors of Brazilian Medical Students and Recent Doctors. PLoS One 2015; 10: 0133585.

20. Baldwin K, Namdari S, Bowers A, et al. Factors affecting interest in orthopedics among female medical students: a prospective analysis. Orthopedics 2011; 34: 919-32.

21. Williams TE, Jr., Satiani B, Thomas A, et al. The impending shortage and the estimated cost of training the future surgical workforce. Ann Surg 2009; 250: 590-7.

22. Marshall DC, Salciccioli JD, Walton SJ, et al. Medical student experience in surgery influences their career choices: a systematic review of the literature. J Surg Educ 2015; 72: 438-45.

23. Sedaghat N, Mondy J, Eslick GD, et al. Exposure of medical students to surgery: the Nepean summer vacation surgical program. J Surg Educ 2012; 69: 580-7.

24. Cloyd J, Holtzman D, O'Sullivan P, et al. Operating room assist: surgical mentorship and operating room experience for preclerkship medical students. J Surg Educ 2008; 65: 275-82.

25. Berman L, Rosenthal MS, Curry LA, et al. Attracting surgical clerks to surgical careers: role models, mentoring, and engagement in the operating room. J Am Coll Surg 2008; 207: 793-800.

26. Redlich PN, Milkowski T, Bragg D, et al. Multiple variables influence the educational value of surgical clerkship sites. Am J Surg 2006; 191: 178-82.

27. Fernando N, McAdam T, Youngson G, et al. Undergraduate medical students'perceptions and expectations of theatre-based learning: how can we improve the student learning experience? Surgeon 2007; 5: 271-4.

28. Wijnen-Meijer M, van der Schaaf M, Nillesen K, et al. Essential facets of competence that enable trust in medical graduates: a ranking study among physician educators in two countries. Perspect Med Educ 2013; 2: 290-7.

29. Anand, R. and P.S. Sankaran, Factors influencing the career preferences of medical students and interns: a cross-sectional, questionnaire-based survey from India. J Educ Eval Health Prof, 2019. 16: 12.

30. Brotherton SE, Rockey PH and Etzel SI. US graduate medical education, 2003-2004. JAMA 2004; 292: 1032-7.

31. Blakemore LC, Hall JM and Biermann JS. Women in surgical residency training programs. J Bone Joint Surg Am 2003; 85: 2477-80.

32. Boyle E, Healy D, Hill AD, et al. Career choices of today's medical students: where does surgery rank? Ir J Med Sci 2013; 182: 337-43.

33. Chew YW, Rajakrishnan S, Low CA, et al. Medical students'choice of specialty and factors determining their choice: a cross-sectional questionnaire survey in Melaka-Manipal Medical College, Malaysia. Biosci Trends 2011; 5: 69-76.

34. Bernstein J, Dicaprio MR and Mehta S. The relationship between required medical school instruction in musculoskeletal medicine and application rates to orthopaedic surgery residency programs. J Bone Joint Surg Am 2004; 86: 2335-8.

35. Egol KA, Collins J and Zuckerman JD. Success in orthopaedic training: resident selection and predictors of quality performance. J Am Acad Orthop Surg 2011; 19: 72-80.

36. Lambert EM and Holmboe ES. The relationship between specialty choice and gender of U.S. medical students, 1990-2003. Acad Med 2005; 80: 797-802.

37. Pico K, Gioe TJ, Vanheest A, et al. Do men outperform women during orthopaedic residency training? Clin Orthop Relat Res 2010; 468: 1804-8.

38. Johnson AL, Sharma J, Chinchilli VM, et al. Why do medical students choose orthopaedics as a career? J Bone Joint Surg Am 2012; 94: 78.

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Evaluation of the relationship between diastolic dysfunction and interatrial block

Diyastolik disfonksiyon ve interatrial blok arasındaki ilişkinin değerlendirilmesi

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ABSTRACT

Background: The interatrial block (IAB) is a condition that occurs due to the delay of conduction in the right atrium to the left atrium, and can be partial (pIAB) or advanced (aIAB), and also is associated with atrial arrhythmia. Diastolic dysfunction (DD) is an important condition frequently encountered in most healthy middle-aged individuals and plays a role in the development of many cardiovascular diseases. It is noteworthy that frequent paroxysmal atrial fibrillation (PAF) attacks are observed especially in individuals with DD in clinical life, and its relationship with the presence of interatrial block is still unclear in these patients. Our aim in this study was to evaluate the relationship between the presence of DD and the development of interatrial block and PAF.

Material and Method: A total of 146; 92 patients with DD and 54 control (proven by echocardiography) were enrolled in this cross-sectional and prospectively study. The properties of the P wave were evaluated in leads D2-3 aVF and V1. Echocardiography and electrocardiography results of the two groups were compared.

Results: The mean age of the DD and the control group was (62.3±0.74 and 61.2±0.61 years, p=0.481) respectively. The frequency of IAB was significantly higher in the DD than the control group (37%-46.7%-16.3%, 77.8%-18.5%-3.7%, and none-pIAB-aIAB, respectively). In the correlation analysis, there was a strong correlation between the presence of DD and IAB (r: 0.439, p<0.001), and the history of PAF and IAB (r: 0.458, p<0.001).

Conclusion: In our study, the frequency of IAB was significantly higher in the DD group. We think that it may be beneficial to evaluate P waves more carefully to determine the risky individuals among those who have DD in clinical life.

Keywords: Interatrial block, diastolic dysfunction, atrial fibrillation

ÖZ

Amaç: Interatrial blok (IAB), sağ atriyumda sol atriyuma iletimin gecikmesi nedeniyle ortaya çıkan bir durumdur ve kısmi (partial-pIAB) veya gelişmiş (advanced-aIAB) olabilir ve ayrıca atriyal aritmi ile ilişkilidir. Diyastolik disfonksiyon (DD), çoğu sağlıklı orta yaşlı bireyde sık karşılaşılan önemli bir durumdur ve birçok kardiyovasküler hastalığın gelişiminde rol oynar. Özellikle klinik yaşamda DD'li bireylerde sık paroksismal atrial fibrilasyon (PAF) ataklarının gözlenmesi dikkat çekicidir ve bu hastalarda IAB varlığı ile ilişkisi hala belirsizdir. Bu çalışmadaki amacımız DD varlığı ile IAB ve PAF gelişimi arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Bu kesitsel ve prospektif çalışmaya DD olan 92 ve 54 kontrol (ekokardiyografi ile kanıtlanmış) olmak üzere toplam 146 kişi dahil edildi. P dalgasının özellikleri, D2-3 aVF ve V1 derivasyonlarında değerlendirildi. İki grubun ekokardiyografi ve elektrokardiyografi sonuçları karşılaştırıldı.

Bulgular: DD ve kontrol grubunun yaş ortalaması sırasıyla (62,3±0.74 ve 61,2±0,61 yıl, p=0,481) idi. IAB sıklığı DD'de kontrol grubuna göre anlamlı olarak yüksekti (sırasıyla, %37-%46,7-%16,3, %77,8-%18,5-%3,7, normal-pIAB-aIAB, p<0,001). Korelasyon analizinde DD varlığı ile IAB arasında (r: 0,439, p<0,001) ve PAF ile IAB öyküsü arasında güçlü bir korelasyon olduğu bulundu (r: 0,458, p<0,001).

Sonuçlar: Çalışmamızda DD grubunda IAB sıklığı anlamlı olarak yüksekti. Klinik hayatta DD olanlarda riskli bireyleri belirlemek için P dalgalarını daha dikkatli değerlendirmenin faydalı olabileceğini düşünüyoruz.

Anahtar Kelimeler: İnteratriyal blok, diyastolik disfonksiyon, atriyal fibrilasyon

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INTRODUCTION

Cardiovascular diseases are common in the general population around the worldwide, affecting the majority of adults older than 60 years, causing most of the deaths in developed countries (1). Diastolic dysfunction (DD) reflects abnormal cardiac relaxation, stiffness or filling, and it plays a key role in the development of heart failure with preserved ejection fraction (HFpEF), atrial fibrillation (AF). Although, preclinical diastolic dysfunction (PDD) is a common finding in older and obese adults. It is a predictor for CVD mortality (2). PDD is a predictor for heart failure and all-cause mortality after controlling for comorbidities (3,4). Also, DD increases LA pressure resulting in atrial dysfunction. Atrial dysfunction, could cause supraventricular arrhythmias and facilitate heart failure (5). Diastolic dysfunction by echocardiography is one of the most important criteria for the diagnosis of HFpEF (6).

The interatrial block (IAB), which was first defined by Bayes de Luna, is a condition that occurs due to the delay of conduction in the right atrium to the LA (7). IAB can be partial (pIAB) or advanced (aIAB) and commonly diagnosed with an electrocardiogram. Because of their association with supraventricular tachyarrhythmia's, electromechanical dysfunction, and embolic stroke, intra and interatrial conduction abnormalities have significant clinical implications (8). Identifying patients with atrial conduction disorders in DD can improve risk classification to guide clinical decisions. Studies have shown that IAB is a predictor for AF development and embolic stroke (9). It has previously been observed that paroxysmal atrial fibrillation (PAF) attacks were more frequent especially individuals with DD in real life, and relation between IAB and DD is still unclear.

This paper argues that there could be a relation between DD and IAB, and this relation could determine the presence of PAF.

MATERIAL AND METHOD

Study Groups

This study was conducted at the Departments of Cardiology of Afyonkarahisar Health Science University between February 1, 2019 and December 1, 2019. This study was approved by the university /local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

A total of 146; 92 patients with DD and 54 control (proven by echocardiography) were enrolled in this cross-sectional and prospectively study. The study population enrolled randomly among the patients who applied to the cardiology outpatient clinic. All participants have echocardiographic measurements. Laboratory findings and demographic variables of all patients were recorded. The study was approved by the local ethics committee (2019/120) and all participating individuals provided written informed consent. This study was performed according to the Declaration of Helsinki II.

Criteria for exclusion the subjects were as follows: pregnancy, under 18 and over 75 age, heart failure with reduced ejection fraction (HFrEF, EF<45%), thyroid and other hormonal disorders, cerebrovascular diseases, serious valve disease, cardiac pacemaker, bundle branch block and supraventricular arrhythmia, drugs known to affect atrial conduction, consuming alcohol, and electrolyte disturbance. The following definitions were used; hypertension, blood pressure ≥140/ 90 mmHg and/ or use of antihypertensive treatment; dyslipidaemia, total cholesterol levels of >200 mg/dl or low density lipoprotein (LDL)-cholesterol levels of ≥130 mg/dl or triglyceride levels of ≥150 mg/dl or HDL cholesterol levels in male ≤40 mg/dl in women ≥50 mg/dl and/or using lipid lowering agents; diabetes mellitus, fasting plasma glucose; ≥126 mg/dl, two-hour plasma glucose ≥200 mg/dL during an OGTT, random (or "casual") plasma glucose ≥200 mg/dL in the presence of symptoms, and/or glucose lowering treatment. Smokers were defined participants who reported smoking currently and regularly (at least five cigarettes per day). Body mass index weight in kilogram divided by the square of height in meters was obtained.

Echocardiographic Measurements

Echocardiography was performed with the Phillips EPIQ CVx (Germany, 2008) with a 3.5 MHz transducer probe. A one-lead ECG was recorded continuously during the echocardiographic examination. The thicknesses of the posterior wall and interventricular septum, LA dimensions, LV end-systolic and end-diastolic diameters were obtained using M-mode in parasternal long axis. LVEF was calculated using Simpson's biplane method. The velocities of the mitral E wave and A wave, deceleration time of E wave and E/A ratio were acquired using pulsed Doppler from the apical four-chamber view on the mitral valve. The Valsalva maneuver test was used to separate grade 1-2 DD. Furthermore, velocities and systolic times of the mitral lateral annular were acquired using pulsed Doppler and Tissue Doppler echocardiography from the apical four-chamber view. All echocardiographic procedures were performed by the same operator. Measurements were made in accordance with the recommendations of the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) (10,11). According to the ASE and the EACVI guidelines, diastolic filling patterns were categorized as normal, grade I (abnormal relaxation), grade II (pseudo normal), and grade III (restrictive filling). DD classification was made according to the proposed measurements (**Table 1**).

Table 1. The recommendations of classification diastolic filling patterns by ASE and EACVI

Variables	Normal	Grade I (abnormal relaxation)	Grade II (pseudo normal)	Grade III (restrictive filling)
Mitral E/A ratio	>0,8	≤0.8	>0.8-<2	>2
Average E/e'ratio	<10	<10	10-14	>14
LA maximum volume index, mL/m^2	<34	Normal or increased	>34	>34
Decelaration time, msec	140-240	>240	Normal or prolonged	<140
TR systolic jet velocity (m/sec)	<2.8	<2.8	>2.8	>2.8
İsovolumetric relaxation time, ms	>90	>90	<90	<70

A: Late diastolic mitral flow velocities, ASE: American Society of Echocardiography, E: Early diastolic mitral flow velocities, EACVI: European Association of Cardiovascular Imaging, LA: Left atrium, TR: Tricuspid regurgitation

Electrocardiographic Measurements

A 12-lead ECG (Nihon Kohden Cardiofax S, Tokyo, Japan) was performed according to established standards of American Heart Association Electrocardiography and Arrhythmias Committee (12). One experienced operator blinded to the Echocardiography data analyzed the ECGs. At rest, 12-lead ECG recordings of 1 mV/cm amplitude and 50 mm/sec were obtained. The properties of the P wave were evaluated in leads D2-3 aVF and V1. And definitions was made according to the following criteria; The pIAB is characterized by a P wave duration ≥120 milliseconds (ms) on a 12-lead (ECG). The diagnosis of aIAB is made by a P-wave duration ≥120 ms and a biphasic or +/− morphology of the P-wave in leads II, III, and aVF of the ECG (13).

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 22.0 software (IBM Corp., Armonk, NY, USA). Variables were investigated using visual and analytic methods to determine normal distribution. Descriptive analysis are presented using the mean±SD for normally distributed variables, median and interquartile ranges for abnormally distributed variables. A chi-square test was used to compare nominal and categorical variables (such as gender, hypertension, hyperlipidaemia) The mean value of variables with normal distribution was tested with a T-test, and abnormally distributed variables were tested with the non-parametric Mann-Whitney U test. Correlation analysis was applied using Spearman and Pearson tests according to distribution. Multivariate analysis using a logistic regression model was performed to determine presence of IAB and odds ratios (OR) with a 95% confidence interval (CI) were calculated. A p-value< 0.05 was considered statistically significant.

RESULTS

The mean age of the DD and the control group was 62.3±0.74 years and 61.2±0.61 years, respectively. There were no significant differences between the groups concerning the variables of gender, smoking, hyperlipidaemia, and diabetes mellitus. However, hypertension frequency was higher in DD group than the control. The frequency of IAB was significantly higher in the DD than the control group (37%-46.7%-16.3%, 77.8%-18.5%-3.7%, and none-pIAB-aIAB, respectively). The demographic characteristics of the participants in the study are summarized in **Table 2**.

As expected in the analysis of the echocardiographic results of the groups, there were significant differences in the parameters showing diastolic functions. There was no significant difference between the groups in terms of left ventricular diameters, ejection fraction value, and valve functions. All 2D and tissue Doppler echocardiography data of the study groups are presented in **Table 3**.

In the correlation analysis, there was a strong correlation between the presence of DD and IAB (r: 0.439, p<0.001), and the history of PAF and IAB (r: 0.458, p<0.001). Also, a significant correlation between DD and IAB with echo parameters were determined as shown in **Table 4**.

Table 4. Correlation analysis between clinical variables

Diastolic DF. –	Spearman's Rho	P value	IAB –	Spearman's Rho	P value
IAB	R:0.439	P<0.001	**PAF**	R: 0.458	P<0.001
PAF	R:0.366	P<0.001	**Age**	R: 0.179	P=0.030
Age	R:0.331	P<0.002	**IVS**	R: 0.166	P=0.045
LVEDD	R:0.186	P=0.024	**PW**	R: 0.189	P=0.022
LA	R:0.288	P<0.001	**E/A**	R:-0.178	P=0.031
AO	R:0.328	P<0.001	**Em**	R:-0.307	P<0.001
IVS	R:0.338	P<0.001	**Am**	R: 0.260	P=0.002
PW	R:0.353	P<0.001	**Em/Am**	R:-0.350	P<0.001
E	R:-0.357	P<0.001	-	-	-
A	R: 0.254	P=0.002	-	-	-
E/A	R:-0.415	P<0.001	-	-	-
E/E m	R: 0.294	P<0.001	-	-	-
IVRT	R:-0.396	P<0.001	-	-	-
Em	R:-0.415	P<0.001	-	-	-
Am	R: 0.294	P<0.001	-	-	-
Em/Am	R:-0.396	P<0.001	-	-	-

p<0.05 statistical significance, A: Late diastolic mitral flow velocities, AO: Aort root, DD: Diastolic dysfunction, E: Early diastolic mitral flow velocities, IAB: Interatrial block, IVRT: Isovolumetric relaxation time, IVS: Interventricular septum, LA: Left atrium, LVEDD: Left ventricular end diastolic diameter, m: Tissue Doppler mitral flow velocities, PAF: Paroxysmal atrial fibrillation, PW: Posterior wall, Rho: Spearman correlation coefficient, TDI: Tissue Doppler Imaging

Table 2. Baseline demographic and clinical characteristics of study groups

Variables	Control (n:54)	DD (n:92)	P value
Gender, Male/Female, n (%)	31/23 (57.4%/42.6%)	48/44 (52.2%/47.8%)	0.540*
Age, year	61.2±0.61	62.3±0.74	0.481#
Diabetes Mellitus, n (%)	5 (9.3%)	17 (18.5%)	0.133*
Hypertension, n (%)	13 (24.1%)	39 (42.4%)	0.026*
Hyperlipidemia, n (%)	9 (16.7%)	19 (20.7%)	0.555*
Thyroid disorder, n (%)	6 (11.1%)	10 (10.9%)	0.964*
CAD, n (%)	12 (22.2%)	18 (18.9%)	0.701*
COPD, n (%)	5 (9.3%)	11 (12%)	0.614*
Paroxysmal AF history, n (%)	7 (13.2%)	40 (43.5%)	0.001*
Inter atrial block, n (%) (None/ Partial/ Advanced)	42/10/2 (77.8%/18.5%/3.7%)	34/43/15 (37%/46.7%/16.3%)	0.001*
Inter atrial block, Post-hoc analysis			
None – Partial	42 (80.8%)-10 (19.2%)	34 (44.2%)-43 (55.8%)	<0.001*
None -Advanced	42 (95.5%)-2 (4.5%)	34 (69.4%)-15 (30.6%)	0.001*
Partial – Advanced	10 (83.3%)-2 (16.7%)	43 (74.1%)-15 (25.9%)	0.499*
Fasting glucose (mg/dl)	81 (75.7-92.9)	86 (81-101)	0.093**
Hemoglobin (g/dl)	13.06±0.15	13.57±0.17	0.056#
Creatinine (mg/dl)	0.89 (0.7-0.9)	0.7 (0.6-0.9)	0.001**
Total cholesterol (mg/dl)	154.5 (140-169)	165 (141-194)	0.090**
Triglyceride (mg/dl)	140 (124-164)	154 (125-186)	0.167**
LDL- cholesterol (mg/dl)	91.5 (75-115)	97.5 (76-125)	0.420**
HDL- cholesterol (mg/dl)	42 (38-49)	41 (38-45)	0.163**
WBC ($x10^3$/uL)	7.92 (6.07-8.9)	7.35 (6.22-9)	0.937**
Mean platelet volume	9.85 (9.05-11.4)	9.65 (8.9-10.5)	0.207**
Neutrophil count ($x10^3$/uL)	4 (3.4-5.07)	4.29 (3.35-5.1)	0.364**
Lymphocyte count ($x10^3$/uL)	2.42±0.10	2.30±0.65	0.285#
Monocyte count ($x10^3$/uL)	0.67±0.25	0.64±0.20	0.408#
Platelet count ($x10^3$/uL)	246.9±7.97	260±7.2	0.244#

* Chi-square test, ** Mann Whitney U test, # Independent simple T-test, ±: standard deviation, n: individual number. p<0.05 statistical significance.
AF: Atrial fibrillation, BMI: Body Mass Index, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, DD: Diastolic dysfunction, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, WBC: white blood cell

Table 3. Echocardiographic findings of DD and control groups

Variables	Control (n:54)	DD (n:92)	P value
LVEDD (mm)	45 (43-48)	47.5 (45-50)	0.027**
LVESD (mm)	28 (27-30)	29 (27-31)	0.268**
LVEF Simpson (%)	63 (61-65)	63 (59-64)	0.067**
IVS (mm)	9.87±0.19	11.02±0.16	<0.001#
PW (mm)	9.59±0.16	10.47±0.14	<0.001#
LA volume (ml/m^2)	33.5 (30-36)	36 (34-38)	<0.001**
AO (mm)	25.06±0.4	26.9±0.3	0.001#
PAB, mmHg	20 (15-24)	24 (18-28)	0.051**
Diastolic degree, 1-2-3	-	60, 22, 10	-
Mitral E, cm/sn	110 (91.5-124)	70 (62.82)	<0.001**
Mitral A, cm/sn	69 (62-75)	85 (72-92)	<0.001**
Mitral E/A ratio	1.56 (1.41-1.68)	0.78 (0.70-1.11)	<0.001**
Deceleration time (msn)	152 (135-174)	189 (156-224)	<0.001**
E m, cm/sn	11.9±0.2	7.46±0.17	<0.001#
A m, cm/sn	7.42±0.19	11.3±0.28	<0.001#
S m, cm/sn	8.92±0.49	11.2±0.29	<0.001#
TDI E/A ratio	1.57 (1.42-1.83)	0.66 (0.57-0.77)	<0.001**
IVRT, m/sn	76.92±1.07	69.79±1.41	0.001#
Mitral E/Em ratio	9.4 (7.7-10.6)	9.3 (8-12)	0.196**
MR degree, n (0-1-2-3-4)	19-31-3-1-0	22-56-12-2-0	0.380*
TR degree, n (0-1-2-3-4)	16-31-7-0-0	26-61-4-1-0	0.222*
AR degree, n (0-1-2-3-4)	49-5-0-0-0	77-15-0-0-0	0.232*
PR degree, n (0-1-2-3-4)	50-4-0-0-0	86-6-0-0-0	0.832*

Independent simple T-test, ** Mann Whitney U test, ±: standard deviation, n: individual number.
A: Late diastolic mitral flow velocities, AR: Aort regurgitation, AO: Aort root, DD: Diastolic dysfunction, E: Early diastolic mitral flow velocities, IVRT: Isovolumetric relaxation time, IVS: Interventricular septum, LA: Left atrium, LVEDD: Left ventricular end diastolic diameter, LVEF: Left ventricular ejection fraction, LVESD: Left ventricular end systolic diameter, m: Tissue Doppler mitral flow velocities, MR: Mitral regurgitation, PAB: Pulmonary artery pressure, PR: Pulmonary regurgitation, PW: Posterior wall, TDI: Tissue Doppler Imaging, TR: Tricuspid regurgitation

In logistic regression analysis; DD [Odds ratio (OR)=1.338, confidence interval (CI) %95 (0.364-2.312); p=0.007], PAF [OR: 2.48 %95, CI (1.32-3.63); p<0.001] were found to be independent predictors for IAB presence. No significant results were observed in other parameters in regression analysis.

DISCUSSION

Atrial conduction irregularity is common outcomes of a variety of cardiovascular conditions. In the majority, they are readily identified by non-invasive electrocardiography as an increased P wave duration as well as characteristic morphologic features. In recent studies have shown that IAB is associated with many different cardiovascular conditions (14,15). Also, aIAB was found to predict all-cause mortality after ischemic stroke (16). DD has seen frequently in daily clinic routine, and there are very few studies in the literature evaluating its relationship with IAB. The main finding of our study was that the frequency of IAB increased in the presence of DD significantly, and there was a strong correlation between IAB and DD. We have also found that DD was an independent determinant for the development of IAB. In the evaluation of these patients, we think that more attention should be paid to the presence of IAB in their ECG. As we know from previous studies, IAB is a predictor of atrial arrhythmias, particularly AF (17). Given that IAB is associated with increased arrhythmic and embolic events, early recognition of IAB can help reduce CV events that may occur in these patients.

Advanced IAB has an estimated prevalence was 0.1–0.5% in the population, with an incidence of 2.27 per 1000 person-years (15). The frequency of pIAB is much higher. In the large ECG studies reported prevalences of pIAB between 20%-47% of individuals on the different population with sinus rhythm (18,19). Although the incidence of IAB is high, its diagnosis is skipped frequently. However, it was shown in studies that this situation led to important results. In the study of Kaykha et al. (20), approximately 40.000 people were evaluated and found that IAB were strong predictors of CV death. In another study, which 7.500 people were evaluated and the follow-up period was 8.6 years, it was found that P wave duration was associated with both CV mortality and all-cause death, after adjustment for cardiovascular risk factors (21). Considering this data, the increased frequency of IAB in individuals with DD indicates that these patients can cause significant clinical events. In another study that evaluates 11.956 individuals, hypertension and overweight/obesity were the main risk factors for DD, and significantly associated with IAB (22). In our study, the frequency of IAB was significantly higher in the DD group. We think that it may be beneficial to evaluate P waves more carefully to determine the risky individuals among those who have DD in clinical life.

As is known, DD is an independent predictor for AF development. It is known that LA dilatation, fibrosis, and remodelling, especially in these patients, lead to this condition (23). In the echo-Doppler investigation of Goyal and Spodick, was found that IAB was associated with a sluggish, poorly contractile LA and that the degree of dysfunction was related to the degree of conduction delay between the RA and LA (24). In a study investigating LA strain and strain rate using speckle tracking echocardiography, reported that IAB correlates directly with LA structural remodelling and a decrease in LA strain patterns (25). Several studies have implicated IAB in the development of new-onset AF, whereas others have reported no significant associations (26). In previous studies were found that IAB diagnosed from a 12-lead electrocardiogram is associated with a high incidence of subsequent AF (27). Also, IAB associated with an increase of supraventricular tachyarrhythmia's and atrial premature beats (7). It was shown in previous studies that the increase in the frequency of IAB was associated with an increase in the frequency of thromboembolic events other than AF. In our study, the history of PAF was more common in the DD group. The reason for this relationship may be LA changes due to DD and subsequent IAB. In these patients, early detection of IAB may alert clinicians earlier in terms of AF. We think that the findings of our study may be useful for DD patients, which are common in daily life. Determining the presence of IAB in ECG for the identification of risky patients can be an easy, practical, useful, and inexpensive marker.

Study limitations

There are some limitations in this study. In our study, the low number of patients, especially the number of control groups, was an important limitation. Other limitations were the evaluation of ECGs and the application of echocardiography. We have not out the high-resolution computer software program for the evaluation of ECG results in this study. Another limitation was the fact that single-center of our study. Also research with a larger number of patients, as well as other contributions, is needed to support our findings.

CONCLUSION

The aim of the present research was to examine the relevance between DD and IAB. And we found that the frequency of IAB increased significantly in the presence of DD and there was a strong correlation between them. The research has also shown that DD is an independent determinant for the development of IAB. Determining the presence of IAB in ECG for the identification of risky patients can be an easy, practical, useful, and inexpensive marker.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Departments of Cardiology of The study was approved by the Afyonkarahisar Health Science University Ethics Committee. University ethics committee (2019/120).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

REFERENCES

1. Laslett LJ, Alagona PJ, Clark BA 3rd, et al. The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. J Am Coll Cardiol 2012; 60: S1-49.
2. Wan S-H, Vogel MW, Chen HH. Pre-clinical diastolic dysfunction. J Am Coll Cardiol 2014; 63: 407–16.
3. Kane GC, Karon BL, Mahoney DW, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. JAMA 2011; 306: 856–63.
4. Redfield MM, Jacobsen SJ, Burnett JCJ, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003; 289: 194–202.
5. Yildirir A, Batur MK, Oto A. Hypertension and arrhythmia: blood pressure control and beyond. Europace 2002; 4: 175–82.
6. Paulus WJ, Tschöpe C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007; 28: 2539–50.
7. Bayes de Luna A, Cladellas M, et al. Interatrial conduction block and retrograde activation of the left atrium and paroxysmal supraventricular tachyarrhythmia. Eur Heart J. 1988; 9: 1112–8.
8. Johner N, Namdar M, Shah DC. Intra- and interatrial conduction abnormalities: hemodynamic and arrhythmic significance. J Interv Card Electrophysiol 2018; 52: 293–302.
9. Lorbar M, Levrault R, Phadke JG, Spodick DH. Interatrial block as a predictor of embolic stroke. Am J Cardiol 2005; 95: 667–8.
10. Sahn DJ, DeMaria A, Kisslo J, Weyman AF. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation. 1978; 58: 1072–83.
11. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016; 29: 277–314.
12. Kligfield P, Gettes LS, Bailey JJ, et al. Recommendations for the standardization and interpretation of the electrocardiogram: part I: The electrocardiogram and its technology: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Cl. Circulation 2007; 115: 1306–24.
13. de Luna AB, Platonov P, Cosio FG, et al. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. J Electrocardiol 2012; 45: 445–51.
14. Ariyarajah V, Asad N, Tandar A, Spodick DH. Interatrial block: pandemic prevalence, significance, and diagnosis. Chest 2005 Aug; 128: 970–5.
15. O'Neal WT, Zhang Z-M, Loehr LR, Chen LY, Alonso A, Soliman EZ. Electrocardiographic advanced interatrial block and atrial fibrillation risk in the general population. Am J Cardiol 2016; 117: 1755–9.
16. Baturova MA, Lindgren A, Shubik Y V, Carlson J, Platonov PG. Interatrial block in prediction of all-cause mortality after first-ever ischemic stroke. BMC Cardiovasc Disord 2019; 19: 37.
17. Russo V, Papa AA, Rago A, et al. Interatrial block to predict atrial fibrillation in myotonic dystrophy type 1. Neuromuscul Disord 2018; 28: 327–33.
18. Nielsen JB, Kühl JT, Pietersen A, et al. P-wave duration and the risk of atrial fibrillation: Results from the Copenhagen ECG Study. Hear Rhythm 2015; 12: 1887–95.
19. Frisella ME, Spodick DH. Confirmation of the prevalence and importance of a 12-lead investigation for diagnosis. Am J Cardiol 2005; 96: 696–7.
20. Kaykha A, Myers J, Desser KB, Laufer N, Froelicher VF. The prognostic importance of isolated P-wave abnormalities. Clin Cardiol 2010; 33: E87–93.
21. Magnani JW, Gorodeski EZ, Johnson VM, et al. P wave duration is associated with cardiovascular and all-cause mortality outcomes: the National Health and Nutrition Examination Survey. Hear Rhythm 2011; 8: 93–100.
22. Sun G, Zhou Y, Ye N, Wu S, Sun Y. Independent associations of blood pressure and body mass index with interatrial block: a cross-sectional study in general Chinese population. BMJ Open 2019; 9: e029463.
23. Eicher J, Laurent G, Mathé A, et al. Atrial dyssynchrony syndrome: an overlooked phenomenon and a potential cause of 'diastolic'heart failure. Eur J Heart Fail 2012; 14: 248–58.
24. Goyal SB, Spodick DH. Electromechanical dysfunction of the left atrium associated with interatrial block. Am Heart J 2001; 142: 823–7.
25. Lacalzada-Almeida J, Izquierdo-Gómez MM, Belleyo-Belkasem C, et al. Interatrial block and atrial remodeling assessed using speckle tracking echocardiography. BMC Cardiovasc Disord 2018; 18: 38.
26. Tse G, Wong CW, Gong M, et al. Predictive value of inter-atrial block for new onset or recurrent atrial fibrillation: A systematic review and meta-analysis. Int J Cardiol 2018; 250: 152–6.
27. Agarwal YK, Aronow WS, Levy JA, Spodick DH. Association of interatrial block with development of atrial fibrillation. Am J Cardiol 2003; 91: 882.

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The effect of erector spinae plane block on cost of percutaneous nephrolithotomy surgery

Erektör spina plan bloğunun perkütan nefrolitotomi cerrahisi maliyetine etkisi

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ABSTRACT

Aim: The analgesic effect of ESPB for percutaneous nephrolithotomy have been reported in a few study. However there is not any study yet in terms of the effect of ESPB on the cost of anesthesia. The aim of the study is to evaluate the effect of ESPB on sevoflurane and opioid consumption and cost for percutaneous nephrolithotomy.

Material and Method: The patients who underwent percutaneous nephrolithotomy were divided into two groups as ESPB group (Group B; N, 30) and non-ESPB group (Group K; N, 31) whether ESPB was performed or not in this prospective observatioanl study. Total consumption of sevoflurane, remifentanyl and total consumption of tramadol was recorded. Total consumption of sevoflurane, remifentanil and tramadol was multiplied by the unit price of the drug (milliliter and milligram) for determining cost estimation.

Results: The total amount of remifentanil, sevoflurane and tramadol consumption were significantly lower in the Group B (respectively; p=0.009, p=0.001, p<0.001). The total remifentanil, sevoflurane and tramadol costs were found to be statistically significantly lower in the Group B (respectively: p=0.006, p=0.001, p<0.001).

Conclusion: The ESPB is a cost-effective procedure and contributes to the multimodal anesthesia.

Keywords: ESPB, cost estimation, percutaneous nephrolithotomy, anesthesia, analgesia

ÖZ

Amaç: ESPB'nun perkütan nefrolitotomi cerrahisinde analjezik etkileri çok az bir çalışma ile rapor edilmiştir. Ancak ESPB'nun anestezi maliyeti üzerine etkisi hakkında henüz bir çalışma yoktur. Bu çalışmanın amacı ESPB'nun perkütan nefrolitotomi cerrahisi için sevofluran ve opioid tüketimi ve maliyeti üzerine etkisini değerlendirmektir.

Gereç ve Yöntem: Bu prospektif gözlemsel çalışmada perkütan nefrolitotomi geçiren hastalar ESPB'u yapılan (Grup B; 30) ve blok yapılmayan (Grup K; 31) şeklinde iki gruba ayrılmıştır. Sevofluran, remifentanil ve tramadol toplam tüketim miktarları kaydedilmiştir. Maliyet tahmini için sevofluran, remifentanil ve tramadolün toplam tüketilen miktarları ilaçların birim fiyatları (mililitre ve miligram) ile çarpılmıştır.

Bulgular: Toplam tüketilen remifentanil miktarı, sevofluran miktarı ve tramadol miktarı Grup B'de anlamlı olarak düşüktü (sırasıyla; p=0.009, p=0.001, p<0.001). Toplam remifentanil, sevofluran maliyeti ve tramadol maliyeti Grup B'de istatistiksel olarak anlamlı derecede düşük idi (sırasıyla; p=0.006, p=0.001, p<0.001).

Sonuç: ESPB'u maliyet etkin bir uygulamadır ve multimodal anesteziye katkı sağlamaktadır.

Anahtar kelimeler: ESPB, maliyet tahmini, perkütan nefrolitotomi, anestezi, analjezi

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INTRODUCTION

Health expenditure is increasing day by day due to developing technology and increasing prices.1 Therefore, cost control becomes inevitable (1). Although anesthesia seems to be a part of the cost of the surgical procedure, the cost-increasing effect of many anesthesia applications can be observed in the long term (2). The surgical procedure, the drugs used in the anesthesia practice and the type of anesthesia are the factors affecting the total anesthesia cost (3). Reducing expensive drug use in anesthesia practice has been shown as an appropriate method for cost control (4).

In clinical practice, inhalation agents are more frequently used both in induction and maintaining of anesthesia. The efficacy and safety of inhalation agents are well established and clinical investigations have continued to define the different interactions between the drugs (5). Due to the higher cost of inhalation agents in total anesthesia-related expenditure, different management methods have been researched for decreasing the inhalation agents's requirements (3,6).

Intravenous (IV) opioids have been used to manage nociception in intraoperative and to treat pain in the early postoperative period (7). Several methods have suggested for anesthesiologists and surgeons to decrease unnecessary opioid use, opioid-related adverse events, and side effects in the perioperative period (8).

Erector spinae plane block (ESPB) is a new technique used for management of pain (9). Local anesthetics were injected interfascial plane of the structures (10). Göktaş et al. (11) reported that the local anesthetic infiltration via epidural catheter after anesthesia induction reduced the consumption of inhaled agent. It is well known that local anesthesics reduce the consumption of inhaled agent due to reducing the minimum alveolar concentration (MAC) of inhalation anesthetics because of their central action after being absorbed from the injection site (11,12).

The analgesic effect of ESPB have been reported (13). However there is not any study regarding the effect of ESPB on the cost. In addition, ultrasound-guided ESPB has been performed in very few studies in patients undergoing percutaneous nephrolithotomy (PCNL) (14,15). In this study, we aimed to evaluate the effect of ESPB on sevoflurane and opioid consumption and cost.

MATERIAL AND METHODS

This prospective observational study was approved by Local Ethics Committee (2019/11, Ref. No: 2019.06.08). Written informed consent form was taken from all patients. ASA (American Society of Anesthesiology) I-II-III, between 18-75 years old, 61 patients who underwent percutaneous nephrolithotomy between August 2019 and December 2019 were included in the present study according to the Declaration of Helsinki. Patients with central nervous system disease, severe cardiovascular system disease, liver failure, kidney failure, impaired coagulation parameters, allergy to any of the study drug, infection of the injection site, obesity (body mass index >35 kg m^{-2}) and open surgery procedures were not included in the study.

Erector spinae plane block is performed in our clinic for postoperative analgesia for patients (who request) who undergoing PCNL surgery. Patients who underwent PNCL between the dates specified in the previous paragraph and who had undergone block and not were included in the present study. The patients were divided into two groups as ESPB (Group B; N, 30) and non-ESPB (Group K; N, 31) whether ESPB was performed or not. In our clinic ESPB was performed as follows;

All patients underwent standard monitoring (heart rate, oxygen saturation, non-invasive blood pressure measurement). In Group B, ESPB (inplane approach) was performed with bilateral ultrasound at T10 level for patients with sitting position under midazolam (0.03 mg/kg) sedation. The ESPB was made using a 7-18 MHz linear ultrasound probe (Esaote My Lab 6 US Machine, Florance, Italy) and a 22 gauge 100 mm needle (B. Braun, Germany). It was performed by another experienced anesthetist who did not manage the perioperative anesthesia of the patients. The skin was sterilized with povidone iodine. The probe covered with aseptic sheath was placed parallel to the T10 vertebral axis and moved medial side to the lateral side. When the shadow of the eight rib and the transvers process was seen, the needle was inserted toward the trapesius and erector spinae mucsle and T10 transvers process. The needle contacted to the transvers process. Two milliliter (ml) of saline was injected and the interfascial plane between erector spinae muscle and the transvers process was confirmed. Thirty ml of 0.25% bupivacaine was applied to one side and local anesthetic spread was observed. After the block procedure, the patients were taken to the operating room. All patients were monitored (peripheral oxygen saturation, heart rate, noninvasive mean blood pressure) and standard general anesthesia was applied. Thiopental sodium 5-7 mg/kg (i.v.) and fentanyl 1.5-2 mg/kg (i.v.) were used in anesthesia induction and 0.6 mg/kg (i.v.) rocuronium was applied to facilitate tracheal intubation. The maintenance of anesthesia was carried out in 2% sevoflurane, 50% air and 50% oxygen, with controlled ventilation in 4 L fresh gas flow. Bispecteral index (BIS) (A-2000, Aspect Medical Systems, USA) was used to control the depth of anesthesia. BIS values were kept between 40-50 with increasing or decreasing sevoflurane

concentrations in both groups. Remifentanil (0.5-1 mcg/kg/min) infusion was administered to patients without sufficient depth who were hemodynamically unstable. Muscle relaxant was applied repeatedly according to the TOF rate (when reached 25%) throughout the operation. In addition to routine monitoring parameters, the MAC values of sevoflurane in the 5th, 10th, 15th, 20th, 25th, 30th, 35th, 40th, 45th, 60th, 90th, 110th, 130th, 150th minutes were recorded. The characteristics (age, gender, ASA) and anesthetic properties (duration of anesthesia, duration of surgery, total sevoflurane consumption, total remifentanil consumption) were also recorded. In addition, tramadol consumption according to postoperative pain follow-ups (24 hour) were recorded. The amount of sevoflurane was calculated according to how long the inhalation anesthesia (sevoflurane) was applied, the varying fresh gas (FG) flow and volatile anesthetic (VA) concentration settings. The total consumption amount of sevoflurane gas was determined by calculating the VA consumption of each time period using the formula reported by Biro (16):

Fluid sevoflurane (ml)=FG flow (ml/dk)1×VA conc (vol%)2×Anesthesia duration (min)/saturated gas volume (ml/ml)3×100 (vol %)

1. FG flow of sevoflurane
2. Sevoflurane concentration
3. Sevoflurane vapor volume

Postoperative analgesia was performed with 1000 milligram (mg) parasetamol and 50 mg dexketoprophene twenty minute before the end of the surgery. Neostigmine (0.05 mg/kg) and atropine (0.01 mg/kg) were applied to restore the patient's muscle strength after spontaneous ventilation was achieved. Patients were extubated and transferred to the post anesthesia care unit. Visual analog scale (VAS) scores (0-3; mild pain, 4-6; moderate pain, 7-10; severe pain) were recorded that indicate no to severe pain of patients at postoperative 0th, 1th, 2th, 6th, 12th and 24th hours (17). Resque analgesic (1 mg/kg intravenous tramadol) was administered when VAS scores were more than four. Total consumption of tramadol was recorded. The total consumption of sevoflurane, remifentanil and tramadol was multiplied by the unit price of the drug (milliliter and milligram) for determining cost estimation.

Sampla size calculation

The results of our preliminary study were used for sample size calculation. Accordingly, consumption of sevoflurane was 42.85±9.86 ml in the Group B and 53.15±14.89 ml in the Group K. According to these data, the minimum sample size required for this study was determined as 54 using G * Power 3.1.9.2 software with an error of 0.05 and a power of 0.90. Sixty one (61) patients were enrolled in the study considering dropout rate of 10%.

Statistical analysis

The statistical analysis was performed with SPSS program for Windows Version 20.0 statistical package (IBM Corporation, Armonk, NY, USA). Data were analyzed with Kolmogorov-Smirnov test for conformity to normal distribution. According to the distribution of the data, if the normal distribution does not fit, the Mann-Whitney-U test was performed. Independent T-test was used for comparison between groups in normally distributed data. Continuous variables were presented as mean±standard deviation or median (minimum-maximum) according to the distribution. For categorical variables, frequency counts and percentages were calculated. P values lower than 0.05 have been considered statistically significant.

RESULTS

Sixty one (61) patients were included in the present study. There was no significant difference between the demographic and anesthtetic characteristics (age, sex, ASA status, anesthesia time, surgery time) of the patients between the groups (p>0.05) (**Table 1**). There was no significant difference between the perioperative follow-up parameters (heart rate, mean blood pressure, BIS values, discharge time) of the patients between the groups (p>0.05) (**Table 2**). The time of the first analgesic was given to the patient was statistically significantly longer in Group B than Group K (p=0.008) (**Table 2**). Mean MAC values were statistically significantly higher in the Group K (p<0.001) (**Table 2**). The total amount of remifentanil consumption, the total amount of sevoflurane consumption and the total amount of tramadol consumption of the patients were significantly lower in the Group B in the perioperative period (respectively; p=0.009, p=0.001, p<0.001) (**Table 3**).

Table 1. Anesthesia and surgical features of patients

	Group B N, 30	Group K N, 31	P value
Age, mean±sd	48.07±14.61	47.23±14.02	0.79
Sex (F/M), n	7/23	7/24	0.75
ASA, n (%)			
I	8 (25.9%)	7 (22.6%)	
II	15 (51.9%)	22 (70.9%)	0.25
III	7 (22.2%)	2 (6.5%)	
Anesthesia duration, min, mean±sd	130.22±17.11	127.76±17.82	0.42
Surgery duration, min, mean±sd	122.59±17.23	120.11±18.55	0.39

Group B, patients with ESPB; group K, patients with non block; F, female; M, male; sd, standart deviation

The total remifentanil cost, sevoflurane cost and tramadol cost obtained by multiplying the unit prices of these drugs used in the perioperative period were found to be statistically significantly lower in the Group B (p=0.006, p=0.001, p<0.001) (**Table 3**).

Table 2. Perioperative follow-up results of patients

	Group B N, 30	Grup K N, 31	P value
HR, beat/min, mean±sd	69.87±2.76	70.09±3.00	0.81
MBP, mmHg, mean±sd	76.91±3.20	76.33±3.16	0.43
MAKmean mean±sd	0.80±0.01	1.10±0.01	<0.001*
BİS, mean±sd	45.77±1.88	45.91±1.84	0.77
First analgesia time, hour, mean±sd	3.78±2.37	2.37±1.00	0.008*
Discharge time, day mean±sd	3.93±1.41	4.38±1.55	0.24

Group B, patients with ESPB; group K, patients without block; N, number; HR, heart rate; MBP, mean blood pressure; MAK, minimum alveolar concentration; BİS, bispecteral index; sd, standart deviation
*, P values for independent t-test

Table 3. Perioperative total consumption and costs of anesthetic agents

	Group B N, 30	Group K N, 31	P value*
Intraop-remifentanyl consumption, µicrogram Median (min-max)	80 (15-375)	200 (80-500)	0.009
Intraop-sevoflurane consumption, milliliter, mean±sd	42.37±9.63	52.65±12.81	0.001
Postop-tramadol consumption, milligram, mean±sd	77.77±42.36	137.14±61.04	<0.001
Intraop-remifentanyl cost, TL, Median (min-max)	3.44 (0.64-16.13)	8.60 (3.44-21.50)	0.006
Intraop-sevoflurane cost, TL, mean±sd	66.52±15.12	82.67±20.11	0.001
Postop-tramadol cost, TL, mean±sd	13.2±7.2	23.31±10.37	<0.001

Group B, patients with ESPB group; group K, patients without block, N, number; intraop, intraoperative; postop, postoperative; TL, turkish liras; sd, standart deviation
*, P values for Independent T-test and Mann Whithey-U test

DISCUSSION

In the present study, preoperative ESPB was found to be cost-effective by reducing opioid and sevoflurane consumption in the patients who underwent percutaneous nephrolithotomy (PCNL) surgery. Recently, the effect of ESPB (which is frequently used for postoperative analgesia) on postoperative pain and opioid consumption is being investigated in different surgical procedures (18). However, in the literature, we find a few study investigating the effect of ESPB administration on perioperative consumption of analgesic agents for PCNL surgery (14,15). In addition, there was not any study that investigated the anesthesia cost effect of ESPB for PCNL surgery. With the present study, we observed that ESPB application reduces intraoperative and postoperative analgesic consumption and inhalation agent consumption and directly reduces the cost.

Balanced anesthesia applications are procedures using the lowest dose of drugs to minimize possible drug side effects (19). Regional analgesia methods are also preferred because of the lower cost and less medication is used (20). Therefore, regional anesthesia has taken its place in multimodal balanced anesthesia (19). In this study a kind of the regional anesthesia that commonly used in recent years for different type of surgeries was used. We observed that the consumption of sevoflurane was lower in patients for whom ESPB was performed who underwent balanced anesthesia. In balanced anesthesia, the inhalation agent contributes to antinociception and supports loss of consciousness in patients with unconsciousness (19). Local anesthetics that used in block procedures show their effects by preventing nerve end stimulation (21). They also act by preventing the potential for action in the peripheral nerves. Thus, they create antinociceptive effects too (21). This suggested that the amount of sevoflurane was low in patients with blockade and MAC values were low due to the antinociceptive additive effect of the local anesthetic agent. In a previous study, the transverse abdominis plane block was performed for post operative analgesia after general anesthesia (22). Kokulu et al. (22) used desflurane (a different inhalation agent) and found that its consumption and cost were lower in the group of patients with blockade. They suggested that, according to the results of their study, local anesthetics prevented the transmission of sensory messages to the central nervous system, thereby the MAC value of the inhalation agent (desflurane) was reduced. In our opinion, in our study, local anesthetic antinociceptive effect was shown by decreasing sevoflurane consumption and MAC values in the block group. Accordingly, performing the ESPB before general anesthesia reduced the cost by contributing to multimodal anesthesia.

Opioids are used in balanced anesthesia with inhalation agents as part of multimodal anesthesia (23). However, due to concerns about opioid overuse and undesirable side effects, additional multiple agents are used to reduce the amount of opioids and manage the nociceptive component of anesthesia (23). Regional anesthesia applications have an important role in maintaining the ERAS protocol after surgery and as a part of perioperative multimodal anesthesia and analgesia (24). Therefore, both central and peripheral nerve blocks can be used for opioid-free anesthesia. In the present study, we observed that opioid consumption (remifentanil consumed intraoperatively and tramadol consumed postoperatively) was lower in patients who had applied ESPB, which is used frequently in recent years, in the preoperative period.

Cost control has become an imperative in all areas of health care in the face of increasing health expenditure. When the cost of anesthesia is calculated annually, it only costs 5-6% of the surgical procedures (25). The cost of anesthesia per surgical procedure appears to be low. However, anesthesia is given for many surgical procedures throughout the year. Also anesthesia is a component of

not only surgical but also medical diagnostic procedures as well as in pain management (26). For this reason, cost studies are carried out by changing the anesthesia type, anesthesia method and combinations of drugs used in anesthesia applications (27). In a previous study, the cost of anesthesia was lower in balanced general anesthesia method compared to the total intravenous anesthesia method (28). In the present study, multimodal balanced general anesthesia was applied too and ESPB was found to be cost-effective in percutaneous nephrolithotomy surgery. In addition, the use of drugs in anesthesia creates a great cost. At this point, cost effectiveness can be achieved by reducing the doses of the drugs (29). In our study, the consumption of the inhalation agent-which attracts attention with its increasing price and the consumption of opioids-which have relatively side effects and which increased the cost due to the subsequent abuse, were found to be lower.

Some amount of local anesthetics that have some systemic effect can also pass into the blood when used in regional anesthesia (30). In our study, it was probably some amount of local anesthetic passed into the blood (we did not analyze the amount). This is the limitation of our study. Because it is not possible to know how much systemic analgesic effects of local anesthetics. The another limitation of the present study is the lack of the sensorial level of block application due to the general anesthesia. Furthermore, the third limitation is that the total drug costs used by the patients during their hospital stay and the cost estimation according to the duration of hospitalization in the intensive care unit were not calculated as they would complicate the estimation. In future studies, evaluations may be made with different surgical procedures, different blocks and different inhalation agents, taking into account the entire hospitalization process and treatment per patient.

CONCLUSION

The preoperative ESPB reduced the consumed inhalation agent and opioid and showed cost effectiveness in the perioperative period.

At the same time, ESPB has been observed as a method that contributes to the basic principles of multimodal anesthesia as well as multimodal analgesia.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Local Ethics Committee (2019/11, Ref. No: 2019.06.08)

Informed Consent: All patients signed the informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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

REFERENCES

1. Visscher SL, Naessens JM, Yawn BP, Reinalda MS, Anderson SS, Borah BJ. Developing a standardized healthcare cost data warehouse. BMC Health Serv Res 2017; 17: 396.
2. French KE, Guzman BA, Rubio AC, Frenzel JC, Feeley TW. Value based care and bundled payments: Anesthesia care costs for outpatient oncology surgery using time-driven activity-based costing. Healthcare 2016; 4: 173-80.
3. Chan SM, Horng Huei-Chi, Huang ST, et al. Drug cost analysis of three anesthetic regimens in prolonged lumbar spinal surgery. J Med Sci 2009: 29; 75-80.
4. Tabing AK, Ehrenfeld JM, Wanderer JP. Limiting the accessibility of cost-prohibitive drugs reduces overall anesthetic drug costs: a retrospective before and after analysis. Can J Anesth 2015; 62: 1045–54.
5. Brioni JD, Varughese S, Ahmed R, Bein B. A clinical review of inhalation anesthesia with sevoflurane: from early research to emerging topics. J Anesth 2017; 31: 764–78.
6. Singh PM, Trikha A, Sinha R, Ramachandran R, Rewari V, Borle A. Pharmaco-economics: Minute-based cost of sevoflurane in pediatric short procedures and its relation to demographic variables. J Anaesthesiol Clin Pharmacol 2013; 29: 328-32.
7. Brown EN, Pavone KJ, Naranjo M. Multimodal general anesthesia: theory and practice. Anesth Analg 2018; 127: 1246-58.
8. Koepke EJ, Manning EL, Miller TE, Ganesh A, Williams DGA, Manning MW. The rising tide of opioid use and abuse: the role of the anesthesiologist. Perioper Med 2018; 7: 16.
9. Tulgar S, Ahiskalioglu A, De Cassai A, Gurkan Y. Efficacy of bilateral erector spinae plane block in the management of pain: current insights. J Pain Res 2019; 12: 2597-613. doi:10.2147/JPR.S182128
10. Forero M, Adhikary SD, Lopez H, Tsui C, Chin KJ. The erector spinae plane block: a novel analgesic technique in thoracic neuropathic pain. Reg Anesth Pain Med 2016; 41: 621–7.
11. Goktas U, Isik D, Kati I, Atik B, Soyoral L. Effects of lidocaine infiltration on cost of rhinoplasty made under general anesthesia. J Craniofac Surg 2011; 22: 2176–8.
12. Senturk M, Pembeci K, Menda F, et al. Effects of intramuscular administration of lidocaine or bupivacaine on induction and maintenance doses of propofol evaluated by Bispectral Index. Br J Anaesth 2002; 89: 849–52.
13. Tulgar S, Kapakli MS, Senturk O, Selvi O, Serifsoy TE, Ozer Z. Evaluation of ultrasound-guided erector spinae plane block for postoperative analgesia in laparoscopic cholecystectomy: A prospective, randomized, controlled clinical trial. J Clin Anesth 2018; 49: 101-6.
14. Gultekin MH, Erdogan A, Akyol F. Evaluation of the Efficacy of the Erector Spinae Plane Block for Postoperative Pain in Patients Undergoing Percutaneous Nephrolithotomy: A Randomized Controlled Trial. J Endourol 2020; 34: 267-72. doi:10.1089/end.2019.0777.

15. Ibrahim M, Elnabtity AM. Analgesic efficacy of erector spinae plane block in percutaneous nephrolithotomy. Anaesthesist 2019; 68: 755–61. doi.org/10.1007/s00101-019-00673-w.

16. Biro P. Calculation of volatile anaesthetics consumption from agent concentration and fresh gas flow. Acta Anaesthesiol Scand 2014; 58: 968–72.

17. Sindhu F. Are non-pharmacological nursing interventions for the management of pain effective? A meta-analysis. J Adv Nurs 1996; 24: 1152-9.

18. Kendall MC, Alves L, Traill LL, Oliveira GS. The effect of ultrasound-guided erector spinae plane block on postsurgical pain: a meta-analysis of randomized controlled trials. BMC Anesthesiol 2020; 20: 99. doi.org/10.1186/s12871-020-01016-8

19. Brown EN, Pavone KJ, Naranjo M. Multimodal general anesthesia: theory and practice. Anesth Analg 2018; 127: 1246-58.

20. Greenberg CP. Practical, cost-effective regional anesthesia for ambulatory surgery. J Clin Anesth 1995; 7: 614-21.

21. Fozzard HA, Lee PJ, Lipkind GM. Mechanism of local anesthetic drug action on voltage-gated sodium channels. Curr Pharm Des 2005; 11: 2671-86.

22. Kokulu S, Bakı ED, Kaçar E, et al. Effect of transversus abdominis plane block on cost of laparoscopic cholecystectomy anesthesia. Med Sci Monit 2014; 20: 2783-7.

23. Egan TD. Are opioids indispensable for general anaesthesia? Br J Anesth 2019; 122: e127-35. doi.org/10.1016/j.bja.2019.03.005.

24. Grant MC, Sommer PM, He C, et al Preserved analgesia with reduction in opioids through the use of an acute pain protocol in enhanced recovery after surgery for open hepatectomy. Reg Anesth Pain Med 2017; 42: 451–7.

25. Johnstone RE, Jozefczk KG. Costs of anesthetic drugs: Experience with a cost education trial. Anesth Analg 1994; 78: 766–71.

26. Hogan PF, Seifert RF, Moore CS, Simonson BE. Cost effectiveness analysis of anesthesia providers. Nurs Econ 2010; 28: 159-69.

27. Li S, Coloma M, White PF, et al. Comparison of the costs and recovery profiles of three anesthetic techniques for ambulatory anorectal surgery. Anesthesiology 2000; 93: 1225-30.

28. Epple J, Kubitz J, Schmidt H, et al. Comparative analysis of costs of total intravenous anaesthesia with propofol and remifentanil vs. balanced anaesthesia with isoflurane and fentanyl. Eur J Anaesthesiol 2001; 18: 20-8.

29. Kaniyil S, Krishnadas A, Parathody AK, Ramadas KT. Financial implications of intravenous anesthetic drug wastage in operation room. Anesth Essays Res 2017; 11: 304-8.

30. Tomin J, Živanov-Čurlis J, Popović D, Glogovac S, Bašić D. Differences in local anesthetic effects of optically active isomers of local anesthetic compounds. Biotechnology & Biotechnological Equipment 2006; 20: 9-14.

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Evaluation of the relationship between uric acid and bone mineral density in postmenopausal women: a single center retrospective study

Postmenopozal kadınlarda ürik asit ile kemik mineral yoğunluğu arasındaki ilişkinin değerlendirilmesi: tek merkezli retrospektif çalışma

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ABSTRACT

Objectives: Osteoporosis is an important public health problem which is characterized by loss of bone mass resulting in susceptibility to fractures. There is much evidence indicating that uric acid, a final enzymatic product of purine metabolism, has beneficial antioxidant effects on several chronic diseases such as diabetes mellitus, hypertension and cardiovascular diseases. We aimed to evaluate the relationship between serum uric acid levels and bone mineral density (BMD) on postmenopausal osteoporosis in the present study.

Material and Method: This study was carried out at the Bolu İzzet Baysal Physical Medicine and Rehabilitation Training and Research Hospital, Department of Physical Medicine and Rehabilitation. The medical records of 1200 postmenopausal women between January 2019 and 2020 who had dual energy x-ray absorptiometry (DEXA) examination and serum uric acid levels recorded were screened retrospectively. In total, 92 individuals with osteoporosis and 399 healthy individuals were included in the study after exclusion of subjects with systemic diseases or taking drugs affecting bone metabolism or uric acid levels. Bone mineral density and T scores of femur neck (F neck) and lumbar spine (L2-L4), glucose, AST, ALT, creatinine, alkaline phosphatase, calcium, phosphate, parathormone (PTH), albumin and total protein were all recorded in individuals.

Results: Serum uric acid concentrations were found to be significantly lower in the osteoporosis group compared with the control group [4.65(2.40-7.80) vs 5.20 (3.80-9.40); p<0.001, respectively]. In correlation analysis, uric acid was significantly associated with fasting blood glucose (r=0.129, p=0.004), creatinine (r=0.374, p<0.001), calcium (r=0.201, p<0.001), total protein (r=0.123, p=0.006) and TSH (r=0.108, p=0.017). Correlation analysis also revealed a significant and positive correlation between uric acid and L2-L4 BMD (r=0.255, p<0.001). L2-L4 BMD was found to be independently related with uric acid in multivariate linear regression analysis after adjustment for confounding factors (B=1.619, p<0.001).

Conclusion: Our findings revealed that serum uric acid levels and lumbar (L2-L4) BMD were independently associated with each other in postmenopausal osteoporosis. Further studies are needed to determine the association of uric acid with osteoporosis and to address the utility of uric acid in clinical practice.

Keywords: Osteoporosis, uric acid, bone mineral density, postmenopausal women

ÖZ

Amaç: Osteoporoz, kemik kütlesi kaybı ve kırıklara yatkınlıkla sonuçlanan önemli bir halk sağlığı sorunudur. Pürin metabolizmasının son enzimatik ürünü olan ürik asitin diyabetes mellitus, hipertansiyon ve kardiyovasküler hastalıklar gibi çeşitli kronik hastalıklar üzerinde faydalı antioksidan etkilere sahip olduğunu gösteren çok sayıda kanıt vardır. Bu çalışmada postmenopozal osteoporozda serum ürik asit düzeyleri ile kemik mineral yoğunluğu (KMY) arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışma Bolu Abant İzzet Baysal Eğitim ve Araştırma Hastanesi, Fizik Tedavi ve Rehabilitasyon Kliniğinde yapıldı. Ocak 2019 ve 2020 yılları arasında çift-enerjili X-ışını absorbsiyometri (DEXA) incelemesi olan ve serum ürik asit düzeyleri kaydedilmiş olan 1200 postmenopozal kadının tıbbi kayıtları retrospektif olarak tarandı. Sistemik hastalıkları olan veya kemik metabolizmasını veya ürik asit düzeylerini etkileyen ilaç alan bireyler dışlandıktan sonra toplamda 92 osteoporozlu ve 399 sağlıklı birey çalışmaya dahil edildi. Tüm bireylerde KMY, femur boynu ve lomber vertebra (L2-4) T skoru, serum glukoz, AST, ALT, kreatinin, alkalen fosfataz, kalsiyum, fosfor, parathormon ve total protein düzeyleri kaydedildi.

Bulgular: Serum ürik asit konsantrasyonları, osteoporoz grubunda kontrol grubuna göre anlamlı derecede düşük bulundu [4.65 (2.40-7.80)-5.20 (3.80-9.40); p<0.001, sırasıyla]. Korelasyon analizinde ürik asit anlamlı bir şekilde açlık kan şekeri (r=0.129, p=0.004), kreatinin (r=0.374, p<0.001), kalsiyum (r=0.201, p<0.001), toplam protein (r=0.123, p=0.006) ve tiroid uyarıcı hormon (TSH) (r=0.108, p=0.017) ile ilişkili idi. Korelasyon analizi ürik asit ile L2-L4 KMY arasında anlamlı ve pozitif bir korelasyon olduğunu ortaya koydu (r=0.255, p<0.001). Çoklu doğrusal regresyon analizinde karıştırıcı faktörlerin etkisi arındırıldıktan sonra L2-L4 KMY ürik asit ile bağımsız olarak ilişkili bulundu (B=1.619, p<0.001).

Sonuç: Bulgularımız, postmenopozal osteoporozda serum ürik asit düzeyleri ve lomber (L2-L4) KMY'nin bağımsız ilişkili olduğunu ortaya koydu. Ürik asit ile osteoporoz arasındaki ilişkiyi belirlemek ve ürik asidin klinik uygulamadaki kullanımını değerlendirmek için daha fazla çalışmaya ihtiyaç vardır.

Anahtar kelimeler: Osteoporoz, ürik asit, kemik mineral yoğunluğu, postmenopozal kadın

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INTRODUCTION

Osteoporosis is a metabolic bone disease causing reduced bone mass and degradation of bone microarchitecture resulting in bone fragility and increased fracture risk (1). The bone remodeling process occurs with equilibrium between osteoclasts and osteoblasts. Cytokines emerging during this cycle increase osteoclastic activity and lower osteoblastic activity (2). Osteoporosis development is observed in the elderly and those with diseases involving systemic inflammation (3).

Uric acid occurs as the final product of purine metabolism, especially in the liver. Mean serum uric acid levels vary according to sex, but are higher in males (4). Uric acid found in tissues may have crystal or soluble structure according to properties and may have antioxidant or prooxidant features (5). Some studies in the literature have reported hyperuricemia is associated with inflammation and plays a role in osteoporosis pathogenesis (6). Additionally, it was associated with gout, metabolic syndrome and cardiovascular diseases due to prooxidant features (7). Furthermore, there are publications stating it has protective effect against diseases with chronic inflammation like osteoporosis and Alzheimer disease (8,9). When the literature is investigated, there are contradictory results about the correlation between serum uric acid levels and osteoporosis. In our study we aimed to investigate the correlation between serum uric acid levels and bone mineral density (BMD) in women with postmenopausal osteoporosis.

MATERIAL AND METHOD

This retrospective study was carried out at the Bolu İzzet Baysal Physical Medicine and Rehabilitation Training and Research Hospital, Department of Physical Medicine and Rehabilitation. The study protocol abided by the principals of the Helsinki Declaration. Electronic records of 1200 postmenopausal women between January 2019 and 2020 who had dual energy X-ray absorptiometry (DEXA) examination were analyzed retrospectively. Participants with a T score ≤ -2.5 were defined as osteoporosis and included in the osteoporosis group. Control subjects were selected among healthy individuals who were referred for routine checkup with a T score of >-2.5 on DEXA examination. Patients using medications affecting bone metabolism were excluded from the study. Participants with systemic diseases such as liver and renal disease, diabetes mellitus, thyroid and parathyroid disease, gout, cancer, inflammatory disease, acute and chronic infectious diseases were also excluded from the study. In total, 92 individuals with osteoporosis and 399 healthy individuals who had BMD and uric acid, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, alkaline phosphatase, calcium (Ca), phosphate (P), parathormone (PTH), albumin and total protein measurements were included in the study. BMD and T scores of femur neck (F neck) and lumbar spine (L2-L4), glucose, AST, ALT, creatinine, alkaline phosphatase, Ca, P, PTH, albumin and total protein were all recorded. Menopause was defined as the loss of menstruation for the last 12 months.

Statistical analysis:

SPSS 25.0 program (Armonk, NY: IBM Corp.) was used for statistical analysis. Distributions were tested for normality using the Shapiro-Wilk test. Variables were analyzed with Mann Whitney U test since they were distributed non-homogeneously. Data were presented as median (min, max). The relationship between plasma uric acid and other variables was investigated by Spearman correlation analysis. Multivariate linear regression analysis was performed to investigate the association of serum uric acid with clinical and laboratory parameters. P values less than 0.05 were considered statistically significant for all statistical analyses.

RESULTS

The median age of the group was 64.00 (40-80) years, and it was comparable between the osteoporosis and control group. There were no differences between the two groups with regards to AST, Ca, P, 25-hydroxyvitamin D (25 (OH) D), PTH, albumin, total protein and thyroid stimulating hormone (TSH). The baseline characteristics of the study population are summarized in **Table 1**. The average serum uric acid concentration was 5.33 (2.40-9.40) mg/dl and was significantly lower in the osteoporosis group compared with the control group [4.65 (2.40-7.80) vs. 5.20 (3.80-9.40); p<0.001, respectively] (**Table1**). Comparison of serum uric acid between patients with osteoporosis and healthy controls is shown in **Figure 1**. In correlation analysis, uric acid was significantly associated with age (r=0.167, p<0.001), creatinine (r=0.374, p<0.001), fasting blood glucose (r=0.129, p=0.004), Ca (r=0.201, p<0.001), total protein (r=0.123, p=0.006) and TSH (r=0.108, p=0.017). Correlation analysis revealed a significant but weak positive correlation between uric acid and L2-L4 BMD (r=0.255, p<0.001) (**Table 2**). Variables correlated with uric acid in correlation analysis were included in multivariate linear regression analysis. L2-L4 BMD (B=1.449, p<0.001), age (B=0.018, p=0.007), Ca (B=0.279, p=0.002) and creatinine (B=2.358, p<0.001) were found to be independently associated with serum uric acid after adjustment for confounding factors (**Table 3**). F neck BMD was not related with uric acid in multivariate regression analysis after adjustment for confounding factors.

Table 1. Clinical and demographic characteristics of individuals

	Osteoporosis (n=92)	Controls (n=399)	P
Age, years	65.55 (49-85)	64.28 (40-87)	0.156
Uric Acid, mg/dL	4.65 (2.40-7.80)	5.20 (3.80-9.40)	<0.001
Glucose, mg/dL	92 (65-234)	94 (26-279)	0.069
ALT, U/L	15 (5-51)	16 (5-87)	0.147
AST, IU/L	19 (3-74)	19 (9-85)	0.575
Creatinine, mg/dL	0.77 (0.58-1.23)	0.80 (0.54-2.13)	0.072
Alkaline Phosphatase, U/L	71 (24-177)	68 (21-169)	0.319
Ca, mg/dL	9.40 (8.10-13.20)	9.40 (7.60-11.90)	0.346
P, mg/dL	3.70 (2.60-5.70)	3.80 (2.10-5.90)	0.126
25 (OH) Vitamin D, ng/dL	16.81 (4.40-84.84)	15.93 (3.16-96.49)	0.522
PTH, pg/mL	55.70 (14.90-215.60)	51.60 (14.20-220.20)	0.411
Albumin, g/L	40.15 (30.10-46.90)	39.90 (21.30-54.50)	0.358
Total Protein, g/L	64.65 (53.10-74.80)	66.20 (42.40-90.60)	0.256
TSH, uIU/mL	1.29 (0.41-9.13)	1.35 (0.40-9.86)	0.573
L2-4 BMD (g/cm^2)	0.76 (0.60-1.45)	1.01 (0.79-1.82)	<0.001
L2-4 T Score	-2.80 (-4.10-3.00)	-0.70 (-2.40-4.10)	<0.001
F Neck T Score	-1.50 (-3.50-0.30)	-0.30 (-2.40-3.30)	<0.001
F Neck BMD(g/cm^2)	0.71 (0.31-1.03)	0.84 (0.53-1.37)	<0.001

Table 2. Correlation analysis showing the association between clinical parameters and serum uric acid levels

Variables	r value	p value
Age	0.167	<0.001
Glucose	0.129	0.004
AST	0.014	0.757
ALT	0.042	0.351
Alkaline Phosphatase	-0.037	0.416
Creatinine	0.374	<0.001
Ca	0.201	<0.001
P	0.056	0.214
25(OH) Vitamin D	-0.013	0.772
PTH	-0.003	0.938
Albumin	0.024	0.602
Total Protein	0.123	0.006
TSH	0.108	0.017
L2-4 BMD	0.255	<0.001
F neck BMD	0.083	0.065

Table 3. Multivariate linear regression analysis for uric acid

Variables	B	P
L2-L4 BMD	1.449	<0.001
F neck BMD	0.053	0.902
Age	0.018	0.007
Glucose	0.001	0.445
Calcium	0.279	0.002
Total protein	0.014	0.121
Creatinine	2.358	<0.001

Dependent variable; uric acid, independent variables; L2-L4 BMD, F neck BMD, age, glucose, calcium, total protein, TSH. p<0.05; statistically significant, BMD; bone mineral density

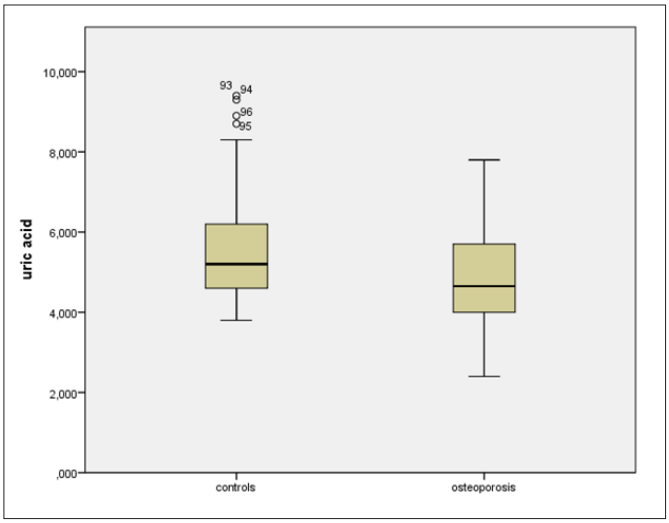

Figure 1. Comparison of serum uric acid levels between patients with osteoporosis and healthy controls

DISCUSSION

Osteoporosis is a public health concern characterized by loss of bone mass and disruption of bone architecture resulting in susceptibility to fractures especially in postmenopausal women. There is growing evidence indicating that uric acid has beneficial effects on bone metabolism. In the present study, we investigated the association of serum uric acid with bone mineral density in postmenopausal women. Our study results indicate that uric acid levels were lower in postmenopausal women with osteoporosis compared with the control group and uric acid was independently associated with BMD in the lumbar (L2-L4) spine, but not with BMD in the F neck.

Many studies have addressed the association of uric acid and bone mineral density in the literature. However, it is remarkable that there are few studies examining this topic especially in postmenopausal women. Chen et al. (10) investigated the correlation of uric acid with BMD in patients with primary osteoporosis in both genders. They stated that uric acid was positively correlated with lumbar (L1-L4) BMD, but not with hip BMD in agreement with our study. In another study, Babaei et al. (11) investigated serum uric acid status and its association with bone mineral density in elderly people aged 60 years and older, and they reported that serum uric acid was negatively associated with osteoporosis in this population. Our study design differs between these two studies, including the patient selection; Chen at al. (10) and Babaei et al. (10) included both men and women in their study while only postmenopausal women were recruited in our study. In a study consisting of 310 healthy Indian participants, Kaushal et al. (12) categorized indiviuals into two groups based on the uric acid levels and found that height, weight and body mass index (BMI) in the group with serum uric acid 5.4 mg/dL and above were statistically significantly higher compared to the group with serum uric acid below 5.4 mg/dL. They noted that alkaline phosphatase, 25 (OH) D, fasting blood glucose and hemoglobin A1c (HBA1c) levels were similar between the two groups. Increased uric acid levels were shown to be consistent with high BMD scores in both the lumbar region and femur neck and this effect was proposed to be due to the antioxidant properties of uric acid. A multicenter study by Lin et al. (13) including 17,735 people demonstrated statistically significant correlations between uric acid with lumbar spine BMD and lumbar spine T scores and Z scores. They reported that high uric acid levels might be protective against both osteoporosis and osteopenia. Another study including men over the age of 70 years in Australia investigated the correlation between uric acid and BMD and obtained similar results (14).

Makovey et al. (15) showed that high uric acid levels were associated with less annual loss of lumbar spine, forearm and total body BMI in studies including peri/postmenopausal women. In contrary to many studies in the literature, this study did not show an association between uric acid with hip BMD. In our study, similar to the one by Makovey et al. (15) uric acid and hip BMD were not shown to be associated with each other. The other two studies investigating the uric acid levels and lumbar spine BMD including pre-perimenopausal and peri-postmenopausal female patients in the Asian population reported similar results to our study (16,17).

When the literature is investigated, studies investigating the correlation between serum uric acid levels with osteoporotic fracture development are notable. In a study by Nabipour, it was stated that higher serum uric acid levels were associated with a lower prevalence of vertebral and nonvertebral fractures in older men (14). Similarly, Chen at al. (10) reported that postmenopausal women with history of fragility fractures had significantly lower levels of uric acid compared to postmenopausal women without fragility fractures and claimed that serum uric acid might be a protective factor for bone health in primary osteoporosis. Lane et al. (18) investigated the correlation of uric acid and fracture risk in older men in the osteoporotic fractures in men (MrOS) study and they demonstrated that higher serum uric acid levels were associated with a reduction in risk of incident nonvertebral fractures despite the fact that it was not related with higher hip BMD and hip fractures. In the Rotterdam study, it was found that higher levels of uric acid were associated with a reduction in incident osteoporotic and nonvertebral fractures in both men and women in agreement with the MrOS study. It was also noted that there was no association between serum uric acid and hip or vertebral fractures. In addition, the relationship of uric acid with favorable hip bone geometry was first demonstrated in this study (19).

Although recent studies have reported that hyperuricemia could help protect against the onset of bone fractures, contradictory results are found when the literature is reviewed. In the Verona study including both female and male individuals with 4±1.2-year follow-up, basal serum uric acid levels were not shown to be associated with new onset osteoporotic fracture development. Furthermore, they indicated that participants with higher serum uric acid levels had significantly less osteoporosis in agreement with most of the studies reported in the literature (20). In another study, Zhang et al. (21) established a rat model of experimental mild hyperuricemia and examined the relationship between uric acid and BMD. They did not find any relationship between hyperuricemic rats and normouricemic rats with respect to BMD, volume density and biomechanical properties, contrary to accumulating evidence supporting possible associations between serum uric acid levels and BMD. The cause of the contradictory results in these studies may be explained by differences in patient selection such as sex, age and ethnicity. Difference in study designs and participant numbers may also cause conflicting results. We think that from this perspective, future prospective studies are required to reveal the reasons underlying the conflicting results.

In the present study, we did not demonstrate an independent relationship between uric acid and serum levels of 25 (OH) vitamin D, PTH and P. We found that uric acid was independently and positively associated with calcium, age and creatinine in the adjustment model on regression analysis. Different from present study, Chen Li reported that uric acid was negatively related with 25 (OH) vitamin D, but not with Ca or P in elderly

people with primary osteoporosis (10). In another study, Xiong also did not demonstrate any causal relationship between serum uric acid and PTH, Ca or P. Contrary to these studies, Hui at al. (22) found an independent relationship between uric acid and PTH levels in a national population study.

Our findings demonstrate a significant positive association between serum uric acid and lumbar (L2-L4) BMD in postmenopausal women in agreement with studies claiming a protective effect of higher uric acid on osteoporosis. It is not clear yet whether postmenopausal women at risk of osteoporosis should be treated in the presence of asymptomatic hyperuricemia because of its protective effect on bone health. Li et al. (23) investigated serum uric acid levels and multiple health outcomes depending on review of evidence from observational studies, randomized controlled trials, and Mendelian randomization studies. They reported that a clear role for serum uric acid levels existed only for gout and nephrolithiasis.

There are, however, some limitations to this study. First, individuals in this study were included from a single tertiary hospital; thus, this may not be representative of the general population. Retrospective design and relatively small study population in osteoporosis group are the second and third limitations.

We think that our findings provide additional data on the beneficial effects of uric acid on bone mineral health in postmenopausal women. Clinical implications of serum uric levels in postmenopausal women with osteoporosis are not clear yet and need to be determined by further larger scale studies with sufficient power.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Bolu Abant İzzet Baysal University Noninterventional Ethics Committee (Permission granted/ date-TUEK: 16.06.2020, Number of meeting: 321, Decision number: 2020/16).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

REFERENCES

1. Varacallo MA, Fox EJ. Osteoporosis and its complications. Med Clin North Am 2014; 98: 817-31.
2. Charles JF, Aliprantis AO. Osteoclasts: more than 'bone eaters'. Trends Mol Med 2014; 20: 449-59.
3. Ginaldi L, Di Benedetto MC, De Martinis M. Osteoporosis, inflammation and ageing. Immun Ageing 2005; 2: 14.
4. Antón FM, García Puig J, Ramos T, González P, Ordás J. Sex differences in uric acid metabolism in adults: evidence for a lack of influence of estradiol-17 beta (E2) on the renal handling of urate. Metabolism 1986; 35: 343-8.
5. Sautin YY, Johnson RJ. Uric acid: the oxidant-antioxidant paradox. Nucleosides Nucleotides Nucleic Acids 2008; 27: 608-19.
6. Kim SC, Paik JM, Liu J, Curhan GC, Solomon DH. Gout and the risk of non-vertebral fracture. J Bone Miner Res 2017; 32: 230-6.
7. Genoni G, Menegon V, Secco GG, et al. Insulin resistance, serum uric acid and metabolic syndrome are linked to cardiovascular dysfunction in pediatric obesity. Int J Cardiol 2017; 249: 366-71.
8. Han W, Bai X, Wang N, Han L, Sun X, Chen X. Association between lumbar bone mineral density and serum uric acid in postmenopausal women: a cross-sectional study of healthy Chinese population. Arch Osteoporos 2017; 12: 50.
9. Du N, Xu D, Hou X, et al. Inverse association between serum uric acid levels and Alzheimer's disease risk. Mol Neurobiol 2016; 53: 2594-9.
10. Chen L, Peng Y, Fang F, Chen J, Pan L, You L. Correlation of serum uric acid with bone mineral density and fragility fracture in patients with primary osteoporosis: a single-center retrospective of 253 cases. Int J Clin Exp Med 2015; 8: 6291-4.
11. Babaei M, Shamsi R, Heidari B, Bijari A. Serum uric acid status and its association with bone mineral density in the elderly people aged 60 years and more. Int J Endocrinol Metab 2019; 17: e80780.
12. Kausal N, Vohora D, Jalali RK, Jha S. Raised serum uric acid is associated with higher bone mineral density in a cross-sectional study of a healthy Indian population Ther Clin Risk Manag 2018; 14: 75-82.
13. Lin X, Zhao C, Qin A, et al. Association between serum uric acid and bone health in general population: a large and multicentre study. Oncotarget 2015; 6: 35395–403.
14. Nabipour I, Sambrook PN, Blyth FM, et al. Serum uric acid is associated with bone health in older men: a cross-sectional population-based study. J Bone Miner Res 2011; 26: 955–64.
15. Makovey J, Macara M, Chen JS, et al. Serum uric acid plays a protective role for bone loss in peri- and postmenopausal women: a longitudinal study. Bone 2013; 52: 400–6.
16. Kim S, Jung J, Jung JH, Kim SK, Kim RB, Hahm JR. Risk factors of bone mass loss at the lumbar spine: a longitudinal study in healthy korean pre- and perimenopausal women older than 40 years. PLoS One 2015; 10: e0136283.
17. Ishii S, Miyao M, Mizuno Y, Tanaka-Ishikawa M, Akishita M, Ouchi Y. Association between serum uric acid and lumbar spine bone mineral density in peri- and postmenopausal Japanese women. Osteoporos Int 2014; 25: 1099–105.
18. Lane NE, Parimi N, Lui LY, et al. Osteoporotic fractures in men study group association of serum uric acid and incident nonspine fractures in elderly men: the osteoporotic fractures in men (MrOS) study. J Bone Miner Res 2014; 29: 1701–7.
19. Muka T, de Jonge EA, Kiefte-de Jong JC et al. The influence of serum uric acid on bone mineral density, hip geometry, and fracture risk: the rotterdam study. J Clin Endocrinol Metab 2016; 101: 1113–22.

20. Veronese N, Bolzetta F, De Rui M, et al. Serum uric acid and incident osteoporotic fractures in old people: The PRO.V.A study. Bone 2015; 79: 183–9.

21. Zhang D, Bobulescu IA, Maalouf NM, et al. Relationship between serum uric acid and bone mineral density in the general population and in rats with experimental hyperuricemia. J Bone Miner Res 2015 ; 30: 992–9.

22. Hui JY, Choi JWJ, Mount DB, Zhu Y, Zhang Y, Cho HK. The independent association between parathyroid hormone levels and hyperuricemia: a national population study. Arthritis Res Ther 2012; 14: R56.

23. Li X, Meng X, Timofeeva M, et al. Serum uric acid levels and multiple health outcomes: Umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. BMJ 2017; 357: j2376.

Original Article/Özgün Makale

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The role of the C-reactive protein/albumin ratio in determining prognosis of patients diagnosed with small cell lung cancer and the relationship with the diameter and SUVmax value of primer mass in PET-CT

Küçük hücreli akciğer kanseri tanısı konulan hastalarda C-reaktif protein/albumin oranının prognoz tayinindeki yeri ile PET-BT'deki primer kitlenin çapı ve SUVmax değeri ile ilişkisi

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ABSTRACT

Introduction: In our study, we aimed to evaluate retrospectively the role of C-reactive protein/albumin rate (CAR) in determining prognosis of patients diagnosed with SCLC and the relationship with the diameter and SUVmax value of primer mass in positron emission tomography/computed tomography. **Material and Method:** A total of 70 patients diagnosed with SCLC between January 2008 and December 2015 in this study. Informations of patients were recorded. Hemogram at the time of first diagnosis, biochemistry values, diameter of the primary mass in PET-CT, SUVmax values, cancer stage, survival times were recorded. NLR: neutrophil lymphocyte, CAR: C-reactive protein/albumin ratios were calculated.

Results: The mean age of the patients was 57.6±7.5. While 59 (84.3%) patients were dead, 11 (15.7%) patients were still alive. The median follow-up time of the patients was 13. 7 (8.1-30.1) month. The mean life span was found to be 21 month in patients with CAR<0.3, and it was found to be 10 month in patients with CAR≥0.3 (p=0.007). Median lifespan was 23 month in patients with LDH<187 and it was 10 month in patients with≥187 (p=0.048). Median life span was found as 19 month in patients with NLR<3 and it was found to be 10 month in patients with NLR≥3. The result was evaluated as close to statistical significance (p=0.073).

Conclusion: We detected that male gender, the stage of disease, the increase of SUVmax value of primary mass and increased CAR, NLR and LDH levels were found to be poor prognostic criterias in SCLC patients. We consider that CAR, NLR and LDH levels can be used for forecasting of mortality at the beginning of the diagnoses of SCLC.

Keywords: Small cell lung cancer, C-reactive protein, albumin, mortality

ÖZ

Giriş: Küçük hücreli akciğer kanseri (KHAK) tüm akciğer kanser türlerinin %15'ini oluşturur. Çalışmamızda KHAK tanısı konulan hastalarda retrospektif olarak ilk tanı anında bakılan C-reaktif protein/albümin (CAR)'ın prognoz tayinindeki yeri ile primer kitlenin PET-BT'deki çapı ve SUVmax değeri ile ilişkisinin değerlendirilmesini amaçladık.

Gereç ve Yöntem: Çalışmamızda hastanemiz 8. kliniğinde Ocak 2008-Aralık 2015 tarihleri arasında KHAK tanısı konulan70 hasta dahil edildi. Hastalara ait bilgiler hasta dosyaları ve hastane bilgi sisteminden retrospektif olarak elde edildi. İlk tanı anında bakılan hemogram, biyokimya değerleri, PET-BT'deki primer kitlenin çapı, SUVmax değerleri, kanser evresi, sağkalım süreleri kayıtedildi. NLR: nötrofil/lenfosit, CAR: C-reaktif protein/albümin oranları hesaplandı.

Bulgular: Hastaların ortalama yaşı 57,6±7,5 olarak hesaplandı. 59 (%84,3) hasta exitus iken, 11 (%15,7) hasta halen sağ idi. Hastaların median izlem süresi 13,7 (8,1-30,1) ay idi. CAR<0,3 olanlarda ortalama yaşam süresi 21 ay iken; ≥0,3 olanlar da 10 ay olarak bulundu (p=0,007). LDH<187 olanlarda median ömür 23 ay; ≥187 olanlarda ise 10 ay olarak bulunmuştur (p=0,048). NLR<3 olanlarda median yaşam süresi 19 ay; ≥3 olanlarda 10 ay olarak bulunmuştur. Sonuç istatistiksel olarak anlamlılık sınırına yakın olarak değerlendirilmiştir (p=0,073).

Sonuç: Erkek cinsiyet, hastalığın evresi ve primer kitlenin SUVmax değerindeki artış, artmış CAR, artmış NLR ve artmış LDH KHAK'lı hastalarda kötü prognoz kriteleri olarak saptadık. CAR, NLR ve LDH düzeylerinin tanı anındaki mortaliteyi öngörmede kullanılabileceklerini düşünmekteyiz.

Anahtar kelimeler: Küçük hücreli akciğer kanseri, c-reaktif protein, albümin, mortalite

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INTRODUCTION

Lung cancer is an increasingly common type of cancer worldwide. It is the most diagnosed cancer type and it is the most frequent cancer type in terms of cancer-related deaths. Five year survival rate is low, despite all the treatment options in lung cancer. Small cell lung cancer (SCLC) accounts for 15% of all lung cancer types. Complete blood count and biochemical tests are commonly used in the routine. The number of white cells, neutrophil and lymphocyte and the ratio of neutrophil/lymphocyte (NLR), hypoalbuminemia and C-reactive protein (CRP) are systemic inflammatory markers (1).

CRP is a positive acute phase reactant while albumin is a negative acute phase reactant. Acute phase proteins are also helpful in diagnosing malignant diseases and in determining the prognosis. The mortality is higher in elderly patients with high positive acute phase proteins or with low albumin value that is the one of the negative acute phase proteins (2,3).

The ratio of CRP/alb (CAR) was found to be associated with prognosis in many types of cancer, and also it was detected that it is independent risk factor in predicting the progression of patients with lung cancer (4). Positron emission tomography/computed tomography (PET-CT) is used to assess staging and the treatment response in patients diagnosed with malignancy. There are some studies that show the maximum standard uptake value (SUVmax) of the primary tumor is an independent prognostic factor.

Tumor size is also accepted to be a prognostic factor in non-small cell lung cancer (NSCLC) (5). It was shown that as tumor size increases, the value of SUVmax increases too (6-8). In one study, it was found that there was a positive correlation between tumor size and SUVmax (8). In our study it was aimed retrospectively to evaluate the relationship between the role of CAR detected at the beginning, in determining the prognosis of patients diagnosed with SCLC and the diameter and SUVmax value of primary mass in PET-CT.

MATERIAL AND METHOD

This study was approved by the university/local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval of our study was received by applying to medical specialty training board of Ataturk Chest Diseases and Thoracic Surgery Education and Research Hospital, Chest Diseases with the date of 12.07.2018 and number of 604.

In our study 70 patients diagnosed with SCLC between January 2008 and December 2015 in 8th clinic of our hospital were included. The datas of the patients were obtained retrospectively from patient files. The hemogram and biochemistry values that detected at the time of initial diagnosis, the diameter and SUVmax value of primer mass in PET-CT used for staging. The stage of cancer, the performance status and smoking histories of patients, BMI and survival times were recorded. The patients with comorbid disease and with infectious disease were excluded from the study. Tumor size, taken into consideration the largest tumor diameter in the CT section, was determined in millimeters (mm). The clinical stage was classified on the basis of the American Joint Committee on Cancer 7th edition.

The following formulas were used:

- BMI: weight/height squared
- NLR: absolute neutrophyl count/absolute lymphocyte count
- CAR: CRP/albumine

PET-CT

A whole body scan was applied with a Siemens Biography 6 HI-REZ PET/CT scanner (Siemens Medical Solutions, Knoxville, Tennessee) to patients after at least 6 hours fast-and with blood glucose level k 180 mg/dL. The images of 6–8 bed positions from the base of the skull to high-thigh were obtained an hour after the intravenous bolus injection of fluorodeoxyglucose (FDG) at a dosage ranging from 370 to 555 MBq (10–15mCi). The patients were positioned with the arms above the head. A whole-body PET study followed an enhanced whole-body CT study and was used for attenuation correction.

Statistical Analyses

Statistical analyses were performed using the SPSS 22. The variables were investigated using histogram, probability plots and analytical methods (Kolmogorov-Smirnov/ Shapiro-Wilk's test) tı determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed and medians and interquartile range (IQR) fort he non-normally distributed and ordinal variables. The univariant analyses to identify variables of patient outcomes was investigated using chi-square, Fisher exact, Student's t and Mann-Whitney U test, where appropiate. For multivariant analyses, the possible factors identified with univariate analyses were further entered into logistic regression analysis to determine independent predictors of mortality. ROC (Receiver Operating Characteristics) curve analysis were used to determine cut-off value of LDH, CAR and NLR. The Kaplan-Meier survival estimates were calculated. A separate log rank test was used to identify the independent effect of LDH, CAR and NLR values on survival. A p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS

In this study, we retrospectively analyzed the prognostic power of CRP/Alb ratio in 70 eligible patients with SCLC. Men were 90% (N:63) of those participating in the study. The mean age of the patients was 57.6±7.5. The number of the exitus patients was 59 (84.3%), while 11 patients (15.7%) were still alive. The median monitoring time of the patients was 13.7 (8.1-30.1) month.

The average smoking history of patients was 40 packets/years. 27 patients were staged as. The number of limited stage patients with SCLC was 27 and 43 patients were staged as extensive stage SCLC. The mean diameter of mass was calculated as 6.68±2.8 cm. The median SUVmax value of the primary mass was 13.43 (13.49-18.18).

The comparison of the general characteristics of limited stage and extensive stage patients with SCLC was shown in **Table 1**. There was a statistically significant difference in terms of the mean LDH levels and the monitoring times between two groups.

Table 1. The comparison of the general characteristics of patients with limited and extensive stage SCLC

	Limited stage	Extensive stage	p
Cigarette Pc-Year	40 (35-50)	40 (30-56)	0.942
SUVmax	13.44 (10.10-16.85)	13.43 (11.1-19.24)	0.567
RDW	14.1 (13.5-14.9)	13.9 (13.4-14.8)	0.763
PLT	289 (242-368)	294 (225-356)	0.484
CRP	1.32 (0.6-5.5)	2.78 (1.1-6.2)	0.319
CAR	0.34 (0.17-1.54)	0.92 (0.27-1.81)	0.275
NLR	2.88 (2.13-4.38)	3.30 (2.41-4.50)	0.175
LDH	187 (168-242)	215 (180-427)	0.026
Monitoring times (month)	23.7 (10.1-37.25)	10.6 (6.2-21.15)	0.009

CAR: CRP/albümine ratio, RDW: Red cell distribution width, PLT:platelet, NLR: neutrophyl count/lymphocyte count ratio, LDH: Lactate dehydrogenase, CRP: C-reactive protein

According to the ROC curve analysis, the cut-off value of CAR was 0.3, the cut-off value of NLR was 3, and also the cut-off value of LDH was 187.

The average life span was 21 months in patients with CAR<0.3, while it was 10 months in patients with CAR≥0.3. The survival distinction was statistically significant (p=0.007) (**Figure 1**). It was found that the median life-span was 23 months in the patients with LDH<187 and it was 10 month in the patients with LDH≥187 (p=0.048) (**Figure 2**).

Median life span was found to be 19 months in patients with NLR<3, it was found to be 10 months in patients with NLR≥3 years. The result was evaluated as close to statistical significance (p=0.073) (**Figure 3**).

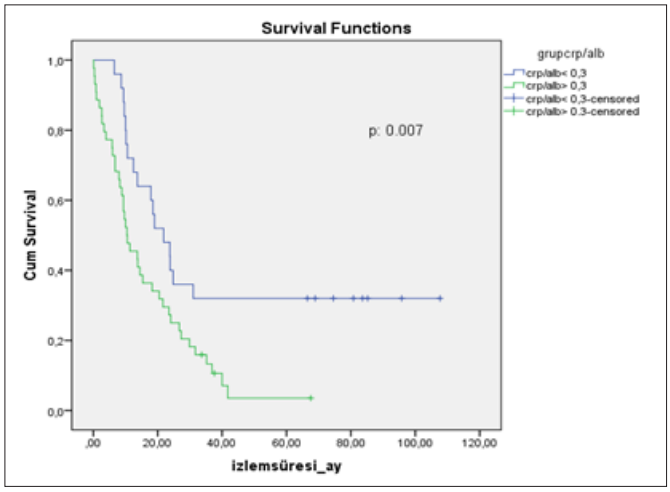

Figure 1. The relationship between the CAR and the survival

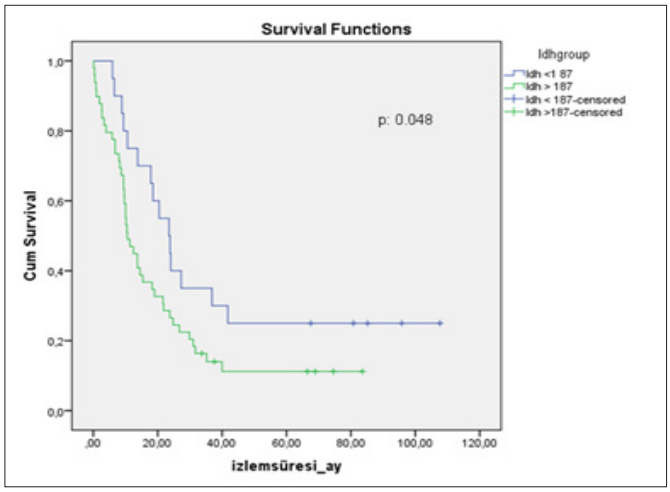

Figure 2. The relationship between the LDH and the survival

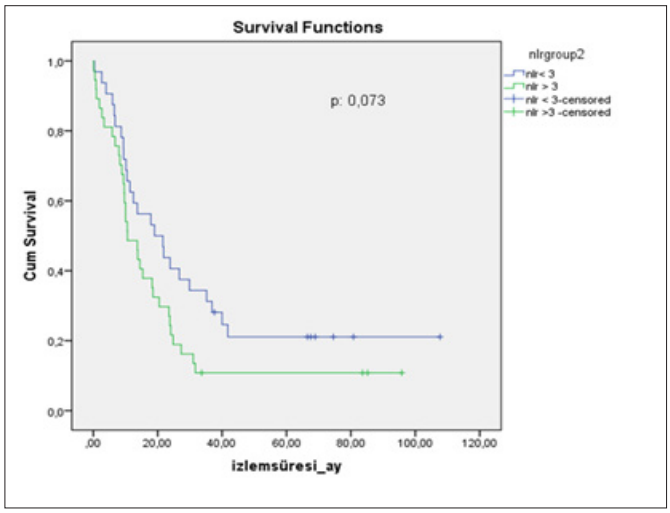

Figure 3. The relationship between the NLR and the survival

Hemogram parameters of both groups were compared and no significant difference was detected. Tumor diameter and SUVmax values were also found to be similar.

The age, the gender and the mortality rates of the patients, the diameter and the SUVmax values of primary mass were compared according to the cut-off value of CAR. They are shown in **Table 2**. No statistical difference was found. The mortality rate was found to be low in patients with CAR<0.3 (p=0.008).

Table 2. The comparison of the properties of SCLC patients according to the high and low CAR values

	CAR<0.3	CAR≥0.3	P
Gender (male %)	88.0%	91.1%	0.487
Age (mean±SD)	59.8±7.05	56.47±7.62	0.076
Diameter of primary mass (mean±SD)	7.18±3.21	6.40±2.64	0.278
SUVmax value of primary mass (Median [IQR 25-75])	13.53 [11.66-17.52]	13.0 [10.00-18.97]	0.695
Stage (limited stage %)	52.0%	31.1%	0.07
Mortality %	68%	93.3%	0.008

CAR: CRP/alb ratio

It was determined that the age, the gender, the stage of disease, the diameter and the SUVmax value of primary mass, the NLR, the CAR and the LDH values didn't affect independently mortality but it was detected that the male gender, the stage, the SUVmax value of the primary mass and the NLR values were close to the statistical significance limit according to the results of logistic regression analysis conducted with the aim of examining the risk factors for mortality in SCLC (**Table 3**).

Table 3. The risk factors affecting mortality in patients with SCLC according to logistic regression analysis

Risk factor	RR (%95 Cl)	p
Age	0.96 (0.836-1.10)	0.587
Gender (male/female)	18.6 (0.93-372.47)	0.055
Stage (limited/extensive)	0.2 (0.06-1.04)	0.057
The diameter of primary mass	1.30 (0.84-2.02)	0.230
SUVmax	0.90 (0.814-1.07)	0.066
NLR	0.57 (0.32-1.00)	0.052
CAR	1.60 (0.81-3,14)	0.160
LDH	1.00 (0.99-1.00)	0.920

CAR: CRP/albumine ratio, NLR: neutrophyl count/lymphocyte count ratio, LDH: Lactate dehydrogenase

DISCUSSION

It is known that elevated LDH levels correlate with inflammation and tumor necrosis and therefore it reflects tumor activity. It is well known that high LDH level is a prognostic factor and detected in many malignancies, especially lymphoma, small cell lung carcinoma and germ cell tumors. Some studies have also shown that high serum LDH level is a poor prognostic factor in patients with NSCLC too (9,10). LDH is a prognostic and potential pro tumor factor in patients with lung cancer. In patients with SCLC, a poor correlation was detected between increased LDH levels and survival and it has been recommended that serum LDH levels and other prognostic factors to be evaluated together (11).

LDH is a biochemical parameter especially high in patients with extensive stage SCLC. Increased LDH levels are associated with short median survival in patients with both limited and extensive stage SCLC. Patients with normal LDH levels have better prognosis than patients with increased LDH levels. The 1-year mortality was determined as 33.1% in cases with normal LDH level and as 60.2% in cases with increased LDH levels. It was found that LDH levels at the beginning of diagnosis were associated with prognosis in patients with SCLC (12). In our study median life span was detected as 23 months in patients with low LDH level and it was detected as 10 month in patients with high LDH level. The LDH levels were found to be lower in patients with limited stage SCLC compared to the patients with extensive stage SCLC (187-215 in order). Analysis of LDH subgroups may provide clearer datas in terms of prognose. Albumin can reflect the nutritional status of patients with cancers and malnutrition is correlated with worse survival (13). It has been shown in several studies that the albumin level detected low at the beginning of the diagnose in patients with cancers is a prognostic factor and it is related to the short duration of survival (14). In our study, the level of albumin was found higher in patients with limited stage than in patients with extensive stage. There was no statistically significant difference. This result may be due to the fact that the numbers of patients were not equal in the two groups.

Systemic inflammation is also linked to poor outcome in cancer patients. CRP is a sensitive and reliable prognostic marker for systemic inflammation that is also convenient for testing with standardized parameters established in clinical laboratories. In a study of 592 lung cancer patients and 670 control subjects, pre-diagnostic elevated CRP was found to be associated with an increased risk of lung cancer development (15). Previous studies have reported that elevated CRP level can affect the growth and progression of cancer. Hong et al. (16) observed that high CRP level is associated with poor prognosis of patients with SCLC. CRP levels were determined lower in patients with limited stage compared to patients with extensive stage. CRP and albumin ratio, a new index, may have prognostic value in inflammation and better predict overall survival of patients with cancer. The CAR is a readily available biomarker. Recently, the effect of CAR on prognosis in the various tumors has been shown in many studies. It is an independent prognostic factor. CAR has been found to be a poor prognostic factor in pancreatic cancer, nasopharyngeal cancer, colorectal

cancer and esophageal cancer (4). In another study, it was detected that CAR was associated with progression and mortality in operable NSCLC and SCLC (4). In this study, a 0.3 cut off value for CAR was used for predicting overall survival in SCLC. The mean life span was 21 month in patients with CAR<0.3, and 10 month in patients with CAR≥0.3. The mortality rate was found to be high in patients with CAR≥0.3. In accordance with the literature, we found that CAR is a prognostic factor in determining mortality in SCLC.

It is thought that PET/CT frequently used in diagnosis and staging of cancer, is a noninvasive method for determining the prognosis of the tumor. In a retrospective study, the average of SUVmax value of primary tumors was 11.1 and it was determined that there wasn't significantly difference between the below and above of this value in terms of survival (17). When the relation between the increase of SUVmax value and mortality was evaluated in the logistic regression analysis performed in our study, it was found to be close to the statistical significance limit. There are some studies having showed that the SUVmax value increases as the tumor size increases (8). In the study of Brown et al. (18) all histological subtypes of lung cancer were evaluated together and it was determined that the increase of SUVmax and tumor size was in positively correlation but when it was evaluated according to the histological subgroups there was a correlation between tumor size and SUVmax value in patients with adenocarcinoma while there was no significant correlation between tumor size and SUVmax value in patients with epidermoid carcinoma and large cell carcinoma. There are also some studies having showed that there is no correlation between tumor size and SUVmax value (19). In our study, we haven't found any relation between tumor size and SUVmax with survival. Leukocyte, neutrophil and lymphocyte count and neutrophil to lymphocyte ratio (NLR) are markers of systemic inflammation that are known to play main roles in cell-mediated destruction of cancer cells (20). NLR is an inexpensive, reproducible and widely available blood test. However elevated peripheral NLR before treatment was an independent prognostic factor of poor progressive free survival and overall survival in SCLC patients (21). In a study conducted in patients with lung cancer and with NLR<3, median survival time (31.08 month) was significantly longer than that of those with NLR≥3 (18 month) (22). In SCLC patients, no relationship could be found between NLR and median survival time (22). In our present study, the median life span was 19 month in patients with NLR<3, and it was 10 month in patients with NLR≥3. The result was evaluated to be close to the significance limit. More meaningful results will be obtained by increasing the number of patients. SCLC is a type of lung cancer that spreads rapidly and has an aggressive course. However it responds to the chemotherapy and radiotherapy well. In extensive stage, the survival rate without treatment is very low. The average life expectancy is longer in those patients with limited stage disease under treatment. Male gender is more prevalent, while female patients have a better prognosis than male patients (23). In our study, it was determined that male gender, stage of disease, SUVmax value of primary mass and NLR affect the prognosis and it is close to the statistical significance limit made by logistic regression analysis with the aim of examining the risk factors for mortality in SCLC. We think that to increase the number of patients will lead to more meaningful results.

CONCLUSION

As a result, we found that male gender, increased SUVmax value of mass, increased CAR, increased NLR, and increased LDH are poor prognostic criterias in patients with SCLC. We believe that CAR, NLR and LDH levels can be used for prediction of mortality at the diagnostic moment.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval of our study was received by applying to medical specialty training board of Atatürk Chest Diseases and Thoracic Surgery Education and Research Hospital, Chest Diseases with the date of 12.07.2018 and number of 604.

Informed Consent: Written informed consent form was obtained from all patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Kacan T, Babacan NA, Seker M, et al. Could the neutrophil to lymphocyte ratio be a poor prognostic factor for non small cell lung cancers? Asian Pac J Cancer Prev 2014; 15: 2089-94.
2. Harris TB, Ferrucci L, Tracy RP, et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. Am J Med 1999; 106: 506-12.
3. Klonoff-Cohen H, Barrett-Connor EL, Edelstein SL. Albumin levels as a predictor of mortality in the healthy elderly. J Clin Epidemiol 1992; 45: 207-12.

4. 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: 6848.
5. Mery CM, Pappas AN, Burt BM, et al. Diameter of non-small cell lung cancer correlates with long-term survival: implications for T stage. Chest 2005; 128: 3255-60.
6. Brown RS, Leung JY, Kison PV, Zasadny KR, Flint A, Wahl RL. Glucose transporters and FDG uptake in untreated primary human non-small cell lung cancer. J Nucl Med 1999; 40: 5565.
7. Dooms C, van Baardwijk A, Verbeken E, et al. Association between 18F-fluoro-2-deoxy-D-glucose uptake values and tumor vitality: prognostic valueof positron emission tomography in early-stage non-small cell lung cancer. J Thorac Oncol 2009; 4: 822-8.
8. Li M, Liu N, Hu M, et al. Relationship between primary tumor luorodeoxyglucose uptake and nodal or distant metastases at presentation in T1 stage nonsmall cell lung cancer. Lung Cancer 2009; 63: 383-6.
9. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group experience. J Clin Oncol 1991; 9: 1618-26.
10. Danner BC, Didilis VN, Wiemeyer S, et al. Long-term survival is linked to serum LDH and partly to tumour LDH-5 in NSCLC. Anticancer Res 2010; 30: 1347-51.
11. Zhang X, Guo M, Fan J, et al. Prognostic significance of serum LDH in small cell lung cancer: a systematic review with meta-analysis. Cancer Biomark 2016; 16: 415-23.
12. Tas F, Aydiner A, Demir C, Topuz E. Serum lactate dehydrogenase levels at presentation predict outcome of patients with limited-stage small-cell lung cancer. Am J Clin Oncol 2001; 24: 376-8.
13. Jin J, Liu D, Zhou Y, Li W. C-reactive protein to albümin ratio as prognostic factors in lung cancer. Int J Clin Exp Med 2017; 10: 16780-7.
14. Chatani M, Matayoshi Y, Masaki N, Inoue T. Radiation therapy for brain metastases from lung carcinoma. prospective randomized trial according to the level of lactate dehydrogenase. Strahlenther Onkol 1994; 170: 155-61.
15. Chaturvedi AK, Caporaso NE, Ktaki HA: C-reactive protein and risk of lung cancer. JCO. 2010; 28: 2719-26.
16. Hong S, Kang YA, Cho BC, Joon D, Yonsei K. elevated serum C-reactive protein as a prognostic marker in small cell lung cancer. Med J 2012; 53: 111-7.
17. Hoang JK, Hoagland LF, Coleman RE, Coan AD, Herndon JE II, Patz EF Jr. Prognostic value of fluorine-18 fluorodeoxyglucose positron emission tomography imaging in patients with advanced-stage nonsmall cell lung carcinoma. J Clin Oncol 2008; 26: 1459-64.
18. Brown RS, Leung JY, Kison PV, Zasadny KR, Flint A, Wahl RL. Glucose transporters and FDG uptake in untreated primary human non-small cell lung cancer. J Nucl Med 1999; 40: 556-65.
19. Soret M, Bacharach SL, Buvat I. Partial-volume effect in PET tumor ımaging. J Nucl Med 2007; 48: 932-45.
20. Kobayashi T, Teruya M, Kishiki T, et al. Inflammation-based prognostic score and number of lymph node metastases are independent prognostic factors in esophageal squamous cell carcinoma. Dig Surg 2010; 27: 232–7.
21. Deng M, Ma X, Liang X, Zhu C, Wang M. Are pretreatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio useful in predicting the outcomes of patients with small-cell lung cancer? Oncotarget 2017; 8: 37200-07.
22. Akinci Ozyurek B, Sahin Ozdemirel T, Buyukyaylaci Ozden S, Erdogan Y, Kaplan B, Kaplan T. Prognostic value of the neutrophil to lymphocyte ratio (NLR) in lung cancer cases. Asian Pac J Cancer Prev 2017; 18: 1417-21.
23. Souhami RL, Law K. Longevity in small cell lung cancer. a report to the Lung Cancer Subcommittee of the United Kingdom Coordinating Committee for Cancer Research. Br J Cancer 1990; 61: 584-9.

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Corneal abrasion risk in septorhinoplasty operations under general anesthesia

Genel anestezi altında yapılan septorinoplasti ameliyatlarında kornea abrazyonu oluşma riski

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ABSTRACT

Aim: Proper care of the eye is required in all anesthetic applications, especially during general anesthesia. Corneal abrasion is the most common ophthalmologic complication in patients undergoing general anesthesia for non-ocular surgery. Corneal protection methods have been developed to reduce and eliminate the rate of this preventable complication. In this study, it was aimed to compare eye closure with hypoallergenic surgical tapes, eye closure with bio-occlusive dressing and antibiotic eye ointment for eye protection in patients undergoing septorhinoplasty under general anesthesia.

Material and Method: The surgical files of all patients with ASA I and ASA II who underwent septorhinoplasty between 1 January 2019 and 31 December 2019 in our hospital were retrospectively analyzed. A total of 721 patients, 403 female, 318 male, were included in the study. The patients were divided into three groups according to the methods used for eye protection. The demographic features of the patients, the duration of the operation and the findings or complaints about the eyes, if any, before and after the operation were listed from the surgery and outpatient files. It was investigated whether the frequency of eye complaints and symptoms had a significant difference between patients with different eye protection methods. $p<0.05$ was considered statistically significant.

Results: In 721 patients included in the study, it was determined that hypoallergenic surgical tape was applied to 198 patients, an eye ointment with antibiotics was applied to 302 patients, and a bio-occlusive dressing was applied to 221 patients. It was determined that two patients in Group I using hypoallergenic surgical tape and one patient in Group II using antibiotic eye ointment was observed to have a sting and rash that did not require treatment on the first day of the operation. These findings evaluated as CA were not statistically significant between the groups ($p=0.264$).

Conclusion: In septorhinoplasty surgery, there is no significant difference between closing the eyelids directly, applying ointment or closing with bio-occlusive material. However, the bio-occlusive dressing can be used in patients at risk of corneal pathology.

Keywords: Bio-occlusive dressing, corneal abrasion, eye care, eye protection, general anesthesia, peri-operative eye injury

ÖZ

Amaç: Tüm anestezik uygulamalarda, özellikle genel anestezi uygulanması sırasında gözün uygun bakımı gereklidir. Nonoküler cerrahi için genel anestezi uygulanan hastalarda en sık görülen oftalmolojik komplikasyon kornea hasarıdır. Bu önlenebilir komplikasyonun oranını azaltmak ve ortadan kaldırmak için kornea koruma yöntemleri geliştirilmiştir. Bu çalışmada genel anestezi altında septorinoplasti uygulanan hastalarda göz korunması amacıyla hipoallerjenik cerrahi flasterle göz kapatma, biyo-oklüzif şeffaf bantla göz kapatma ve antibiyotikli göz pomadı uygulanmasının karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Hastanemizde 1 Ocak 2019/31 Aralık 2019 arasındaki Septorinoplasti yapılmış ASA I ve ASA II olan tüm hastaların ameliyat dosyaları retrospektif olarak incelendi. 403 kadın 318 erkek toplam 721 hasta çalışmaya dahil edildi. Hastalar, göz koruma için kullanılan yöntemlere göre 3 gruba ayrıldı. Ameliyat ve poliklinik dosyalarından hastaların demografik özellikleri, operasyon süreleri, operasyondan önce ve operasyondan sonraki dönemde varsa gözleri ile ilgili bulgu ya da şikâyetleri listelendi. Göz şikâyet ve bulgularının görülme sıklığının farklı göz koruma yöntemleri uygulanan hastalar arasında anlamlı bir farkları olup olmadığı araştırıldı. İstatiksel olarak $p<0,05$ anlamlı olarak kabul edildi.

Bulgular: Çalışmaya dahil edilen 721 hastada göz koruma yöntemi olarak 198 hastaya nonallerjik flaster, 302 hastaya antibiyotikli göz pomadı, 221 hastaya biyo-oklüzif şeffaf bant uygulandığı tespit edildi. Nonallerjik flaster kullanılan Grup I'de 2 ve antibiyotikli göz pomadı kullanılan Grup II'de 1 hastada operasyonun 1. gününde tedavi gerektirmeyen batma ve kızarıklık görüldüğü tespit edildi. CA olarak değerlendirilmiş olan bu bulgular gruplar arasında istatiksel olarak anlamlı değildi ($p=0,264$).

Sonuç: inoplasti cerrahisinde göz kapaklarını doğrudan bantlayarak kapatmak, merhem sürmek veya biyooklüzif malzeme ile kapatmak arasında anlamlı bir fark yoktur. Ancak kornea patolojisi riski olan hastalarda biyo-oklüzif şeffaf bantlar kullanılabilir.

Anahtar Kelimeler: Bio-occlusive şeffaf bant, genel anestezi, göz bakımı, göz koruması, kornea hasarı, perioperarif göz yaralanması

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INTRODUCTION

Proper care of the eye is required in all anesthetic applications, especially during general anesthesia. Corneal abrasion (CA) is the most common ophthalmologic complication in patients undergoing general anesthesia for non-ocular surgery (1). CA is defined as a defect on the epithelial surface of the cornea, the anterior part of the eye (2).

Patients complain of eye pain, blurred vision, headache, discomfort during blinking or opening, excessive tearing, light sensitivity, feeling of sand, stinging and foreign body sensation. Factors contributing to the formation of CA can be direct irritation of the cornea with a chemical substance, as well as the lack of protective corneal reflex during operation and a decrease in basal tear production can be counted as the main reasons (3).

In rare cases, direct trauma to the eye with mask and laryngoscope, head and neck operations and operations other than the supine position of the patient can be counted among other reasons (4).

Visual loss secondary to trauma or irreversible corneal opacification has been reported after chemical injury during general anesthesia (5).

Various methods have been proposed for peri-operative ocular surface protection. These are manual closure of closed eyelids with or without eye ointment with tapes, application of oil-based lubricant ointments, aqueous solutions such as methylcellulose or viscous gels, wearing protective glasses, wearing hydrophilic contact lenses, tarsore sutures, geliperm dressing (5).

There are studies showing the prevalence of CA between 0.01% and 59% during non-ocular surgery (6,7).

Rhinoplasty is one of the most commonly performed cosmetic procedures around the world (8). In literature searches, no study on the frequency of CA was found during rhinoplasty surgeries.

Corneal protection methods have been developed to reduce and eliminate the rate of this potentially preventable complication.

In this study, it was aimed to compare eye closure with hypoallergenic surgical tape, eye closure with bio-occlusive dressing and antibiotic eye ointment for eye protection in patients undergoing rhinoplasty under general anesthesia.

MATERIAL AND METHOD

In this study, the surgical files of all patients with ASA I and ASA II who underwent septorhinoplasty between 1 January 2019/31 December 2019 in our hospital with local ethical approval (MH 2.1.2020 date 2020/39 number) were analyzed retrospectively. Patients using steroids and antihistamines in the last 24 hours before the operation, patients with ocular pathology were excluded from the study. A total of 721 patients, 403 female, 318 male, were included in the study.

In all patients, anaesthesia was induced with propofol 2 mg kg and maintained with isoflurane.

It was observed that three different methods were applied in our hospital to protect the eye from possible complications during general anesthesia at various time intervals. The patients were divided into three groups according to the methods used. Patients who undergo eye closure with hypoallergenic surgical tapes (Octamed Fix, Octacare, Turkey) Group I; patients who only used eye ointment with antibiotics (paraffin-based ointment including Terramycine, Pfizer, Turkey) were considered as Group II; and patients with bio-occlusive dressing (Tegaderm™, 3M Healthcare, Germany) were considered as Group III. The demographic features of the patients, the duration of the operation and the findings or complaints about the eyes, if any, before and after the operation were listed from the surgery and outpatient files. It was investigated whether the frequency of eye complaints and symptoms had a significant difference between patients with different eye protection methods.

Statistical analysis

Statistical analysis of the data was performed using IBM SPSS for Windows 23.0 (USA) software, and statistical significance was accepted as $p<0.05$. Chi-square and ANOVA tests were used for statistical evaluation.

RESULTS

As an eye protection method in 721 patients included in the study, hypoallergenic surgical tape was used to 198 patients, only eye ointment with antibiotics in 302 patients, and bio-occlusive dressing in 221 patients. The demographic characteristics of the groups were as given in Table. There was no statistical difference in terms of demographic data and operation times of the three groups ($p>0.05$). A total of 3 (0.42%) patients were found to develop CA. It was determined that two patients in Group I using hypoallergenic surgical tape and one patient in Group II using antibiotic eye pouch were observed to have a sting and rash that did not require treatment on the first day of the operation. These findings evaluated as CA were not statistically significant between the groups ($p=0.264$).

Table. Demographic features and operation times of patients

	Group 1 (antibiotic eye ointment)	Group 2 (bio-occlusive dressing)	Group3 (hypoallergenic surgical tape)	p
Age,year (mean±SD)	25.28±5.70	24.47±4.84	24.72±6.32	0.242
Female/male (n)	130/172	98/123	90/108	0.866
Operation time (min) (mean±SD)	132.61+12.90	132.57+12.59	131.39+12.95	0.534

DISCUSSION

Corneal abrasion is a condition where the integrity of the cornea is impaired. It facilitates the penetration of pathogenic organisms, which can lead to microbial keratitis and permanent scarring (9). In a meta-analysis in which 16 articles were examined, the most important risk factors for CA formation in non-ocular surgery were stated to be longer surgery>3.5 hours, advanced age, Trendelenburg positioning, robotic cases and general anesthesia (10).

Although CA is one of the minor complications of general anesthesia, it can be very painful and adversely affect the patient's hospital stay and surgery experience (11). Surgical drapes, oxygen facial masks and foreign bodies play a role in wear (1).

Longer surgery> It has been shown that after 1 hour of general anesthesia, basic changes occur in the protein content of the tear film layer and the incidence of corneal wear increases (7).

In a study conducted during the years when eye protection methods were not widely used, the incidence of CA was reported to be 44% (12). The incidence reported in studies conducted after the spread of eye protection methods decreased to numbers such as 0.01%-0.11% (6,13).

Perioperative CAs often occur secondary to insufficient closing of the eyelids (14). During normal sleep, the orbicularis muscle keeps the eyelid closed; general anesthesia prevents contraction (14).

In some studies, tracheal intubation with PEEP increased intraocular pressure. It has been reported to increase the risk of CA in patients with the combined effects of corneal edema and increased intraocular pressure (15).

One-fifth of the peri-operative CAs are directly related to trauma or chemical injury. Accidental spillage of antiseptic or skin cleansing agent (the most common skin antiseptic is povidone-iodine 10% aqueous solution) into the eyes can cause chemical injury (16).

There is no standard mode of protecting the cornea during general anesthesia for non-eye surgery. The methods described in the literature are not entirely effective and may be associated with undesirable side effects (3).

In a study where eye protection was provided to the study group with ocular tape or ocular ointment and no eye protection method was applied to the control group, 90% of CA occurred in the control group without any eye protection form. The same study found that the greatest reduction in tear production occurred in the unprotected eye (17).

In a study on corneal protection techniques during non-ocular surgery, simple tape application to closed eyelids has been found to provide equal or superior protection to other interventions such as petroleum jelly application (3).

It has been stated that using lubricants in addition to covering the eyelids and taping does not reduce the risk of CA, but may cause side effects (18,19).

One study has shown that many bands used in the operating room allow chlorhexidine solution to penetrate through the tape, but 3M Durapore, 3M Tegaderm Film and Hy-Tape products do not allow fluid to penetrate through the tape (20).

In contrast, in a study of seventy-six patients comparing hydro-gel eye patch and adhesive tape; the authors concluded that the hydro-gel eye patch was superior to the adhesive tape in preventing corneal abrasions (21).

In a study of 72 patients, manual eye closure, adhesive tape, just applying ointment and applying ointment and then applying adhesive tape were compared. The authors reported that in this study, they did not find a significant difference between the groups in CA incidence (22).

In a study where it was stated that the main thing in eye protection was to close the eye completely, Tegaderm ™ Film was suggested to be used in patients at risk of fluids getting into the eyes (23). In one study, it was concluded that horizontal banding had more protective effect than vertical when taping to protect the eye (24).

In another study, the authors stated that they only applied eye ointment to prevent CA (25).

In a study on patients undergoing robotic prostatectomy in the Trendelenburg position, the authors reported that CA did not develop in patients who used Tegaderm during general anesthesia; however, 2.3% CA developed in patients using a valve banding and ocular lubricant (26).

In one study, they found that Hypoallergenic tape, paraffin-based ointment including Terramycin, polyacrylic acid liquid gel and Artificial tears including hydroxy- propyl methylcellulose are equally effective in preventing corneal abrasions as an eye protection method (27).

In our study, similar to many publications in the literature, no statistical significance was found between just closing the eye, using antibiotic ointment and using bio-occlusive (p=0.264).

Iodine-containing solutions applied to the nose and around the nose to clear the surgical area in septorhinoplasty surgeries may increase chemical injuries in the eyes. We think that the frequency of CA in our study is higher than some studies due to the iodized solution applied to the face. In a study comparing povidone-iodine with isotonic solution, it has been reported that iodized solution can cause minimal corneal damage (28).

The main limitations of our study are that it is retrospective and those eye findings are recorded only due to patient complaints.

CONCLUSION

Various measures have been taken to prevent corneal abrasion. In rhinoplasty surgery, there is no significant difference between closing the eyelids directly, applying ointment or closing with bio-occlusive material. However, if the patient has a risk of corneal pathology, protection with eyelid banding or lubricating ointment may not be optimal. In such cases, the use of bio-occlusive dressings can be considered.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Meltem Hospital Ethics Committee (MH 2.1.2020 date 2020/39 number).

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

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. Martin DP, Weingarten TN, Gunn PW, et al. Performance improvement system and postoperative corneal injuries: incidence and risk factors. Anesthesiology 2009; 111: 320-6.
2. Morris A, Bonanno L, Bennett M. Effectiveness of corneal abrasion prevention interventions for adults undergoing general anesthesia for more than one hour: a systematic review protocol. JBI Database System Rev Implement Rep 2018; 16: 1785-90.
3. Grixti A, Sadri M, Watts MT. Corneal protection during general anesthesia for nonocular surgery. Ocul Surf 2013; 11: 109-18.
4. Taylor T, Major E. Hazards of reversal of neuromuscular blockade. Hazards and complications of anaesthesia 2nd ed Edinburgh: Churchill Livingstone. 1993: 234-5.
5. Cuddihy PJ, Whittet H. Eye observation and corneal protection during endonasal surgery. J Laryngol Otol. 2005; 119: 556-7.
6. Yu HD, Chou AH, Yang MW, Chang CJ. An analysis of perioperative eye injuries after nonocular surgery. Acta Anaesthesiol Taiwan. 2010; 48: 122-9.
7. Anderson DA, Braun TW, Herlich A. Eye injury during general anesthesia for oral and maxillofacial surgery: etiology and prevention. J Oral Maxillofac Surg. 1995; 53: 321-4.
8. Alharethy S, Aldrees T, Aljrid R, Alanazi A, Algaryan SK, Jang YJ. Common nasal deformities among rhinoplasty patients in a university hospital in Saudi Arabia. Ann Saudi Med. 2017; 37: 2017-211.
9. Wilson SA, Last A. Management of corneal abrasions. Am Fam Physician. 2004; 70: 123-8.
10. Papp AM, Justin GA, Vernau CT, et al. Perioperative Corneal Abrasions After Nonocular Surgery: A Systematic Review. Cornea. 2019; 38: 927-32.
11. Moos DD, Lind DM. Detection and treatment of perioperative corneal abrasions. J Perianesth Nurs. 2006; 21: 332-41.
12. Batra YK, Bali IM. Corneal abrasions during general anesthesia. Anesth Analg 1977; 56: 363-5.
13. Segal KL, Fleischut PM, Kim C, et al. Evaluation and treatment of perioperative corneal abrasions. J Ophthalmol. 2014; 2014: 901901.
14. Palte HD. Revisiting perioperative corneal abrasion. ASA Newsletter. 2018; 82: 22-5.
15. White E, Crosse MM. The aetiology and prevention of peri-operative corneal abrasions. Anaesthesia. 1998; 53: 157-61.
16. Gild WM, Posner KL, Caplan RA, Cheney FW. Eye injuries associated with anesthesia. A closed claims analysis. Anesthesiology. 1992; 76: 204-8.
17. Grover VK, Kumar KV, Sharma S, Sethi N, Grewal SP. Comparison of methods of eye protection under general anaesthesia. Can J Anaesth. 1998; 45: 575-7.
18. Kaye AD, Renschler JS, Cramer KD, et al. Postoperative Management of Corneal Abrasions and Clinical Implications: a Comprehensive Review. Curr Pain Headache Rep 2019; 23: 48.
19. Snow JC, Kripke BJ, Norton ML, Chandra P, Woodcome HA. Corneal injuries during general anesthesia. Anesth Analg 1975; 54: 465-7.
20. Reimer C. Eye taping during anesthesia and chlorhexidine exposure. Can J Anaesth 2017; 64: 1159-60.
21. Wan T, Wang Y, Jin X-M. Corneal injury and its protection using hydro-gel patch during general anesthesia. Int J Ophthalmol 2014; 7: 964.
22. Lee S-J, Im Kim S, Chung JK, et al. Comparison of eye protection methods for corneal abrasion during general anesthesia. Anesth Pain Med 2016; 11: 99-103.

23. Prakash S. Perioperative eye protection under general anesthesia. J Anaesthesiol Clin Pharmacol 2013; 29: 138.

24. Herbert L. Ophthalmology in anaesthesia and intensive care. Anaesth Intensive Care Med 2004; 5: 304-7.

25. Demir N, Muluk NB, Velentin PT. Anesthesia for Rhinoplasty. All Around the Nose: Springer; 2020. p.783-7.

26. Laverv H, Samadi D, Gainsburg D. 800 preventing ocular injuries during robotic prostatectomy: A simple technique. Eur Urol Suppl 2010; 9: 257.

27. Ganidagli S, Cengiz M, Becerik C, Oguz H, Kilic A. Eye protection during general anaesthesia: comparison of four different methods. Eur J Anaesthesiol 2004; 21: 665-7.

28. Shimmura S, Matsumoto K, Yaguchi H, et al. Acidic electrolysed water in the disinfection of the ocular surface. Exp. Eye Res 2000; 70: 1-6.

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Is there a relationship between chondroid neoplasia and AB0 blood groups?

Kondroid neoplazi ile AB0 kan grupları arasında bir ilişki var mı?

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ABSTRACT

Aim: AB0 and Rh blood groups have been associated with various malignancies. This study aims to investigate the relationship between AB0/Rh blood groups and chondroid neoplasia.

Material and Method: We evaluated 276 patients with chondroid neoplasia retrospectively. The blood groups and tumor localization of the patients who were operated between 2014-2019 were recorded. 129 patients who donated blood to our hospital in 2019 constituted the control group. We compared the demographic characteristics and blood groups of the patients with the control group using the chi-square test.

Results: The mean age was 52±14.6, 49±15.9, and 37±10.3 years, respectively, for enchondroma, chondrosarcoma and the control group. The tumor was mostly localized to the distal femur in both enchondroma and chondrosarcoma patients. Although the 0 Rh (+) blood group rate was higher and the B Rh (+) blood group rate was lower in patients with enchondroma and chondrosarcoma compared to the control group, this difference was not statistically significant. The A and AB blood group rates of the case and control groups were similar.

Conclusion: There was no relationship between AB0 blood groups and chondroid neoplasia. Studies investigating the relationship of different benign and malignant bone tumors with AB0 and Rh blood groups in large patient series are needed.

Keywords: Enchondroma, chondrosarcoma, AB0 blood groups, malignancy

ÖZ

Amaç: AB0 ve Rh kan grupları, çeşitli malignitelerle ilişkilendirilmiştir. Bu çalışmada AB0 kan grupları ile kondroid neoplazi arasındaki ilişkinin araştırılması amaçlanmıştır. 276 kondroid neoplazili hastayı retrospektif olarak değerlendirdik.

Gereç ve Yöntem: 2014-2019 yılları arasında ameliyat edilen hastaların kan grupları ve tümör lokalizasyonu kaydedildi. Kontrol grubunu 2019 yılında hastanemize kan bağışı yapan 129 hasta oluşturdu. Ki-kare testi ile hastaların demografik özelliklerini ve kan gruplarını kontrol grubu ile karşılaştırdık.

Bulgular: Enkondrom, kondrosarkom ve kontrol grubu için ortalama yaş sırasıyla 52±14,6, 49±15,9 ve 37±10,3 yıldı. Tümör hem enkondrom hem de kondrosarkom hastalarında çoğunlukla distalfemurda lokalizeydi. Enkondroma ve kondrosarkomlu hastalarda 0 Rh (+) kan grubu oranı daha yüksek ve B Rh (+) kan grubu oranı kontrol grubuna göre daha düşük olmasına rağmen, bu fark istatistiksel olarak anlamlı değildi.

Sonuç: Kondroid neoplaziler ile AB0 kan grupları arasında ilişki yoktu. Geniş hasta serilerinde farklı benign ve malign kemik tümörlerinin AB0 ve Rh kan grupları ile ilişkisini araştıran çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Enkondrom, kondrosarkom, AB0 kan grupları, malignite

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INTRODUCTION

Enchondroma is usually found incidentally in the appendicular skeleton in young adults (1). Solitary enchondroma is a benign chondroid lesion representing 3 to 13% of all primary bone tumors in large biopsy series (1). Enchondroma is most common in the small bones in hand (40-65%) (2) Most hand lesions are found in proximal phalanges (40-50%) followed by metacarpals (15-30%), middle phalanges (20-30%) and distal phalanx (5-15%) (1,2). Carpal bone involvement is very rare (1). The next most common place for enchondroma is tubular bones, which make up 25% of cases. It is located most frequently in the femur, humerus and tibia from the tubular bones (1,2).

Chondrosarcoma is associated with pain and tends to occur in the axial skeleton of middle-aged adults (3). Chondrosarcoma is the second most common primary osseous neoplasm and constitutes 8 to 17% of the primary bone tumors that are biopsied (3). The most common involvement sites are pelvis, femur, humerus, ribs, tibia, scapula and spine (4). Hand and foot involvement of the chondrosarcoma is rare (1-4%), frequently seen in metacarpals and proximal phalanx (5,6). Chondrosarcoma has a different clinical course than enchondroma. Patients are on average ten years older than patients with enchondroma. Pain is almost always present and is generally insidious, progressive, worse (7).

Matrix mineralization types of bone neoplasms are divided into two main groups as chondroid and osseous. In chondroid matrix mineralization, punctate, linear, crescent shaped or annular calcifications are seen. Chondroid neoplasms are enchondoma, osteochondroma, chondroblastoma, chondromyxoid fibroma and chondrosarcoma (5-7). Numerous studies investigating the relationship between blood group and malignancies have been reported to increase the risk of malignancy with some blood groups (8-15). However, blood group was found to be unrelated to skin cancer, salivary gland cancer and malignant mesothelioma in other studies (16-18). There is only one study investigating the relationship between blood group and bone tumors (2). Of the 449 patients included in that study, only 38 had chondroid neoplasia (192). To the best of our knowledge, there is no study that investigate the relationship between blood group and chondroid neoplasms. Due to the contradictory results between the blood group and malignancy, we aimed to investigate the relationship between blood type and chondroid neoplasms.

MATERIAL AND METHOD

Patients and study design

This study is a case-control study. We retrospectively evaluated 129 (31.8%) patients with enchondroma and 147 (36.3%) with chondrosarcoma who were operated between the years 2014-2019. Blood groups, tumor localization, age, and gender of the patients were recorded from archive files. A control group was formed from 129 (31.8%) healthy volunteers who applied to the blood donation center of our hospital in 2019 and had similar characteristics with the case group in terms of age and gender. Patients whose records or pathology results could not be achieved, and those conservatively followed for enchondroma were excluded from the study. The study protocol was signed on August 18, 2020 at HSU Dr. Abdurrahman Yurtaslan Oncology Hospital was approved by the institutional review board. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

SPSS 22.0 (Chicago) was used for statistical analysis of research data. In the descriptive statistics section, categorical variables are presented as numbers, percentages, and continuous variables are presented with mean±standard deviation and median (range). The consistency of continuous variables to normal distribution was evaluated via Kolmogorov-Smirnov and Shapiro-Wilk tests. Mann-Whitney U test was used for comparison of continuous variables of two groups. Chi-square tests were used in comparison analysis for categorical variables between independent groups. In this study, the level of statistical significance was set at $p< 0.05$.

RESULTS

The mean age was 52±14.6, 49±15.9, and 37±10.3, respectively, for enchondroma, chondrosarcoma, and the control group. There was no statistically significant difference between age, gender, and tumor site of enchondroma and chondrosarcoma patients (**Table 1**). Distal femur was the most common location of both enchondroma and chondrosarcoma (**Table 2**).

Table 1. The characteristics of patient groups

	Enchondroma (n=129)	Chondrosarcoma (n=147)	p value
Mean age±sd	52.1±14.6	48.7±15.9	0.088
Gender	-	-	-
Male, n (%)	68 (52.7)	78 (53.1)	0.953
Female, n (%)	61 (47.3)	69 (46.9)	
Tumor site of the extremity	-	-	-
Right, n (%)	70 (54.3)	81 (55.1)	0.888
Left, n (%)	59 (45.7)	66 (44.9)	

Table 2. Tumor localization of the patients

Localization	Enchondroma (n=129)	Chondrosarcoma (n=147)	p value
Distal femur, n (%)	62 (48)	42 (28)	p<0.001
Proximal humerus, n (%)	36 (28)	28 (20)	p<0.001
Phalanges, n (%)	18 (14)	11 (7)	p<0.001
Proximal tibia, n (%)	10 (7)	2 (1)	p<0.001
Pelvic, n (%)	-	31 (22)	p<0.001
Proximal femur, n (%)	-	22 (15)	p<0.001
Proximal fibula, n (%)	1 (1)	9 (6)	p<0.001
Foot, n (%)	2 (2)	2 (1)	p<0.001

The blood group distribution of the patients and the control group were shown in **Table 3.** The blood type A Rh (+) was the highest among both patients and the control group. The AB Rh (-) was the least blood group among both patients and the control group. Although the 0 Rh (+) blood group rate was higher and the B Rh (+) blood group rate was lower in patients with enchondroma and chondrosarcoma compared to the control group, this difference was not statistically significant. The A and AB blood group rates of the case and control groups were similar.

Table 3. Distribution of the ABO blood groups

Blood Groups	Enchondroma(%)	Chondrosarcoma(%)	Control group(%)	p value
A Rh (+)	38.0	34.0	37.2	0.646
B Rh (+)	10.1	10.9	16.3	0.646
AB Rh (+)	8.5	7.5	8.5	0.646
0 Rh (+)	32.6	31.3	24.8	0.646
A Rh (-)	4.7	6.8	5.4	0.646
B Rh (-)	1.6	3.4	3.1	0.646
AB Rh (-)	0.0	2.7	0.0	0.646
0 Rh (-)	4.7	3.4	4.7	0.646

DISCUSSION

Hereditary AB0 and Rh blood group antigens have been associated with various malignancies (9-11). However, as far as we know, there is no study in the literature investigating the relationship between chondroid neoplasm and blood group. So, this study is the first to investigate the relationship between blood group and chondroid neoplasm. As a result of the presented study, there was no relationship between the blood group and the chondroid neoplasms.

Human blood group antigens are glycoproteins expressed on the surface of red blood cells and in addition to their expression on the surface of red blood cells, ABO antigens are highly expressed on the surface of epithelial cells of the gastrointestinal, bronchopulmonary and urogenital systems (20). Sugar residues of these glycoproteins are added to a protein backbone, H antigen, by a glycosyltransferase encoded by the ABO gene on the 9q34 chromosome (21). Changes in surface glucoconjugates can lead to intercellular adhesion and membrane signals, which may have important effects on tumor development and spread (22). The association of the AB0 blood group system with cancer is unclear and difficult to understand (20). There are several hypotheses to explain its relationship with cancer. A and B antigens can somehow help cancers grow more aggressively (23). The presence of antigens A and B has been shown to increase cellular motility and facilitate interactions between tumor cells (23). In addition, it has been observed that AB0 antigens may contribute to apoptosis (23). For this reason, there are many publications in the literature investigating the relationship between AB0 and Rh groups and cancers, but this study is important because it is the first study to investigate the relationship between AB0 and Rh blood groups and bone tumors.

Several studies demonstrated that AB0 and Rh blood groups are protective against certain malignancies (12-19). Iodice et al. (8) showed a 47% risk reduction for exocrine pancreatic cancer in patients with 0 blood group. Huang et al. (9) showed that the B and AB blood groups could be protective against gastrointestinal, colorectal, gastric, and bladder cancers in their cohort study in 2017. Wolpin et al. (10) demonstrated that 0 blood groups were protective in pancreatic cancer in their cohort study in 2009. There are many studies investigating the relationship between blood groups and cancer risk (11). Marinaciio et al. (11) interpreted blood groupA as a risk factor for endometrial and ovarian cancer. Previous studies showed that blood group A increases the risk of gastric cancer (12,13). A similar relationship was demonstrated in colorectal cancers and studies showed that blood group A also increases the risk of colorectal cancer (14,15). Huang et al. (9) showed that the AB0 blood group increased the risk of liver cancer by 45%.

Some studies investigating the relationship between blood group and malignancy have yielded negative results (16-18). Pinkston et al. (16) showed no relationship between salivary gland tumors and AB0 and Rh blood groups. Tursen et al. (17) showed no relationship between skin cancer and AB0 and Rh blood groups. Similarly, Utkan et al. (18) could not find a relationship between the blood group and the risk of malignant mesothelioma.

This study has its strengths and some limitations. One of its strengths is the first original study in the literature to investigate the relationship between bone tumors and the AB0 and Rh blood group. Another strong thing is that blood groups are obtained from blood center data, not verbal expression. Limitation is that it requires more patients. Because the number of patients in rare blood groups is very low. Another limitation is that enchondroma patients who were conservatively followed up in the outpatient clinic without surgery were excluded because the blood groups were unknown.

CONCLUSION

As a result, enchondroma and chondrosarcoma are chondroid lesions with unique clinical, radiological and pathological findings. There is no relationship between AB0 and Rh blood group and enchondroma and chondrosarcoma. In addition, studies investigating the relationship between different benign and malignant bone tumors with AB0 and Rh blood groups in large patient series are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dr. Abdurrahman Yurtaslan Oncology Hospital Ethics Committee (Permission granted: 18.08.2020, Decision no: 100).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

REFERENCES

1. Hakim DN, Pelly T, Kulendran M, Caris JA. Benign tumours of the bone: A review. J Bone Oncol 2015; 4: 37-41.
2. Mulligan ME. How to Diagnose Enchondroma, Bone Infarct, and Chondrosarcoma. CurrProbl Diagn Radiol 2019; 48: 262-73.
3. Campanacci M. Bone and soft tissue tumors. Springer; 2013.
4. Brien EW, Mirra JM, Kerr R. Benign and malignant cartilage tumors of bone and joint: their anatomic and theoretical basis with an emphasis on radiology, pathology and clinical biology. Skeletal Radiol 1997; 26: 325-53.
5. Atalay İB, Yılmaz S, Şimşek MA, Ekşioğlu MF, Güngör BŞ. Chondrosarcomas of the phalanges of the hand. Jt Dis Relat Surg 2018; 29: 34-9.
6. Öztürk R, Ulucaköy C, Atalay İB, Yapar A, Karakoç Y. Management and retrospective analysis of pelvic ramus tumors and tumor-like lesions: Evaluation with 31 cases. Jt Dis Relat Surg 2020; 31.
7. Murphey MD, Flemming DJ, Boyea SR, Bojescul JA, Sweet DE, Temple HT. Enchondroma versus chondrosarcoma in the appendicular skeleton: differentiating features. Radiographics 1998; 18: 1213-37.
8. Iodice S, Maisonneuve P, Botteri E, Sandri MT, Lowenfels AB. ABO blood group and cancer. Eur JCancer 2010; 46: 3345-50.
9. Huang JY, Wang R, Gao Y-T, Yuan J-M. ABO blood type and the risk of cancer–Findings from the Shanghai Cohort Study. PloS one 2017; 12.
10. Wolpin BM, Chan AT, Hartge P, et al. ABO blood group and the risk of pancreatic cancer. J Natl Cancer I 2009; 101: 424-31.
11. Marinaccio M, Traversa A, Carioggia E, et al. Blood groups of the ABO system and survival rate in gynecologic tumors. Minerva ginecologica 1995; 47: 69-76.
12. Edgren G, Hjalgrim H, Rostgaard K, et al. Risk of gastric cancer and peptic ulcers in relation to ABO blood type: a cohort study. Am J Epidemiol 2010; 172: 1280-5.
13. Sun W, Wen C-P, Lin J, et al. ABO blood types and cancer risk—a cohort study of 339,432 subjects in Taiwan. Cancer Epidemiol 2015; 39: 150-6.
14. Hsiao LT, Liu NJ, You SL, Hwang LC. ABO blood group and the risk of cancer among middle-aged people in T aiwan. Asia-Pac J Clin Oncol 2015; 11: 31-6.
15. Labarriere N, Piau J, Otry C, et al. H blood group antigen carried by CD44V modulates tumorigenicity of rat colon carcinoma cells. Cancer Res 1994; 54: 6275-81.
16. Pinkston JA, Cole P. ABO blood groups and salivary gland tumors (Alabama, United States). Cancer Cause Control 1996; 7: 572-4.
17. Tursen U, Tiftik EN, Unal S, et al. Relationship between ABO blood groups and skin cancers. Dermatol Online J 2005; 11: 44.
18. Utkan G, Urun Y, Cangir AK, et al. Clinicopathological features of patients with malignant mesothelioma in a multicenter, case-control study: no role for ABO-Rh blood groups. Asian Pac J Cancer P 2013; 14: 249-53.
19. Jia D. Bone tumor and ABO blood type. Zhonghuazhongliu za zhi 1991; 13: 220-2.
20. Hakomori S-i. Antigen structure and genetic basis of histo-blood groups A, B and O: their changes associated with human cancer. Biochim Biophys Acta (BBA)-General Subjects 1999; 1473: 247-66.
21. Reid ME, Mohandas N. Red blood cell blood group antigens: structure and function. Semin Hematol 2004; 41: 93-117.
22. Zhang S, Zhang HS, Cordon-Cardo C, Ragupathi G, Livingston PO. Selection of tumor antigens as targets for immune attack using immunohistochemistry: protein antigens. Clin Cancer Res 1998; 4: 2669-76.
23. Melzer D, Perry JR, Hernandez D, et al. A genome-wide association study identifies protein quantitative trait loci (pQTLs). PLoS Genet. 2008; 4: e1000072.

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Factors affecting grade point average among nursing students at college of applied medical science

Uygulamalı tıp bilimleri fakültesinde hemşirelik öğrencileri arasında not ortalamasını etkileyen faktörler

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ABSTRACT

Introduction: Academic performance of the students is very important. Hence, this study aims to assess the Factors affecting Grade Point Average (GPA) among nursing students at the college of applied medical science.

Material and Method: A descriptive study design was adopted in this study. A total of 134 students undergoing a 4 years of Baccalaureate nursing program at the College of Applied Medical Sciences, King Khalid University (KKU), Saudi Arabia was selected using convenience sampling. This study was carried out during the academic year of 2018-2019. The data were collected using a questionnaire such as the five-point Likert scale. The responses obtained were subjected to statistical analysis using SPSS.

Results: The results indicated that the factors which influence the GPA were teacher factor highest mean score 61.32, followed by student factors represented 54.77, home, the college factor is not showing many influencing factors.

Conclusion: Based on the study findings, the results revealed that the teacher-related factor had the highest grand mean value of 61.32 followed by item student-related factor had the grand mean value of 54.77, home factor grand mean value of 47.27, and college factor grand mean value of 20.17. Result revealed that teacher plays a key role in the academic performance of the students. So the present study concludes that the teacher should get feedback from the students at the end of each class to make sure whether the students understood the lecture and clarify the doubt of the students at the end of each lecture.

Keywords: Factors, grade point average (GPA), nursing students

ÖZ

Giriş: Öğrencilerin akademik performansı çok önemlidir. Bu nedenle bu çalışma, uygulamalı tıp bilimleri kolejindeki hemşirelik öğrencileri arasında not ortalamasını (NO) etkileyen faktörleri değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Bu çalışmada betimsel çalışma tasarımı benimsenmiştir. Suudi Arabistan Kral Halid Üniversitesi (KKU) Uygulamalı Tıp Bilimleri Koleji'nde 4 Yıllık Bakalorya hemşireliği programına giren toplam 134 öğrencinin uygunluk durumuna göre örneklem seçildi. Bu çalışma 2018-2019 eğitim öğretim yılında yapılmıştır. Veriler, beş noktalı Likert ölçeği gibi bir anket kullanılarak toplanmıştır. Elde edilen yanıtlar SPSS kullanılarak istatistiksel analize tabi tutulmuştur.

Bulgular: Sonuçlar, not ortalamasını etkileyen faktörlerden öğretmen faktörünün en yüksek ortalama puan 61,32 olduğunu, ardından öğrenci faktörlerinin 54,77'yi temsil ettiğini, üniversite faktörünün önemli ölçüde etkileyici özelliği olmadığını gösterdi.

Sonuç: Araştırma bulgularına göre, sonuçlar öğretmenle ilişkili faktörün en yüksek genel ortalama değeri olan 61,32 olduğunu, öğrenciyle ilişkili faktörün genel ortalama değeri 54,77 olduğunu, ev faktörünün büyük ortalama değerinin 47,27 olduğunu ve üniversite faktörünün büyük ortalama değerinin 20,17 olduğunu gösterdi. Sonuçta öğretmenin, öğrencilerin akademik performansında önemli bir rol oynadığını ortaya konulmuştur. Bu nedenle mevcut çalışma öğretmenin, öğrencilerin dersi anlayıp anlamadıklarından emin olmak ve her dersin sonunda öğrencilerin şüphelerini açıklığa kavuşturmak için öğrencilerden geribildirim alması gerektiği sonucuna varmaktadır.

Anahtar Kelimeler: Faktörler, not ortalaması, hemşirelik öğrencileri

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INTRODUCTION

Students are the future leader of the nation. Academic achievement of the students play an important role in producing best quality graduate nurses. Baccalaureate nursing student nurses are the future healthcare professionals to save the life of the patient. Student performance is one of the important factors to know the quality of education and also the guiding post to know about the lack of education. If the performance is the measure and it is possible to rectify the factor which reduces the performance and helps not only students and also the teacher to identify the problem in education. Few investigators also described that a student who is successful in their required profession has good study habits. In addition to this, she explained that students should apply these habits to in their daily studies. She also suggested that the students should not try to study all the subjects in a single period of time (1).

A study found that the student's previous educational outcome had the most important sign of students'upcoming achievement. This indicates that the highest the previous appearance, the better academic performance of the student in future endeavors (2).

Academic success has a great influence on a student's self- esteem, motivation, and perseverance in higher education. Poor academic performance or highest failure rates may lead to undesirable levels of school dropping, less graduation, and high cost of education. This may also decrease the chance of higher education. Parents'participation has been measured in different ways. The study found that increase occurrence of performance was linked with poor performance or misbehavior in the classroom (3).

An efficient and good Teachers are continuously on the improvement of teaching or instructional material, which may result in efficient learning of students. A sensible and clever choice of a selection of teaching material or audiovisual aids leads to good level of understanding. Some of the factors affecting the student's academic performance such as personal condition, school-related aspect, study habits, home-related aspect, and teacher-related aspect. These factors have highly effect on students'performance, the degree of impact of these factors differs according to personality and culture. Regarding, school-related factor, it was found that unqualified and less efficient teachers, lack of facilities, and inadequate instructional materials were mainly affecting the academic achievement of students. Non-school factors include poverty, low educational achievement, lack of education of parents, poor health, and dietary pattern were the major factors that affect the academic performance (4).

Factors affecting students'academic performance arise for several reasons. Thinking skills primarily affect students learning factors. If they do not learn what they need to learn. If the teacher does not know how to catch the attention of the students, the more students cannot make attention to the subject. The students get lazy if they perceive the topic is not relevant to their subject (5).

The higher education performances depend on the academic achievement of graduate students (6). The outcome of student previous education has the most significant sign of student's upcoming performances, It indicates that the higher previous appearance the better student academic performance in future activities (2). Social and economic background of parents may be linked with the academic performance of school students, they noticed that parents or guardians who have well established social, educational and economic background definitely make stronger the level of a successful career in the future (7).

The students who are successful in their preferred career have interest in reading habits. The researcher stated that students should follow these reading habits to all of their subjects. She also suggested that the students should try to study all their subjects in a different period of time. The personal characteristics of learners and the environment play an important role in their academic success (8). The family members, school personnel, and community provide help and support to improve the quality of the academic performance of the students. This social assistance plays a vital role in the accomplishment of the performance of students at school (9).

Students whose parents are educated secured higher score on standardized tests than those whose parents were not educated (10). Educated parents can well communicate with their children regarding completing schoolwork, activities, and information being taught at school (11). The home environment also influences the academic performance of students. Educated parents can provide such an environment suitable for the academic success of their children. The academic performance of students profoundly depends upon parental involvement in their academic activities to attain the highest level of quality in academic success (12).

A lot of research has been done on factors affecting the academic performance of the college students but there is less information about the academic performance of the students. There are many factors which affect the learning process of learner. The literature suggests that there are many variables that affect learning such as environment, nutrition, emotions, gender, sleep, culture, learning style, and previous learning experience (13). The teacher should know how to make the students understand

more about the subject which they are teaching and also identify the factors which affect their learning and guide them to overcome the problem. This makes the students perform well in their examinations. Hence, students, academic performance has always been a topic of interest for educator. Educators and researchers have identified demographic, socio-economic, family and school factors as variable contributing to students academic performance. Keeping this in mind, the researcher selected this topic to identify the factors which affect their learning and reduce the GPA.So this study aims to identify the factor that leads to reduce the GPA among female nursing students and to associate the demographic data and GPA.

MATERIAL AND METHOD

All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles. The study was carried out with the permission of King Khalid University (Permission date: 11.2.2019, No: HA-06-B-001).

A quantitative, descriptive –survey method was adopted for this study. The study was conducted in the College of applied medical science, Saudi Arabia. The college is providing 4 years Baccalaureate degree nursing program. Students from level 3 to level 8 were (2^{nd} year -4^{th} year) recruited to participate in the study based on the inclusion criteria such as willing to participate in the study and the exclusion criteria was level 1 & 2 (1^{st} year) students because in the first year the subjects were related to basic science not the nursing subject. A total of 134 students consent to participate in the study from level 3 to level 8 (2^{nd} year-4^{th} year) between the age group of 18-23 years. The sample were selected based on convenient sampling technique. The tools used for the study was totally 10 questions regarding personal information, Such as Student age, marital status, number of family members, family income, number of the family at home, Family chronic disease, Selection of nursing course, Respondent chronic illness, A number of hours traveling from home to college, GPA and also rating scale for assessing the factors influencing the academic performance of the students. The questionnaire used for assessing the factors affecting GPA is composed of 49 questions classified as student related factor (14 questions), college related factor (6 questions), Home related factor (14 question) and Teacher related factor (15 questions). The scale is composed of five-point Likert as 1 (Never), 2 (rarely), 3 (sometime), 4 (often), 5 (always). The questionnaire used for data collection was translated to the Arabic version. The tool was validated by the expert in the field of nursing, Using Cronbach Alpha, the instrument was found to be highly reliable as indicated by the value of 0.84.

Method of Data Collection

The researcher got permission from the college Administrative authority. Thereafter, it was subjected to review by the Research Ethics Committee of the university. Based on approval the researcher preceded the data collection. The researcher informed the purpose of the study and the confidentiality of the personal data. The data will be used only for study purpose and the benefit of the study explained to the students and informed consent collected from the students. The researcher explained that their participation was entirely voluntary, that there was no monetary compensation for their participation, and that any information resulting from the study was strict confidentiality. The researcher provided detail about the questionnaire and how to rate the questionnaire themselves and their personal information. Arabic version of a questionnaire distributed to the students individually according the willingness, consent for participating in the study also collected before starting to filling the data and instructed them to rate the scale according to their experience about these factors and also said this is about their individual opinion should not discuss with their friends. Each students taken 30-45 minutes to complete the questions and the data collection period was 3 weeks. The obtained data were reviewed, prepared for computer processing, coded, analysed, and tabulated. Data entry and data analysis were done using SPSS version 16. Data were presented as Frequency distribution, Mean, Standard Deviation, correlation.

RESULTS

Figure shows the distribution of students participation in the study according to the academic levels , level 3, level 4 8%and 25% level 5, level 6 16% & 24%, level 7, level 8 14% & 13%. The results demonstrate that 2nd & 3rd students participation is high than final year students (**Figure 1**).

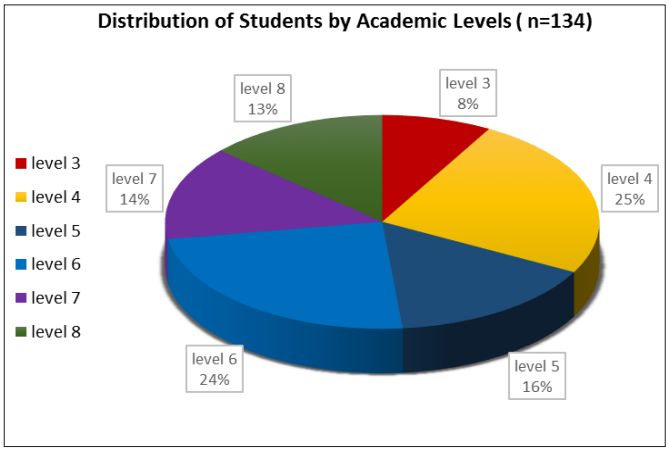

Figure 1. Distribution of students by academic levels

Total number of students was 134, majority of them (84.3%) were single, 87.3% were free from chronic diseases, 91.8% were selecting nursing specialty by themselves and 63.4% their family income was > 10000 SR. This shows that majority of the students selected nursing course on their own so they shows the interest in studying the nursing subject and also sickness of the family members and the financial aspect of the family members also is good and it is not the factor to influence the study (**Figure 2**).

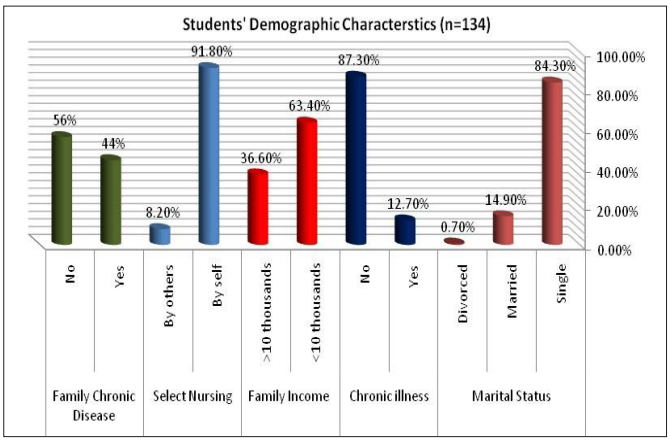

Figure 2. Distribution of students by academic levels

As regard students'demographic characteristics mean score, students'mean age was 21.52 years, number of family members 7. 94, GPA Mean score was 3.13 and Mean hours the students spent to reach college was 1.38. This shows majority of the participants between the age group of 21 years (**Table 1**).

Table 1. Students Demographic Characteristics Mean Score

Items	Mean ($\overline{X}$ ±SD)
Age	21.52+1.193
Family number	7.94+3.117
GPA	3.13+0.758
Hours to college	1.38+0.805

There are 4 factors such as Student, College, Home and Teacher identified to know which factor affecting the students GPA. The result revealed that the teacher-related factor had the highest Grand Mean Value of 61.32 followed by item student related factor had the Grand Mean Value of 54.77,Home factor Grand Mean Value of 47.27 and college factor Grand Mean Value of 20.17. This shows that teacher factor influence on GPA of the students. (**Table 2**).

Table 2. Factors Affecting Students GPA Mean Score

Items	Mean ($\overline{X}$ ±SD)
Student factors	54.7761±7.01517
College factors	20.1716±3.07189
Home factors	47.2761±9.55978
Teacher factors	61.3284±11.87768

It shows the correlation between factors and students'GPA, there was positive correlation between college factors and students'factors (r=.353, p=0.01), students'factors and teacher factors (r=.327, p=0.01), teacher factors and college factors (r=.399, p=0.01), while no correlation founded between home factors and students'GPA. This implies Student, College and Teacher factors play a important role in the improving students GPA (**Table 3**).

Table 3. Bivariate Correlations between Factors and Students GPA

Item	Student factors	Home factors	College factors	Teacher factors	GPA
Student factors	1	.088	.353**	.327**	.021
Home factors	.088	1	-.125-	.096	.030
College factors	.353**	-.125-	1	.399**	.052
Teacher factors	.327**	.096	.399**	1	.024
GPA	.021	.030	.052	.024	1

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

It shows the correlation between demographic characteristics and GPA of the students. The result shows negative correlation between students'age (r=-.258, p=0.01) and GPA, so the age of the students is not matter for the GPA of the students, age and year of study shows positive correlation (r=.628, p=0.01), so the year of the study increases the understanding and interest of the study will be good and thus the students GPA also increases and number of family members have positive correlation to hours to college (r=.190, p=0.05) (**Table 4**).

Table 4. Bivariate Correlations between demographic Characteristics of the students and GPA

Item	GPA	Age	Level	Family Number	Hours to College
GPA	1	-.258**	.021	-.046-	.018
Age	-.258**	1	.628**	.034	-.003-
Level	.021	.628**	1	-.048-	-.131-
Family members	-.046-	.034	-.048-	1	.190*
Hours to college	.018	-.003-	-.131-	.190*	1

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

This study was conducted to explore the important factor that affects the students Grade Point Average. The aim of nursing education is to acquire knowledge, attitude, and skills to provide quality nursing care to needy people. The students should perceive the importance of education and improve professional standards. The current study was conducted to explore the factors which affect the GPA. The current study revealed that most of the nursing students in the age group of 21 years. Regarding the Grade Point Average most of the students were in the category of 3.13.The results show that the average number of family members have seven to nine members in the family.

Findings indicate that all the factors to students, school, home, and teacher have an extensive effect on the academic performance of the student's respondents. Results further revealed that among the four given factors, teacher-related factors have the greatest impact on the academic performance as indicated by the mean value of 61.32. This further indicates that the respondents felt that teaching strategies, student-teacher relationships, and communication barriers hinder their academic performance. This results supported by the study conducted by Alos et al. (14) (2015) which concluded some of the factors have a great impact on the performance of the students, teacher-related factor top the list. This shows that teacher plays an important role in the performance of the students.

Ganyaupfu (15) (2013) also indicates that teacher competence in teaching is a combination of paradigm in the sense that it measures a variety of interrelated aspects in teaching which includes mastery in the subject, preparing the subject in detail, presentation of the content, and effective communication with the students. Lack of knowledge in the subject matter by the teacher leads frustration among students by fulfilling the expectation of the students. Richardson (16) (2006) drawn from the research results teachers have impact on the student's academic performance and from the results, they recommended commitment in preparing the subject and pacing the information, maintain good communication is very important.

The second factor which affects the performance of the students was student-related factors. Manizheh Alami (17) (2016) who said that there could be any reason for students'boredom in the class untouchable topics to read or write and mismatch between students'current information and the presented material in the classroom, I study only there is exam. Moreover et al. (18) (2015) said that high-performance students study in a calm and lonely place most of the time, the study at a consistent time throughout the semester, note an important point in the lecture and clarify the doubt. Meenu (19) (2016) indicated that family structure has a great influence on the student's academic achievement. It is generally reported that the un-conducive environment at home reduces the possibility of learning capabilities.

The third factor which affects student performance was a home-related factor. Bonci (20) (2008) noted in her study that home plays a major role in the achievement of the students. Other researchers also noted that the lack of support from the home leads to a decline in the performance of the students. This normally happens in the urban area most of the parents used to be busy in their office work and it is difficult for them to spend time with their children for guiding them to prepare for the studies. The parents have no attention towards students and therefore spend most of their time in the social media. Using social media distraction from the studies and the students are not ready to prepare the lesson on a daily basis this makes them prepare the lesson only during the exam time.

The last factor which affects the performance of the students is college-related factors. These factors include the availability and perceived quality of learning facilities such as the library, computer, laboratory, clinical environment. Schools without basic facilities also affect the student's performance. The classroom physical environment is very important for students to concentrate in the class and also the facility in the laboratory. Nursing students spend most of their hours in the laboratory and in hospitals. If they practice in the hospital whatever they learned in the classroom makes them understand well and also it give confidence about the subject matter. Owoeye et al. (21) (2011) said that the main purpose of a school library is to make all books, periodicals and other reproduced materials available to the students to improve their study habits. They further indicated that school libraries may not be effective if the books therein are not adequate and up to date. The library environment should have a comfortable environment, chairs and rich in literature with adequate books, journal, periodicals, magazine, computer copy machines and other learning aids that help the students to perform well and that they may need sufficient space for their study so that they do not need to squeeze themselves together. Studies show that students will not perform well if the environment is too hot or too cold, the environment should be conducive for concentrating the class lecture. The inadequate facility in the college environment also leads to health problems.

CONCLUSION

Based on the study findings, the results revealed that teacher-related factor was highly influencing and the other factor such as student, home and college followed that. Among the teacher factor there are two statements

shown highest score such as Do your teacher provide an explanation in the class and Do your teacher clarify the doubt if you have any doubt in the subject matter has highest mean score, it is considered as highly influencing factor. so at the end of each class the teacher should get feedback from the students and modify their teaching strategy according to the need.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of King Khalid University (Permission date: 11.2.2019, No: HA-06-B-001).

Informed Consent: Consent form was obtained from the students.

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

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Author Contribution: All of the authors declare that they have all participated in the design, execution, analysis of the data.

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REFERENCES

1. Marquez VC, Romero C, Ventura S. Predicting School Failure Using Data Mining. In Proceedings of the 4th International Conference on Educational Data Mining. 2011; 6: 271-6.
2. Bratti M, Staffolani S. Student time allocation and educational production functions, Conference paper at the XIV annual EALE conference. 2002.
3. Schlee BM, Mullis AK, Shriner M. Parents Social and Resource Capital: Predictors of academic achievement during early childhood. Children and youth services review. J Educ Psychol 2008; 96: 778-84.
4. Alos SB, Caranto LC, David JJT. Factors Affecting the Academic Performance of the Student Nurses of BSU. Int J Nurs Sci 2015; 5: 60-5
5. Stomberg M, Nilsson K. Nursing students'self-graded motivation to complete their programme of study. Open Nurs J 2010; 4: 42-7.
6. Soares AP, Guisande MA, Almeida LS, Paramo M.F. Academic Achievement in first-year Portuguese college students: The role of academic preparation and learning strategies. Int J Psychol 2009; 44: 204-12.
7. Zhonglu L, Zeqi Q. How does family background affect children's Educational achievement? Evidence from Contemporary China. Chin J Sociol 2018; 5: 13
8. Hayden K, Ouyang Y, Scinski L, Olszewski B, Bielefeldt T. Increasing student interest and attitudes in STEM: Professional development and activities to engage and inspire learners. CITE 2011; 11: 47-69.
9. Goddard RD. Relational networks, social trust, and norms: A social capital perspective on students'chances of academic success. Educ Eval Policy Anal 2003; 25: 59-74.
10. Krashen S. The hard work hypothesis: Is doing your homework enough to overcome the effects of poverty? Multicult Educ 2005; 1: 16-9.
11. Fantuzzo J, Tighe E. A family involvement questionnaire. J Educ Psychol 2000; 92: 367-376.
12. Barnard WM. Parent involvement in elementary school and educational attainment. Child Youth Serv Rev 2004; 26: 39- 62.
13. Jensen B, Seltzer A. Neighbourhood and family effects in educational progress. Aust Econ Rev 2000; 33: 17-31.
14. Alos SB, Caranto LC, David JJT. Factors affecting the academic performance of the student nurses of BSU. Int J Nurs Sci 2015; 5: 60-5.
15. Elvis MG. Factors influencing academic achievement in quantitative courses among business students of private higher education institutions.J Educ Pract 2013; 4: 57-60.
16. Richardson JTE. Investigating the relationship between variations in students' perceptions of their academic environment and variations in study behaviour in distance education. Br J Educ Psychol 2006; 76: 867–893
17. Manizheh A. Causes of poor academic performance among omani students. Int J Soc Sci Res 2016; 4: 8-11.
18. Miguel AC, Ksenia P. Influence of study habits on academic performance of International college students in Shanhai. CCSE 2015; 5: 42-55
19. Meenu D. Factors affecting the academic achievement: A study of elementary school students of NCR Delhi, India. J Educ Pract 2016; 7: 70-4
20. Bonci A. A research review: The importance of families and the home environment, National Literacy Trust. 2008; Retrieved from https://files.eric.ed.gov/fulltext/ED521654.pdf
21. Joseph S, Owoeye Y. School facilities and academic achievement of secondary school agricultural science in Ekiti state, Nigeria. Asya Soc Sci 2011; 7: 64-74.

Original Article/Özgün Makale

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The effect of Pilates performed during pregnancy on delivery outcomes

Pilatesin gebelikte doğum sonuçları üzerine etkisi

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ABSTRACT

Aim: The aim of this study was to investigate the effect of clinical pilates on delivery outcomes in pregnant women.

Material and Method: Eighty-three pregnant women were included in the study. The study comprised pregnant women who voluntarily agreed to perform Pilates (n: 26, age: 28.77±4.43 years) and a control group (n: 57, age: 28.18±4.69 years) that did not perform pilates. Pilates training was provided by a physiotherapist two days a week (1 h/session). Height, weight, weight gained during pregnancy, hemoglobin level, education level, duration of labor, type of delivery, birth week, induction requirement and duration, birth weight of infants, and APGAR (appearance, pulse, grimace response, activity, respiration) scores were retrospectively recorded from the patient files.

Results: It was found that Pilates did not have a negative effect on gestational age, birth week, birth weight of infants and APGAR scores. Pregnant women who performed pilates gained less weight during pregnancy compared with those in the control group ($p<0.05$).

Conclusion: This study supports the conclusion that pilates performed by pregnant women has a positive effect on delivery outcomes.

Keywords: Pregnancy, delivery, pilates

ÖZ

Amaç: Bu çalışmanın amacı, gebelerde klinik pilatesin doğum sonuçları üzerine etkisini araştırmaktır.

Gereç ve Yöntem: Çalışmaya seksen üç gebe dahil edildi. Çalışma grupları, pilates yapmayı gönüllü olarak kabul eden (n: 26, yaş: 28,77±4,43 yıl) çalışma grubu ve pilates yapmayan (n: 57, yaş: 28,18±4,69 yıl) kontrol grubundan oluşturuldu. Pilates eğitimi haftada iki gün fizyoterapist tarafından sağlandı (1 saat/seans). Retrospektif olarak boy, kilo, gebelikte kazanılan kilo, hemoglobin düzeyi, eğitim düzeyi, doğum süresi, doğum şekli, doğum haftası, indüksiyon gereksinimi ve süresi, bebeklerin doğum ağırlığı ve APGAR (görünüm, nabız, grimace yanıtı, aktivite, solunum) puanları hasta dosyalarından kaydedildi.

Bulgular: Pilates'in gebelik yaşı, doğum haftası, bebeklerin doğum ağırlığı ve APGAR skorları üzerinde olumsuz bir etkisi olmadığı bulundu. Pilates yapan gebeler hamilelikte kontrol grubuna göre daha az kilo aldı ($p<0.05$).

Sonuç: Bu çalışma, hamile kadınlar tarafından yapılan pilatesin doğum sonuçları üzerinde olumlu bir etkisi olduğu sonucunu desteklemektedir.

Anahtar Kelimeler: Gebelik, doğum, pilates

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INTRODUCTION

Although exercise during pregnancy is recommended by authorities, there are limited studies on this topic in the literature. A woman's body will experience many changes during pregnancy. These changes include changes in posture, weight gain and weakness of joints and ligaments (1). Exercise has been associated with better outcomes in mothers and their children in addition to protection against the development of chronic disease. According to the American College of Obstetricians and Gynecologists (ACOG), despite the physiologic and anatomic changes in the maternal body, physical exercise should be encouraged during pregnancy (2). Among exercise programs, the Pilates method has become more popular worldwide (3). This method was developed by Joseph Pilates in the early 1900s (4). In 2002, it was modified by Australian physiotherapists under the name of modified (clinical) Pilates and made clinically compliant. Clinical Pilates is a method used by physiotherapists (4). In Pilates, the body is defined as a system originating from a central column. This column consists of muscles that most fundamentally represent the body. Initially, these muscles are trained. Clinical Pilates develops body awareness. Because of the principles forming its philosophy, Pilates strengthens mind–body coalescence by offering a holistic approach.

Exercises are slowly ended under the control of the patient and not under the effect of gravity. This reduces the risk of injuries. The most important reason why clinical Pilates has gained popularity in recent years is its mind–body coalescence feature. With the effect of behavior training, Pilates enables women's lives to be balanced physically, physiologically and emotionally (5). Pilates is a technique that emphasizes spinal stabilization, pelvic floor control, breathing and posture. The effects of Pilates on pelvic floor muscle strength have been investigated. It has been concluded that these exercises can be used to treat pelvic floor dysfunction (6). Most pregnant women have difficulty in breathing, particularly during the second and third trimesters. Pilates increases lung capacity and reduces the feeling of shortness of breath. One of the most important issues during pregnancy is balance. There are many studies reporting that the ability to balance is decreased during pregnancy. A woman gains weight equal to 25%–30% of her total body weight during pregnancy, and therefore, her center of gravity changes. This change is caused by two conditions: changing hormonal balance and its effect on the mental state. Testosterone is important for balance, spatial perception and hand-eye coordination. When Pilates is performed, testosterone levels increase and balance improves (5).

Performing Pilates regularly during pregnancy creates body awareness, improves posture, protects the body against musculoskeletal problems caused by posture disorder, helps the body be more flexible, improves coordination along with balance, enables less weight gain, reduces the risk of premature birth and strengthens the immune system (5).

Based on this information, the aim of this study was to investigate the effects of clinical Pilates on delivery and maternal fetal outcomes.

MATERIAL AND METHOD

The study was retrospectively performed in a tertiary referral center. The study was approved by the local Institutional Review Boards (01/06/2012, acception no.8) and written informed consent of all participants were obtained. This study was conducted according to the Declaration of Helsinki. A total of 83 patients (n: 26 Pilates group and n: 57 control group) were included in this study. The Pilates group comprised 26 patients who volunteered to perform Pilates under the supervision of a physiotherapist starting from gestational weeks 16–18 until gestational weeks 34–36. The control group comprised pregnant women who were admitted for delivery during the same period, but were not included in the Pilates exercise program. Patients with systemic diseases, such as hypertension and goiter, and maternal complications, such as preeclampsia, gestational diabetes, membrane rupture, multiple pregnancy and placenta previa, were excluded from the study. In the Pilates group, exercises were taught at the hospital by a physiotherapist for at least 8 weeks, 2 days a week and 1 h per session in the form of moderate intensity exercise (Borg Scale 12–14) recommended by ACOG guidelines. The Pilates exercise program was designed so that exercise sessions included a warm-up phase, main exercise program and cooling phases. The program was held at the mat level against gravity and resistance (along with the use of an exercise band and exercise ball). The first 10 min of the 1-h exercise program consisted of warm-up exercises, mid-load period (Clinical Pilates) exercises were performed for 30-40 min and cooling exercises were performed for 10 min. Age, height, weight, weight gained during pregnancy, hemoglobin level, education level, duration of labor, type of delivery, birth week, induction requirement and duration, birth weight of infants and APGAR scores were retrospectively recorded from the patient files. Statistical analysis was performed using SPSS version 20 software (SPSS Inc, Chicago, IL, USA). For descriptive statistics, number and percentage were used to present categorical variables, whereas mean±standard deviation was used for continuous variables with normal distribution. In cases where parametric test assumptions were fulfilled, Student t-test was used for intergroup comparisons, and Mann–Whitney U test was used if parametric test assumptions were not fulfilled. Significance level (p value) was accepted as 0.05.

RESULTS

The mean age of pregnant women in the pilates and control groups was 28.77±4.43 and 28.18±4.69 years, respectively. No difference was found between the two groups in terms of mean age (p: 0.574) (**Table 1**). The mean gestational age of pregnant women in the study group at the onset of Pilates was 20 (min. 16, max. 27) weeks. There was a significant difference between the two groups in terms of education level of pregnant women. In the study, 17 (65.4%) of the pregnant women in the Pilates group were university graduates, 7 (26.9%) were high school graduates and 2 (7.7%) were primary school graduates, whereas 6 (10.5%) of the pregnant women in the control group were university graduates, 17 (29.9%) were high school graduates and 34 (59.6%) were primary school graduates (**Table 1**) (p<0.001).

Table 1. Demographic characteristics

Variables	Pilates Group (n=26)	Control Group (n=57)	P-value
Age (Years) (mean±SD)	28.77±4.43	28.18±4.69	0.574
Initial BMI (kg/cm²)	25.70±1.75	26±2.54	0.432
Weight gain (kg)	10.69±2.24	14.11±4.39	<0.001
Gestational age (weeks)	39.35±1.23	38.88±1.40	0.157
Gravida	1.54±0.72	1.84±0.80	0.21
Education (n, %)	-	-	-
Primary	2 (7.7%)	34 (59.6%)	<0.001
High School	7 (26.9%)	17 (29.9%)	<0.001
University	17 (65.4%)	6 (10.5%)	<0.001

Demographic data: age, initial body mass index, gestational age, gravida, education

Body mass index (BMI) at the beginning of pregnancy was 25.70±1.75 and 26±2.54 for pregnant women in the study and control groups, respectively. There was no significant difference between the two groups in terms of body mass index at the beginning of pregnancy (p>0.05) (**Table 1**). The mean weight gain during pregnancy was 10.69±2.24 kg for pregnant women in the study group and 14.11±4.39 kg for those in the control group. There was a significant difference between the two groups in terms of weight gained during pregnancy (**Table 1**) (p<0.001).

There was no difference between the groups in terms of gravida and parity (**Table 1**) (p: 0.21). Considering the type of delivery, there was no significant difference between the groups in terms of primary Cesarean rates (**Table 2**) (p: 0.272). However, the percentage of primary Cesarean rates was 15.4% in the Pilates group and 26.3% in the control group. There was no difference between the groups in terms of Cesarean indications (p: 1).

When labor time was compared between the groups, it was found that there was no difference in the latent phase (p: 0.313), whereas a difference was found in the active phase. The active phase was significantly shorter in the study group (**Table 2**) (p: 0.042).

There was also a significant difference between the groups in terms of induction time (**Table 2**) (p<0.01). In the study group, 46% of the patients underwent labor induction and the mean induction time was 5.33 (min 2, max 11) hours. Conversely, 26 patients in the control group underwent labor induction and the mean induction time was 10.88 (min 6, max 18) hours.

There was no significant difference between the groups in terms of gestational age (p: 0.157) (**Table 2**). There was no significant difference between the groups in terms of birth weights of infants (p: 0.498) (**Table 2**). In comparing APGAR evaluations at min 1 and 5 after delivery, no significant difference was found between the groups (p>0.05). There was a significant difference between the groups in terms of hemogram values. (p: 0.045) (**Table 2**).

Table 2. Clinical characteristics

Variables	Pilates Group (n=26)	Control Group (n=57)	P-value
Delivery Type	-	-	-
Vaginal birth (n, %)	22(84.6%)	42(73.7%)	-
Cesarean	4(15.4%)	15(26.3%)	0.272
Labor	-	-	-
Latent phase (h) (mean±SD)	7.92±2.46	9.35±4.5	0.313
Active phase (h)	3.54±1.33	4.19±1.49	0.042
Induction time (h) (Median) (min; max)	5h (2-11)	11h (6-20)	<0.001
Hb (gr/dL) (Median) (min, max)	12.57 (10.20-14.10)	12.08 (9.20-13.9)	0.045
Infant weight (g) (SD)	3454± 73.9	3378±66.6	0.498

Note: Values are presented as mean±standard deviation. (p< 0.05).

DISCUSSION

The age range of the pregnant women included in this study was 20–39 years. Fourteen studies in the ACOG guideline reported an important correlation between exercise during pregnancy and the age of pregnant women. It has been observed that young pregnant women perform high level exercises (7-10). In contrast to these studies, four studies reported that the older age group exercised with higher intensity (11-14). In these studies, it was reported that adult women (26–35 years old) were more interested in high intensity exercises and increased their level of exercise during the period from pre-pregnancy to pregnancy, and women who had been doing sports before pregnancy continued their sportive activities during pregnancy (11,12). In some studies, no correlation was found between gestational age and exercise level (15-18).

In this study, 17 (65.4%) of the pregnant women in the Pilates group were university graduates, whereas only 6 (10.5%) pregnant women in the control group were university graduates. In other words, it is noteworthy

that the education level of the pregnant group receiving exercise training was higher. In a study conducted in Portugal, despite the decrease in physical activity during pregnancy, it was shown that pregnant women with nulliparous pregnancy were working, had a higher education level and the age range was 25–34 years (19). In another study conducted with 616 pregnant women who were mostly Spanish (94.3%), the mean age was 31.3 (SD: 4.2) years and the majority of them were high school (44.3%) or university (38.5%) graduates (20). These results are consistent with those of our study.

In this study, when body mass indices at the beginning of pregnancy were examined, no statistical difference was found between the groups. When weight gained during pregnancy was compared between the groups, it was found that weight gain during pregnancy was lower in the study group than in the control group. In other words, it was concluded that the exercise program provided in this study reduced weight gain during pregnancy.

In another study, it was reported that pregnant women in the active group gained 12.4 kg of weight during pregnancy and those in the control group gained 10.5 kg of weight. There was no significant difference between the groups in terms of weight gain (21). In our study, it was found that pregnant women in the Pilates group gained 10.6 kg of weight during pregnancy and those in the control group gained 14.1 kg of weight.

When we look at studies in general, a contradictory correlation is seen between exercise during pregnancy and weight gain. In a few studies, no correlation was found between exercise and weight gain during pregnancy (22,23). However, other studies concluded that weight gain was lower in pregnant women who exercised than in those who did not exercise at all (24-26).

In the study by Clapp and Little (25) on pregnant women, it was found that weight gain was lower when exercise was performed during the first trimester, but weight gain was higher when exercise was performed during the second and the third trimesters. In our study, the exercises were started in the second trimester. The second trimester is preferred because pregnancy is definite, the risk of abortion is less, and physical changes start to occur in the body. Ideally, it may be advisable to start exercising before pregnancy and to continue the exercises during pregnancy at a personally adjusted intensity level. In fact, results of the medium-severity personal exercise program used in this study support this view.

Conversely, when the duration of labor between the groups was compared, it was found that there was no difference between the latent phases, but the active phase in the Pilates group was significantly shorter (p: 0.042). When induction times were examined, a significant difference was found between the groups ($p<0.001$). There are limited studies in the literature comparing the induction period of labor. In fact, we expected pregnant women in the Pilates group to have a shorter duration of labor. However, in many studies, there was no positive effect of exercise on shortening the duration of labor (27-32). However, our study supports the fact that pregnant women who perform Pilates require shorter induction and they have a shorter duration of labor. According to the study conducted by Horns et al. (33) it was concluded that pregnant women who exercised during the third trimester gave birth with a shorter duration of labor than those in the control group. In our study, 22 (84.6%) of the pregnant women who performed Pilates had a normal birth and 42 (73.7%) of those in the control group had a normal birth. The primary cesarean ratios were 15.4% and 26.3% in the Pilates and control groups, respectively. There was no statistically significant difference between the groups in terms of the delivery type. However, when the percentages were examined, it was noteworthy that the normal birth rate was higher among pregnant women in the Pilates group. We believe that this difference would be significant in a larger sample. In the literature, the number of studies on this subject is limited.

No significant difference was found between the groups in terms of gestational age ($p>0.157$). The mean gestational age was 275.4 days (39.3 weeks) in the Pilates group and 272.1 days (38.8 weeks) in the control group. In our study, preterm birth (before 36 weeks) or post-term birth (after 42 weeks) was not observed in any of the groups. All pregnant women in the study had term delivery, and there was no significant difference between them in terms of gestational age. This result supports the notion that there is no risk of preterm birth in pregnant women who receive Pilates exercise training. In another study that was similar to our study, it was reported that the mean gestational age of the active pregnant group was 39.2 weeks and the mean gestational week of the control group was 39.4 weeks (21). In other words, there was no preterm birth in the active group. In the study by Gollenberg et al. (34) it was emphasized that there was no difference between the active pregnant and control groups in terms of gestational age or preterm birth results.

There was no difference between the groups in terms of birth weights. In other words, exercise during pregnancy had no effect on decreasing the birth weight of infants. In the study by Pivarnik et al. (35) it was found that there was no relationship between infant birth weight and physical activity. In addition, Clapp et al. (27) reported that infant birth weight was lower in pregnant athletes who exercised 6 days a week, at least for 1 h a day, than in

those who stopped exercising after 28 weeks. Similarly, in another study, it was reported that regular exercise during pregnancy had a negative effect on infant birth weight. In this study, it was reported that infant birth weight was lower in pregnant women who attended exercise sessions regularly until 28 weeks of pregnancy and attended at least one third of the exercise sessions during the remainder of their pregnancy than in those who reduced their physical activity during pregnancy (36). In another study, it was reported that infant birth weights of pregnant women who exercised heavily during pregnancy were higher than those who did not exercise (37). In a prospective randomized controlled trial by Clapp et al. (27) severe aerobic exercises were performed from early to late term of pregnancy. It was reported that infant birth weight of pregnant women who performed this exercise program was 460 g higher than that of those in the control group (24). Bradley et al. (21) emphasized that infant birth weight was 3329 g in active pregnant women and 3308 gr in inactive pregnant women.

Considering that all pregnant women had similar levels of physical activity at the onset of the study, the fact that the exercise program did not affect birth weight supports the conclusion that this program is highly safe for pregnant women, and therefore, is a noteworthy finding.

In this study, it was found that there was no significant difference between APGAR scores at min 1 and 5 for infants of pregnant women who did or did not perform clinical Pilates. Previous studies have mostly focused on the effects of exercise during pregnancy on birth weight, birth week, and APGAR score. In these studies, aerobic dance and strengthening exercises were performed by sedentary pregnant women twice a week for a minimum of 12 weeks, and it was found that exercise training had no negative effect on AGPAR score (38,39). In this study, delivery outcomes of pregnant women performing clinical Pilates were compared with those of pregnant women not performing Pilates, and it was found that Pilates had no lowering effect on gestational age, there was no difference between infant birth weights between pregnant women in the exercise group and those in the control group, and APGAR scores were similar in both groups.

One of the limitations of this study was the small sample size. Furthermore, the physical activity level of pregnant women in the control group during pregnancy could not be determined. Prospective studies with a larger number of pregnant women will be more satisfactory in terms of study results.

Although the importance of exercise in pregnant women has been emphasized in recent years, the lack of a standardized exercise program in the literature is a serious shortcoming.

CONCLUSION

Clinical Pilates can be a suitable exercise model when applied to pregnant women within an appropriate period of pregnancy since it has a positive effect on the pregnant women and their infants. We believe that this exercise model should be given more importance by obstetricians and physiotherapists in Turkey. Dissemination of these trainings is important for the continuation of future studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the local Institutional Review Boards (01/06/2012, acception no.8).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

REFERENCES

1. Foti T, Davids JR, Bagley A. A biomechanical analysis of gait during pregnancy. J Bone Joint Surg Am 2000; 82: 625-32.
2. ACOG Committee Opinion No. 650: Physical activity and exercise during pregnancy and the postpartum period. Obstet Gynecol 2015; 126: e135-e142.
3. Bird ML, Hill KD, Fell JW. A randomized controlled study investigating static and dynamic balance in older adults after training with Pilates. Arch Phys Med Rehabil 2012; 93: 43-9.
4. Unal E. Romatizmal Hastalıkalrda Biyopsikososyal Model: Bilişsel Egzersiz Terapi Yaklaşımı (BETY). Ankara: Pelikan Yayıncılık. 2014.
5. Winsor M, Laska M. The pilates pregnancy: Maintaining strength, flexibility, and your figure. Da Capo Press; 2001.
6. Culligan PJ, Scherer J, Dyer K, et al. A randomized clinical trial comparing pelvic floor muscle training to a Pilates exercise program for improving pelvic muscle strength. Int Urogynecol J 2010; 21: 401-8.
7. ACOG Committee Obstetric Practice. ACOG Committee opinion. Number 267, January 2002: exercise during pregnancy and the postpartum period. Obstet Gynecol 2002; 99: 171-3.
8. Zhang J, Savitz DA. Exercise during pregnancy among US women. Ann Epidemiol 1996; 6: 53-9.
9. Evenson KR, Savitz DA, Huston SL. Leisure-time physical activity among pregnant women in the US. Paediatr Perinat Epidemiol 2004; 18: 400-7.

10. Petersen AM, Leet TL, Brownson RC. Correlates of physical activity among pregnant women in the United States. Med Sci Sports Exerc 2005; 37: 1748-53.

11. Fell DB, Joseph KS, Armson BA, Dodds L. The impact of pregnancy on physical activity level. Matern Child Health J 2009; 13: 597-603.

12. Hinton PS, Olson CM. Predictors of pregnancy-associated change in physical activity in a rural white population. Matern Child Health J 2001; 5: 7-14.

13. Rutkowska E, Łepecka-Klusek C. The role of physical activity in preparing women for pregnancy and delivery in Poland. Health Care Women Int 2002; 23: 919-23.

14. Rose NC, Haddow JE, Palomaki GE, et al. Self-rated physical activity level during the second trimester and pregnancy outcome. Obstet Gynecol 1991; 78: 1078-80.

15. Watson PE, McDonald BW. Activity levels in pregnant New Zealand women: relationship with socioeconomic factors, well-being, anthropometric measures, and birth outcome. Appl Physiol Nutr Metab 2007; 32: 733-42.

16. Chasan-Taber L, Schmidt MD, Pekow P, et al. Correlates of physical activity in pregnancy among Latina women. Matern Child Health J 2007; 11: 353-63.

17. Clarke PE, Gross H. Women's behaviour, beliefs and information sources about physical exercise in pregnancy. Midwifery 2004; 20: 133-41.

18. Mottola MF, Campbell MK. Activity patterns during pregnancy. Can J Appl Physiol 2003; 28: 642-53.

19. Gouveia R, Martins S, Sandes AR, et al. Pregnancy and physical exercise: myths, evidence and recommendations. Acta medica portuguesa 2007; 20: 209-14.

20. Artieta-Pinedo I, Paz-Pascual C, Grandes G, et al. The benefits of antenatal education for the childbirth process in Spain. Nurs Res. 2010; 59: 194-202.

21. Price BB, Amini SB, Kappeler K. Exercise in pregnancy: effect on fitness and obstetric outcomes-a randomized trial. Med Sci Sports Exerc 2012; 44: 2263-9.

22. Kramer MS, McDonald SW. Aerobic exercise for women during pregnancy. Cochrane Database Syst Rev 2006; 2006: CD000180.

23. Magann EF, Evans SF, Weitz B, Newnham J. Antepartum, intrapartum, and neonatal significance of exercise on healthy low-risk pregnant working women. Obstet Gynecol 2002; 99: 466-72.

24. Clapp JF 3rd, Kim H, Burciu B, Schmidt S, Petry K, Lopez B. Continuing regular exercise during pregnancy: effect of exercise volume on fetoplacental growth. Am J Obstet Gynecol 2002; 186: 142-7.

25. Clapp JF 3rd, Little KD. Effect of recreational exercise on pregnancy weight gain and subcutaneous fat deposition. Med Sci Sports Exerc 1995; 27: 170-7.

26. Haakstad LA, Voldner N, Henriksen T, Bø K. Physical activity level and weight gain in a cohort of pregnant Norwegian women. Acta obstetricia et gynecologica Scandinavica 2007; 86: 559-64.

27. Clapp JF 3rd, Dickstein S. Endurance exercise and pregnancy outcome. Med Sci Sports Exerc 1984; 16: 556-62.

28. Collings CA, Curet LB, Mullin JP. Maternal and fetal responses to a maternal aerobic exercise program. Am J Obstet Gynecol 1983; 145: 702-7.

29. Hall DC, Kaufmann DA. Effects of aerobic and strength conditioning on pregnancy outcomes. Am J Obstet Gynecol 1987; 157: 1199-203.

30. Rice PL, Fort IL. The relationship of maternal exercise on labor, delivery and health of the newborn. J Sports Med Phys Fitness 1991; 31: 95-9.

31. Bungum TJ, Peaslee DL, Jackson AW, Perez MA. Exercise during pregnancy and type of delivery in nulliparae. J Obstet Gynecol Neonatal Nurs 2000; 29: 258-64.

32. Kardel KR, Kase T. Training in pregnant women: effects on fetal development and birth. Am J Obstet Gynecol 1998; 178: 280-6.

33. Horns PN, Ratcliffe LP, Leggett JC, et al. Pregnancy outcomes among active and sedentary primiparous women. J Obstet Gynecol Neonatal Nurs 1996; 25: 49-54.

34. Gollenberg AL, Pekow P, Bertone-Johnson ER, et al. Sedentary behaviors and abnormal glucose tolerance among pregnant Latina women. Med Sci Sports Exerc 2010; 42: 1079-85.

35. Pivarnik JM, Perkins CD, Moyerbrailean T. Athletes and pregnancy. Clin Obstet Gynecol 2003; 46: 403-14.

36. Cléroux J, Feldman RD, Petrella RJ. Lifestyle modifications to prevent and control hypertension. 4. Recommendations on physical exercise training. Canadian Hypertension Society, Canadian Coalition for High Blood Pressure Prevention and Control, Laboratory Centre for Disease Control at Health Canada, Heart and Stroke Foundation of Canada. CMAJ 1999; 160: S21-S28.

37. Hatch MC, Shu XO, McLean DE, et al. Maternal exercise during pregnancy, physical fitness, and fetal growth. Am J Epidemiol 1993; 137: 1105-14.

38. Nascimento SL, Surita FG, Parpinelli MÂ, Siani S, Pinto e Silva JL. The effect of an antenatal physical exercise programme on maternal/perinatal outcomes and quality of life in overweight and obese pregnant women: a randomised clinical trial. BJOG 2011; 118: 1455-63.

39. Haakstad LA, Bø K. Exercise in pregnant women and birth weight: a randomized controlled trial. BMC Pregnancy Childbirth. 2011; 11: 66.

Original Article/Özgün Makale

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Prevalence and risk factors of otitis media with effusion in primary school children in Mersin

Mersin'de ilkokul çocuklarında efüzyonlu otitis media prevalansı ve risk faktörleri

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ABSTRACT

Aim: To investigate the prevalence of otitis media with effusion (OME) and related risk factors among primary school children in Mersin.

Material and Method: The study was conducted at eight primary government schools in the distinct socioeconomic district between October 2018 and December 2018. Using the combined physical examination and otoscopic evaluations, a total of 960 children included the study.

Findings: Of the children who were screened, 53.2% were girls and the mean age was 7.57±0.45 years (min:5-max:11 years). In this study, otitis media with effusion prevalence was 2.6% (20 of 761 children) and all children had bilateral otitis media with effusion. There was no statistically significant difference between the presence of otitis media with effusion and the number of people at home, incoming level, month of birth, birth weight, duration of breastfeeding, age average, class, gender, smoking in the house, presence of hearing loss in the family, history of otitis in the family, use of pacifier, use of baby bottle, presence of allergy, previous history of otitis, the presence of open mouth, snoring and tonsil grades.

Conclusion: Although the low prevalence of otitis media with effusion in our study, considering that otitis media with effusion and its possible preventive severe complications, screening for otitis media with effusion should be a part of preventive health services, particularly for primary school children.

Keywords: Children, school nursing, otitis media with effusion, prevalence, primary schools

ÖZ

Amaç: Mersin'deki ilkokul çocukları arasında efüzyonlu otitis media (EOM) prevelansını ve ilgili risk faktörlerini araştırmak.

Gereç ve Yöntem: Çalışma Ekim 2018-Aralık 2018 tarihleri arasında farklı sosyoekonomik bölgedeki sekiz ilköğretim okulunda gerçekleştirildi. Fizik muayene ve otoskopik değerlendirmeler birlikte kullanılarak toplam 960 çocuk çalışmaya dahil edildi.

Bulgular: Tarama yapılan çocukların %53,2'si kız ve ortalama yaş 7,57±0,45 yıl idi (min:5-max:11 yıl). Bu çalışmada efüzyonlu otitis media prevalansı %2,6 idi (761 çocuğun 20'si) ve tüm çocuklarda bilateral efüzyonlu otitis media vardı. efüzyonlu otitis media varlığı ile evdeki kişi sayısı, gelir düzeyi, doğum ayı, doğum kilosu, emzirme süresi, yaş ortalaması, sınıf, cinsiyet, evde sigara kullanımı, ailede işitme kaybı varlığı, ailede otit öyküsü, emzik kullanımı, biberon kullanımı, alerji varlığı, önceki otit öyküsü, açık ağız varlığı, horlama ve bademcik evreleri arasında istatistiksel olarak anlamlı bir fark yoktu.

Sonuç: Çalışmamızda efüzyonlu otitis media prevalansı düşük olmasına rağmen, efüzyonlu otitis media ve olası önleyici ciddi komplikasyonları düşünüldüğünde, efüzyonlu otitis media taraması özellikle ilkokul çocukları için koruyucu sağlık hizmetlerinin bir parçası olmalıdır.

Anahtar Kelimeler: Çocuklar, hemşirelik, efüzyonlu otitis media, prevalans, ilkokul

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INTRODUCTION

Hearing loss in childhood occurring from birth to late childhood and it can be classified as conductive, sensorineural and mixed type. The signs of hearing loss include delays in speech or language, vestibular problems and academic failure in children. Also hearing loss can affect children's social interactions and academic life (1,2). Early diagnosis of hearing loss is essential for warranting early intervention and development of normal language and academic skills in children. For this reason, hearing screening and ear examination are important in school-age children and appropriate follow-up care should be provided to detected children (3,4).

Otitis media with effusion (OME) is defined as the accumulation of fluid in the middle ear cavity without any signs and symptoms of acute infection and it causes conductive type hearing loss. Hearing loss in children is most commonly related to OME in developed countries. Hearing loss may affect speech, cognitive, and psychological development of the children. Since OME symptoms can be insidious, diagnosis is difficult and often delayed. The disease is an important public health problem because there are many risks of complications such as tympanosclerosis, chronic otitis media (COME), retraction pockets and adhesive otitis media (5). There are many environmental risk factors including smoking, poor socio-economic conditions, seasonal conditions, daycare, race, sex, adenoid tissue hypertrophy, eustachian tube dysfunction, immunodeficiency, allergy, mastoid pneumatization and craniofacial abnormalities in the development of OME. Epidemiologic data may be contributory and complementary in determining the etiopathogenesis of OME. There are several studies reported the prevalence of OME as 1.3 to 31.3% in primary school children depending on the countries (2,6-8).

The school health nurse serves an important role in the overall health and education of the children in their school and hearing screening in school-age children is a part of this role. Handling hearing loss early offers better results and an opportunity for success at school. Since the most common cause of conductive hearing loss in children is OME, it is an important health problem in school-age children (9). With this viewpoint, the study aimed to determine the prevalence of OME in primary school children in Mersin and to investigate the association between OME and related risk factors.

MATERIAL AND METHOD

Patient Selection

This cross-sectional study was conducted by Department of Public Health Nursing and Otorhinolaryngology between October 2018 and December 2018. This study was approved by the Ethics Committee of Mersin University. There were approximately 120000 children in 139 primary schools covering the first four years of education. The minimum number of samples (768) was calculated by statistical software (Epi-Info version 7; www.cdc.gov). The population of the universe was 120000 and the prevalence of OME was 10%, 95% confidence interval, 3% sampling error and design effect as 2. A total of 960 students sampled due to predict of 20% loss. In this study, multistage sampling method was used. Each district was evaluated as a cluster and location of schools divided to a low, medium and high level according to land price of districts. Each school was selected from each district on low and high socioeconomic level (among the lowest and highest of 20% segment) by simple random sampling method. One class was determined with randomly from each first, second, third and fourth's class on each school. There were 960 students in 32 classes in eight schools included in the study and 761 students receiving parental consent were included in the study. The participation rate was 79.3%.

Questionnaire

In this study, data collected with middle ear disorders risk factors questionnaire and physical examination findings. Twenty-one questions included in this questionnaire which includes the child's health status, breastfeeding, bottle-pacifier use, number of individuals living at home, smoking in the house, family ear disease history accordance with the literature (6-8). The questionnaire and the parental leave form were sent to the families by the school nurse the day before the examination. Children of the families were examined who signed the informed consent form and completed the form.

Examination

All the children were examined in the suitable place of each school by otorhinolaryngology specialist. Physical examination was carried out by otoscope (ear and nasal examination) and abeslang (oral cavity examination). Children with obstructed external ear canal by cerumen excluded from the study. The ear examination findings divided as normal ear, OME, COME and adhesive otitis media. Oral cavity examination findings divided as tonsillar hypertrophy, according to Brodsky (from grade 0 to grade 4). The children diagnosed as OME were referred to the hospital for follow-up and treatment.

Statistical Analysis

The data were analyzed by E-Picos (Medicres.org) using descriptive statistics as number, percentage, arithmetic mean, median (25%-75%) and materiality test as Chi-square test. $p \leq 0.05$ was considered significant.

RESULTS

In this study, 45.9% of the schools with low socioeconomic status, and 54.1% of with high socioeconomic status. According to classes of students, 26.3% of the students were 1st grade, 23.8% were 2nd grade, 22.5% were 3rd grade and 27.5% were 4th grade (**Table 1**).

Table 1. Introductory features of children

		n	%
Location of schools according to incoming level	Low	349	45.9
	High	412	54.1
Class	1. class	200	26.3
	2. class	181	23.8
	3. class	171	22.5
	4. class	209	27.5
Sex	Female	405	53.2
	Male	356	46.8

Of the children who were screened, 53.2% were girls and the mean age was 7.57±0.45 years (min: 5-max: 11 years). The average of income level of family (n=578) 2334.82±67.172 TL (min: 60-max: 13000 TL). The average number of people living at home (n=723) 4.90±0.06 (min: 2-max: 12 person). The average birth weight of the children (n=710) 3198.50±23.18 gr (min: 800-max: 6000, median: 3200 gr) and average breastfeeding time (n=615) 15.63±0.36 months (min: 1, max: 48, median: 15 months).

In this study, OME prevalence was 2,6% (20 of 761) and all children had a bilateral OME. Also, one child had bilateral perforated tympanic membrane (0.1%) and six children had a retraction of the tympanic membrane (1.5%) (**Table 2**).

Table 2. Examination findings of children

Examination finding		n	%
Otoscopic examination (n:761)	Normal	698	91.8
	Pathologic	27	3.5
	Could not be assessed	36	4.7
Otitis media with effusion (n:725)	Yes	20	2.7
Perforated tympanic membrane (n:725)	Yes	1	0.1
Retraction of tympanic membrane (n:725)	Yes	6	0.8
Tonsillar size (n:761)	Grade-0	172	22.6
	Grade-1	328	43.2
	Grade-2	183	24.0
	Grade-3	49	6.4
	Grade-4	3	0.4
	Tonsillectomised	26	3.4

There was no significant difference between the presence of OME and the number of people at home, the amount of income, month of birth, birth weight, duration of breastfeeding, age average, income status, class, gender, smoking in the house, presence of hearing loss in the family, history of otitis in the family, use of pacifier, use of baby bottle, presence of allergy, previous history of otitis, the presence of open mouth, snoring and tonsillar grades (**Table 3**).

Table 3. Risk factors of otitis media with effusions

		Yes, n (%)	No, n (%)
Is anyone smoking in the house? (n:758)		330 (43.5)	428 (56.5)
Is mother smoking? (n:758)		166 (21.9)	592 (78.1)
Is father smoking? (n:758)		419 (55.3)	339 (44.7)
Hearing loss in family? (n:746)		72 (9.7)	674 (90.3)
Who has hearing loss? (n:73)	Father	25 (34.2)	
	Mother	29 (39.7)	
	Sibling	19 (26.1)	
Otitis media in family? (n:717)		100 (13.9)	617 (86.1)
Who has otitis media? (n:100)	Father	19 (19.0)	
	Mother	34 (34.0)	
	Sibling	47 (47.0)	
Breastfeeding (n:745)		703 (94.4)	42 (5.6)
Pacifier usage (n:731)		274 (37.5)	457 (62.5)
Bottle feeding? (n:741)		484 (65.3)	257 (34.7)
Has your child ever had otitis media? (n:730)		100 (13.7)	630 (86.3)
Does your child have hearing loss? (n:725)		23 (3.2)	702 (96.8)
Recurrent upper airway infection (n:720)		270 (37.5)	450 (62.5)
Open mouth sleeping (n: 736)	Always	105 (14.3)	330 (44.8)
	Only when sick	301 (40.9)	
Snoring (n:736)	Always	66 (9.0)	459 (62.4)
	Only when sick	211 (28.7)	
Sleep apnea (n:734)	Always	12 (1.6)	620 (84.5)
	Only when sick	102 (13.9)	

DISCUSSION

This study is an epidemiologic investigation of the prevalence of OME in school-age children, another ear disease, and tonsillar hypertrophy. OME is one of the most common health problems seen in children and it may lead to sequelae or complications such as hearing loss, delay of speech and language. These probable complications may be prevented by early diagnosis of OME. The etiology of OME is multifactorial and various factors effected this process (6-8).

In this study, OME prevalence in primary school children was 2.6% and this rate was low as according to previous literature from Turkey and other countries. The reported prevalence of OME in Turkey is variable depending on the cities. The reported prevalence was 11.2% to 13.3% in Ankara (10-12), 7% to 8.7% in Istanbul (13,14), 16.9% in Denizli (15), 6.5% in Kahramanmaras (8), 11.44% in Trabzon (16), 14,5% in Diyarbakir (4). Our prevalence rates were lower than those reported results and various climatic and environmental factors may explain this low rate. Also, we made diagnosis of OME only by otoscopic examination, if portable tympanometry was used as auxiliary method the rate might have been different. The fact that now parents are conscious and that children are diagnosed earlier can also explain these low rates. Also, some public health initiatives, such as prevention through vaccination, may be responsible for reducing the OME rates. In our study, the incidence of OME was lower than in previous studies, suggesting that vaccination programs may be successful. Also, the low prevalence of OME in our study support the recommendations of guideline that clinicians should not routinely screen children for OME who are not at risk for OME (17).

In the literature, the prevalence of OME is variable on the world, ranging from 1.3 to 31.3%, depending on the countries. In a study from China, the OME prevalence was found 1.3%, while in a study from Kuwait, it was found 31.3% (18,19). The prevalence rates reported in other studies were as follows: 6.5% in the Greece (20), 9.5% in the Netherlands (21), 10% in Easter Island (22), 13.8% in Saudi Arabia (23), and 2.2% in Hong Kong (24). Our prevalence rate was 2.6% in the similar age group. These different results may be related to climatic and environmental factors. Also, some genetic predisposition may be involved. For example, some studies suggest that the Eustachian tube functions may better in the African races and therefore, low rates of OME seen in this region (25,26).

Some authors found that OME was encountered more frequently in boys or girls, whereas others found no differences (18-22). In this study, there is no gender difference in the prevalence of OME. This result is due to the low rate of OME prevalence in our study.

In our study found no relationship between OME and duration of breastfeeding. The most likely explanation for this is that in our study, there were children who have been breastfed for at least one year and breastfeeding is protective against middle ear infections. Breastfeeding of children for at least three months from birth reduces the risk of developing middle ear infections (27). Also, there was no difference in middle ear infections between the breastfed and non-breastfed children. This finding can be explained by our study includes a few children never breastfed, because breast-feeding is very common in Turkey.

Feeding bottle or pacifier usage may play an etiologic role in the development of OME (28,29). In our study found no relationship between OME and feeding bottle or pacifier usage. However, while our results showed a predisposition of increased OME with bottle use, it was not statistically significant. This could be explained by the low prevalence of OME in our study.

Recurrent upper respiratory infections and passive smoking increase the risk of middle ear infection by promoting colonization with pathogens (2,3). The effect of smoke on mucociliary function and consequent risk for OME has been known, but in our study, there is no statistically significant difference between the children had smoking and non-smoking parents.

Some studies show that low incoming level and poor sociodemographic features are risk factors for developing OME related to overcrowding in house, malnutrition, and poor hygiene of home (7,8). Although epidemiologic studies suggest that genetic susceptibility to middle ear diseases such as OME and COME, environmental factors and population characteristics should be taken into consideration. In our study, the prevalence of OME is higher at low incoming level, but this difference statistically insignificant.

Adenotonsillar pathology may be a risk factor for developing OME (30). In this study, we did not evaluate the adenoid size due to this examination needs the endoscope; therefore, we evaluated the only tonsillar sizes. In our study, there was no significant difference between the presence of OME and the presence of open mouth, snoring and tonsil grades. In this study, there is no significant difference between the OME and tonsillar sizes. This issue due to low OME prevalence of our study population.

There are some limitations in our study. First, OME can be diagnosed by otoscopy in the clinic, but if there is any diagnostic doubt, auxiliary diagnostic methods such as pneumatic otoscopy, otomicroscopy, tympanometry and audiometry can be used. In our study, auxiliary diagnostic methods could not be used because otoscopic examinations were performed in schools. Second, children can be more affected auditory and cognitively in chronic OME, while acute OME may appear physiologically after URI and regress spontaneously and its negative effect on the child may be minimal. The distinction between acute and chronic OME can be made with clinical follow-up. We recorded instant condition of the middle ear during the examination, but not differentiate between acute and chronic OME.

CONCLUSION

Though the low prevalence of OME in our study, considering that OME and its possible preventive severe complications screening for OME should be a part of preventive health services particularly for primary school children. The low prevalence of OME in our study support the recommendations of guideline that clinicians should not routinely screen children for OME who are not at risk for OME. However, identifying children with symptoms that can be associated with OME, such as hearing difficulties, vestibular problems, poor academic performance, behavioral problems, or ear discomfort, is still important issue.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethics Committee of Mersin University (Permission granted: 07.11.2018, Decision no: 2018/450)

Informed Consent: Informed consent was obtained from the parents of the children evaluated in this study.

Referee Evaluation Process: Externally peer-reviewed.

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

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REFERENCES

1. Schilder AG, Chonmaitree T, Cripps AW, et al. Otitis media. Nat Rev Dis Primers 2016; 2: 16063.
2. DeAntonio R, Yarzabal JP, Cruz JP, Schmidt JE, Kleijnen J. Epidemiology of otitis media in children from developing countries: a systematic review. Int J Pediatr Otorhinolaryngol 2016; 85: 65-74.
3. Erdivanli OC, Coskun ZO, Kazikdas KC, Demirci M. Prevalence of otitis media with effusion among primary school children in Eastern Black Sea, in Turkey and the effect of smoking in the development of otitis media with effusion. Indian J Otolaryngol Head Neck Surg 2012; 64: 17-21.
4. Guzel R, Meric F, Toprak SF, Yorgancilar AE, Gün R. Prevalence and risk factors of otitis media with effusion in primary school and kindergarten children in provincial and district centers of Diyarbakir. J Med Updates 2012; 2: 1-8.
5. Kaspar A, Newton O, Kei J, Driscoll C, Swanepoel W, Goulios H. Prevalence of ear disease and associated hearing loss among primary school students in the Solomon Islands: Otitis media still a major public health issue. Int J Pediatr Otorhinolaryngol 2018; 113: 223-8.
6. Kiris M, Muderris T, Kara T, Bercin S, Cankaya H, Sevil E. Prevalence and risk factors of otitis media with effusion in school children in Eastern Anatolia. Int J Pediatr Otorhinolaryngol 2012; 76: 1030-5.
7. Ozkiriş M, Kapusuz Z, Saydam L. The prevalance of middle ear diseases among 7- to 13-year-old primary school students in Yozgat province. Turk J Pediatr 2012; 54: 493-6.
8. Okur E, Yildirim I, Akif Kilic M, Guzelsoy S. Prevalence of otitis media with effusion among primary school children in Kahramanmaras, in Turkey. Int J Pediatr Otorhinolaryngol 2004; 68: 557-62.
9. Sekhar DL, Beiler JS, Schaefer EW, et al. Certified school nurse perspectives on state-mandated hearing screens. J Sch Health 2016; 86: 612-9.
10. Jones AL, Lambert AW, Barnett M. Nursing students: Training and maintaining universal newborn hearing screening knowledge. Nurse Educ Pract 2018; 32: 72-7.
11. Ozbilen S, Beder E, Akyildiz N, Koybasoglu A, Goksu N. Ankara Balgat cevre ilkokul ögrencileri arasinda kulak burun bogaz hastaliklari prevalansi. Proceedings of the 17th Turkish Otorhinolaryngology National Congress; 1985; Istanbul, Turkey. 1985. pp. 128-33.
12. Goksu A. Park Egitim Saglik ocagi bolgesine bagli ilkokullarda sekretuar otitis media prevalans arastirmasi. A.Ü. Halk Sağlığı Departmanı, Doktora Tezi. 1992.
13. Gultekin E, Develioğlu ON, Yener M, Ozdemir I, Kulekci M. Prevalence and risk factors for persistent otitis media with effusion in primary school children in Istanbul, Turkey. Auris Nasus Larynx 2010; 37: 145-9.
14. İnanlı S, Özer E, Öztürk Ö, et al. Istanbul'da okul öncesi ve okul çağındaki çocuklarda sekretuar otitis media prevalansı ve risk faktörleri. Turk Arch Otorhinolaryngol 2000; 38: 9-16.
15. Özüer MZ, Topuz B, Kara CO, Bayramoğlu I. Denizli merkez anaokullarında sekretuar otitis media prevalansı ve risk faktörleri. Kulak Burun Bogaz Ihtis Derg 1999; 6: 63-5.
16. Caylan R, Bektas D, Atalay C, Korkmaz O. Prevalence and risk factors of otitis media with effusion in Trabzon, a city in northeastern Turkey, with an emphasis on the recommendation of OME screening. Eur Arch Otorhinolaryngol 2006; 263: 404-8.
17. Rosenfeld RM, Shin JJ, Schwartz SR, et al. Clinical practice guideline: otitis media with effusion (update). Otolaryngol Head Neck Surg 2016; 154: 1–41.
18. Rushton HC, Tong MC, Yue V, Wormald PJ, van Hasselt CA. Prevalence of otitis media with effusion in multicultural schools in Hong Kong. J Laryngol Otol 1997; 111: 804–6.
19. Holmquist J, Al Fadala S, Qattan Y. Prevalence of secretory otitis media among school children in Kuwait. J Laryngol Otol 1987; 101: 116–9.
20. Apostolopoulos K, Xenelis J, Tzagaroulakis A, Kandiloros D, Yiotakis J, Papafragou K. The point prevalence of otitis media with effusion among school children in Greece. Int J Pediatr Otorhinolaryngol 1998; 44: 207-14.
21. Schilder AG, Zielhuis GA, Van Den Broek P. The otological profile of a cohort of Dutch 7.5-8-year-olds. Clin Otolaryngol Allied Sci 1993; 18: 48-54.
22. Goycoolea HG, Goycoolea MV, Farfan CR. Racial and familial factors in otitis media. A point prevalence study on Easter Island. Arch Otolaryngol Head Neck Surg 1988; 114: 147-9.
23. El-Sayed Y, Zakzouk S. Point prevalence of type B tympanogram in Riyadh. Int J Pediatr Otorhinolaryngol 1995; 31: 53-61.
24. Tong MC, Yue V, Ku PK, Lo PS, van Hasselt CA. Screening for otitis media with effusion to measure its prevalence in Chinese children in Hong Kong. Ear Nose Throat J 2000; 79: 626-30.

25. Okeowo PA. Observations on the incidence of secretory otitis media in Nigerian children. J Trop Pediatr 1985; 31: 295-8.

26. Halama AR, Voogt GR, Musgrave GM. Prevalence of otitis media in children in a black rural community in Venda (South Africa). Int J Pediatr Otorhinolaryngol 1986; 11: 73-7.

27. Karunanayake CP, Albritton W, Rennie DC, et al. Ear infection and related risk factors in first nations and rural school-aged Canadian children. Int J Pediatr 2016; 2016: 1523897.

28. Salah M, Abdel-Aziz M, Al-Farok A, Jebrini A. Recurrent acute otitis media in infants: analysis of risk factors. Int J Pediatr Otorhinolaryngol 2013; 77: 1665-9.

29. Owen MJ, Baldwin CD, Swank PR, Pannu AK, Johnson DL, Howie VM. Relation of infant feeding practices, cigarette smoke exposure, and group child care to the onset and duration of otitis media with effusion in the first two years of life. J Pediatr 1993; 123: 702-11.

30. Els T, Olwoch IP. The prevalence and impact of otitis media with effusion in children admitted for adeno-tonsillectomy at Dr George Mukhari Academic Hospital, Pretoria, South Africa. Int J Pediatr Otorhinolaryngol 2018; 110: 76-80.

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Pelvic inflammatory disease and contraception: a cross-sectional study in teritary center

Pelvik inflamatuvar hastalık ve kontrasepsiyon: üçüncü basamak merkezde kesitsel bir çalışma

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ABSTRACT

Aim: To investigate the relationship between the contraceptive methods used in the patient population treated for pelvic inflammatory disease (PID) in a tertiary center with clinical and laboratory features and clinical outcome of PID.

Material and Method: This is a cross-sectional study using the anamnesis, examination findings, microbiological and pathological evaluation results of vaginal and cytological samples recorded in the hospital database of 974 patients treated with a diagnosis of PID in a tertiary center between 2017 and 2019.

Results: Copper-intrauterine device (Cu-IUD) was the most commonly used contraceptive method in women with a history of PID. When the cervicovaginal culture results are evaluated; *E.coli* positivity was more frequent in patients using CU-IUD and levonorgesterone IUD (LNG-IUD) (<0.001). The frequency of reproduction was higher in Group B *Streptococcus* (<0.001) and other *Streptococcus* species (=0.006) in those using condoms. While *Staphylococcus* (=0.041) and *Chlamydia trochomatis* positivity was higher in combined oral contraceptives (COC) users, *C. Trochomatis* growth was frequent in depot medroxyprogeterone acetate (DMPA) users (<0.001). Re-hospitalization was more common in the DMPA group compared to the other groups (p=0.008).

Conclusion: Contraceptive methods may affect the genital flora and may be a predisposing factor for the development of PID or prevent the development of PID.

Keywords: Contraceptive agents, intrauterine devices, long-acting reversible contraception, pelvic inflammatory disease

ÖZ

Amaç: Üçüncü basamak bir merkezde pelvik inflamatuvar hastalık (PID) için tedavi edilen hasta popülasyonunda kullanılan kontraseptif yöntemler ile PID'nin klinik ve laboratuvar özellikleri ve klinik sonuçları arasındaki ilişkiyi araştırmak.

Gereç ve Yöntem: Üçüncü basamak bir merkezde 2017-2019 yılları arasında PID tanısı ile tedavi edilen 974 hastanın hastane veri tabanına kaydedilen anamnez, muayene bulguları, vajinal ve sitolojik örneklerin mikrobiyolojik ve patolojik değerlendirme sonuçlarının kullanıldığı kesitsel bir çalışmadır.

Bulgular: Bakır-rahim içi araç (Cu-RİA), PID öyküsü olan kadınlarda en sık kullanılan kontraseptif yöntemdi. Servikovajinal kültür sonuçları değerlendirildiğinde; *E.coli* pozitifliği CU-RİA ve levonorgesteron RİA (LNG-RİA) kullanan hastalarda daha sıktı (<0.001). Prezervatif kullananlarda Grup B *Streptococcus* (<0.001) ve diğer *Streptococcus* türlerinde (=0.006) üreme sıklığı daha yüksekti. *Staphylococcus* (=0.041) ve *Chlamydia trochomatis* pozitifliği kombine oral kontraseptif (COC) kullananlarda daha yüksek iken, *C. Trochomatis* büyümesi depo medroksiprogeteron asetat (DMPA) kullanıcılarında daha sık görülmüştür (<0.001). Diğer gruplarla karşılaştırıldığında (p=0.008).

Sonuç: Kontraseptif yöntemler genital florayı etkileyebilir ve PID gelişimi için predispozan bir faktör olabilir veya PID gelişimini önleyebilir.

Anahtar Kelimeler: Kontraseptif ajanlar, pelvik inflamatuvar hastalık, rahim içi araçlar, uzun etkili geri dönüşümlü kontrasepsiyon

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INTRODUCTION

Pelvic inflammatory disease (PID) is a serious complication of sexually transmitted infections and some gynecological procedures and is observed in 2-4% of women of reproductive age (1,2). PID is a term that includes upper genital tract infections such as endometritis, salpingitis, and oophoritis. It is caused by the spread of infections in the vagina and cervix to the uterine cavity (3). The diagnosis of PID should refer to the diagnostic criteria recommended by the Centers for Disease Control and Prevention (CDC), which consider abnormal vaginal discharge, fever, adnexal tenderness, cervicovaginal culture and laboratory data (1). Although PID is associated with sexually transmitted diseases, it can also be caused by endogenous infections of the vaginal flora. Risk factors for PID have been identified such as the use of an intrauterine device (IUD), curettage, multiple sexual partners, and sexually transmitted diseases (4), and barrier methods have been reported to be protective (5,6). PID is an important cause of gynecological morbidity (7); adhesion secondary to tubal infection leads to tubal infertility, ectopic pregnancy and chronic pelvic pain (8-10).

Copper intrauterine device (Cu- IUD) is one of the most effective birth control methods and is frequently used in all age groups (11). There are studies reporting an increased risk of PID in women using Cu-IUD (12,13). On the other hand, it has been reported that the risk of PID decreases in women who use levonorgesterone IUD (LNG-IUD) (14). It has been reported that the use of oral hormonal contraceptives reduces the risk of PID and the severity of inflammation decreases in these users (15). However, there is a lack of a current study that compares the effects of intrauterine, hormonal and barrier contraceptive methods on the clinical and outcomes of PID.

The purpose of our study in the light of this information; to investigate the relationship between the contraceptive methods used in the patient population treated for PID in a tertiary center with clinical and laboratory features and treatment outcome of PID.

MATERIAL AND METHOD

This is a cross-sectional study using the anamnesis, examination findings, and microbiological and pathological evaluation results of vaginal and cytological specimens recorded in our hospital database of patients admitted to our gynecology outpatient clinic in a tertiary center between January 2017 and December 2019. Ethics committee approval was received for this study from the Adıyaman University Non-interventional Clinical Researches Ethics Committee (No: 2020/6-23). This study was carried out in accordance with the Helsinki Declaration of Principles.

Among these patients, 1294 patients aged 18-45 years who had at least one minimum criteria and additional criteria were accepted as PID in accordance with the diagnostic criteria published in the latest guidelines by the United States Centers (1). In our center, patients who are diagnosed with severe disease, have nausea, vomiting and fever, have complications such as tubo-ovarian abscess, and those who do not comply with the outpatient regimen are hospitalized. Patients who were diagnosed with PID but had recently received outpatient oral antibiotic therapy, had a history of diabetes mellitus, had a history of minor or major surgery in the last 6 months, a history of immunosuppressive disease, or a history of immunosuppressive drug use in the last 6 months were excluded from the study. Based on these criteria, 974 female patients were included in the study. The patients were divided into the following groups according to the contraceptive method they used: copper IUD (Cu-IUD), combined oral contraceptive drug (COC), depot medroxyprogeterone acetate (DMPA), condom and LNG-IUD.

Clinical and Laboratory Tests Reviewed

Hospital entrance records taken from the electronic medical record database in our study center were made with service follow-up charts, laboratory results and discharge records.

Patient characteristics (age, parity, marital status, contraceptive method used, educational level) and PID clinical and laboratory characteristics (body temperature, C-reactive protein (CRP) serum level, white blood cell count (WBC), erythrocyte sedimentation rate (ESR) and physical examination findings (pelvic tenderness, fundal tenderness, cervical motion tenderness, abnormal cervical discharge) and cervicovaginal culture results) were noted. Cervicovaginal culture results; standard flora, *Escherichia coli (E. coli), group B Streptococcus, Enterococcus faecalis (E. faecalis), Staphylococcus and its species, Streptococcus and species, Chlamydia trachomatis* were noted for each group.

Clinical results such as hospitalization time and re-hospitalization were noted. Body temperature measured at admission was recorded as measured in degrees Celsius centigrade. 38 and above was accepted as fever. Hospitalization was accepted as re-hospitalization within the first 30 days after discharge (16). Clindamycin/gentamicin (900 mg IV clindamycin every eight hours plus a single daily dose (5 mg/kg) gentamicin) was administered, and after clinical improvement, the treatment regimen of oral clindamycin (450 mg orally four times daily) or doxycycline (100 mg twice daily) was administered.

Statistical Analysis

SPSS 22 (IBM SPSS version 22, IBM Corp., Armonk, NY) program was used to analyze the data. Pearson's Chi-square test was used for significance between groups and Fisher's exact test was used for categorical variables. Student t test and Mann-Whitney U test were used for analysis of continuous variables. A two-sided p value<0.05 showed statistical significance. A value of p<0.05 was considered statistically significant.

RESULTS

The demographic characteristics of the groups are given in **Table 1**. Accordingly, Cu-IUD was the most commonly used contraceptive method in women with a history of PID. Other preferred methods were COC, LNG-IUD, Condom and DMPA in order of frequency. The most preferred contraceptive method in the 18-25 age group was COC, the most preferred method in the 25-35 age group was Cu-IUD and the most preferred method in the 35-45 age group was LNG-IUD.

In the analyzes made according to the PID clinical and laboratory results; Fever was more frequent in Cu-IUD and DMPA groups (0.047). Pain and increased ESR, CRP, WBC values were common in those using COC and DMPA (p=<0.001). When the cervicovaginal culture results are evaluated; *E.coli* positivity was more frequent in patients using CU-IUD and LNG-IUD (p<0.001). The frequency of reproduction was higher in Group B *Streptococcus* (p<0.001) and other *Streptococcus* species (p=0.006) in those using condoms. While *Staphylococcus* (p=0.041) and *Chlamydia trochomatis* positivity was higher in COC users, *C. Trochomatis* growth was frequent in DMPA users (p<0.001) (**Table 2**).

When hospitalization times of the patients were compared according to the groups, there was no significant difference (p>0.05). However, re-hospitalization was more common in the DMPA group compared to the other groups (p=0.008) (**Table 2**).

DISCUSSION

PID occurs with ascending spread of cervical infections. *N. Gonorrhoeae*, *C. Trochomatis* and anaerobic and facultative bacteria found in the vaginal flora were isolated in the fallopian tubes of women with acute PID (17). PID is affected by many mechanisms such as reduction in normal vaginal lactobacilli, development of bacterial vaginosis, reproduction of anaerobic microflora. The presence of bacterial vaginosis may affect the cervical barrier and cause the progression of microorganisms in the upper genital tract (18,19). It has been shown in various previous publications that the risk of PID increases with the use of IUD (20,21). In a recent study conducted in a large group of patients in Turkey bacterial colonization increases with use Cu-IUD, but the frequency of the PID has not been shown to increase with the IUD (22).

Table 1. Demographic characteristics of the patients

	Cu-IUD n=412	COC n=239	DMPA n=43	Condom n=117	LNG-IUD n=163
Age					
18-25	55 (13.4%)	151 (63.1%)	19 (44.2%)	47 (40.2%)	28 (17.2%)
25-35	263 (63.8%)	74 (31%)	15 (34.9%)	14 (12%)	31 (19%)
35-45	94 (22.8%)	14 (5.9%)	9 (20.9%)	56 (47.8%)	104 (63.8%)
Marial Status					
Married	354 (85.9%)	164 (68.6%)	9 (20.9%)	63 (53.9%)	146 (89.6%)
Divorced	58 (14.1%)	75 (31.4%)	34 (79.1%)	35 (29.9%)	17 (10.4%)
Single	-	-	-	19 (16.2%)	-
Obstetric History					
Gravida	3.19±1.90	2.34±2.00	3.66±1.91	2.12±1.81	2.07±2.00
Parity	2.56±1.54	1.67±1.35	2.88±1.42	1.87±1.23	1.74±1.09
Abortus	0.62±0.71	0.67±0.91	0.83±1.23	0.62±0.71	0.63±0.89
Educational Level					
Middle school and pre-school	151 (36.6%)	17 (7.1%)	4 (9.3%)	33 (28.2%)	86 (52.8%)
High school	138 (33.5%)	93 (38.9%)	9 (20.9%)	39 (33.3%)	29 (17.8%)
License	74 (18%)	81 (33.9%)	19 (44.2%)	17 (14.5%)	21 (12.9%)
Graduate	49 (11.9%)	48 (20.1%)	11 (25.6%)	28 (23.9%)	27 (16.5%)
Body Mass Index					
<25	69 (16.7%)	19 (7.9%)	21 (48.8%)	61 (52.1%)	47 (28.8%)
25-29.99	294 (73.4%)	173 (72.4%)	19 (44.3%)	35 (29.9%)	83 (51%)
>30	49 (11.9%)	47 (19.7%)	3 (6.9%)	21 (18%)	33 (20.2%)

Cu-IUD:Copper intrauterine device; COC: Combined oral contraceptives; DMPA: Depot medroxyprogeterone acetate;LNG-IUD; levonorgesterone intrauterine device

Table 2. Disease characteristics and treatment outcomes according to contraceptive method relationship

	IUD n=412	COC n=239	DMPA n=43	Condom n=117	LNG-IUD n=163	p
Clinicsl Features						
Fever (>38)	324 (78.6%)	207 (86.6%)	40 (93%)	63 (53.9%)	51 (31.3%)	0.047
Pain (lower abdominal. fundal. cervikal motion)	247 (59.9%)	224 (93.7%)	37 (86%)	71 (60.7%)	84 (51.5%)	<0.001
Laboratory value (WBC. CRP ve ESR%)	379 (92%)	171 (71.5%)	43 (100%)	98 (83.8%)	102 (62.6%)	<0.001
Cervicovaginal Culture						
Escherichia coli	73 (17.8%)	9 (3.8%)	5 (11.7%)	13 (11.1%)	41 (25.2%)	<0.001
Group B *Streptococcus*	53 (12.9%)	29 (12.1%)	6 (14%)	24 (20.5%)	21 (12.8%)	<0.001
Enterococcus faecalis	28 (6.8%)	7 (2.9%)	1 (2.3%)	12 (10.3%)	19 (11.7%)	0.51
Staphylococcus spp.	17 (4.1%)	26 (10.9%)	-	3 (2.6%)	9 (5.5%)	0.041
Streptococcus spp.	8 (1.9%)	19 (7.9%)	2 (4.6%)	13 (11.1%)	5 (3.1%)	0.006
Chlamidya trochomatis	70 (17%)	47 (19.7%)	12 (27.9%)	8 (6.8%)	21 (12.9%)	<0.001
Standart flora	163 (39.5%)	102 (42.7%)	17 (39.5%)	44 (37.6%)	47 (28.8%)	0.17
Treatment Outcome						
Hospitalization duration	5.02±1.14	3.87±1.01	3.03±1.21	4.07±1.83	5.84±2.03	0.29
Re-hospitalization	109 (26.5%)	23 (9.7%)	19 (44.2%)	29 (24.8%)	47 (28.8%)	0.008

Cu-IUD:Copper intrauterine device; COC: Combined oral contraceptives; DMPA: Depot medroxyprogeterone acetate;LNG-IUD; levonorgesterone intrauterine device WBC: White Blood Cell; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate

There are some factors preventing the full understanding of the role of Cu-IUD in the development of gynecological infections. Many genital infections are asymptomatic. One of the most important examples among these is *C. Trochomatis*. It is difficult under these conditions to determine whether PID, which develops secondary to this microbial agent, which can cause tubal infertility and chronic pelvic pain, due to the upper genital tract infection that causes tubal damage and adhesions (23), is caused by Cu-IUD (24). In addition, in another study, it was shown that *C. Trochomatis* positivity did not contribute to the development of PID in Cu-IUD users (24). Considering our study results, the most common contraceptive method used in patients with a history of PID was Cu-IUD. This finding is not a surprise when compared with the data in previous studies, but the fact that Cu-IUD is one of the contraceptive methods frequently used in our country may explain the high number of patients in the group. However, although *C. Trochomatis* was the most common bacterium grown in cervicovaginal culture in this study, there was no correlation with *C. Trochomatis* positivity in PID patients using Cu-IUD.

In a previous study examining microbial cultures in patients with PID, the most frequently grown bacteria were *E. Coli* (26.4%) and other *Enterococcus* species (24%) (25). In another study, S. Aureus was the most common bacteria (26). In another study conducted with a large patient population in Asia, bacteria that multiplied frequently in PID patients; *E. coli*, *Proteus mirabilis*, *S. aureus*, Group B *Streptococcus* and *Klebsiella pneumoniae* (27). In our study, the second most common bacterium that multiplied in cervicovaginal cultures was *E. Coli* after *C. Trochomatis*. It has been reported in various publications that oral hormonal contraceptive methods have positive effects on the vaginal microflora and reduce the risk of PID (28,29).

Estrogen in the content of COC increases the amount of glycogen in vaginal epithelial cells and increases the growth of *Lactobacillus* bacteria and contributes to the reproduction of healthy vaginal microbial flora (30-33). In a study conducted among women using COC as a contraceptive method and women using a barrier method, it was shown that Lactobacillus reproduce more in the vaginal microflora of COC users (31). In the data in our study, *C. Trochomatis* and *Staphylococcus* positivity were found in the cervicovaginal cultures of PID patients using COC. These changes can be explained depending on the effects of COC on flora.

Information on the effects of progesterone-containing contraceptive methods on the vaginal microflora is still contradictory. In a study examining the vaginal flora of patients using oral contraceptive drugs containing progesterone and using LNG-IUD; It has been determined that due to atrophy caused by progesterone, glycogen content in vaginal epithelial cells decreased and vaginal microflora was negatively affected (34). However, some studies have shown that the use of LNG-IUD has no effect on vaginal microflora (35,36). In a study conducted with DMPA users, it was stated that there was a decrease in the prevalence of lactobacilli in the vaginal microflora, while another study reported that it had no effect on microflora (37,38). In our study, positivity of *E. Coli* in cervicovaginal culture in PID patients using LNG-IUD, positivity of group B *Streptococcus* in condom users and *C. Trochomatis* positivity in DMPA users were frequent. These findings may be related to the negative effects of progesterone and barrier methods mentioned in publications on the vaginal microflora.

In addition, considering the re-hospitalization rates of the patients, we found that this rate increased in DMPA users. This may be related to the persistent infection of *C. Trochomatis*, which is the most common agent in patients using DMPA.

This study has some limitations. Firstly our study is single-centered, and common contraceptive methods used among patients admitted to our center were investigated. Secondly, the study is a cross-sectional study. The data registered in the hospital database were analyzed retrospectively. In the light of these findings, the data should be considered before generalizing to the society.

CONCLUSION

In women presenting with acute PID clinic, contraceptive methods may have an impact on treatment selection and results. It should be kept in mind that contraceptive methods to be chosen in patients with a history of PID may affect the genital flora and may be a predisposing factor for the development of PID or prevent the development of PID.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was received for this study from the Adıyaman University Non-interventional Clinical Researches Ethics Committee (No: 2020/6-23).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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REFERENCES

1. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR. Recommendations and reports: Morbidity and mortality weekly report. Recommendations and Reports 2015; 64: 1-137.
2. Ford GW, Decker CF. Pelvic inflammatory disease. Disease-a-month: DM 2016; 62: 301.
3. Campbell S, Monga A. (Eds.). Gynaecology by ten teachers. London: Arnold. 2000, (pp. 41-54).
4. Kansagara D, Englander H, Salanitro A, et al. Risk prediction models for hospital readmission: a systematic review. JAMA 2011; 306: 1688-98.
5. Lee NC, Rubin GL, Grimes DA. Measures of sexual behavior and the risk of pelvic inflammatory disease. Obstet Gynecol 1991; 77: 425-30.
6. Kreisel K, Torrone E, Bernstein K, Hong J, Gorwitz R. Prevalence of pelvic inflammatory disease in sexually experienced women of reproductive age—United States, 2013–2014. MMWR Morb Mortal Wkly Rep 2017; 66: 80–3.
7. Trent M, Haggerty CL, Jennings JM, Lee S, Bass DC, Ness R. Adverse adolescent reproductive health outcomes after pelvic inflammatory disease. Arch Pediatr Adolesc Med 2011; 165: 49-54.
8. Goyal M, Hersh A, Luan X, Localio R, Trent M, Zaoutis T. National trends in pelvic inflammatory disease among adolescents in the emergency department. J Adolesc Health 2013; 53: 249-52.
9. Matters JS, Catchpole M, Smith C. Chlamydia trachomatis: summary and conclusions of CMO's Expert Advisory Group. 1998. London: Department of Health.
10. Centers for Disease Control and Prevention 1998 Guidelines for the Treatment of Sexually Rransmitted Diseases, MMWR Morb Mortal Wkly Rep 1997; 47: 1- 111.
11. Jatlaoui TC, Riley HEM, Curtis KM. The safety of intrauterine devices among young women: a systematic review. Contraception 2017; 95: 17–39.
12. Stanwood NL, Garrett JM, Konrad TR. Obstetriciangynecologists and the intrauterine device: A survey of attitudes and practice. Obstet Gynecol 2002; 99: 275–80.
13. Madden T, Allsworth JE, Hladky KJ, Secura GM, Peipert JF. Intrauterine contraception in Saint Louis: A survey of obstetrician and gynecologists'knowledge and attitudes. Contraception 2010; 81: 112–6.
14. Fraser IS. Non-contraceptive health benefits of intrauterine hormonal systems. Contraception, 2010; 82: 396–403.
15. Schindler AE. Non-contraceptive benefits of oral hormonal contraceptives. Int J Endocrinol Metab 2013; 11: 41-7.
16. Havens JM, Olufajo OA, Cooper ZR, Haider AH, Shah AA, Salim A. Defining rates and risk factors for readmissions following emergency general surgery. JAMA Surg 2016; 151: 330–6.
17. Brunham RC, Gottlieb SL, Paavonen J. Pelvic inflammatory disease. N Engl J Med 2015; 372: 2039-48.
18. McGregor JA, French JI, Jones W, et al. Bacterial vaginosis is associated with prematurity and vaginal fluid mucinase and sialidase: results of a controlled trial of topical clindamycin cream. Am J Obstet Gynecol 1994; 170: 1048-59.
19. Draper DL, Landers DV, Krohn MA, Hillier SL, Wiesenfeld HC, Heine RP. Levels of vaginal secretory leukocyte protease inhibitor are decreased in women with lower reproductive tract infections. Am J Obstet Gynecol 2000; 183: 1243-8.
20. Hubacher D. Intrauterine devices and infection: review of the literature. Indian J Med Res 2014; 140: S53–7.
21. Liabsuetrakul T, Peeyananjarassri K. Mechanical dilatation of the cervix during elective caeserean section before the onset of labour for reducing postoperative morbidity. Cochrane Database Syst Rev 2018; 8: CD008019.
22. Sel G, Harma MI. Bacterial colonization of intrauterine device samples from patients without a history of pelvic inflammatory disease. Ann Med Res 2020; 27: 1036-9.
23. Witkin SS, Minis E, Athanasiou A, Leizer J, Linhares IM. *Chlamydia trachomatis*: the persistent pathogen. Clin Vaccine Immunol 2017; 24: e00203-17.
24. Birgisson NE, Zhao Q, Secura GM, Madden T, Peipert JF. Positive Testing for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* and the risk of pelvic inflammatory disease in IUD users. J Womens Health (Larchmt) 2015; 24: 354-9.

25. Lurie S, Asaala H, Harari OS, Golan A, Sadan O. Uterine cervical non-gonococcal and non-chlamydial bacterial flora and its antibiotic sensitivity in women with pelvic inflammatory disease: did it vary over 20 years? Isr Med Assoc J 2010; 12: 747–50.

26. Audu BM, Kudi AA. Microbial isolates and antibiogram from endocervical swabs of patients with pelvic inflammatory disease. J Obstet Gynaecol 2014; 24: 161–4.

27. Judlin P, Liao Q, Liu Z, Reimnitz P, Hampel B, Arvis P. Efficacy and safety of moxifloxacin in uncomplicated pelvic inflammatory disease: the MONALISA study. BJOG 2010; 117: 1475–84.

28. Schindler AE. Non-contraceptive benefits of hormonal contraceptives. Minerva Ginecol 2010; 62: 319-29.

29. Huber JC, Bentz EK, Ott J, Tempfer CB. Non-contraceptive benefits of oral contraceptives. Expert Opin Pharmacother 2008; 9: 2317-25.

30. Brooks PJ, Edwards DJ, Blithe DL, et al. Effects of combined oral contraceptives, depot medroxyprogesterone acetate, and the levonorgestrel releasing Intrauterine system on the vaginal microbiome. Contraception 2017; 95: 405-13.

31. Rifkin SB, Smith MR, Brotman RM, Gindi RM, Erbelding EJ. Hormonal contraception and risk of bacterial vaginosis diagnosis in an observational study of women attending STD clinics in Baltimore, MD. Contracept 2009; 80: 63–7.

32. O'Hanlon DE, Lanier BR, Moench TR, Cone RA. Cervicovaginal fluid and semen block the microbicidal activity of hydrogen peroxide produced by vaginal lactobacilli. BMC Infect Dis 2010; 10: 120.

33. O'Hanlon DE, Moench TR, Cone RA. In vaginal fluid, bacteria associated with bacterial vaginosis can be suppressed with lactic acid but not hydrogen peroxide. BMC Infect Dis 2011; 11: 200.

34. Donders G, Bellen G, Janssens D, Van Bulck B, Hinoul P, Verguts J. Influence of contraceptive choice on vaginal bacterial and fungal microflora. Eur J Clin Microbiol Infect Dis 2017; 36: 43-8.

35. Jacobson JC, Turok DK, Dermish AI, Nygaard IE, Settles ML. Vaginal microbiome changes with levonorgestrel intrauterine system placement. Contraception 2014; 90: 130–5.

36. Hashway SA, Bergin IL, Bassis CM, et al. Impact of a hormone-releasing intrauterine system on the vaginal microbiome: a prospective baboon model. J Med Primatol 2014; 43: 89–99.

37. Borgdorff H, Verwijs MC, Wit FWNM et al. The impact of hormonal contraception and pregnancy on sexually transmitted infections and on cervicovaginal microbiota in african sex workers. Sex Transm Dis 2015; 42: 143–52.

38. Mitchell CM, McLemore L, Westerberg K, et al. Long-term effect of depot medroxyprogesterone acetate on vaginal microbiota, epithelial thickness and HIV target cells. J Infect Dis 2014; 210: 651–5.

Original Article/Özgün Makale

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The assessment of the cardioprotective effectiveness of levosimendan on patients with impaired left ventricle functions and less than %40 of ejection fraction who will receive coronary artery bypass graft operation

Sol ventrikül fonksiyonları bozulmuş, ejeksiyon fraksiyonu %40'ın altında olan, koroner arter by-pass greft operasyonu yapılacak hastalara verilen levosimendan tedavisinin, kardiyoprotektif etkinliğinin postoperatif olarak değerlendirilmesi

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ABSTRACT

Aim: The purpose of this study is to demonstrate the postoperative cardioprotective efficacy of preoperative levosimendan treatment in patients with impaired left ventricular function undergoing coronary by-pass surgery.

Material and Method: This study was performed prospectively between November 2008 and September 2009 in Eskişehir Osmangazi Univercity Department of Cardiovascular Surgery. Twenty patients with coronary artery disease (CAD) between the ages of 48-78 and ejection fraction (EF) below 40% were included in the study. levosimendan was given to the first group preoperatively(experimental group). Group 2 was the control group. Coronary artery bypass graft (CABG) surgery was performed in all of them. One group received additional levosimendan infusion, preoperatively. Age, comorbidity, cardiopulmonary by-pass (CPB) time, cross clamp (CC) time, patient vessel number, anastomosis number, extubation times, intensive care stay and hospital stay were recorded. Preoperative, postoperative 1st day and postoperative 7th day nt-proBNP values and preoperative and postoperative 15th day ejection fraction (EF) values with echocardiography (ECHO) were measured. The cardioprotective efficacy of the drug was evaluated by comparing the data of the control group and the experimental group.

Results: No statistically significant difference was found between the two groups in terms of CPB time, CC time, age, comorbidity, number of sick vessels, number of anastomosis, extubation time, length of stay in intensive care and hospital stay. (p>0.05). There was no significant difference between the groups in preoperative EF values (p>0.05). The mean values of EF measurements on the postoperative 15th day were calculated as 39% in the experimental group and 40% in the control group. The increase in EF values was greater in the experimental group. This increase was found to be more significant in the experimental group (P=0.008). There was a significant difference between the groups in preoperative and postoperative 1st day n-tproBNP values (p<0.05). A significant increase was observed in nt-proBNP values in the groups until the 7th postoperative day. (p<0.001). Although this increase was statistically significant in both groups, it was observed that the increase in the control group was higher. After the nt-proBNP measurements on the postoperative 7th day, there was no significant difference between the two groups (p>0.05).

Conclusion: As a result of this study, it was determined that levosimendan has a positive effect on myocardial protection and contractility in patients with low EF in CABG surgery.

Keywords: Levosimendan, coroner by-pass surgery, left ventricle dyusfunction

ÖZ

Amaç: Bu çalışmanın amacı koroner by-pass ameliyatı yapılacak, sol ventrikül fonksiyonu bozulmuş hastalarda preoperatif levosimendan tedavisinin postoperatif kardiyoprotektif etkinliğini göstermektir.

Gereç ve Yöntem: Bu çalışma Kasım 2008- Eylül 2009 tarihleri arasında, Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Kalp ve Damar Cerrahisi Anabilim Dalında prospektif olarak gerçekleştirildi. Çalışmaya yaşları 48-78 arasında, ejeksiyon fraksiyonu (EF) %40'ın altında koroner arter hastalığı (KAH) olan 20 hasta alındı. Hastalar iki gruba ayrıldı. 1. gruba preoperatif levosimendan verildi (deney grubu). 2. grup kontrol grubuydu. Hepsine koroner arter bypass greft (KABG) cerrahisi uygulandı. Yaş, komorbidite, kardiyopulmoner by-pass (KPB) zamanı, kros klemp (KK) zamanı, hasta damar sayısı, anastomoz sayısı, ekstübasyon süresi, yoğun bakımda ve hastanede kalış süreleri kaydedildi. Preoperatif, postoperatif 1.gün ve postoperatif 7. gün nt-proBNP değerleri ve preoperatif ve postoperatif 15. gün ejeksiyon fraksiyon (EF) değerleri ekokardiyografiyle (EKO) ölçüldü. Kontrol grubu ve deney grubunun verileri karşılaştırılarak ilacın kardiyoprotektif etkinliği değerlendirildi.

Bulgular: İki grup arasında komorbidite, KPB zamanı, KK zamanı, yaş, hasta damar sayısı, anastomoz sayısı, ekstübasyon süresi, yoğun bakımda kalış süresi ve hastanede kalış süresi açısından istatistiksel olarak anlamlı farklılık saptanmadı. (P>0,05). Preoperatif ölçülen EF değerlerinde gruplar arasında anlamlı farklılık gözlenmedi (P>0,05). Postoperatif 15. gündeki EF ölçümlerinin ortalama değerleri deney grubunda %39, kontrol grubunda %40 olarak hesaplandı. EF değerlerindeki artış deney grubunda daha fazlaydı. Bu artışın deney grubunda daha anlamlı olduğu tespit edildi (P=0,008).

Gruplar arasında preoperatif ve postoperatif 1. gün bakılan nt-proBNP değerleri arasında anlamlı farklılık vardı (p<0,05). Gruplarda nt-proBNP değerlerinde postoperatif 7. güne kadar anlamlı bir artış gözlendi. (p<0,001). İstatistiksel olarak bu artış her iki grupta da anlamlı olmasına karşın kontrol grubundaki artışın daha fazla olduğu görüldü. Postoperatif 7. gün bakılan nt-proBNP ölçümleri sonrası 2 grup arasında anlamlı farklılık yoktu (P>0,05).

Sonuç: Bu çalışma sonucunda KABG cerrahisinde düşük EF'li hastalarda levosimendaın myokardiyal koruma ve kontraktilite üzerine olumlu etkinliği olduğu saptandı.

Keywords: Levosimendan, koroner by-pass cerrahisi, sol ventrikül disfonksiyonu

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INTRODUCTION

CABG surgery is the main treatment for ischemic heart disease. Over the past 30 years, advances in surgical techniques have improved the quality of life. It has decreased the morbidity and mortality associated with CABG surgery and facilitated postoperative care (1). CABG still has high postoperative mortality and morbidity for patients with left ventricular dysfunction (LVD) compared to patients with normal left ventricular function (2). However, after long-term patient results and clinical follow-ups, it has been shown that coronary revascularization is superior to medical treatment for patients with low EF (3). CPB and cardioplegic arrest have disadvantages. These can be listed as systemic inflammatory response, myocardial damage, neurological damage, renal and pulmonary insufficiency.

Despite these disadvantages, the most important advantage of CPB is to reach the target vessels in the immobile, hollow heart and to perform complete revascularization by working in a bloodless environment (4) The improvement in left ventricular functions begins on the 1st and 3rd days. İt has been shown that significant improvement occurs at the end of 10-15 days. (5). Regardless of the cause of LVD, it has been reported that there is a significant improvement in left ventricular ejection EF after myocardial revascularization in 25-40% of CAD (6). Classical inotropic agents used in heart failure are α-β agonists (dobutamine, dopamine, epinephrine, norefinephrine) and phosphodiesterase III inhibitors (amrinone, milrinone). These drugs improve the cardiac output by increasing the stroke volume. They exert these effects by increasing the level of cyclic adenosine mono phosphate in cardiac myocytes (7). Levosimendan, which has been recently used in acute decompensated heart failure, increases the sensitivity of cardiac troponin-c to cytoplasmic calcium (8-6). The most important feature is that the intracellular calcium level does not increase during this inotropic effect. In this way, important side effects such as cardiac myocyte dysfunction and arrhythmia due to increased intracellular calcium during the effect of adrenergic inotropic agents are prevented. (9). Levosimendan causes arterial and venous dilatation by opening ATP-sensitive potassium channels in vascular smooth muscle cells (10). The contractile level effects caused by levosimendan provide a corrective effect on both preload and afterload of the heart. During this procedure, there is no increase in the oxygen consumption of the myocardium. Thanks to its vasodilation effect in coronary arteries, it also has anti-ischemic activity (11). Studies have shown that elevated brain natriuretic peptide (BNP) levels in patients with chronic heart failure reflect an increased risk of mortality. BNP is released from cardiomyocytes with its prepro hormone form, with increased left ventricular volume load and ventricular expansion. As a result of the studies, it was observed that plasma proBNP levels in left ventricular dysfunction correlated with the severity of symptoms and prognosis. Since BNP disappears from the blood in a very short time, measuring proBNP levels gives much more reliable results (12).

Our aim in this study is to investigate the cardioprotective efficacy of Levosimandan, which is given preoperatively to CAD with LVD undergoing CABG operation, by evaluating the nt-proBNP value and ECHO measurements.

MATERIAL AND METHOD

The study was carried out on 20 patients undergoing CABG at Eskişehir Osmangazi University Faculty of Medicine, Department of Cardiovascular Surgery, between November 2008 and September 2009. This study was approved by the university/local human research ethics committee and all procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee, the 1964 Declaration of Helsinki and subsequent amendments or comparable ethical standards. All patients included in the study signed the Informed Consent Form. It was approved by Eskişehir Osmangazi University Faculty of Medicine Ethics Committee (Date: 10.11.2008, No: 2008/454).

A total of 20 patients (1 female and 19 male) with LVD (EF<40%) undergoing CABG were included in the study. It was divided into 2 groups of 10 people, namely the experimental group and the control group. Preoperative routine tests were performed for CABG. CABG operation had not been applied to any patient before. The same team did all the surgeries.

Levosimendan was started 24 hours before the operation. Solution for infusion 12.5 mg in 500 ml dextrose. It was prepared by adding levosimendan. The solution was given a 12 μgr/kg (microgram/kilogram) loading infusion in the first 10 minutes. There were no complications. In the following period, a maintenance infusion at a dose of 0.2 μgr/kg/min was given.

Blood samples for Nt-proBNP level were taken 1th day after the operation, 24 hours after the operation and on the 7th day. Blood samples for Nt-proBNP level were taken 1 day after the operation, 24 hours after the operation and on the 7th day. Plasma NT-proBNP measurements were made in Elecsys 2010 using Roche Diagnostics'NT-proBNP kit. In both groups, ventricular EF measurements were made by transthoracic echocardiography before the operation and on the 15th postoperative day.

For anesthesia, 30 minutes before the operation, 0.05 mg/kg morphine was administered intramuscularly for premedication. During induction, 0.3 mg/kg etomidate was given intravenously to all patients. Neuromuscular blocker 0.9 mg/kg rocuronium was administered. Sevoflurane anesthetic was started at 2-4% MAC value. İntubation was performed. Patients were connected to a mechanical ventilator. Remifentanil infusion at 0.1-0.4 µgr/kg/min was started to the patients.

Median sternotomy was performed in operations. İnternal mammarian artery and saphenous vein were prepared as grafts. Terumo® Advanced Perfusion System 1 heart-lung machine was used in CPB. Standard cannulation was performed for CBP. Hot blood cardioplegia was given after distal anastomoses. Moderate (30-32 Co) hypothermia was applied. Diastolic cardiac arrest was performed. Cold blood cardioplegia was administered at 20-minute intervals for myocardial protection. Hot blood cardioplegia was administered after the distal anastomoses were made and before the cross-clamp was removed. Proximal anastomoses were performed with a side clamp. The patients were taken to the cardiovascular surgery intensive care unit. Patients who were hemodynamically and surgically stable were extubated.

Shapiro Wilk test was used to examine the distribution of variables. For normally distributed variables t test, two way variance analysis and Holm Sıdak multiple comparison test were used. Descriptive statistics were given as mean±standard error (MEAN±SD). Mann Whitney U test, Wilcoxon T test, Chi-square test and Spearman Correlation analysis were used for variables that were not normally distributed. Median 25% and 75% percentiles were given as descriptive statistics.

RESULTS

The ages of the patients participating in the study were between 48 and 78; The average age of the experimental group was 66.50±9.95 and the average age of the control group was 59±7.28. Biochemical analysis of nt-proBNP measurements measured on preoperative 1st day and postoperative 1st and 7th days from patients in both groups were Performed. At the same time, preoperative EF (EF0) and postoperative EF (EF15) of patients in both groups. measurements were made. The data are given in **Table 1.**

No statistically significant difference was found between the groups in terms of age, comorbitidity, CPB time, CC time, number of patient vessels, number of anastomosis, extubation times, length of stay in intensive care and hospital stay. No significant difference was observed between the groups in preoperative EF values (p>0.05). The data are shown in **Table 2-3.**

Table 1. T-proBNP and ejection fraction values

	P0	P1	P7	EF0	EF15
L1	438	3009	3248	32	46
L2	1798	2854	2075	38	43
L3	3164	5798	10984	16	25
L4	2775	6820	5691	35	35
L5	1118	3677	3097	25	35
L6	2017	2674	6660	38	45
L7	1671	3696	4100	20	26
L8	793	3449	3113	35	51
L9	434	6361	3300	24	34
L10	1784	9618	9891	37	51
K1	1500	2099	3415	38	41
K2	2088	2882	2673	30	32
K3	492	4681	5718	32	35
K4	371	2415	6520	38	40
K5	1078	2517	3388	39	40
K6	53	1132	3501	39	44
K7	178	4047	7171	38	36
K8	415	1468	2779	39	44
K9	116	3077	4686	32	39
K10	1664	2355	3850	35	44

L: Levosimendan given group, K: Control grubu, P0: Preoperative nt-proBNP measurement, P1: Postoperative 1st day nt-proBNP measurement, P7: Postoperative 7th day nt-proBNP measurement
EF0:Preoperative EF measurement, EF15:Postoperative EF measurement.

Table 2. Comorbidity in experimental group and control group

	L (n:10)	L (%)	K (n:10)	K (%)	p
DM	3	30	2	20	>0.05
HT	4	40	3	30	>0.05
COPD	3	30	2	20	>0.05
PAH	1	10	2	20	>0.05
RD	2	20	1	10	>0.05
HL	4	40	3	30	>0.05

DM: Diabetes mellutus, HT: Hypertension COPD: Chronic obstructive pulmonary disease, PAD: Peripheral artery disease, RD: Renal dysfunction, HL: Hyperlipidemia, L: Levosimendan given group; K: Control group.

Table 3. Experimental group and control group perioperative data

	Experimental group mean±sd	Control grup mean±sd	p
AGE	66.5±9.95	59±7.28	0.071
CBP (minute)	112.6±41.02	105.8±35.66	0.697
CCT	66.4±28.14	64.9±18.6	0.890
EF15 (%)	39.1±9.49	39.5±4.11	0.905
-	median (25%-75%)	median (25%-75%)	-
Number of patient veins	4 (4-4)	4 (3-4)	0.435
Number of Anastomosis	3 (3-4)	3.5 (3-4)	0.630
Extubation time (hours)	4.5 (4-5)	5 (5-5)	0.251
Intensive care stay (days)	1.5 (1-2)	2 (1-2)	0.661
Hospital length of stay (days)	6.5 (5-7)	6.5 (6-7)	0.548

KKT: Cross Clamp Time, mean±sd: mean, standard deviation, CBP: kardiyopulmoner by-pass time, EF15: postoperative 15th day ejection fraction

There was a significant difference between the groups in preoperative and postoperative 1st day nt-proBNP values (p<0.05). There was no significant difference between the 2 groups after nt-proBNP measurements on the postoperative 7th day (p>0.05). A significant increase in ntproBNP values was observed in both groups until the 7th postoperative day (p<0.001). It was observed that the median values of preoperative nt-proBNP measurements increased 2.99 times on the postoperative 1st day and 3.26 times on the postoperative 7th day in the experimental group. In the control group, it was found that it increased 3.35 times on the postoperative 1st day and 5.50 times on the 7th day. Although this increase was statistically significant in both groups, it was observed that the increase in the control group was higher. Change values are shown in **Table 4.**

Table 4. Average nt-proBNP values in control and experimental groups

	P	mean±sd	P0	P1	P7
Experimental group	P0	1599.2±923.2	·	0.002	0.000
	P1	4795.6±2274.1	0.002	·	0.928
	P7	5215.9±3073.2	0.000	0.928	·
Test results	-	p<0.001	-	-	-
Control group	P0	795.5±731.2	·	0.005	0.000
	P1	2667.3±1078.8	0.005	·	0.010
	P7	4370.1±1588	0.000	0.010	·
Test	-	p<0.001	-	-	-

P0: Preoperative nt-proBNP measurement, P1: Postoperative 1st day nt-proBNP measurement, P7: Postoperative 7th day nt-proBNP measurement

The mean EF was 33.5 in the experimental group and 38 in the control group. It was observed that postoperative EF values increased in both groups compared to preoperative data. The mean values of EF measurements measured on the postoperative 15th day were 39 in the experimental group and 40 in the control group. The increase in EF values was greater in the experimental group. İt was observed that this increase was more significant in the experimental group (P=0.008). The data are shown in **Table 5.**

Table 5. EF values in the experimental group and the control group

	Experimental group median (25-75%)	Control group median (25-75%)
EF 0	33.50	38
EF 15	39	40
p value	P=0.008	P=0.012

EF: Ejection fraction.

Mean CC time was 66.4±28.14 minutes in the experimental group, while it was 64.9±18.6 minutes in the control group. There was no statistically significant difference between the groups in terms of CC times (p>0.05).

While the average number of sick vessels was 4 in the experimental group, it was 4 in the control group. The median value of the number of anastomoses performed was calculated as 3 in the experimental group and 3.5 in the control group. There was no significant difference (p>0.05).

Dopamine and dobutamine infusion was started in 5 patients who developed low cardiac output postoperatively in the experimental group and 8 patients in the control group. Despite the need for more inotropics in the control group, there was no significant difference between the groups as a result of the statistical analysis (p>0.05).

Intraaortic balloon pump support was provided to 2 patients in the experimental group and to 1 patient in the control group due to low cardiac output. There was no statistically significant difference between the groups in terms of the need for intraaortic balloons (p>0.05).

DISCUSSION

Studies have shown that CABG provides improvement in long-term surveillance in patients with impaired ventricular function (13). Despite advanced surgical techniques, myocardial protection and postoperative care, the surgical risk is still high. It is known that surgical manipulation, global ischemia, reperfusion injury, hypothermia and CPB have damaging effects on myocardium (14).

No statistically significant difference was found between the groups in terms of age, comorbitidity, CPB time, CC time, number of patient vessels, number of anastomosis, extubation times, length of stay in intensive care and hospital stay. No significant difference was observed between the groups in preoperative EF values (p>0.05).

In this study, nt-proBNP levels, which are considered to be an indicator of left ventricular dysfunction, were examined perioperatively. The efficacy of the levosimendan treatment given in terms of protecting myocardial functions was investigated by making simultaneous EF measurements. Due to the damaging effects of CABG on the myocardium, an increase in postoperative nt-proBNP values is observed. It is known that postoperative high nt-proBNP values are associated with intraoperative and postoperative complications in patients undergoing CABG surgery (15). Similarly, in our study, an increase in nt-proBNP levels was found in the postoperative period. However, it was observed that the increase in mean nt-proBNP values in the experimental group was lower than the control group. After 24 hours, an average increase of 2.99 times in the experimental group and 3.35 times in the control group was noted in the nt-proBNP value. Similarly, the increase in the values

measured on the 7th postoperative day was less in the experimental group (3.26 in the experimental group, 5.50 in the control group). Although this increase was statistically significant in both groups, it was observed that the increase in the control group was higher ($p<0.001$). In many studies evaluating the treatment of congestive heart failure with levosimendan, nt-proBNP was used as a neurohormonal marker and it was observed that the improvement in symptoms and the decrease in nt-proBNP levels were parallel to each other (16). Levosimendan, developed for the short-term treatment of acute exacerbations of heart failure, has been shown in many studies to be more effective than conventional inotropic treatment methods. It has been observed that the maximum benefit from treatment after levosimendan infusion takes 24-48 hours after infusion (17-18). CABG complications due to ischemia and reperfusion (such as low cardiac output) are most common in the first 48 hours postoperatively (19). Therefore, it is inevitable that the drug will be most beneficial in these patients during this period. As seen in our data analysis, similar to other studies, the change in nt-proBNP values increased less significantly in the experimental group than in the control group in the first 24 hours after the operation. In the experimental group, it was observed that the median values of preoperative nt-proBNP measurements increased 2.99 times on the postoperative 1st day and 3.26 times on the postoperative 7th day. In the control group, it was found to increase 3.35 times on the postoperative 1st day and 5.50 times on the 7th day ($p<0.001$). Although this increase was statistically significant in both groups, it was observed that the increase in the control group was higher. This shows the cardioprotective activity of levosimendan.

It is accepted that CABG improves postoperative symptoms and survival in patients with LVD (20). Similar data were obtained in this study that we conducted. In both groups, it was found that there was an increase in EF values measured on the postoperative 15th day, statistically, the increase in the experimental group was found to be more significant ($p=0.002$). The reason for this change in EF value in the experimental group was thought to be the result of the beneficial effect of levosimendan on the myocardium alone (such as global ischemia, reperfusion, hypothermia, CC. systemic inflammatory response), as well as its beneficial effect on ischemic myocardium and hyperne myocardial functions at the end of the first 2 weeks postoperatively. We found that there was a significant increase in postoperative EF values of patients with low EF in both groups.

Although levosimene has been shown to be effective in acute heart failure, its use in open heart surgery is still not standard, according to recent studies. Studies are needed to demonstrate the cardioprotective activity of levosimendan in subgroups of open heart surgery (21). We think that levosimendan treatment will significantly contribute to CABG in long-term surveillance but data analysis will be healthier with similar studies to be conducted in a larger patient group.

CONCLUSION

As a result of this study, it has been shown that levosimendan has a positive effect on myocardial protection and contractility in CAD with LVD when combined with CABG.

ETHICAL DECLARATIONS

Ethics Committee Approval: This prospective research was approved by the Ethics Committee of Eskişehir Osmangazi University Faculty of Medicine (Date: 10.11.2008, No: 2008/454).

Informed Consent: All patıents partıcıpatıng ın the study have sıgned the İnformed Consent Form

Referee Evaluation Process: Externally peer-reviewed.

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

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REFERENCES:

1. Trachiotis MD, Weintraub MD, Johnston MD, Jones MD, et al. Coranary artery bypass grafting in patients with advanced left ventriculer dysfunction. Ann Thorac Surg 1998; 66: 1632-9.
2. Kirklin JK. Prospects for understanding and eliminating the deleterious effects of cardiopulmonary bypass. Ann Thorac Surg 1991; 51: 529–31.
3. Temporelli PL, Scapellato F, Corra U, et al. Perioperative and Postoperative Predictors Of Outcome in Patient in low Ejection Fraction Early After Coronary Artery By Pass Grefting. EAPC 2008; 15: 441-7.
4. Allman K.C. Shaw LJ, Hachamovitch. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary arter disease and left ventrikular dysfonction: A meta analysis. J Am Coll Card. 2002; 39: 1151-8.
5. Anderson JL, Marshal HW, Bray BE. A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. N. Engl. J. Med. 1983 308: 1312-8.
6. Bonow RO. The hibernating myocardium: Implications for management of congestive heart failure. AJC 1995; 75: 17-25.
7. Packer M, Leier CV. Survival in congestive heart failure during treatment with drugs with positive inotropic actions. Circulation 1987; 75: 55-63.
8. Haikala H, Linden IB. Mechanisms of action of calcium-sensitizing drugs. JBF 1998; 60: 10-9.

9. Sorsa T, Heikkinen S, Abbot MB, Abusamhadneh E, Laakso T, Tilgman C. Binding of levosimendan, a calcium sensitizer, to cardiac troponin C. JBC 2001; 276: 9337-43.

10. Kaheinen P, Polleselo P, Levijoki J, Haikala H. Levosimendan increases diastolic coronary flow in isolated guinea-pig heart by opening ATP-sensitive potassium channels. JCP 2001; 37: 367-74.

11. Korkmaz H, Yilmaz M. "The effects of levosimendan use on high-sensitivity C-reactive protein in patients with decompensated heart failure", AMS 2019; 4: 174-9.

12. Kivikko M, Antila S, Eha J, Lehtonen L, Pantikainen PJ. Pharmacokinetics of levosimendan and its metabolites during and after a 24-hour continuous infusion in patients with severe heart failure. JCPT 2002; 40: 465-71.

13. Carr JA, Haithcokk BE, Paone G. Long term out come after coronary artery by pass garfting in patients with severe left ventrikular dysfonction: Ann Thorac Surg 2002; 74: 1531-6.

14. Allman K.C. Shaw LJ, Hachamovitch D. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary arter disease and left ventrikular dysfonction: A meta analysis. J Am Coll Card. 2002; 39: 1151-8.

15. Lu YF, Qi HW, Tang CZ, Wu MY, Wang Y, Zhao FY. Change of N-terminal pro-brain natriuretic peptide and big endothelin in patients undergoing coronary artery bypass grafting. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2007; 19: 667-70.

16. Parissis J.T, Adamopoulos S, Farmakis D, at al. G. Effect of serial levosimendan infusions on left ventricular performance and plasma biomarkers of myocardial injury and neurohormonal and immune activation in patients with advanced heart failure. Heart 2006; 92: 1768-72.

17. Kyrzopoulos S, Adamapoulos S, Parissis J.T, at al. Levosimendan reduces plasma B-type natriuretic peptide and interleukin 6 and improves central hemodynamics in severe heart failure patients. International JC 2004; 99: 409-13.

18. Çelik T, İyisoy A, Yüksel UÇ, Kardeşoğlu E. The prolonged lowering effect of levosimendan on brain natriuretic peptide levels in patients with decompansated heart failure: Clinical implications. İJC 2008; 128: 97-9.

19. Cheshire C, Bhagra CJ, Bhagra SK. "A review of the management of patients with advanced heart failure in the intensive care unit". Ann Transl Med 2020; 8: 828-42.

20. J. Skorpil, Brat R, Docekal B, Motyk O. Myocardial revascularisation in patients with severe left ventricular dysfunction. Early and midterm results. Biomed Papers 2004; 148: 55-8.

21. Santillo E, Migale M, Massini C, Incalzi RA. Levosimendan for Perioperative Cardioprotection: Myth or Reality? CCR 2018; 14: 142-52.

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Radiologic features of symptomatic cholelithiasis: a current perspective

Semptomatik kolelitiyazisin radyolojik özellikleri: güncel bir bakış

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ABSTRACT

Aim: The aim of this study was to investigate the radiological features of symptomatic cholelithiasis with use radiography, ultrasonography (USG), and computed tomography (CT).

Material and Method: From January 2014 and September 2019, 543 patients with cholelithiasis were identified. Of these, 174 who also underwent radiography and CT were included in the study. During the 3-year follow-up of the 174 patients, 80 patients had symptomatic cholelithiasis, identified according to USG and/or CT examinations, as well as clinical findings. Findings suggesting cholecystitis, cholangitis, pancreatitis, and choledocholithiasis were accepted as symptomatic. Radio-opaque stones were identified on radiography and stones were visible on CT. The stones were divided into groups according to their calcification types. The Hounsfield unit (HU) values of the stones were measured and the number and size of the stones were determined by CT and USG.

Findings and Results: Symptomatic findings included radio-opaque stones, multiple stones, stones with HU values above 100 HU, and cholelithiasis of the uniform calcification type ($p<0.05$). However, the relationship between symptomatic cholelithiasis and stone size was not significant ($p>0.05$).

Conclusion: The radiological features of symptomatic cholelithiasis are important in terms of follow-up, treatment plan and prevention of complications.

Keywords: Cholelithiasis, radio-opaque, symptomatic, complication, radiography

ÖZ

Amaç: Bu çalışmanın amacı, radyografi, ultrasonografi (USG) ve bilgisayarlı tomografi (BT) kullanarak semptomatik kolelitiazisin radyolojik özelliklerini araştırmaktır.

Gereç ve Yöntem: Ocak 2014 ve Eylül 2019'dan itibaren 543 kolelitiyazisli hasta belirlendi. Bunlardan hem radyografi hem de BT'si çekilen 174'ü çalışmaya dahil edildi. 174 hastanın 3 yıllık takibinde 80 hastada USG ve/veya BT incelemelerine ve klinik bulgulara göre tespit edilen semptomatik kolelitiyazis vardı. Kolesistit, kolanjit, pankreatit ve koledokolitiazisi düşündüren bulgular semptomatik olarak kabul edildi. Radyografide radyoopak taşlar belirlendi ve BT'de taşlar görüldü. Taşlar kalsifikasyon türlerine göre gruplara ayrıldı. Taşların Hounsfield birimi (HU) değerleri ölçülerek taş sayısı ve boyutu BT ve USG ile belirlendi.

Bulgular ve Sonuç: Radyoopak taşlar, çoklu taşlar, HU değerleri 100 HU'nun üzerinde olan taşlar ve tek tip kalsifikasyon tipinde safra taşlarında semptomatik bulgular vardı ($p<0,05$); ancak semptomatik kolelitiazis ile taş boyutu arasındaki ilişki anlamlı değildi ($p>0,05$). Semptomatik kolelitiyazisin radyolojik özellikleri takip, tedavi planı ve komplikasyonların önlenmesi açısından önemlidir.

Anahtar kelimeler: Kolelitiyazis, radyo-opak, semptomatik, komplikasyon, radyografi

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INTRODUCTION

Cholelithiasis is the most common disease of the digestive tract after peptic ulcer, and cholelithiasis diseases are encountered in 10% of the general population (1-3). Approximately 70–80% of patients with cholelithiasis have asymptomatic cholelithiasis that remains silent for life (2-5). Symptoms of asymptomatic cholelithiasis initially occur in 10% of patients in the first 5 years after diagnosis and in 25.8% in 10 years (5). The most common complaint in symptomatic cholelithiasis is recurrent abdominal pain, sometimes accompanied by nausea and vomiting. Abdominal swelling and belching may also occur. Mostly, complications such as cholecystitis and pancreatitis develop. Other complications, such as empyema and gallbladder perforation, occur in only 0.1% of cases (3,5). The gold standard for noninvasive diagnosis of cholelithiasis is ultrasonography (USG), with a specificity and sensitivity above 95% (3,4). In some cases, radiographic examination or computed tomography (CT) is used, as well as diagnostic procedures such as magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography (ERCP) and cholangioscopy for the biliary and common bile duct stones (3,6,7).

Gallstones are composed mainly of cholesterol, bilirubin, and calcium salts, with smaller amounts of protein and other materials (8-10). Three types of gallstones are recognized: (I) Pure cholesterol stones, which contain at least 90% cholesterol, (II) pigment stones, which are either brown or black and contain at least 90% bilirubin, and (III) mixed composition stones, which contain varying proportions of cholesterol, bilirubin, and other substances (such as calcium carbonate, calcium phosphate, and calcium palmitate) (8). Brown pigment stones are mainly composed of calcium bilirubinate, whereas black pigment stones contain bilirubin, calcium, and/or tribasic phosphate (8-13). The composition of the stones also affects the treatment. Pigment stones are easily removed by endoscopic lithotripsy, whereas cholesterol stones, which are harder in texture, are more difficult to remove by endoscopic treatment (7). Oral dissolution therapy with bile acids is used in selected patients, but the primary treatment for symptomatic cholelithiasis disease is surgery (4-6).

The components of cholelithiasis determine the radiological features, which may be useful in treatment planning. To the best of our knowledge, no recent studies in the literature have explored the radiographic features of cholelithiasis (14-17). The aim of the present study was to use radiography, USG, and CT to investigate the radiological features of symptomatic cholelithiasis.

MATERIAL AND METHOD

This retrospective study was conducted in Kırıkkale University Faculty of Medicine according to the principles of the Declaration of Helsinki. Abdominal USG, radiography and CT scans were examined from the database of the Kırıkkale University Faculty of Medicine Radiology Department. Approval for the study was granted by the Ethics Committee of Kırıkkale University Faculty of Medicine (Date: 24.10.2018, Number: 18/8).

Study Design

A total of 543 patients with cholelithiasis underwent abdominal ultrasonography between January 2014 and September 2019, and 174 patients with both radiography and CT scans were included in the study. The demographic, radiological and clinical information of the patients was obtained by scanning the files in the hospital registry system. The 3-year follow-up of the 174 patients revealed 80 patients with symptomatic cholelithiasis, identified according to USG and/or CT examinations, together with clinical findings.

Patients under 18 years of age, with primary malignancies of the liver and biliary tract, with metastatic lesions, or with gallbladder malignancy were excluded from the study.

Equipment and Evaluations

Ultrasonographic examinations were performed with a convex probe of 3–5 MHz (Toshiba Aplio 500; Canon Medical Systems, USGA). Radiography and digital X-ray (XGEO GC80, Samsung, Korea) images were obtained with the patient in the supine position. All patients were scanned using a 64-Multislice Computed Tomography (MSCT) instrument (Brilliance 64; Philips Medical System, Best, the Netherlands). The CT scans were acquired in a craniocaudal direction with the following parameters: collimation, 16 mm×1.5 mm; section thickness, 3.0 mm; transverse and coronal reconstruction interval, 3 mm; pitch, 1.2; tube current, 120 kVp; and 200–300 mAs. Enhanced and nonenhanced CT scans were examined in all patients. The enhanced CT examinations were conducted using 350 mg/mL iohexol at a total dose of 90 mL and an injection rate of 3 to 4 mL/s.

The radiographic examinations of the patients with the ultrasound stone were evaluated for the presence or absence of radio-opaque stones. The CT images were also examined for the presence of stones visible on the CT images. The presence or absence of calcification evident on CT images was used to divide the patients into two groups. According to Federle et al. (2) calcification types can be classified into four groups, (I) Uniform type, with homogeneous calcification, (II) laminar type,

with round, layered calcification, (III) annular type, with central, hypodense, round calcification, and (IV) central nidus, with surrounding hypodense, central calcification (**Figure 1**). The Hounsfield unit (HU) values of the stones were also measured. The region of interest (ROI) of the HU includes the entire stone (radiolucent and radiopaque components). The mean value of multiple stones was taken.

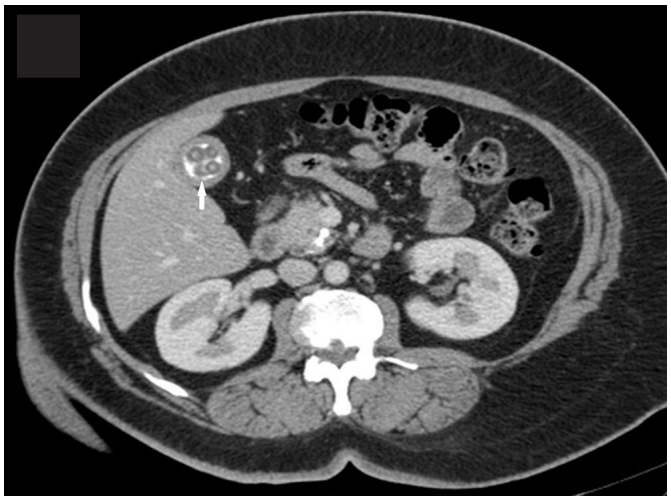

Figure 1. Laminar types of calcification of cholelithiasis as seen by abdominal CT (white arrows).

The sizes of the stones were determined based on both CT and USG findings; however, stones that were not visible on CT were measured based only on the USG findings. The maximum diameter of a stone was measured from the CT images on which the stone was most prominent. The stone sizes and the maximum diameter of the largest stone were measured in the USG examination, whereas the number of stones was recorded as single, a few pieces (2–4 pieces), and multiple stones (≥ 5 pieces) using both USG and CT. The stone sizes were divided into the following 5 groups: 5 mm, 5–15 mm, 15–20 mm, 20–25 mm, and 25 mm. The numbers and sizes of the stones were classified according to the cholelithiasis guideline proposed by Tazuma et al. (6) in 2016.

Patients with symptomatic cholelithiasis were identified according to their USG and/or CT examinations, together with their clinical findings. In general, the clinical findings in all patients were severe abdominal pain (upper abdomen or right upper quadrant pain, epigastric), nausea, vomiting, and/or jaundice and were supported by the laboratory findings (biluribin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GT), amylase, lipase etc.). Those with findings of cholecystitis, cholangitis, pancreatitis and choledocholithiasis were considered symptomatic (4,6,18) (**Table 1**).

Table 1. The distribution of diagnosis associated with cholelithiasis.

Diagnosis	N (%)	Accompanying, N (%)
Acute cholecystitis	64 (80%)	6/2 (choledocholithiasis/ pancreatitis) (10%)
Chronic cholecystitis	11 (13.75%)	
Cholangitis/ choledocholithiasis	4 (5%)	
Pancreatitis	1 (1.25 %)	
Totally	80 (100%)	

In the USG images, a gallbladder wall thickness greater than 3 mm and the presence of pericolecystic fluid and gallbladder distension (transverse diameter >40 mm) were considered diagnostic criteria for acute cholecystitis (3,4,6,18). In the CT images, these criteria were gallbladder wall thickening (>3–5 mm), excessive contrast enhancement in the wall or mucosa, inflammatory changes in the adjacent soft tissues and pericolecystic fluid, and abnormal gallbladder distention (**Figure 2**) (4,6,18,19). The diagnosis of chronic cholecystitis was made based on a gallbladder wall thickness greater than 3 mm observed in the USG and CT images, without gallbladder distension (transverse diameter<40 mm) (**Figure 3**) (19). These criteria were standardized according to a previously published study guideline (4,6,18,19).

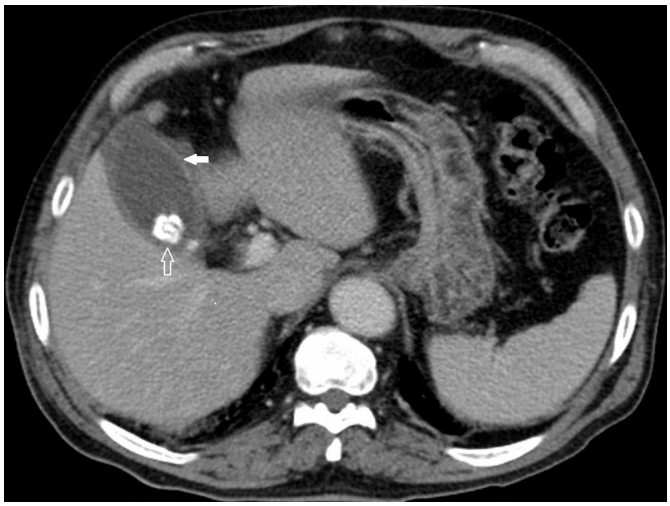

Figure 2. A 78-year-old male patient. Acute cholecystitis was evident on abdominal CT, as indicated by the increased wall thickness of the gallbladder, mucosal enhancement (white arrow), and a calcified stone (open arrow)

Diagnosis of cholangitis/choledocholithiasis: Bile duct wall thickening, dilatation and/or sludge, CT thickening of the bile duct walls, inflammatory changes around the bile duct, and the presence of stones in the biliary tract were evaluated in the USG images (4,6,18,19). Pancreatitis was diagnosed with clinical and laboratory findings along with radiological findings. All pancreatitis patients had severe epigastric pain accompanied by nausea and vomiting. Edematous, hypoechoic, pancreatic

enlargement and heterogeneity in the pancreas were evaluated in the USG images. The presence of contrast-repellent areas suggestive of necrosis or enhancement of the parenchyma and lines of inflammation due to inflammation in the surrounding fat tissue planes (**Figure 4**), or with or without cystic formation, were evaluated in the CT images (3,6,14,18,19).

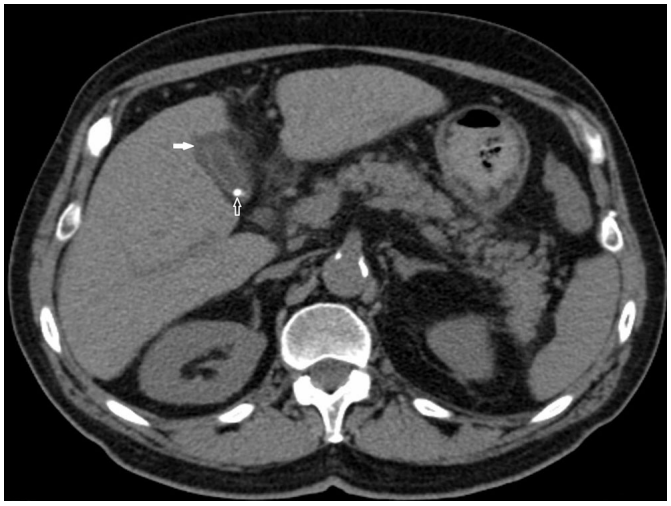

Figure 3. A 71-year-old female patient. Chronic cholecystitis was evident on abdominal CT, as indicated by the increased wall thickness of the gallbladder, without distention (white arrow), and a millimeter-scale calcified stone (open arrow)

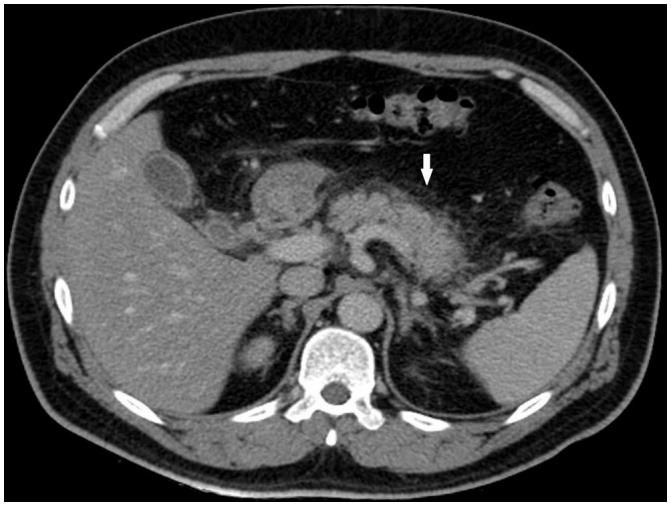

Figure 4. A 46-year-old male patient, Pancreatitis on abdominal CT, inflammation lines due to inflammation in the fat tissue planes surrounding the pancreas (white arrow)

The follow-up USG and CT images of the patients after the first cholelithiasis diagnosis were also examined, and symptomatic cholelithiasis was detected during follow-up. A routine cholelithiasis follow-up protocol, as well as radiological examinations, was performed according to the clinical findings (4-6). The relationship between the different radiological features of cholelithiasis and symptomatic patients was evaluated. All USG, radiographic, and CT scanning images were examined as blinded to clinical data by a radiologist (AÖ) with 10 years of experience in general radiology.

Statistical Analysis

We used the SPSS software package program (SPSS, Chicago, Illinois, USGA), version 20.0, for statistical analyses. Data were expressed as the arithmetic mean±standard deviation (SD) and range. The independent t-test was utilized to compare patient ages with symptomatic and asymptomatic cholelithiasis. The radiological features of cholelithiasis were compared using the $\chi 2$ test to determine the relationship between symptomatic and asymptomatic cholelithiasis. Gender differences among the groups were also compared with the $\chi 2$ test. A P value of less than 0.05 was considered statistically significant.

RESULTS

Of the 174 patients with cholelithiasis, 101 were female (mean age 63.43±17.23) and 73 were male (mean age 63.19±14.29). The demographic characteristics of the patients with symptomatic and asymptomatic cholelithiasis are shown in **Table 2**.

Table 2. Demographic characteristics of symptomatic and asymptomatic patients with cholelithiasis.

	Asymptomatic (N=94)	Symptomatic (N=80)	*P* value
Age, years	61.78±15.7 (23-91)	65.15±16.1 (25-100)	0.167[a]
Gender male/female	40/54	33/47	>0.05[b]

Values are expressed as mean±SD (range) where applicable
[a]Independent t test
[b]χ^2 analysis

The evaluation of symptoms related to cholelithiasis revealed cholecystitis in 75 patients (acute cholecystitis in 64 patients and chronic cholecystitis in 11 patients), choledocholithiasis in 3 patients, pancreatitis in 1 patient, and cholangitis in 1 patient. Six of the patients with acute cholecystitis also showed concurrent cholangitis/choledocholithiasis. Two of the patients with findings of acute cholecystitis also had concomitant findings of pancreatitis. The distribution of diagnosis associated with the cholelithiasis is shown in **Table 1**.

The radiological features of radio-opacity, multiple stones, stones with HU values above 100, and cholelithiasis of a uniform calcification type were found to be symptomatic ($p<0.05$). However, the relationship between symptomatic cholelithiasis and stone size was not statistically significant ($p>0.05$). A comparison of the radiological features between symptomatic and asymptomatic cholelithiasis is shown in Table 3. In our study, no significant difference was noted in the sizes and numbers of stones obtained with CT and USG measurements ($p>0.05$).

Our patients with cholelithiasis showed no symptoms other than cholecystitis, cholangitis, choledocholithiasis, and pancreatitis. A total of 26 (14.9%) of our patients with cholelithiasis underwent cholecystectomy during their follow-up periods.

DISCUSSION

In general, 20–30% of cholelithiasis cases eventually show symptoms and complications, such as acute cholecystitis, chronic cholecystitis, choledocholithiasis, cholangitis, and acute pancreatitis (5). Patients with asymptomatic cholelithiasis can continue their lives without any clinical findings for years (5), and many cases are diagnosed incidentally with USG (6). In our study, 80 (45.9%) of the 174 patients were radiologically symptomatic. This rate is higher than previously reported in the literature because of the higher number of radiographs and CT examinations conducted in symptomatic patients.

Cholelithiasis occurs two times more frequently in women than in men (2-4). In our study, 58% of the patients with cholelithiasis and 58.8% of the patients with symptomatic cholelithiasis were women. No significant difference was detected between the sexes for symptomatic cholelithiasis ($p>0.05$).

The size and the components of the stone affect the radiological features, and 15–20% of the cholelithiasis cases are radio-opaque (2,7). The high level of calcium in the stone increases the likelihood of it being detected by radiography examination (2,7,14,15,20). In our study, 38.5% of the cholelithiasis stones were radio-opaque and 61.5% were radiolucent. Significant increases in symptomatic rates of radio-opaque cholelithiasis were found ($p<0.05$). The reason for the high rate of radio-opaque cholelithiasis in our study could be that radio-opaque stones are symptomatic and are detected more frequently due to recent developments in radiographic techniques. An abdominal digital X-ray revealed millimeter-scale opaque stones (21).

Detection of cholelithiasis by CT is less likely when stones have a high cholesterol ratio and a low calcium ratio (2,7,14,15,20). Pure cholesterol stones are isodense with bile (2). So they are usually invisible on CT. However, if pure cholesterol stones are large in size or contain some calcification, they can be visualized by CT. Cholelithiasis visualization by CT can be as high as 80% (14); in our study, 64.9% of the stones could be visualized by CT. Significant increases were observed in the symptomatic rates in patients with stones that could be visualized by CT. Significant increases were found in the symptomatic rates of patients with cholelithiasis visible in CT scans ($p<0.05$).

In our study, CT could not visualize the stones in 19 patients who had calcified stones less than 5 mm in size. The reason for this is that small stones may not be visualized on abdominal radiography due to their size, even if they are entirely calcified. Stones with HU values below 100 may be visible in CT scans, but may not be visualized by radiography. In our study, cholelithiasis could not be visualized in radiographs of 38 of the 46 patients with cholelithiasis with HU values below 100. The stones with a HU of less than 100 were also less symptomatic (**Table 3**).

Table 3. Comparison of radiological features between symptomatic and asymptomatic cholelithiasis.

Cholelithiasis features	Subtypes	Asymptomatic N (%)	Symptomatic N (%)	Totally	P
Radiography	Radiolucent	73 (77.7)	34 (42.5)	107 (61.5)	<0.001
	Radio-opaque	21 (31.3)	46 (57.5)	67 (38.5)	
	Totally	94 (100)	80 (100)	174 (100)	
CT	Invisible	45 (47.9)	16 (20)	61 (35.1)	<0.001
	Visible	49 (52.1)	64 (80)	113 (64.9)	
	Totally	94 (100)	80 (100)	174 (100)	
Size	<5 mm	21 (22.3)	21 (26.2)	42 (24.1)	0.559
	5-15 mm	37 (39.4)	31 (38.8)	68 (39.1)	
	15-20 mm	25 (26.6)	18 (22.5)	43 (24.7)	
	20-25 mm	9 (9.6)	5 (6.25)	14 (8)	
	>25 mm	2 (2.1)	5 (6.25)	7 (4)	
	Totally	94 (100)	80 (100)	174 (100)	
Number	Single	53 (56.4)	21 (26.25)	74 (42.5)	<0.001
	A few pieces (2–4 pieces)	27 (28.7)	41 (51.25)	68 (39.1)	
	Multipl (≥ 5 pieces)	14 (14.9)	18 (22.5)	32 (18.4)	
	Totally	94 (100)	80 (100)	174 (100)	
HU values	<50	18 (36.7)	10 (15.4)	28 (16.1)	<0.001
	50-100	12 (24.5)	6 (9.2)	18 (10.3)	
	>100	19 (38.8)	49 (75.4)	68 (39.1)	
	Totally	49 (100)	65 (100)	114 (65.5)	
Calcification type	Uniform	20 (46.5)	43 (71.7)	63 (36.2)	0.035
	Laminar	4 (9.3)	6 (10)	10 (5.7)	
	Annular	16 (37.2)	10 (16.7)	26 (14.9)	
	Central Nidus	3 (7)	1 (1.6)	4 (2.3)	
	Totally	43 (100)	60 (100)	103 (59.1)	

P values according to χ^2 analysis. CT- computed tomography. HU- Hounsfield unit

The stones observed by CT were grouped into four calcification types: uniform, laminar, annular, and central nidus. The uniform type was the most frequently seen, while the central nidus type was the least frequently seen. The symptomatic rates were highest for the uniform calcification type (**Table 3**).

Stones larger than 2.5 cm carry a high risk of becoming symptomatic and causing complications (4-6,16,22). In our study, no significant relationship was noted between symptoms and the size of the stone (p=0.559). Patients with more than one cholelithiasis had a high symptomatic rate (**Table 3**).

Cholecystectomy is the first choice treatment for symptomatic cholelithiasis (6). In our study, cholecystectomy was performed on 26 of 80 patients who were symptomatic during their follow-up periods. Oral dissolution therapy (ursodeoxycholic acid) or extra-corporeal shock wave lithotripsy (ESWL) is recommended for non-surgical patients (6), whereas bile acid dissolution therapy is recommended for floating stones (<15 mm in diameter), for radiolucent or<60 HU stones detected by CT scans, and in patients with normal gallbladder function (6). In our study, 12 patients met these criteria. Of these, 5 patients with underwent ursodeoxycholic acid treatment, 3 patients underwent cholecystectomy, and 4 patients were followed up without any treatment.

ESWL therapy is recommended for single stones (<20mm in diameter), radiolucent pure cholesterol stones (<50 HU on CT scan, typical USG image), and in patients with normal gallbladder function (6). In our study, 38 patients met these criteria; however, only 4 patients were treated with ESWL. We think that the low rates of ursodeoxycholic acid and ESWL treatment in our study reflected the neglect of the radiological features of cholelithiasis in the treatment plan.

Current recommendations are that cholelithiasis should be monitored until symptoms develop (4,5). However, the risk of developing symptoms or complications has increased in some patients, and these patients can undergo a prophylactic cholecystectomy. Considerations include the pediatric age group, sickle cell anemia, nonfunctioning gallbladder, porcelain gallbladder, and genetic susceptibility to gallbladder cancer, as well as the radiological features of cholelithiasis (2,5,6,13).

The present study had some limitations, including the small sample size, the short duration of follow-up, and a lack of knowledge about the patients before and after the treatment. The assessment of the symptomatic cholelithiasis patients also did not include an evaluation between clinical and laboratory findings. Another limitation was that interobserver variability could not be determined because the examinations were performed by a single radiologist. Furthermore, the data and images are retrospective records. Nevertheless, the results of our study are meaningful, but additional comprehensive prospective studies are required that will involve detailed clinical findings with long follow-up periods.

CONCLUSION

No recent studies have reported the radiological features of cholelithiasis revealed by the technological advances in imaging devices. Our study shows the radiological features of cholelithiasis and its relationship with clinical symptoms. It can be considered determining factors in the treatment algorithm of cholelithiasis and are therefore important in terms of follow-up, treatment plan, and prevention of complications.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethics Committee of Kırıkkale University Faculty of Medicine (Date: 24.10.2018, Number: 18/8).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Catalano OA, Sahani DV, Kalva SP, et al. MR imaging of the gallbladder: a pictorial essay. Radiographics 2008; 28: 135-55.
2. Federle MP and Raman SP. Diagnostic Imaging: Gastrointestinal E-Book. Elsevier Health Sciences 2015.
3. Rumack CM, Wilson S, Charboneau JW, Levine D. Diagnostic Ultrasound: 2-Volume Set. Missouri: Elsevier Mosby 2010.
4. EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones. J Hepatol 2016; 65: 146-81.
5. Bellows CF, BErGEr DH and Crass RA. Management of gallstones. Am Fam Physician 2005; 72: 637-42.
6. Tazuma S, Unno M, Igarashi Y, et al. Evidence-based clinical practice guidelines for cholelithiasis 2016. J Gastroenterol 2017; 52: 276-300.
7. Tsai HM, Lin XZ, Chen CY, Lin PW, Lin JC. MRI of gallstones with different compositions. AJR Am J Roentgenol 2004; 182: 1513-9.

8. Njeze GE. Gallstones. Niger J Surg 2013; 19: 49-55.
9. Trotman BW. Pigment gallstone disease. Gastroenterol Clin North Am 1991; 20: 111-26.
10. Trotman BW, Petrella EJ, Soloway RD, Sanchez HM, Morris TA 3rd, Miller WT. Evaluation of radiographic lucency or opaqueness of gallstones as a means of identifying cholesterol or pigment stones. Correlation of lucency or opaqueness with calcium and mineral. Gastroenterology 1975; 68: 1563-6.
11. Chan WC, Joe BN, Coakley FV, et al. Gallstone detection at CT in vitro: effect of peak voltage setting. Radiology 2006; 241: 546-53.
12. Stewart L, Griffiss JM and Way LW. Spectrum of gallstone disease in the veterans population. Am J Surg 2005; 190: 746-51.
13. Venneman NG and van Erpecum KJ. Pathogenesis of gallstones. Gastroenterol Clin 2010; 39: 171-83.
14. Brink JA, Kammer B, Mueller PR, Balfe DM, Prien EL, Ferrucci JT. Prediction of gallstone composition: synthesis of CT and radiographic features in vitro. Radiology 1994; 190: 69-75.
15. Dolgin SM, Schwartz JS, Kressel HY, et al. Identification of patients with cholesterol or pigment gallstones by discriminant analysis of radiographic features. New Eng Jo Med 1981; 304: 808-11.
16. Plaisier PW, Brakel K, van der Hul RL, Bruining HA. Radiographic features of oral cholecystograms of 448 symptomatic gallstone patients: implications for nonsurgical therapy. Eur J Radiol 1994; 18: 57-60.
17. Ros E, Valderrama R, Bru C, Bianchi L, Teres J. Symptomatic versus silent gallstones. Radiographic features and eligibility for nonsurgical treatment. Dig Dis Sci 1994; 39: 1697-703.
18. Demehri FR and Alam HB. Evidence-Based Management of Common Gallstone-Related Emergencies. J Intensive Care Med 2016; 31: 3-13.
19. Raptopoulos V, Compton CC, Doherty P, et al. Chronic acalculous gallbladder disease: multiimaging evaluation with clinical-pathologic correlation. Am J Roentgenol 1986; 147: 721-4.
20. Fidler J, Paulson EK and Layfield L. CT evaluation of acute cholecystitis: findings and usefulness in diagnosis. Am J Roentgenol 1996; 166: 1085-8.
21. O'Kane D, Papa N, Manning T, et al. Contemporary Accuracy of Digital Abdominal X-Ray for Follow-Up of Pure Calcium Urolithiasis: Is There Still a Role? J Endourol 2016; 30: 844-9.
22. Ozbalci G, Tanrikulu Y, Kismet K, Dinc S, Akkus M. Gallstone ileus with a giant stone and associated multiple stones. Bratisl Lek Listy 2012; 113: 503-5.

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Comparison of affective temperament profiles in male patients with chronic obstructive pulmonary disease according to groups

Kronik obstrüktif akciğer hastalığı olan erkek hastalarda afektif mizaç profillerinin gruplara göre karşılaştırılması

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ABSTRACT

Introduction: The aim of this study was to determine the temperament profiles of male patients with chronic obstructive pulmonary disease (COPD) according to disease groups.

Material and Method: A total of 80 male COPD patients without any additional disease were included in the study. Patients were staged as group A, group B, group C and group D according to 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. The Turkish version of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Auto (TEMPS-A) and the Hospital Anxiety Depression Questionnaire scales (HADS) were used to determine the dominant affective temperaments.

Results: Totally 80 COPD patients including 20 from each group were recruited into our study. The majority of COPD patients did not have any dominant temperament (n:28). Depressive temperament was found in 18 patients (22.5%) as the most common dominant affective temperament, followed by anxious temperament in 10 patients (12.5%). Anxious temperament was significantly dominant in group A, while there wasn't any significant difference between groups for depressive temperament (p=0.034, p=0.36). Cyclothymic and irritable temperaments were found to be more common in group A (p=0.006, p=0.048). According to the HADS, depression scores were significantly higher in group B than in other groups (p=0.03).

Conclusion: Our study demonstrated that there is a negative correlation between COPD severity and incidence of affective temperaments. To cope with the disease better, COPD patients in early stages are in need of psychological support at least patients in advanced stage.

Keywords: Affective temperament profiles, chronic obstructive pulmonary disease

ÖZ

Giriş: Bu çalışmanın amacı, kronik obstrüktif akciğer hastalığı (KOAH) tanısı olan erkek hastaların hastalık gruplarına göre mizaç profillerini araştırmaktır.

Gereç ve Yöntem: Kronik obstrüktif akciğer hastalığı tanısı olup, ek hastalığı olmayan 80 erkek hasta çalışmaya dahil edildi. Hastalar 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) kriterlerine göre A grubu, B grubu, C grubu ve D grubu olarak evrelendirildi. Baskın mizacı belirlemek için Memphis, Pisa, Paris ve San Diego Oto Mizaç Değerlendirme (TEMPS-A) Türk versiyonu ve Hastane Anksiyete Depresyon anket ölçeği (HADS) kullanıldı.

Bulgular: Her gruptan 20 olmak üzere toplam 80 KOAH hastası çalışmaya dahil edildi. KOAH hastalarının büyük çoğunluğunda herhangi bir baskın mizaç yoktu (n:28). Depresif mizaç 10 hastada (%12,5) görülürken, endişeli mizaç en sık baskın mizaç olarak 18 hastada (%22,5) saptandı. Endişeli mizaç profili grup A'da baskın iken, depresif mizaç için gruplar arasında anlamlı bir fark olmadığı görüldü (p=0.034, p=0.36). Siklotimik ve irritabl mizaç grup A'da daha sık olarak saptandı (p=0.006, p=0.048). HADS ölçeğine göre grup B hastaları diğer gruplara göre daha depresifti (p=0.03).

Sonuç: Çalışmamız KOAH şiddeti ve afektif mizaç sıklığı arasında negatif bir korelasyon olduğunu göstermiştir. KOAH hastalarının hastalıkla daha iyi başa çıkabilmeleri için, sadece ileri evrede değil, erken evrelerde de psikolojik desteğe ihtiyacı vardır.

Anahtar Kelimeler: Afektif mizaç profilleri, kronik obstrüktif akciğer hastalığı

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder that is characterized by persistent airflow obstruction. Worldwide the most commonly encountered risk factor for COPD is tobacco smoking. Nonsmokers may also develop COPD (1).

In order to COPD development takes many years and is not exactly reversible, these patients may have severe physical limitations and substantial psychosocial trouble. There are various studies investigating the relationship between psychological and emotional distresses and COPD.

The 2019 global initiative for chronic obstructive pulmonary disease (GOLD) guidelines considers symptoms and history of exacerbation rather than the degree of airflow obstruction for classification of COPD (1). At the same time comorbidities as anxiety and depression have been included in to new guideline. It is also possible that other psychological variables, such as personality traits and temperaments may influence the progression of the illness, as well as rehabilitation and treatment achievement. Nevertheless, psychological characteristics and temperaments are not given enough importance in guidelines.

Temperament has been defined as a biologically determined, hereditary core of the personality, being stable and relatively unchangeable throughout life, which determines the basic level of reactivity, mood and energy of given individual (2). It is possible to see it as a feature of personality without affective disorders or a basis of affective disorders, like depression or bipolar disease, throughout life. Five dominant affective temperaments are described: depressive, hyperthymic, cyclothymic, irritable and anxious (3). The temperament characteristics of the patient may influence success in competing with stress and may also affects keeping the disease under control.

The aim of this study is to compare the dominant temperament profiles between groups in Turkish patients with COPD in accordance with the new classification.

MATERIAL AND METHOD

The study comprised 80 COPD patients aged 45-70 years. In order to form a homogenous group, only male participants were included. Individuals enrolled in study did not have any comorbid disease. Exclusion criteria were based on the inability of the patient to reliably respond to questionnaires in the interview. All of them were recruited from our chest outpatient clinic where they were regularly followed-up and fulfilled the GOLD criteria for the classification of COPD. This study was approved by the university/local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was carried out with the permission of Research Ethics Committee of Kahramanmaraş Sütçü İmam University faculty of medicine University faculty of medicine (Permission granted/CAAE number: 2014/30.04, Decision no: 72).

Classification of Patients

Patients were grouped as A, B, C, D according to 2019 GOLD guideline. Twenty patients from each group, who have been in the same control group for at least one year were enrolled.

Symptom burden is measured by modified Medical Research Council questionnaire (mMRC)

- A=Low symptom burden (mMRC of 0-1) and and low exacerbation rate (0-1/year).
- B=Higher symptom burden (mMRC of 2) and low exacerbation rate (0-1/year).
- C=Low symptom burden (mMRC of 0-1) and high exacerbation rate (2 or more/year)
- D=Higher symptom burden (mMRC of 2) and high exacerbation rate (2 or more/year)

Questionnaire Scales

The Turkish version of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Auto Questionnaire scale (TEMPS-A) was used to determine the dominant affective temperament, and the Hospital Anxiety Depression Scale (HADS) was used also. Each interview took about 15 minutes.

The HADS is a four Likert-type scale identifying the level and intensity variation which developed by Zigmond and Snaith to measure patient anxiety and the risk of depression. Comprises a total of 14 questions and contains anxiety (HADS-A) and depression (HADS-D) subscales. In studies conducted in Turkey for cutting the anxiety subscale score was found 10/11, while the depression subscale was 7/8. Accordingly, these points are considered to be at risk on the field. The scoring of each item in the scale is different. 1, 3, 5, 6, 8, 10, 11 and 13 show a gradually decreasing intensity and 3, 2, 1, 0 scoring format. On the other hand, the 2nd, 4th, 7th, 9th, 12th, and 14th amendments are scored 0, 1, 2, 3 format.

The Turkish version of TEMPS-A scale was used to determine the dominant affective temperament in the subjects. The validity and reliability of TEMPS-A has been proven in many languages, and in Turkish by Vahip et al. (2). The Turkish version of the scale consists of 99

items. This scale is a self-report instrument consisting of five subscales. It's 99 constituent items inquire about the subject's whole life about traits along depressive, cyclothymic, hyperthymic, irritable and anxious lines. Individuals answer 'yes'or 'no'when considering their life experience. Cutoff scores to determine the dominant temperament are 13 for depressive mood (18 items), 18 for cyclothymic (19 items), 20 for hyperthymic (20 items), 13 for irritable (18 items) and 18 for anxious (24 items). It is possible to have more than one dominant affective temperament (4,5).

Description of Temperaments

1. Hyperthymic Temperament: described in those individuals who display this type of affective temperament as usually cheerful and overoptimistic, warm and extroverted, as having high energy levels, overinvolved in several activities, uninhibited, sensation seeking and with promiscuous tendency, and their length of sleep is commonly short (6).

2. Depressive Temperament: The depressive (or dysthymic) temperament has been classically described in those subjects who are usually unable to see the lighter side of things, are self-denying, have low energy levels and are critical, negativistic and highly introverted, don´t like changes, meeting new people or exploring new situations (7,8).

3. Cyclothymic Temperament: The basic trait of the cyclothymic temperament is a pattern of alternation between hypomanic or irritable, and depressive subclinical moods, cognitions, and behaviors. Emil Kraepelin (9) has described this temperament as the alternation of the previous two temperaments described above (hyperthymic and depressive).

4. Irritable Temperament: The irritable temperament was classically defined by Emil Kraepelin (9) as the lifelong combination, at the same time, of both hyperthymic and depressive temperaments. The irritable temperament is characterized by depressive mood with periods of irritability, high emotional implication in different activities, in the sense that they become very difficult to afford, impulsive, with inner tension and dysphoric restlessness, insatisfaction, unhappiness and bitter disposition, often hypercritical and complaining to others, obtrusiveness, habitually moody and bite disposition, tendency to brood, intrusive and untimely (11).

5. Anxious Temperament: It is characterized as the continuous presence of harm avoidance, dependency, shyness, inability to relax, insecurity, uncontrollable worrying about mundane matters, hypervigilance, tension and gastrointestinal distress, and irritability (10).

Statistical Analysis

In this study SPSS 11.5 (SPSS Inc., Chicago , IL, USA) statistical analysis was performed. Significance levels were evaluated in p≤0,05. Descriptive statistics data reported by percentage or mean±SD. McNemar test was used to assess the compliance categorically. The chi-square test was used in order to compare categorical variables.

RESULTS

The mean age was 60.7±8.13. From 80 COPD patients who were recruited into our study, depressive temperament was found in 18 patients (22.5%) and was the most common dominant affective temperament, followed by anxious temperament in 10 patients (12.5%). Cyclothymic temperament was found in 4 patients, hyperthymic in 4 and irritable temperament was found in 4 patients also. The majority of COPD patients (n:22) did not have any dominant temperament (27.5%). (**Table 1**). According to HADS, anxiety (n:44) was seen more than depression (n:26). (**Table 2**).

Table 1. Distribution of temperament according to the COPD groups

		COPD groups				
Temperament		**A**	**B**	**C**	**D**	**p**
Depressive	Yes	6	4	6	2	0,36
	No	14	16	14	18	
Cyclothymic	Yes	0	4	0	0	0,006*
	No	16	20	20	20	
Irritable	Yes	4	0	2	0	0,048*
	No	16	20	18	20	
Hyperthymic	Yes	2	2	0	0	0,24
	No	18	18	20	20	
Anxious	Yes	6	2	2	0	0,034*
	No	14	18	18	20	
Lack of temperament	Yes	8	12	14	18	0,010*
	No	12	8	6	2	

COPD: Chronic obstructive pulmonary disease
Mann-Whitney U test was used for statistical analysis
*p<0,05 statistically significant

Table 2. Mean values of HADS score according to COPD groups.

	COPD groups				
HADS	**A**	**B**	**C**	**D**	**p**
HAD-A	9,8±3,7	9,6±3,4	11±4,8	10,6±5,2	0,92
HAD-D	5,5±4,1	10,6±5,2	7,6±2	7,9±4,2	0,03*

HADS: Hospital Anxiety and Depression Scale, HAD-A: Hospital Anxiety and Depression- Anxiety, HAD-D: Hospital Anxiety and Depression- Depression
Chi-square test was used for statistical analysis
*p<0,05 statistically significant

When we considered the results according to groups, the number of depressive temperament in groups A, B, C, D was 6, 4, 6, 2 respectively (p=0.36). There was no statistically significant differences between groups in terms of depression. Anxious temperament seen in groups A, B, C, D was respectively 6, 2, 2, 0. That result was statistically significant (p=0.034). Fifty-two patient

hasn't got any temperament (p=0.01). Cyclothymic temperament was seen in 4 patients and all of them were from group B. That result was statistically significant (p=0.006). Irritable temperament was seen in 4 patient in group A, in 2 patient in group C and none in groups B and D. That result was statistically significant also (p=0.048). Hyperthymic temperament was seen in 2 patients in group A and 2 patients in group B. This results were not statistically significant (p=0.24). Lack of temperament was seen most in group D and C (p=0.01) (**Table 1**).

According to HADS, anxiety was seen most in group C. But the result was not statistically significant (p=0.92). Depression was seen significantly higher in group B (p=0.03). (**Table 2**).

COPD groups are also compared separately as: A and B, A and C, A and D, B and C, D and B, C and D. There is a statistically significant difference between groups A and B according to cyclothymic, irritable, and the mixed temperaments (p=0.03), between groups A and C according to cyclothymic temperament (p=0.03), between groups A and D according to cyclothymic, irritable and mixed temperaments (p=0.03) and between groups B and D according to lack of temperament (p=0.03). (**Table 3**).

Table 3. Comparison of COPD subgroups

	A-B	A-C	A-D	B-C	B-D	C-D
Depression	0.47	1.00	0.11	0.47	0.38	0.11
Cyclothymic	*0.03	*0.03	*0.03	1.00	1.00	1.00
Irritability	*0.03	0.38	*0.03	0.15	1.00	0.15
Hypertimic	1.00	0.15	0.15	0.15	0.15	1.00
Anxious	0.11	0.11	*0.009	1.00	0.15	0.15
Lack of temperament	0.21	0.06	*0.001	0.51	*0.03	0.11
Mixed temperament	*0.03	0.38	*0.03	0.15	0.15	1.00
Depression	0.47	1.00	0.11	0.47	0.38	0.11

COPD: Chronic obstructive pulmonary disease
Mann-Whitney U test was used for subgroup analysis. Significance was evaluated at the level of *p<0,05

DISCUSSION

Our study is the first one using the TEMPS-A and HADS questionnaire to compare temperament characteristics of COPD patients between groups. There are several studies related to temperament and character profiles of personality in patients with COPD. However there isn't any that using TEMPS-A and HADS between COPD groups according to new guideline.

Temperament is affected by genetic and environmental factors (12). COPD is also known to be affected by genetic, socioeconomic and environment factors too (13). Before starting to study we thought that affective temperaments especially anxiety and depression would be more frequent in the advanced stages of COPD patients than in the early stages. But the statistical results showed the opposite. In our study, we found that depression was the most common temperament in whole COPD patients. However there was no statistically significant difference in incidence between the groups according to TEMPS. Depression scores found to be significantly higher in group B according to HADS.

In general practice, there seems to be a relationship between depression and the severity of the COPD, with 25% of patients with severe COPD also having depression, 19.6% of those with mild COPD, and 17.5% of those in the control group (14). In a study of Turkey, the prevalence of depression in COPD male patients was 29.6% (15). A meta-analysis from England identified a prevalence of major depression in patients with moderate-to-severe COPD in an out-patient setting of 40% (16). Some studies reported a significant increase in the prevalence of depression, but others reported no significant differences between COPD patients and controls (17). In our study, the prevalence of depression was 22.5%, and this result is similar to other studies.

In our study anxious temperament was seen most in group A. Because of they are worrier, anxious patients applies to clinician even if they have minor complaint. Perhaps a bit of anxiety is needed, especially for early diagnosis of COPD. However, respiratory distress develops in very long time period, patients (especially does not care about the health) usually refer to clinician in the advanced stages of the disease. It can be the reason for anxiety was determined less in advanced stages of COPD.

The symptom of dyspnea, which is a major complaint of COPD patients, is accepted to be a potent stimulus for anxiety (18). Inability to perform daily activities or expected social roles may also lead them to feel anxious. In our country, Celik et al. (19) found the prevalence of anxiety to be about 44% in COPD patients. In the USA, unadjusted prevalence of anxiety was higher among those with COPD (15%) than in controls (6%) (20). In our study, the incidence of anxiety was 12.5% generally, and according to groups it was seen most in group A patients. According to HADS we didn't find any significant difference between groups. These results are similar to those of other studies.

Cyclothymic, hyperthymic and irritable temperaments were found to be less common in patients with COPD. Hyperthymic temperament was seen in only 4 patient and this was not statistically significant. Irritable temperament was seen in 6 patients, 4 from group A and 2 from group C. Cyclothymic temperament was seen in 4 patients including all in group B. So irritable and cyclothymic temperament was more frequent in the early

stages of the disease. Only a few studies investigated the role of personality in COPD. In one study, COPD patients were found to be more neurotic than healthy controls (21). The basic trait of the cyclothymic temperament is a pattern of alternation between hypomanic or irritable, and depressive subclinical moods, cognitions, and behaviors (9). Compared to the advanced stages of COPD, respiratory function and blood oxygen level is less impaired in early stages, subclinical depressive or manic mood disorder that may have resulted in the emergence of mild depression or hypomania. The irritable temperament was classically defined by Emil Kraepelin (9) as the lifelong combination, at the same time, of both hyperthymic and depressive temperaments. The irritable temperament is characterized by depressive mood with periods of irritability, high emotional implication in different activities, in the sense that they become very difficult to afford, impulsivity (11). Because of significant physical and psychosocial impairment secondary to severe dyspnea in advanced COPD, life expectancy decreases. The prevalence of cognitive impairment in patients with COPD was found to be associated with the severity of the disease (22). This may explain why irritability, mood changes like aggressiveness seen less in the advanced stages of COPD.

Similar to these results there was a positive correlation between disease severity and lack of temperament. It is possible that patients become unresponsive or too weak to give response due to perseverance in coping with the disease is reduced.

Study Limitations

This is a single-center study with a relatively small study population, both of which limit the power of our research findings. There was no control group in our study as we compared the groups among themselves and we also excluded the patients with chronic additional diseases, and therefore, our results cannot be extrapolated to all COPD patients. Further studies are required to clarify this subject.

CONCLUSION

Our study showed that in early stage of COPD, dominant affective temperaments are seen much more than advanced stages of disease. Psychological support should be given to COPD patients even though they were in early stages.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Research Ethics Committee of Kahramanmaraş Sütçü İmam University faculty of medicine University faculty of medicine (Permission granted/CAAE number: 2014/30.04, Decision no: 72).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

REFERENCES

1. Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease. GINA-2019.
2. Strelau J. Psychologia temperamentu. Warszawa: Wydawnictwo Naukowe PWN 2009.
3. Vahip S, Kesebir S, Alkan M, Yazici O, Akiskal KK, Akiskal HS. Affective temperaments in clinically-well subjects in Turkey: initial psychometric data on the TEMPS-A. J Affect Disord 2005; 85: 113–25.
4. Akiskal HS, Akiskal KK. TEMPS: Temperament evaluation of Memphis, Pisa, Paris and San Diego. J Affect Disord 2005; 85: 1–2.
5. Kurt E, Karacan I, Ozaras N, Alatas G. Affective temperament in stroke patients. J Acta Neuropsychiatrica 2008; 20: 295-9.
6. Akiskal KK, Akiskal HS. The theoretical underpinnings of affective temperaments: implications for evolutionary foundations of bipolar disorder and human nature. J Affect Disord 2005; 85: 231-9.
7. Akiskal HS, Akiskal KK. Cyclothymic, hyperthymic and depressive temperaments as subaffective variants of mood disorders. In: Tasman A, Riba MB, Eds. Annual Review, vol II. Washington, D.C.: American Psychiatric Press 1992; pp. 43-62.
8. Possl J, von Zerssen D. A case history analysis of the "manic type" and the "melancholic type" of premorbid personality in affectively ill patients. Eur Arch Psychiatry Clin Neurosci 1990; 23: 347-55.
9. Kraepelin E. Manic-depressive illness and paranoia. Edinburgh: Livingstone 1921.
10. Akiskal HS. Toward a definition of generalized anxiety disorder as an anxious temperament type. Acta Psychiatr Scand Suppl 1998; 393: 66-73.
11. Akiskal HS, Mallya G. Criteria for the "soft" bipolar spectrum: treatment implications. Psychopharmacol Bulletin 1987; 23: 68-73.
12. Gillespiea NA, Cloningerb CR, Heathc AC, Martina NG. The genetic and environmental relationship between Cloninger's dimensions of temperament and character. J Pers Individ Diff 2003; 35: 1931-46.
13. Hynninen KM, Breitve MH, Wiborg AB, Pallesen S, Nordhus IH. Psychological characteristics of patients with chronic obstructive pulmonary disease: a review. J Psychosom Res 2005; 59: 429-43.
14. Van Manen JG, Bindels PJ, Dekker FW, Jzermans CI, van der Zee J S, Schade E. Risk of depression in patients with chronic obstructive pulmonary disease and its determinants. Thorax 2002; 57: 412–6.
15. Kömürcüoğlu B, Balıoğlu M, Öztuna I, Büyükşirin M, Işık E, Kunter P. KOAH'lı erkek olgularda depresyon (Depression among male COPD patients). J Toraks 2000; 2910: 31-4.
16. Yohannes AM, Connolly MJ. Do antidepressants work in patients with chronic obstructive pulmonary disease with comorbid depression? Expert Rev. J Respir Med 2011; 5: 727-9.
17. Van Ede L, Yzermans CJ, Brouwer HJ. Prevalence of depression in patients with chronic obstructive pulmonary disease: a systematic review. J Thorax 1999; 54: 688-92.

18. Hill K, Geist R, Goldstein RS, Lacasse Y. Anxiety and depression in end-stage COPD. Eur Respir J 2008; 31: 667-77.

19. Çelik P, Esen A, Akın M. Kronik obstrüktif akciğer hastalığı olgularında depresyon. (Depression in COPD patients). J Solunum Hastalıkları 1998; 9: 25-32.

20. Eisner MD, Blanc PD, Yelin EH, et al. Influence of anxiety on health outcomes in COPD. J Thorax 2010; 65: 229-34.

21. Rutter BM. Some psychological concomitants of chronic bronchitis. Psychol Med 1977; 7: 459-64.

22. Thakur N, Blanc PD, Julian LJ, et al. COPD and cognitive impairment: the role of hypoxemia and oxygen therapy. Int J Chron Obstruct Pulmon Dis 2010; 5: 263-9.

Case Report/Olgu Sunumu

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Cardiac presentations mimicking acute coronary syndrome of a giant pheochromocytoma case

Akut koroner sendromu taklit eden dev feokromositoma olgusu

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ABSTRACT

Pheochromocytomas are benign tumors which originate from adrenal chromaffin cells. The classical triad of the pheochromocytoma includes headache, palpitations, and diaphoresis. Cardiac complications as arrhythmias, cardiomyopathy, ST elevated myocardial infarction, non-ST elevated myocardial infarction and myocardial infarction with non-obstructive coronary arteries (MINOCA) may be seen. Herein, we present a case of a 28-year-old male patient who admitted to an emergency department with chest pain and tachycardia one year ago. Coronary angiography was performed to diagnose a possible acute coronary syndrome. Urgent cardiac catheterization did not demonstrate an obstructive cardiac artery. Any intervention for revascularization was not needed. Nevertheless, the symptoms of the patient continued in the past year after this admission and he was admitted to the hospital a few times more with similar cardiac symptoms mimicking acute coronary syndrome. When the patient referred to our department, we determined that his plasma and urinary catecholamine levels were elevated. Magnetic resonance imaging (MRI) demonstrated a 167x70 mm sized heterogeneous mass including cystic components in the right adrenal gland, which pushes the right kidney towards inferior. After the pre-medication, a 170 mm in size 990-g weighted mass was successfully removed with open surgery. Histopathological findings confirmed the pheochromocytoma diagnosis. However, we presented a case of an exceptional giant pheochromocytoma mimicking acute coronary syndrome.

Keywords: Pheochromocytoma, acute coronary syndrome, giant adrenal mass

ÖZ

Feokromositomalar, adrenal kromaffin hücrelerinden kaynaklanan genellikle benign tümörlerdir. Feokromositomanın klasik triadı baş ağrısı, çarpıntı ve terlemeyi içerir. Aritmiler, kardiyomiyopati, ST segment elevasyonlu miyokard enfarktüsü, ST segment elevasyonu olmayan miyokard enfarktüsü ve obstrüktif olmayan koroner arterlerle miyokard enfarktüsü (MINOCA) gibi kardiyak komplikasyonlar görülebilir. Bir yıl önce göğüs ağrısı ve çarpıntı nedeni ile acil servise başvuran 28 yaşında erkek hastaya akut koroner sendrom ön tanısı ile koroner anjiyografi yapılmış. Koroner anjiyografide obstrüktif hastalık saptanmamış. Benzer şikayetlerinin devam etmesi üzerine tarafımıza refere edilen hastanın yapılan tetkiklerinde katekolamin düzeyleri yüksek saptandı. Manyetik rezonans görüntülemede sağ adrenal glandda 167x70 mm boyutlarında kistik heterojen kitle mevcuttu. Preoperatif medikasyon sonrasında 170 mm boyutunda ve 990 g ağırlığındaki kitle laparotomi ile başarılı bir şekilde çıkarıldı. Histopatolojik bulgular feokromositoma tanısını doğruladı. Bu bildiride genç bir hastada akut koroner sendromu taklit eden dev feokromositoma vakası sunulmaktadır.

Anahtar Kelimeler: Feokromositoma, akut koroner sendrom, dev adrenal kitle

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INTRODUCTION

Pheochromocytoma is a rare catecholamine secreting tumor which originates from adrenal chromaffin cells and affects 0.1-0.6% of hypertensive patients (1). The classical triad of the pheochromocytoma includes headache, palpitations, and diaphoresis. Cardiac complications as arrhythmias, cardiomyopathy, ST elevated myocardial infarction, non-ST elevated myocardial infarction and myocardial infarction with non-obstructive coronary arteries (MINOCA) may be seen (2). The average tumor size is approximately 4.9 cm (3). Giant pheochromocytomas are seen rarely and generally present silent, unlike the classic symptoms of catecholamine-releasing tumors. In many cases, they are incidentally discovered. The algorithm to diagnose a pheochromocytoma consists of the biochemical evaluation and imaging of a possible retroperitoneal mass (4). Herein, we presented a male patient with a giant pheochromocytoma, who manifests cardiac symptoms mimicking acute coronary syndrome before the diagnosis.

The abstract of this case report was presented as "poster presentation" in Endobridge 2019, 24-27 October 2019, Antalya, Turkey.

CASE

A 28-year old male admitted with uncontrolled hypertension, palpitations, and irritability with one year of symptom history. One year ago, he was admitted to the emergency department with chest pain and palpitation. Electrocardiogram demonstrated ST depressions in anterior derivations. Troponin I level was normal. Urgent cardiac catheterization showed slow coronary flow in the left anterior descending artery. An intervention for revascularization was not needed. Nevertheless, the symptoms of the patient continued for one more year after the first attack and he was admitted to the hospital a few times more with similar cardiac symptoms mimicking acute coronary syndrome. When the patient referred to our department, his blood pressure was 140/90 mmHg. Heart rate was 120 beats/minute and electrocardiogram showed sinus rhythm. The physical examination was normal. The patient was evaluated for a possible catecholamine-secreting tumor. We determined an elevation on 24 hours urinary catecholamine metabolites; metanephrine, 5587 µg/24 hours (50-250), normetanephrine, 9233 µg/24 hours (100-500), and dopamine, 728 µg/24 hours (65-400). Urinary adrenaline and noradrenaline levels were normal. Magnetic resonance imaging demonstrated a 167x70 mm sized heterogeneous mass including cystic components in the right adrenal gland, which pushes the right kidney to inferior (**Figure 1**). MIBG scan showed increased uptake in the right adrenal localized mass.

Four mg/day doxazosin treatment was initiated before surgery. 40 mg/day propranolol was added to achieve a much better tachycardia control. After ensuring the efficiency and tolerability of the therapy, the patient underwent to right adrenalectomy by open surgery. A 990 g weighted mass excised totally with its capsule (**Figure 2**). The histopathological evaluation confirmed pheochromocytoma. Capsule invasion was not seen and the Ki67 index was<5. The patient had an uneventful recovery period. Catecholamine levels measured 2 weeks after surgery decreased to normal. We continue to follow the patient as asymptomatic, normotensive, and with normal catecholamine levels.

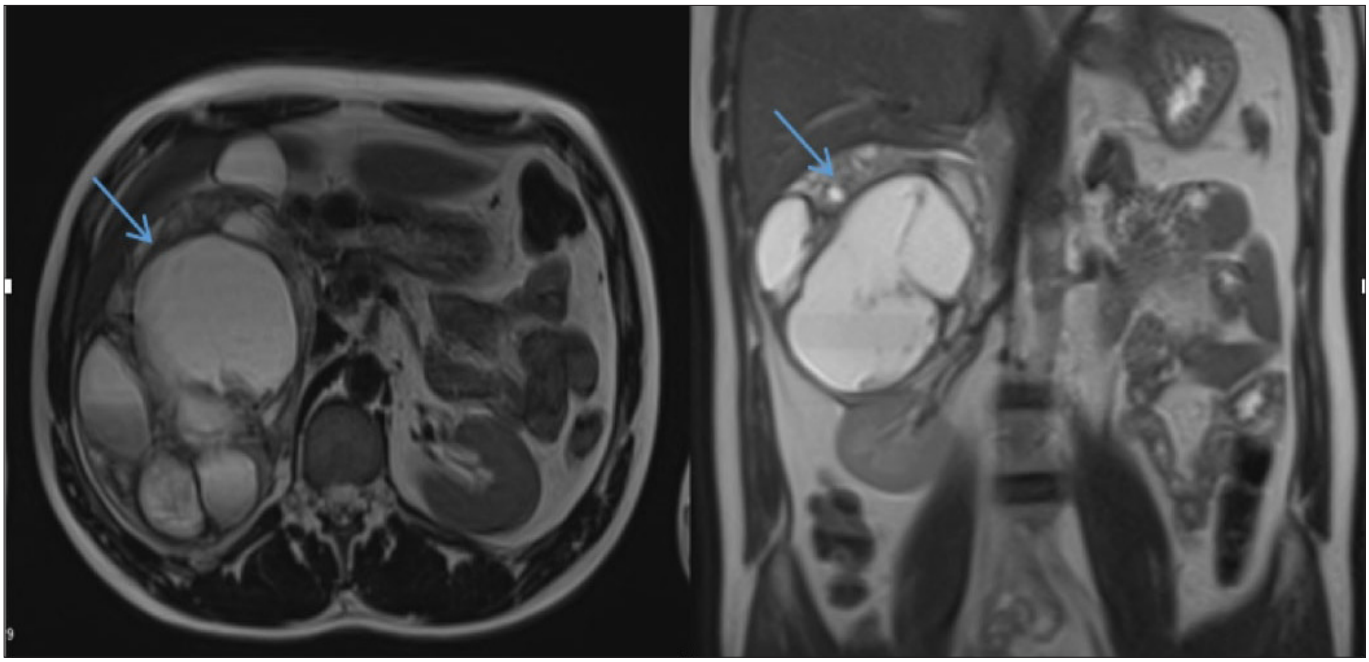

Figure 1. The heterogeneous mass 167x70 mm in sized including cystic components in the right adrenal gland

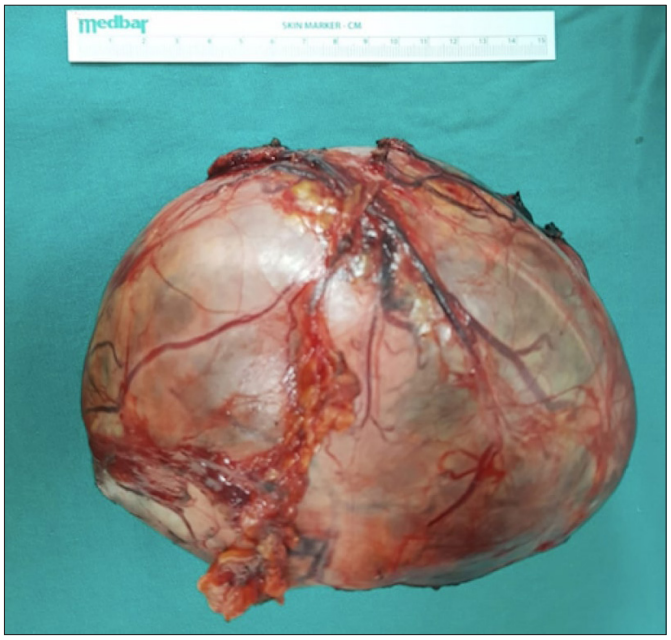

Figure 2. The macroscopic apperance of 17 cm-sized excised mass

DISCUSSION

Pheochromocytomas have rarely seen tumors originating from adrenal chromaffin cells, The estimated pheochromocytoma incidence is 0.8 per 100.000 people/ year (5). Although most of them are benign tumors, 10 % of the cases can be malign (6). They appear in 4.-5. decades and the men-women ratio are seen equal (7). While most of these tumors being sporadic, they can also be seen as a component of hereditary syndromes such as Von Hippel-Lindau, neurofibromatosis type 1, MEN 2 (8). Even though classic symptoms are palpitations, sweating, headache, with the ever-growing usage of the imaging methods, they can be incidentally determined (9). Symptoms include tremor, dyspnea, pallor, generalized weakness, and panic attack-type symptoms as well as orthostatic hypotension, visual blurring, papilledema, weight loss, polyuria, polydipsia, constipation (10). Pheochromocytoma symptoms appear based on the excessive secretion of epinephrine, norepinephrine, and dopamine. The increased central symptomatic activity of the affected patients also contributes to this situation. They also cause laboratory abnormalities such as increased erythrocyte sedimentation rate, insulin resistance, hyperglycemia, leukocytosis, psychiatric disorders, and rarely, secondary erythrocytosis due to overproduction of erythropoietin (11). Circulating high catecholamine metabolites can lead to various cardiac or metabolic problems. While electrocardiogram is usually seen normal, there can also be some pathological findings as ST elevation, T inversions, abnormal Q waves (12). Diagnosing of the pheochromocytoma is usually based on the measurements of the urinary and plasma fractionated metanephrines and catecholamines levels and is followed by the localization of the tumor with abdominal and pelvic MRI or CT (13). If tumors are in size over 10 cm, MIBG or FDG-PET may perform to see whether there are extra-adrenal, multifocal or with any metastatic illnesses (14). Although 15% of pheochromocytomas are extra-adrenal, 95% of them can be abdominal or pelvic. As the size becomes larger, the possibility of malignancy increases. For tumors over 6 cm, the ratio of the benign-malign tumor is 1:8 (15). Despite the secretion of intensive vasoactive metabolites, they can also be asymptomatic and can be detected during an autopsy (16). Extensive necrosis of the adrenal gland, decreasing the production of catecholamines, and the retention of these hormones within the capsular mass after secretion may be the explanations of why these patients are asymptomatic. These factors may lead to delayed diagnosis and late detected tumors can be seen in larger sizes (4). Following the pheochromocytoma diagnosis, all patients should do the appropriate and necessary medical preparations for the resection. In a study evaluating 312 cases of pheochromocytoma, the average tumor size was found 4.5±2.9 (17). Another study analyzing 20 pheochromocytoma cases larger than 10 cm shows that the average age of the patients was 49. In this case series, while 8 patients were asymptomatic, 4 cases presented hypertension, and only 1 case presented chest pain (6). In a recent study of 34 pheochromocytoma cases over 10 cm, the average age was 49. While 31% of the cases presented asymptomatic, 21% had hypertension and back pain, %17 had hypertension and abdominal pain (4). In the report of Korgali et al. (18) a 63-year-old male presented similar symptoms mimicking acute coronary syndrome. Coronary angiography did not show obstructive coronary artery and further examination revealed a 20x17x9 cm pheochromocytoma. According to Uysal et al. (19) 37-year-old male presented hypertension and palpable mass in left upper quadrant. Further examination revelated a 18x8x13 cm malign pheochromocytoma with liver metastasis. Soufi at al. (20) report, a 17-year female patient presented with a 21x15 cm malign pheochromocytoma with liver metastasis while having no symptoms. Our case was 28-year-old and with 167x70 mm sized tumor. Cases under the age of 30 with benign masses in these sizes are seldom in literature. This is also the youngest giant pheochromocytoma case in Turkey among the reported cases with similar sizes. Although most of the cases over 10 cm are asymptomatic, our case was admitted to emergency service with chest pain, palpitation, hypertension symptoms which mimic acute coronary syndrome. In pheochromocytoma patients, electrocardiogram abnormalities appear due to excessively secreted catecholamine levels which stimulate myocardium (21). Exogenous epinephrine and norepinephrine are also cardiotoxic based on the dosage

(22). Pheochromocytoma had a relatively high incidence of cardiovascular complications. These complications include cardiac arrhythmia, ST and non-ST elevation MI, heart failure, hypertensive urgency, TIA, stroke, and subarachnoid hemorrhage. Rarely MINOCA may be seen (2).

Troponin levels may increase mildly while electrocardiogram has seen normal in many of the cases. However, clinical presentation and electrocardiogram findings can mimic acute coronary syndrome. In cases in which pheochromocytoma mimics acute coronary syndrome, coronary angiography does not show obstructive coronary artery. In our case, the patient was admitted to emergency service with typical chest pain and anterior ST depressions were observed in the electrocardiogram. Even though the patient was young, coronary angiography was performed to exclude a possible acute coronary syndrome, but any pathological finding was not revealed in angiography.

CONCLUSION

When physicians confront patient, who have uncontrolled hypertension or unexplained heart diseases, pheochromocytoma diagnosis should be kept in mind especially in younger patients.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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

REFERENCES

1. Widimský J. Recent advances in the diagnosis and treatment of pheochromocytoma. Kidney Blood Press Res 2006; 29: 321–6.
2. Melson E, Amir S, Shepherd L, Kauser S, Freestone B, Kempegowda P. Myocardial Infarction with non-obstructed coronaries-atypical presentation of pheochromocytoma. Endocrinol Diabetes Metab Case Rep 2019; 2019.
3. Guerrero MA, Schreinemakers JMJ, Vriens MR, et al. Clinical spectrum of pheochromocytoma. J Am Coll Surg 2009; 209: 727–32.
4. Maharaj R, Parbhu S, Ramcharan W, et al. Giant cystic pheochromocytoma with low risk of malignancy: a case report and literature review. Case Rep Oncol Med 2017; 2017: 4638608.
5. Beard CM, Sheps SG, Kurland LT, Carney JA, Lie JT. Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. Mayo Clin Proc 1983; 58: 802–4.
6. Ambati D, Jana K, Domes T. Largest pheochromocytoma reported in Canada: A case study and literature review. Can Urol Assoc J 2014; 8: E374-7.
7. Reisch N, Peczkowska M, Januszewicz A, Neumann HPH. Pheochromocytoma: presentation, diagnosis and treatment. J Hypertens 2006; 24: 2331–9.
8. Goldstein RE, O'Neill JA, Holcomb GW, et al. Clinical experience over 48 years with pheochromocytoma. Ann Surg 1999; 229: 755–64.
9. Yu R, Nissen NN, Chopra P, Dhall D, Phillips E, Wei M. Diagnosis and treatment of pheochromocytoma in an academic hospital from 1997 to 2007. Am J Med 2009; 122: 85–95.
10. Bravo EL, Gifford RW. Pheochromocytoma. Endocrinol Metab Clin North Am 1993; 22: 329–41.
11. Bravo EL. Pheochromocytoma: new concepts and future trends. Kidney Int 1991; 40: 544–56.
12. Komamura K, Fukui M, Iwasaku T, Hirotani S, Masuyama T. Takotsubo cardiomyopathy: Pathophysiology, diagnosis and treatment. World J Cardiol 2014; 6: 602–9.
13. Lenders JWM, Duh Q-Y, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99: 1915–42.
14. Eisenhofer G, Rivers G, Rosas AL, Quezado Z, Manger WM, Pacak K. Adverse drug reactions in patients with phaeochromocytoma: incidence, prevention and management. Drug Saf 2007; 30: 1031–62.
15. Alexandraki KI, Grossman AB. Adrenal incidentalomas: "the rule of four." Clin Med (Lond) 2008; 8: 201–4.
16. Arnaldi G, Boscaro M. Adrenal incidentaloma. Best Pract Res Clin Endocrinol Metab 2012; 26: 405–19.
17. Ichijo T, Ueshiba H, Nawata H, Yanase T. A nationwide survey of adrenal incidentalomas in Japan: the first report of clinical and epidemiological features. Endocr J 2020; 67: 141-52. doi: 10.1507/endocrj.EJ18-0486
18. Korgali E, Dundar G, Gokce G, et al. Giant malignant pheochromocytoma with palpable rib metastases. Case Rep Urol 2014; 2014: 354687.
19. Uysal E, Kırdak T, Gürer AO, İkidağ MA. Giant multicystic malignant pheochromocytoma. Turk J Surg 2015; 33: 296–8.
20. Soufi M, Lahlou MK, Benamr S, et al. Giant malignant cystic pheochromocytoma: a case report. Indian J Surg 2012; 74: 504–6.
21. Agarwal V, Kant G, Hans N, Messerli FH. Takotsubo-like cardiomyopathy in pheochromocytoma. Int J Cardiol 2011; 153: 241–8.
22. Paulin FL, Klein GJ, Gula LJ, Skanes AC, Yee R, Krahn AD. QT prolongation and monomorphic VT caused by pheochromocytoma. J Cardiovasc Electrophysiol 2009; 20: 931–4.

Case Report/Olgu Sunumu

HEALTH SCIENCES
MEDICINE

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Unilateral low-frequency hearing loss after spinal anesthesia: a case report

Spinal anestezi sonrası tek taraflı düşük frekanslı işitme kaybı: olgu sunumu

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ABSTRACT

Spinal anesthesia is a frequently used anesthesia technique, which brings an increased risk of associated complications. Hearing loss after spinal anesthesia is rare and usually seen in low-frequency. It can occur uni- or bilaterally and have a permanent or temporary course. This study presents a case who underwent ankle arthroscopy with spinal anesthesia and had a hearing loss at the postoperative 30rd hour and discusses the results in the light of current literature.

Keywords: Hearing loss, spinal anesthesia, unilateral

ÖZ

Günümüzde spinal anestezinin yaygın olarak kullanımı komplikasyonlarındaki artışı da beraberinde getirmektedir. Spinal anestezi sonrası işitme kaybı ile nadir olarak karşılaşılmaktadır. Spinal anestezi sonrası görülen işitme kaybı, genellikle düşük frekanstaki seslerde görülmekte, tek ya da çift tarafı tutabilmekte ve kalıcı ya da geçici seyir gösterebilmektedir. Bu çalışmada ayak bileği artroskopisi nedeniyle spinal anestezi uygulanan ve postoperatif 30. saatte işitmede kaybı görülen olgu sunulmuş ve sonuçlar literatür verileri eşliğinde tartışılmıştır.

Anahtar Kelimeler: İşitme kaybı, spinal anestezi, unilateral

INTRODUCTION

Spinal anesthesia is widely preferred in infraumblical surgeries for its clinical advantages and ease of application. Hearing loss after spinal anesthesia is one of the rare complications of spinal anesthesia. However, it is now encountered more frequently than in previous years due to the increased frequency of spinal anesthesia (1). Sudden hearing loss is defined as 30 dB or more sensorineural hearing loss over at least three consequent audiometric frequencies occurring within three days or less (2). Hearing loss after spinal anesthesia is usually diagnosed only by audiological examinations without any clinical findings. However, patients can also present to health centers with the complaint of hearing loss in the postoperative period (3,4). Hearing loss after spinal anesthesia usually occurs in the low-frequency, exhibits a uni- or bilateral involvement and may follow a temporary or permanent course (5). Various studies have reported that it can be seen between the postoperative 24 hours and six days after spinal anesthesia (4). Although different approaches are used in its treatment, cases may also show spontaneous recovery (6).

Our study aimed to present the diagnosis and treatment approaches in a case with unilateral, sudden, and transient hearing loss that developed on the first postoperative day after ankle arthroscopy with spinal anesthesia.

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CASE

A 43-year-old man of 75 kg, who had no known systemic disease was planned ankle arthroscopy under spinal anesthesia. Physical examination and laboratory tests were evaluated as normal during the preanesthetic consultation. He had no history of a previous operation. He was classified with American Society of Anesthesiologists physical status I and Modified Mallampati score of II. After the patient who was planned to have spinal anesthesia was informed about the procedure, verbal and written consent was obtained. He did not receive premedication on the day of the operation. The subarachnoid space was reached at once via a midline approach at the L4-5 interspace using a 25 G Quincke spinal needle in the sitting position. After free cerebrospinal fluid (CSF) drainage was obtained, 12.5 mg (2.5 ml) of 0.5% hyperbaric bupivacaine was administered. The sensory block level was determined by the pinprick test and the operation started when it reached the T8 level. Oxygen was given with 2 L/min by nasal cannula during the operation. Hemodynamic parameters remained stable throughout the operation and the operation was completed at the 45th minute without any complications.

The patient was hospitalized for one night after the operation. We observed that spinal anesthesia completely disappeared in the postoperative fourth hour. The patient was consulted to us due to a decrease in hearing in the left ear at the postoperative 30rd hour. He had no complaints accompanying hearing loss such as nausea, dizziness, and headache, and no neurological pathology. His cranial nerve examination findings were normal. We learned that the patient had no hearing or balance problems and had not used autotoxic drugs such as aminoglycoside and diuretics before. The audiological examination revealed a normal hearing in the right ear. However, there was a mild sensorineural hearing loss, a 60 dB at 125 Hz, a 55 dB at 250 Hz, a 45 dB at 500 Hz, and a 40 dB at 1000 Hz in the left ear (**Figure 1**).

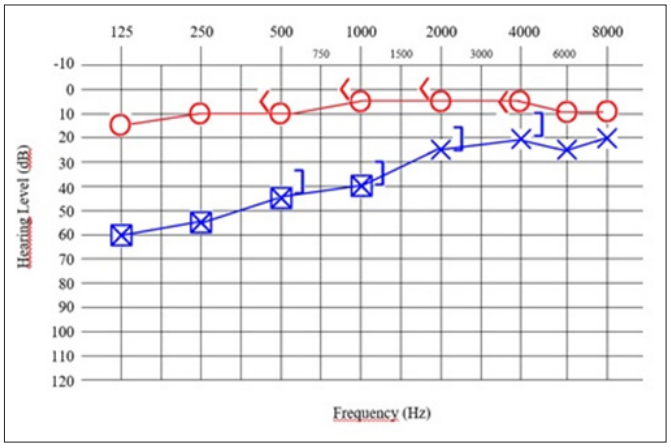

Figure 1. Audiogram on the first postoperative day after spinal anesthesia

Based on the data obtained, the patient was started on medical treatment. He received methylprednisolone 1mg/kg intravenously. When he was checked on the fifth day of the treatment, his complaints had completely disappeared and his audiological examination findings were normal (**Figure 2**). His steroid treatment was reduced and terminated on the 14th day. He had no hearing problems in his follow-up period.

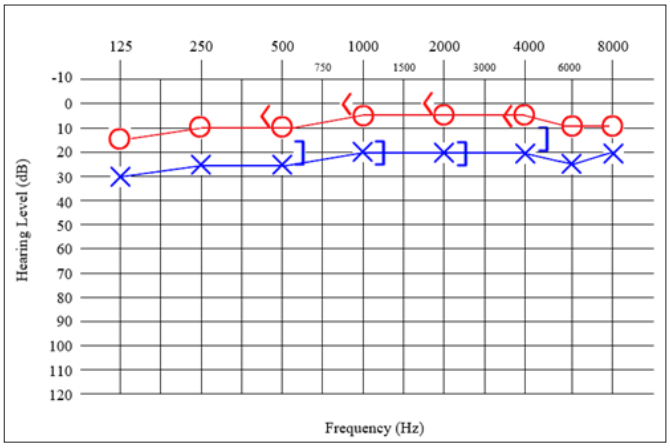

Figure 2. Audiogram on the fifth postoperative day after medical treatment

DISCUSSION

Hearing loss is one of the rare and late complications of spinal anesthesia. The first case of hearing loss after spinal anesthesia was reported by Terrien et al. (7) in 1914. The cases often have no clinical symptoms and the diagnosis is determined by hearing tests. Therefore, the incidence of hearing loss after spinal anesthesia is observed in a wide range, such as 9-93% (3). However, the incidence of patients presenting with hearing loss after spinal anesthesia has been reported as 0.2-8% (4). Although the mechanism of hearing loss due to spinal anesthesia remains uncertain, it is possible to discuss various factors. The side effects of the medications used in anesthesia may be effective in the formation mechanism. It has also been suggested that accompanying ischemic conditions or cerebrospinal fluid leakage due to dural puncture may have a role in hearing loss after spinal anesthesia (8). CSF loss as a result of dural perforation due to lumbar puncture causes a decrease in CSF pressure during spinal anesthesia. In response to CSF loss, perilymphatic fluid passes into the subarachnoid space via the cochlear aqueduct due to the close relationship between middle ear pressure and intracranial pressure, resulting in a decrease in perilymphatic pressure. The relative increase in the endolymphatic pressure observed against the decrease in the perilymphatic pressure causes endolymphatic hydrops. Endolymphatic hydrops leads to displacement in hairy cells in the basilar membrane, resulting in a low-frequency hearing loss (7,8). Hearing loss after spinal anesthesia can be uni- or bilateral and

may follow a permanent or temporary course. Studies have indicated that hearing loss can be seen between the postoperative 24 hours and six days (4). In our case, the hearing loss occurred on the first postoperative day, and a normal hearing was observed on the fifth day of follow-up and treatment.

The type and diameter of the needles used in spinal anesthesia are also effective factors in the mechanism of hearing loss due to CSF drainage. Several studies have shown that the use of spinal needles of a large diameter, such as 22 G, results in a higher incidence of hearing loss than that of spinal needles of a smaller diameter, such as 25 G (3). Erol et al. (9) stated that the incidence of hearing loss was higher after the use of sharp needles than pencil point needles. We encountered a transient low-frequency hearing loss in our case after using a sharp-tip spinal needle of 25 G. However, in a study where the spinal needles were of the same diameter and type, the frequency of hearing loss after spinal anesthesia was higher in patients under the age of 30 compared to those over the age of 60 (10). On the other hand Ok et al. (11) stated that patients between 20 to 40 years of age did not have hearing loss after spinal anesthesia.

It is thought that anesthetic agents used also cause hearing loss after spinal anesthesia. A study showed that the use of prilocaine in spinal anesthesia causes hearing loss more frequently than the use of bupivacaine (12). Middle ear pathologies, the use of nonsteroidal anti-inflammatory drugs, diuretics, aminoglycosides, and antineoplastics are also included in the etiology of sudden hearing loss. Hearing loss that develops depending on the duration, dosage and rate of use of these ototoxic drugs often occurs in the high frequencies (4). In our case, hearing loss was observed at low frequencies and there was no known middle ear pathology in the preoperative or ototoxic drug use in the perioperative period.

There is currently no clear consensus algorithm in the treatment of hearing loss after spinal anesthesia. While some clinicians prefer spontaneous recovery without treatment, others emphasize the necessity of treatment (6). There are treatment options such as maintaining the supine position, hydration, intravenous colloid, use of cochlear vasodilator, systemic steroids, or betahistine, hyperbaric oxygen therapy and epidural blood patch (6,13). Although there are different treatment protocols in the literature, the only treatment accepted by everyone is the administration of steroids, which causes a decrease in the endolymphatic pressure and has an anti-inflammatory effect (14). In our study, the patient was diagnosed and started to receive an intravenous steroid treatment on the first postoperative day. When his hearing functions improved on the fifth day of the treatment, his steroid treatment was reduced and terminated, and he was discharged with healing.

CONCLUSION

Hearing loss after spinal anesthesia is rare; however, as spinal anesthesia becomes more widespread due to its advantages, its complications will increase. It is important to use appropriate equipment, take the necessary precautions and preparations, and inform the surgeon and the patient about possible complications to minimize the complications.

ETHICAL DECLARATIONS

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

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

REFERENCES

1. Cosar A, Yetiser S, Sizlan A, Yanarates O, Yildirim A. Hearing impairment associated with spinal anesthesia. Acta Otolaryngol 2004; 124: 1159-64.
2. Sara SA, Teh BM, Friedland P. Bilateral sudden sensorineural hearing loss: review. J Laryngol Otol 2014; 128: 8-15.
3. Malhotra SK, Joshi M, Grover S. Auditory function following spinal analgesia. Comparison of two spinal needles. Eur J Anesth 2002; 19: 69-72.
4. Sprung J, Bourke DL, Contreras MG, Warner ME, Findlay J. Perioperative hearing impairment. Anesthesiology 2003; 98: 241-57.
5. Schaffartzik W, Hirsch J, Frickmann F, Kuhly P, Ernst A. Hearing loss after spinal and general anesthesia: a comparative study. Anesth Analg 2000; 91: 1466-72.
6. Kilickan L, Gürkan Y, Ozkarakas H. Permanent sensorineural hearing loss following spinal anesthesia. Acta Anaesthesiologica Scandinavica 2002; 46: 1155–7.
7. Vilhena D, Pereira L, Duarte D, Oliveira N. Sudden sensorineural hearing loss after orthopedic surgery under combined spinal and epidural anesthesia. Case Rep Otolaryngol 2016; 2016: 4295601.
8. Michel O, Brusis T. Hearing loss as a sequel of lumbar puncture. Ann Otol Rhinol Laryngol 1992; 101: 390-4.
9. Erol A, Topal A, Arbag H, Kilicaslan A, Reisli R, Otelcioglu S. Auditory function after spinal anaesthesia: the effect of differently designed spinal needles. Eur J Anaesthesiol 2009; 26: 416-20.
10. Gültekin S, Ozcan S. Does hearing loss after spinal anesthesia differ between young and elderly patients? Anesth Analg 2002; 94: 1318-20.

11. Ok G, Tok D, Erbuyun K, Aslan A, Tekin I. Hearing loss does not occur in young patients undergoing spinal anesthesia. Reg Anesth Pain Med 2004; 29: 430-3.

12. Gültekin S, Yilmaz N, Ceyhan A, Karamustafa I, Kiliç R, Unal N. The effect of different anaesthetic agents in hearing loss following spinal anaesthesia. Eur J Anaesthesiol 1998; 15: 61-3.

13. Yildiz TS, Solak M, Iseri M, Karaca B, Toker K. Hearing loss after spinal anesthesia: the effect of different infusion solutions. Otolaryngology Head and Neck Surgery 2007; 137; 79-82.

14. Tezer MS, Baran Y, Erdur Ö, Ata N, Arslanhan M. Comparison of systemic, ıntratympanic and combination therapy of the steroids for the treatment of sudden sensorineural hearing loss. Turkiye Klinikleri J Med Sci 2013; 33: 353-9.

Case Report/Olgu Sunumu

HEALTH SCIENCES
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A case of multisystem sarcoidosis on 18F-FDG PET/CT

F18-FDG PET/BT'de multisistem sarkoidozlu bir olgu

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ABSTRACT

We described a 67-year-old woman with uncommon distribution of multisystem sarcoidosis to disseminated lymph node, lung, liver and sinonasal region on 18F-FDG PET/CT imaging, which showed confounding scintigraphic features of mimicking widespread malignancy due to high metabolic uptake. The present case emphasizes the importance of whole-body assessment by PET/CT in multisystem sarcoidosis associated with rare sinonasal involvement and also the selection of the biopsy site by PET-guidance.

Keywords: Sinonasal sarcoidosis, extrapulmonary sarcoidosis, 18F-FDG PET/CT

ÖZ

18F-FDG PET/BT görüntülemede multisistem sarkoidozun yaygın olmayan lenf nodu, akciğer, karaciğer ve sinonazal bölgeye dağılımı olan ve yüksek metabolik tutulum nedeniyle yaygın maligniteyi taklit eden karıştırıcı sintigrafik özellikler gösteren 67 yaşında bir kadın tanımladık. Bu vaka, nadir sinonazal tutulumla ilişkili multisistem sarkoidozda PET/BT ile tüm vücut değerlendirmesinin ve PET kılavuzluğunda biyopsi yerinin seçilmesinin önemini vurgulamaktadır.

Anahtar Kelimeler: Sinonazal sarkoidoz, ekstrapulmoner sarkoidoz, F18-FDG PET/BT

INTRODUCTION

Sarcoidosis, a chronic inflammatory disease of unknown etiology, characterized by noncaseating granulomas, most commonly affects pulmonary and mediastinal involvement (1-5). Extrapulmonary sarcoidosis is seen in 25-50 % of cases, usually associated with thoracic involvement (1). Extrapulmonary sarcoidosis can be involved multiple organ systems, such as the peripheral lymph nodes, liver, spleen, bones, heart, kidneys, skin, eyes, muscles and central nervous system (2-7).

18F-FDG PET is a non-invasive diagnostic imaging technique widely used in oncological clinical practice, and also provides a valuable assessment of infectious and inflammatory diseases (1-5). Sarcoidosis may exhibit characteristic thoracic PET findings related to its predominant pulmonary and mediastinal involvement (1-5). Disseminated lymph node and extrathoracic lesions may mimic widespread high metabolic metastases or diffuse lymphomatous disease on 18F-FDG PET imaging (4-7). This case report illustrates an example of uncommon distribution of multisystem sarcoidosis to disseminated lymph node, lung, liver and sinonasal region on 18F-FDG PET/CT imaging, which showed confounding scintigraphic features of mimicking widespread malignancy due to high metabolic uptake.

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CASE REPORT

A 67-year-old woman without a significant medical history, non-smoker admitted with fatigue and dyspnea. Physical examination and initial laboratory results were unremarkable. Abdominal CT revealed hypodense lesion in the left lobe of liver and wall thickening in the caecum localization. However, no malignancies were determined by colonoscopy. Chest CT showed bilateral multiple pulmonary nodules, and enlarged mediastinal and hilar adenopathy, prompting referral for PET/CT to assess for malignancy of unknown origin. PET imaging revealed widespread foci of intense 18F-FDG uptake in multiple lymph nodes, lung, liver, and sinonasal region (**Figure 1**). No primary malignancy was identified, findings were interpreted as highly concerning for granulomatous disease, and recommended transbronchial or inguinal lymph node biopsy for differential diagnosis from malignancy. Histopathological examination of excisional biopsies from the right inguinal lymph node led to a diagnosis of nonnecrotizing granuloma with asteroid body which is highly suggestive of sarcoidosis (**Figure 2**). The patient was started on a regimen of systemic steroids.

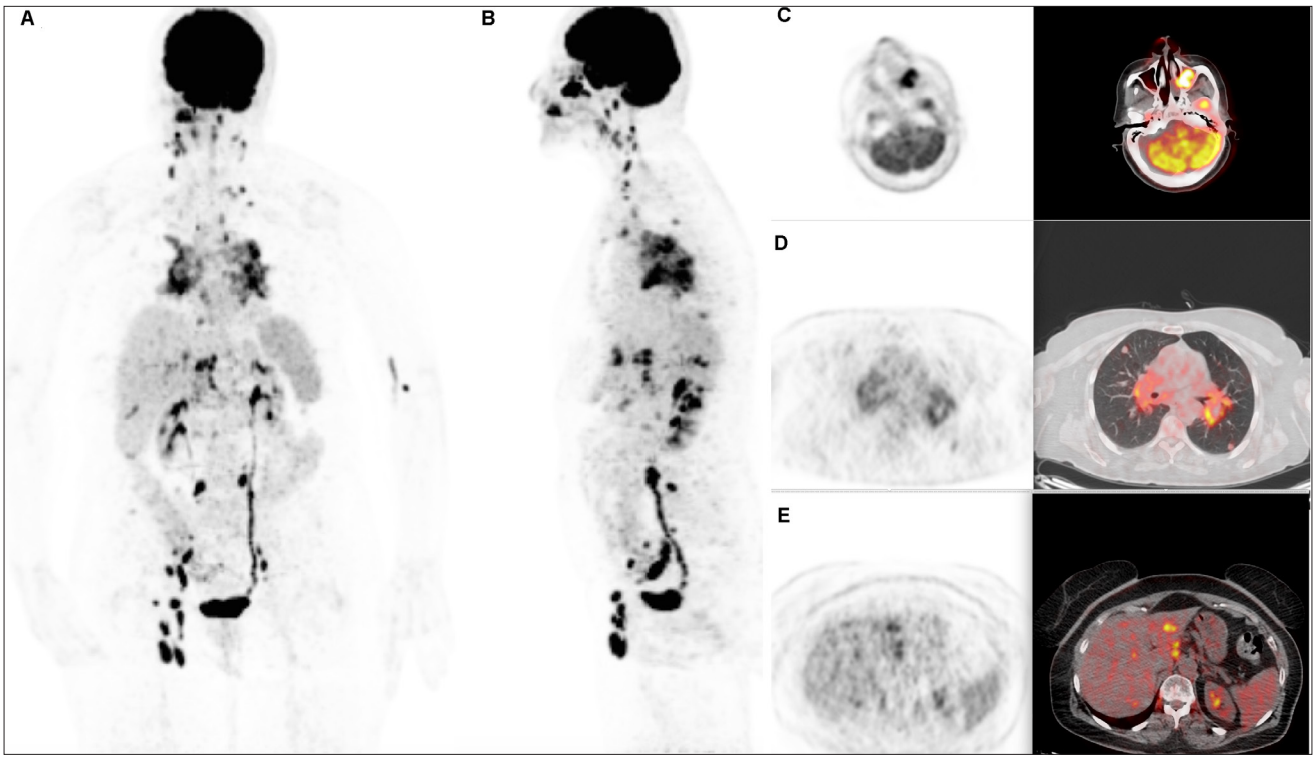

Figure 1. Maximum intensity projection anterior (A) and lateral (B), transaxial PET and fusion PET/CT (C-E) images revealed widespread foci of high 18F-FDG uptake in multiple lymph nodes including bilateral cervical, supraclavicular, mediastinal, hilar, abdominal and right inguinal nodes (largest was 2.0 cm in diameter with SUVmax=18.5), in left maxillary sinus and left nasal concha (SUVmax=31.4); in numerous peribronchovascular region (SUVmax=11.8) and parenchymal nodules in both lungs, in the liver (SUVmax=11.7). No primary malignancy was identified.

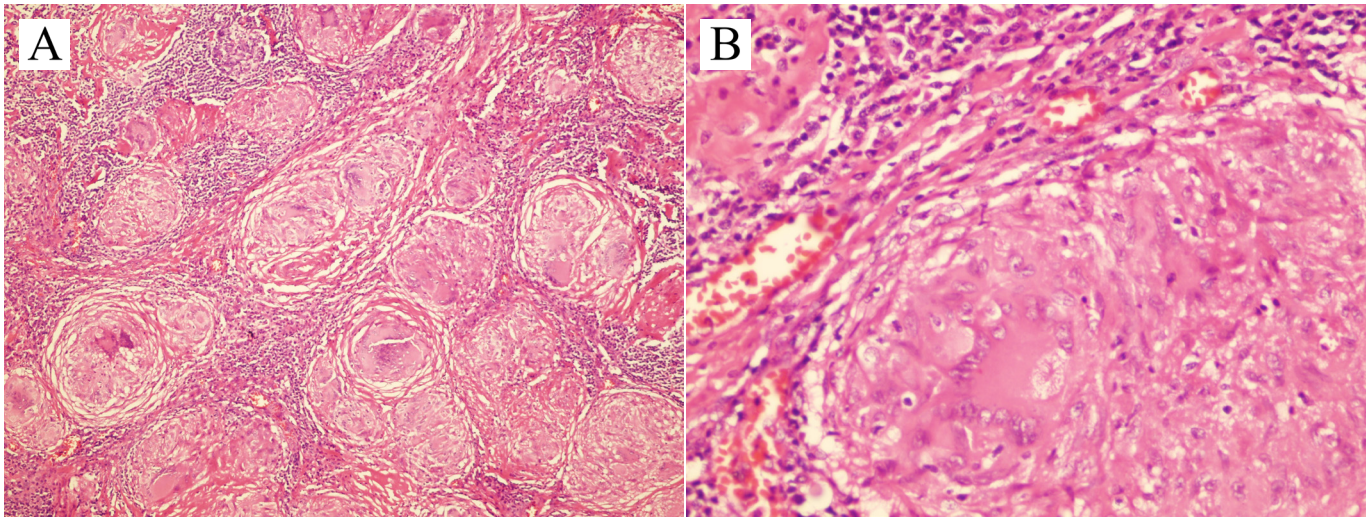

Figure 2. (A) Hematoxylin-eosin stain (original magnification × 100): Nodal effacement by numerous well-defined, small nonnecrotizing granulomas composed of epithelioid cells with Langhans giant cells and lymphocytes. (B) Hematoxylin-eosin (original magnification × 400): Star-like asteroid body within giant cell not specific but compatible with sarcoidosis.

DISCUSSION

18F-FDG PET/CT can significantly contribute to the management of multisystem sarcoidosis because it can detect active inflammatory granulomatous disease (1-3). 18F-FDG PET/CT can increase the accuracy of the diagnosis of extrathoracic involvement due to whole-body functional mapping of active inflammatory sites (4). However, active sarcoidosis lesions are known to be hypermetabolic like malignancies on 18F-FDG PET/CT, and may cause to misinterpretation on imaging (5-7). Malignancies can not be ruled out based on hypermetabolic lesions; therefore, a biopsy was required to confirm the diagnosis. 18F-FDG PET/CT may guide the selection of the biopsy site.

Extrathoracic sarcoidosis is most often associated with thoracic involvement (1-3). Detecting extrathoracic lesions is sometimes difficult by physical examination, standard thoracic radiography or CT. 18F-FDG PET/CT may be helpful in patients with sarcoidosis for determining the intrathoracic and extrathoracic extensity of disease, detecting active disease and accessing the response to treatment (2-4). In the current case, thoracic involvement and also extrathoracic disseminated lymph node, liver and sinonasal involvement was successfully revealed by 18F-FDG PET/CT imaging. The most common extrathoracic involvement was reported the abdomen, which includes liver, spleen, biliary tree, peritoneum, and lymphatic sarcoidosis (2-7). Hepatic involvement is encountered in 50-80% of cases in autopsy specimens (3). Hepatic involvement usually asymptomatic until advanced stage of the disease, is characterized by enlargement, mottled pattern of FDG accumulation, or scattered small nodular granulomatous lesions on cross-sectional imaging (1-8). This may be associated with an enlargement of abdominal lymph nodes close to the liver hilus or in celiac regions, as in our case.

Sinonasal involvement in sarcoidosis is uncommon, account for less than 5% of cases, and is usually seen with advanced stage of the disease (9). Involvement of sinonasal mucosa could be isolated, or a part of multisystem involvement. Sinonasal involvement is most likely underdiagnosed type of sarcoidosis because it is usuallly occult lesion. Even if a biopsy is required to confirm sarcoidosis, PET/CT imaging may play an important role in diagnosis and treatment follow-up (9). Unfortunately, biopsy can not be performed on newly detected sinonasal areas due to technical and ethical reasons. The changes in FDG uptake intensity on 18F-FDG PET/CT may reflect the effectiveness of medical treatment and provide a change in therapeutic strategy.

The present case emphasizes the importance of whole-body assessment by 18F-FDG PET/CT in multisystem sarcoidosis associated with rare sinonasal involvement and also the selection of the biopsy site by PET-guidance. In addition, PET/CT provides prognostic information and guides the therapeutic management.

ETHICAL CONSIDERATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Soussan M, Augier A, Brillet PY, Weinmann P, Valeyre D. Functional imaging in extrapulmonary sarcoidosis: FDG-PET/CT and MR features. Clin Nucl Med 2014; 39: 146-59.
2. Braun JJ, Kessler R, Constantinesco A, Imperiale A. 18F-FDG PET/CT in sarcoidosis management: review and report of 20 cases. Eur J Nucl Med Mol Imaging 2008; 35: 1537-43.
3. Rubini G, Cappabianca S, Altini C, Notaristefano A, Fanelli M, Stabile Ianora AA, Niccoli Asabella A, Rotondo A. Current clinical use of 18FDG-PET/CT in patients with thoracic and systemic sarcoidosis Radiol Med 2014; 119: 64-74.
4. Makis W, Palayew M, Rush C, Probst S. Disseminated Multisystem Sarcoidosis Mimicking Metastases on 18F-FDG PET/CT Mol Imaging Radionucl Ther 2018; 27: 91-5.
5. Nguyen BD. F-18 FDG PET imaging of disseminated sarcoidosis. Clin Nucl Med 2007; 32: 53-4.
6. Palmucci S, Torrisi SE, Caltabiano DC, et al. Clinical and radiological features of extra-pulmonary sarcoidosis: a pictorial essay. Insights Imaging 2016; 7: 571-87.
7. Mapelli P, Mangili G, Picchio M, et al. Sarcoidosis mimicking metastatic gynaecological malignancies: a diagnostic and therapeutic challenge?. Rev Esp Med Nucl Imagen Mol 2013; 32: 314-7.
8. Yonenaga Y, Kushıhata F, Inoue H, et al. Sarcoidosis manifesting as hepatic and splenic nodules mimicking ovarian cancer metastases: A case report. Oncol Lett 2015; 10: 2166-70.
9. Braun JJ, Imperiale A, Riehm S, Veillon F. Imaging in sinonasal sarcoidosis: CT, MRI, 67Gallium scintigraphy and 18F-FDG PET/CT features. J Neuroradiol 2010; 37: 172-81.

Case Report/Olgu Sunumu

HEALTH SCIENCES
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Skin rashes in COVID-19: a report of three cases

COVID-19'da deri döküntüleri: üç olgu sunumu

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ABSTRACT

The novel coronavirus disease (COVID-19) that emerged in Wuhan, China in December 2019 quickly escalated to a global pandemic. Several studies have described its typical clinical manifestations, including fever, cough, diarrhea, and fatigue. In this article, we wanted to draw attention to the cutaneous findings associated with COVID-19, to reveal the place of skin findings in the diagnosis of the disease, and to pioneer research on the subject. We examined the skin findings of 3 patients (3 female). None had additional disease. Cutaneous findings included urticarial lesions in 1 patient, vesicular lesions on the oral mucosa in 2 patients. Cutaneous rashes in COVID-19 are primarily non-specific and similar to cutaneous involvement seen in common viral infections. Therefore, dermatologists' differential diagnosis during the Covid-19 outbreak should include Covid-19. Thus, the awareness of dermatologists in the COVID-19 pandemic will increase and it will be provided to avoid delayed or misdiagnosis.

Keywords: COVID-19, skin changes, urticaria, enanthema, virus

ÖZ

Aralık 2019'da Çin'in Wuhan şehrinde ortaya çıkan yeni koronavirüs hastalığı (COVID-19) hızla küresel bir pandemiye dönüştü. Bazı çalışmalarda ateş, öksürük, ishal ve yorgunluk gibi tipik klinik bulgular tanımlanmıştır. Biz bu makalede COVID-19 ile ilişkili kutanöz bulgulara dikkat çekmek, hastalığın tanısında deri bulgularının yerini ortaya koymak ve konuyla ilgili yapılacak araştırmalara öncülük etmek istedik. Üç hastanın (3 kadın) cilt bulgularını inceledik. Hiçbirinde ek hastalık yoktu. Kutanöz bulgular arasında 1 hastada ürtikeryal lezyonlar, 2 hastada oral mukozada veziküler lezyonlar vardı. COVID-19'daki deri döküntüleri spesifik değildi ve yaygın viral enfeksiyonlarda görülen deri bulgularına benzemekteydi. Bu nedenle, dermatologların Covid-19 salgını sırasındaki ayırıcı tanıları Covid-19'u da içermelidir. Böylece dermatologların COVID-19 pandemisinde ki farkındalıkları artarak gecikmiş veya yanlış tanıdan uzaklaşmaları sağlanacaktır.

Anahtar Kelimeler: COVID-19, cilt değişiklikleri, ürtiker, enantem, virüs

INTRODUCTION

In December 2019, an unexplained outbreak of severe pneumonia occurred in China (1). Suspicion of COVID-19 is based primarily on clinical signs (fever, fatigue, dry cough, anorexia, dyspnea, rhinorrhea, ageusia, anosmia, etc.) and radiology findings. Diagnosis is confirmed by detecting the virus in nasopharyngeal and oropharyngeal swab samples (1). Here, we report the cutaneous manifestations of 3 patients with confirmed diagnosis of COVID-19.

We reviewed electronic medical records, nursing records, laboratory findings, and radiologic examinations for all patients with SARS-CoV-2 infection and collected data on their age, sex, comorbidities (hypertension, diabetes, cardiac or cerebrovascular disease, malignancy, and chronic kidney disease), and typical symptoms from onset to hospital admission (fever, cough, anorexia, diarrhea, throat pain, abdominal pain). All laboratory testing and chest CT were performed according to the clinical care needs of the patient. Visits were made directly or indirectly (due to the high risk of contagion) to collect the patient's history and obtain photographs when possible. Images taken of inpatients'lesions were evaluated remotely using a mobile communication application (WhatsApp).

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CASE REPORTS

Case 1:

A 34-year-old woman with no history of urticaria and or angioedema presented with pruritic erythematous plaques on her face and upper body as well as edema of the lips and eyelids (**Figure 1**). She reported that her edematous rash had started 2 days earlier, followed by dry cough without fever. Her Covid-19 test result was negative but she had radiological findings. Dermatology consultation was requested and the diagnosis of acute urticaria and angioedema was confirmed by a dermatologist. Only antihistaminic therapy was initiated because of the risk of systemic corticosteroids and other immunosuppressants in the infectious process.

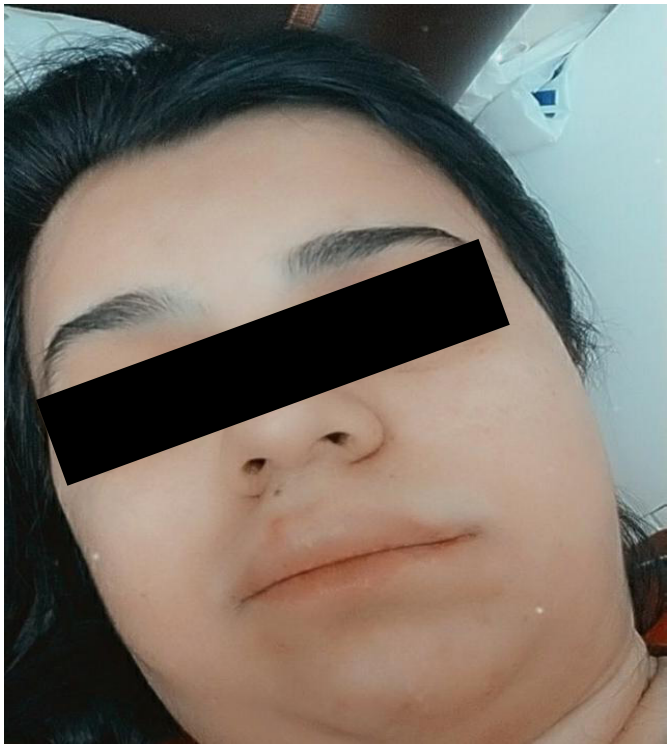

Figure 1. Erythematous plaques on face and upper body as well as edema of the lips and eyelids.

Case 2:

A 12-year-old girl was admitted to the emergency department with fever, cough, and shortness of breath. She tested positive for COVID-19. Dermatology consultation was requested for the patient based on images sent via WhatsApp. There was a stretched vesicle on the lower lip mucosa (**Figure 2**). She was hospitalized due to respiratory distress. We also recommended she use antiseptic and analgesic mouthwashes.

Case 3:

A 43-year-old female healthcare worker suffered from severe dry cough without shortness of breath, arthralgia, myalgia, sore throat, chills, flu-like symptoms, and weakness. Mouth sores appeared at approximately the same time as the onset of these symptoms. She had both intact and ruptured vesicles in the oral mucosa. Her nasopharyngeal and oropharyngeal swab test was positive for COVID-19, while other common viral panels were negative (**Figure 3**). Treatment with oral hydroxychloroquine 400 mg/day and azithromycin 500 mg/day was initiated and home isolation was recommended. We also suggested antiseptic and analgesic mouthwash and intensive hydration for her mouth sores.

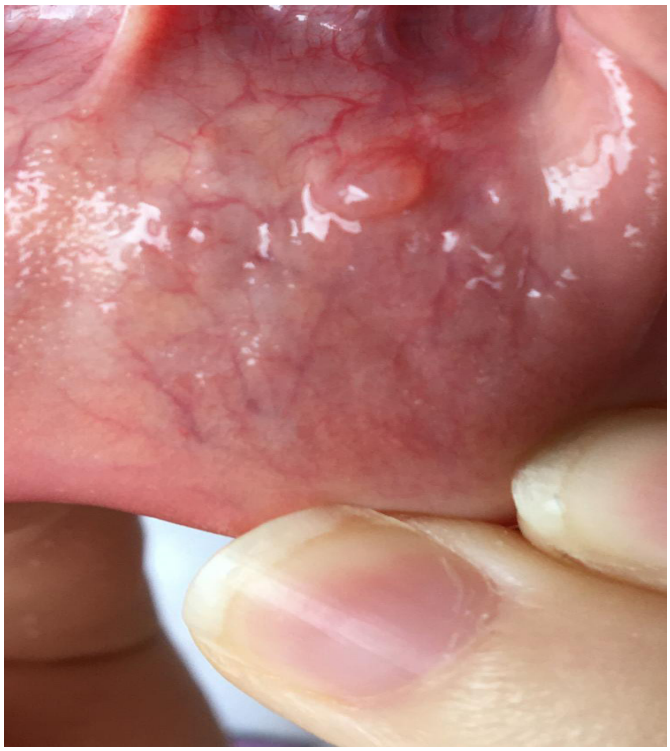

Figure 2. A stretched vesicle on the lip mucosa.

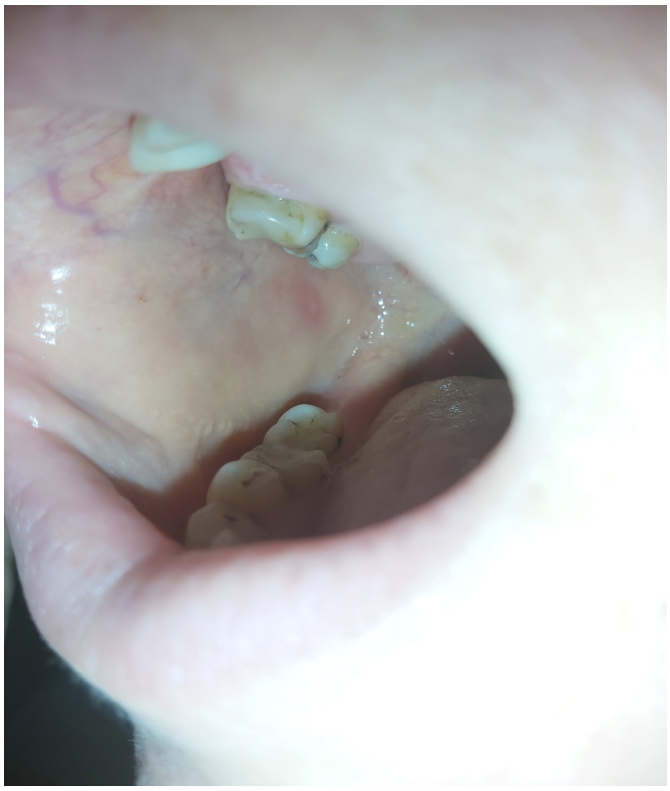

Figure 3. An opened vesicle on the oral mucosa.

DISCUSSION

It is possible for COVID-19 patients to initially present with a skin rash that may be misdiagnosed as another disease. Drug reactions, urticaria and enanthema are among its clinical manifestations (2). Erythematous rashes similar to drug reactions were observed in a report, suggesting that dermatologists must also consider COVID-19 in the differential diagnosis of cutaneous drug reactions (3).

In a report, cutaneous findings were observed during COVID-19 infection in 52 of the patients. Urticarial lesion rates were reported as 13.5% and also enanthema and apthous stomatitis were 5.8% (4).

A report from Spain presented a 32-year-old woman who had extensive urticariform rash with COVID-19 (5). In another report, a 64 year old female patient was admitted to hospital with difficult breathing, fever and cough. She was diagnosed as COVID-19 and treated with hydroxychloroquine, azithromycine and oseltamivir. During the course of the disease, she had severe urticarial reactions. It was difficult to detect whether the rash was due to the drug or viremia (2). Unlike the previous article; erythematous plaques eruption with particular face and acral involvement were started before fever or any respiratory symptom. So it is essential to take into account and promote the potential recognition among clinicians of this possible skin manifestation of covid-19, and lead to think about testing COVID-19 in these cases (6). In our case, her edematous rash had started 2 days earlier, followed by dry cough without fever. Also she had no history of drug use.

Carreras-Presas et al. (7) published a paper presenting three case reports describing oral mucosa vesiculobullous lesions developed by COVID-19 positive or suspected to be positive patients.

CONCLUSSION

The COVID-19 patients who presented with skin findings in our study had mild clinical courses. We think it depends on the absence of additional pathologie and their younger age. Nonetheless, clinicians should be aware of these skin symptoms to optimize COVID-19 detection.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerg Microbes Infect 2020; 9: 687-90.
2. Aktaş H, Hamidi AA. Urticaria in a patient with COVID-19: Therapeutic and diagnostic difficulties [published online ahead of print, 2020 May 17]. Dermatol Ther 2020; e13610. doi:10.1111/dth.13610.
3. Mahé A, Birckel E, Krieger S, Merklen C, Bottlaender L. A distinctive skin rash associated with coronavirus disease 2019?. J Eur Acad Dermatol Venereol 2020; 34: e246-e247. doi:10.1111/jdv.16471
4. Askin O, Altunkalem RN, Altinisik DD, Uzuncakmak TK, Tursen U, Kutlubay Z. Cutaneous manifestations in hospitalized patients diagnosed as COVID-19 [published online ahead of print, 2020 Jun 24]. Dermatol Ther 2020; e13896. doi:10.1111/dth.13896.
5. Fernandez-Nieto D, Ortega-Quijano D, Segurado-Miravalles G, Pindado-Ortega C, Prieto-Barrios M, Jimenez-Cauhe J. Comment on: Cutaneous manifestations in COVID-19: a first perspective. Safety concerns of clinical images and skin biopsies. J Eur Acad Dermatol Venereol 2020; 34: e252-e254. doi:10.1111/jdv.16470
6. Henry D, Ackerman M,, Sancelme E,. Finon A, Esteve E. Urticarial Eruption in COVID-19 Infection. J Eur Acad Dermatol Venereol 2020; 34: 244-5. doi:10.1111/jdv.16472.
7. Martín Carreras-Presas C, Amaro Sánchez J, López-Sánchez AF, Jané-Salas E, Somacarrera Pérez ML. Oral vesiculobullous lesions associated with SARS-CoV-2 infection [published online ahead of print, 2020 May 5]. Oral Dis 2020; 10.1111/odi.13382. doi:10.1111/odi.13382.
8. Martín Carreras-Presas C, Amaro Sánchez J, López-Sánchez AF, Jané-Salas E, Somacarrera Pérez ML. Oral vesiculobullous lesions associated with SARS-CoV-2 infection. Oral Dis 2020; 10.1111/odi.13382. doi:10.1111/odi.13382

Case Report/Olgu Sunumu

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An extremely rare gastric lesion: gastritis cystica profunda

Oldukça nadir bir gastrik lezyon: gastritis cystica profunda

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ABSTRACT

Gastritis cystica profunda (GCP) is an uncommon, benign lesion which looking a cancer-like lesion. This lesion is localized in gastric mucosa and characterized by polypoid hyperplasia or ulcerated mucosal lesion and cystic dilatation of the mucosal glands spreading into the submucosa of the stomach. Exact etiology and pathogenesis of GCP is still incompletely explained. In this case report we present a case of 70-year-old female with proton pump inhibitor resistant upper gastrointestinal symptoms who was diagnosed as GCP after upper gastrointestinal system endoscopy examination. This rare benign entity should be kept in mind in the differential diagnosis of gastric mural mass lesions.

Keywords: Gastric lesion, endoscopy, cancer, gastritis cystica profunda

ÖZ

Gastritis cystica profunda (GCP), kansere benzer bir görünüme sahip nadir, iyi huylu bir lezyondur. Bu lezyon mide mukozasında lokalizedir ve polipoid hiperplazi veya ülsere mukozal lezyon ve midenin submukozasına yayılan mukozal bezlerin kistik dilatasyonu ile karakterizedir. GCP'nin kesin etiyolojisi ve patogenezi hala tam olarak açıklanamamıştır. Bu olgu sunumunda, üst gastrointestinal sistem endoskopi incelemesi sonrası GCP tanısı alan, proton pompa inhibitörüne dirençli üst gastrointestinal semptomları olan 70 yaşında bir kadın olguyu sunuyoruz. Nadir görülen bu benign antite, gastrik mural kitle lezyonlarının ayırıcı tanısında akılda tutulmalıdır.

Anahtar kelimeler: Gastrik lezyon, endoskopi, kanser, gastritis cystica profunda

INTRODUCTION

Gastritis cystica profunda (GCP) is an uncommon, benign gastric submucosal pathology characterized by polypoid hyperplasia and cystic dilatation of the gastric glands spreading into the submucosa of the stomach. Accurate diagnosis of this lesion can be confused with some other common stomach diseases (1,2). Silent clinical symptoms and nonspesific endoscopic and radiographic appearance of this tumor mimic that of other hyperproliferative conditions making diagnosis difficult (3). Herein we report a very rare case of gastritis cystica profunda which we had presumed as a gastric cancer and emphasize the differential diagnosis of this rare entity.

CASE REPORT

A 70-year-old woman was referred to our outpatient clinic with the complaints of abdominal fullness, heartburn, nausea and belching regardless of proton pump inhibitor drugs (PPIs) for the last three months. She had only a past history of hypertension however she had never used tobacco or alcohol. Her family history was negative for gastric pathologies including gastric cancer. Her detailed physical examination revealed no pathological findings. Whole blood, routine blood and stool blood test showed no abnormalities. Because of ongoing dyspeptic symptoms she underwent upper gastrointestinal endoscopy. During upper gastrointestinal system endoscopy, it was noticed that there were nodular lesion at greater curvature of the antrum with an irregular

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depressed centre and a slightly elevated margin and focal flat elevated lesion at anterior wall of the corpus. The lesion had an intriguing appearance and also, she had PPIs resistant dyspepsia. Thus, our prediagnosis was as an early gastric cancer. Multiple biopsies were obtained by the senior endoscopist and no mucosal hemorrhage was occured. Pathological findings were polypoid cystic ectasia of the submucosal layer with cystic dilatation of the glandular structures without mitoses or atypia (**Figure**). Finally, 'gastritis cystica profunda'was the pathological diagnosis. She was not undergoing a surgical operation, and outpatient follow up is ongoing with PPI use.

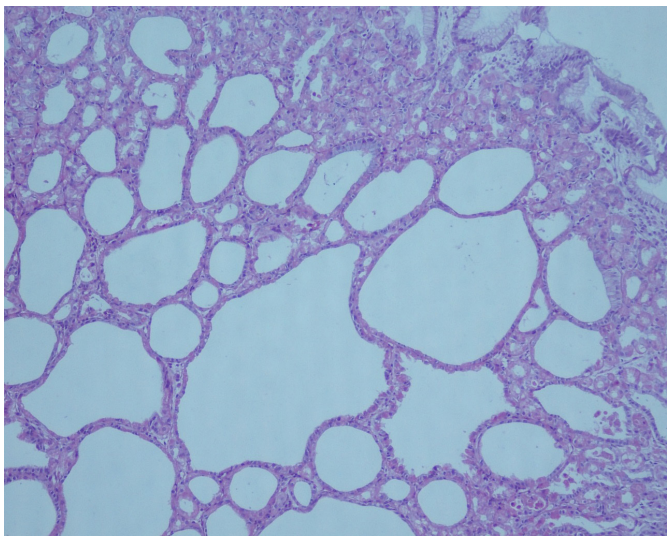

Figure. Polypoid cystic ectasia of the submucosal layer with cystic dilatation of the glandular structures without mitoses or atypia, HEx100.

DISCUSSION

In this rare gastric case report, we have exhibited the dilemma in exact diagnosing a lesion with upper gastrointestinal system endoscopic visuality of an 'early gastric cancer'but which was completely histologically benign. Usually, in case of this cancer mimicking benign lesion, a number of gastroscopies and radiological interventions are needed to be confident of an accurate diagnosis (2,3).

GCP is a rare gastric pathology characterized by the presence of gastric glands in the submucosa of the stomach with normal overlying mucosa and is often mistaken for other more common gastric problems (4). Clinical manifestations and symptoms of GCP are typically nonspecific, leading to significant diagnostic uncertainty. Histological examination of biopsy specimen is nearly non-diagnostic and a formal surgical excision is generally required (5,6).

A globally accepted treatment strategy for GCP has not been well described given the uncommon manner of these gastric lesions and the exact difficulty of diagnosing them (7). GCP is generally benign, although there have been some reports of GCP associated with cancer, but this hypothesis remains difficult to prove (8,9). Moon et al. reported two cases of GCP accompanied by synchronous multiple early gastric cancers occurred in patients without previous gastric surgery (4). In a pathological study of Choi et al. examining 10728 patients with gastric cancer, it was found in 161 patients (10). There are some case reports of GCP coexisting with Ménétrier disease or gastric inverted hyperplastic polyps (11,12).

The natural course of GCP is ambiguous and needs more molecular and histopathological exploration. This rare entity should be kept in mind in the differential diagnosis of patients presenting with suspicious submucosal gastric lesions.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Littler ER, Gleibermann E. Gastritis cystica polyposa. (Gastric mucosal prolapse at gastroenterostomy site, with cystic and infiltrative epithelial hyperplasia) Cancer 1972; 29: 205–9.
2. Franzin G, Novelli P. Gastritis cystica profunda. Histopathology 1981; 5: 535–47.
3. Butt MO, Luck NH, Hassan SM, Abbas Z, Mubarak M. Gastritis profunda cystica presenting as gastric outlet obstruction and mimicking cancer: A case report. J Transl Int Med 2015; 3: 35-7.
4. Moon SY, Kim KO, Park SH, et al. Gastritis cystica profunda accompanied by multiple early gastric cancers. Korean J Gastroenterol 2010; 55: 325-30.
5. Ozenc AM, Ruacan S, Aran O. Gastritis cystica polyposa. Arch Surg. 1988; 123: 372–3.
6. Tuncer K, Alkanat M, Musoglu A, Aydin A. Gastritis cystica polyposa found in an unoperated stomach: An unusual case treated by endoscopic polypectomy. Endoscopy 2003; 35: 882.

7. Park JS, Myung SJ, Jung HY, et al. Endoscopic treatment of gastritis cystica polyposa found in an un-operated stomach. Gastrointest Endosc 2001; 54: 101–3.
8. Park CH, Park JM, Jung CK, et al. Early gastric cancer associated with gastritis cystica polyposa in the unoperated stomach treated by endoscopic submucosal dissection. Gastrointest Endosc 2009; 69: e47–50.
9. Aoyagi K, Koufuji K, Yano S, et al. Two cases of cancer in the remnant stomach derived from gastritis cystica polyposa. Kurume Med J 2000; 47: 243–8.
10. Choi MG, Jeong JY, Kim KM, et al. Clinical significance of gastritis cystica profunda and its association with Epstein-Barr virus in gastric cancer. Cancer 2012; 118: 5227–33.
11. Soares JB, Bastos P, Goncalves R. Menetrier disease with antrum polyposis and gastritis cystica profunda. Endoscopy 2012; 44: E56–7.
12. Yamashita M, Hirokawa M, Nakasono M, et al. Gastric inverted hyperplastic polyp report of four cases and relation to gastritis cystica profunda. APMIS 2002; 110: 717–23.

Case Report/Olgu Sunumu

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MEDICINE

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Imaging features of catastrophic temporomandibular joint disorder in a case with new classification

Katastrofik temporomandibular eklem hastalığı, yeni sınıflama ile bir olguda radyolojik özellikleri

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ABSTRACT

Temporomandibular joint disorders (TMJD) have complex and diverse etiologies. Various classifications have been created in order to better describe and to guide the treatments correctly of these disorders. Wilkes classification is the most accepted among these classifications. A more comprehensive and understandable classification has been developed by Dimitroulis to eliminate the short comings of other classifications. In this case we aimed to present category 5 catastrophic temporomandibular joint disorders with radiological findings according to this new classification.

Keywords: Temporomandibular joint, radiology, MRI, CT

ÖZ

Temporomandibular eklem bozukluklarının (TMJD) karmaşık ve çeşitli etiyolojik sebepleri vardır. Bu bozuklukların daha iyi tanımlanması ve tedavilerinin doğru bir şekilde yönlendirilmesi için çeşitli sınıflandırmalar oluşturulmuştur. Wilkes sınıflandırması, bu sınıflandırmalar arasında en çok kabul gören sınıflamadır. Diğer sınıflandırmaların eksikliklerini ortadan kaldırmak için Dimitroulis tarafından daha kapsamlı ve anlaşılır bir sınıflandırma geliştirilmiştir. Bu vakada bu yeni sınıflandırmaya göre kategori 5 katastrofik temporomandibular eklem bozukluklarını radyolojik bulgularla sunmayı amaçladık.

Anahtar Kelimeler: Temporomandibular eklem hastaliği, radyoloji, MRG, BT

INTRODUCTION

Temporomandibular joint disorders (TMJD) have complex and sometimes controversial etiologies and treatment methods (1-3). TMJD were tried to be categorized by various classification methods (3-6). By making classifications, it is aimed to create appropriate and standard treatment methods that will be accepted worldwide at different stages or in situations with different etiologies (5-8). These classifications are also important for standardization in order to compare the clinical results of the treatments and surgical techniques applied (9). There are 3 main classifications related to TMJD; the Research Diagnostic Criteria (RDC) for TMJD, the Wilkes Classification for TMJD internal derangement, and the American Academy of Orofacial Pain (AAOFP) Classification of TMJD (8-11). The Wilkes classification is the most widely used classification that has been adopted by surgeons who treat TMJD (3,9). Its widespread adoption is linked to its simplicity in describing escalating joint pathology in 5 stages, but it concentrates on only 2 disorders (internal derangement and osteoarthritis) and fails to include other TMJD such as ankylosis and tumours (10). Therefore, in 2013, Dimitroulis developed

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a new surgical classification that includes all TMJ-specific disorders that can be applied to future studies on TMJ surgery. The main features and surgical treatment options of this classification are shown in **Table** (9).

In this article, we aimed to present the radiological findings of a case with category 5 catastrophic TMJD which we reported according to a new surgical classification and thus hoped to guide surgeons more accurately.

Table. Surgical classification of TMJD

Category 1	TMJ normal No surgery required or indicated
Category 2	TMJ minor changes (all joint components are salvageable) TMJ arthrocentesis/arthroscopic lavage
Category 3	TMJ moderate changes (most joint components are salvageable) TMJ operative arthroscopy/TMJ arthroplasty
Category 4	TMJ severe changes (few joint components are salvageable) TMJ discectomy±condylar surgery
Category 5	TMJ catastrophic changes (nothing in the joint is salvageable) TMJ resection±total joint replacement

TMJ: Temporomandibular joint, TMJD: Temporomandibular joint disorders

CASE

A 46-year-old woman presented to the otolaryngology clinic with complaints of swelling, not being able to chew anything, locking and mild pain in left TMJ. On physical examination, swelling, malocclusion and crepitus were noticed at the localization of TMJ. Afterwards, Computer tomography (CT) and Magnetic Resonance Imaging (MRI) was performed and reporting was done by evaluating two investigations together.

Enlargement on the TMJ face of the left temporal bone, narrowing in the joint space, osteophytic tapering at the joint corners, sclerotic appearance and expansion were observed. A marked increase in left mandibular condyle width, cortical irregularity and sclerotic appearance were observed on the articular face. On the left, the joint disc could not be visualized and TMJ was ankylosed. In line with these findings, we reported category 5 TMJ by catastrophic changes in the left TMJ (**Figure**).

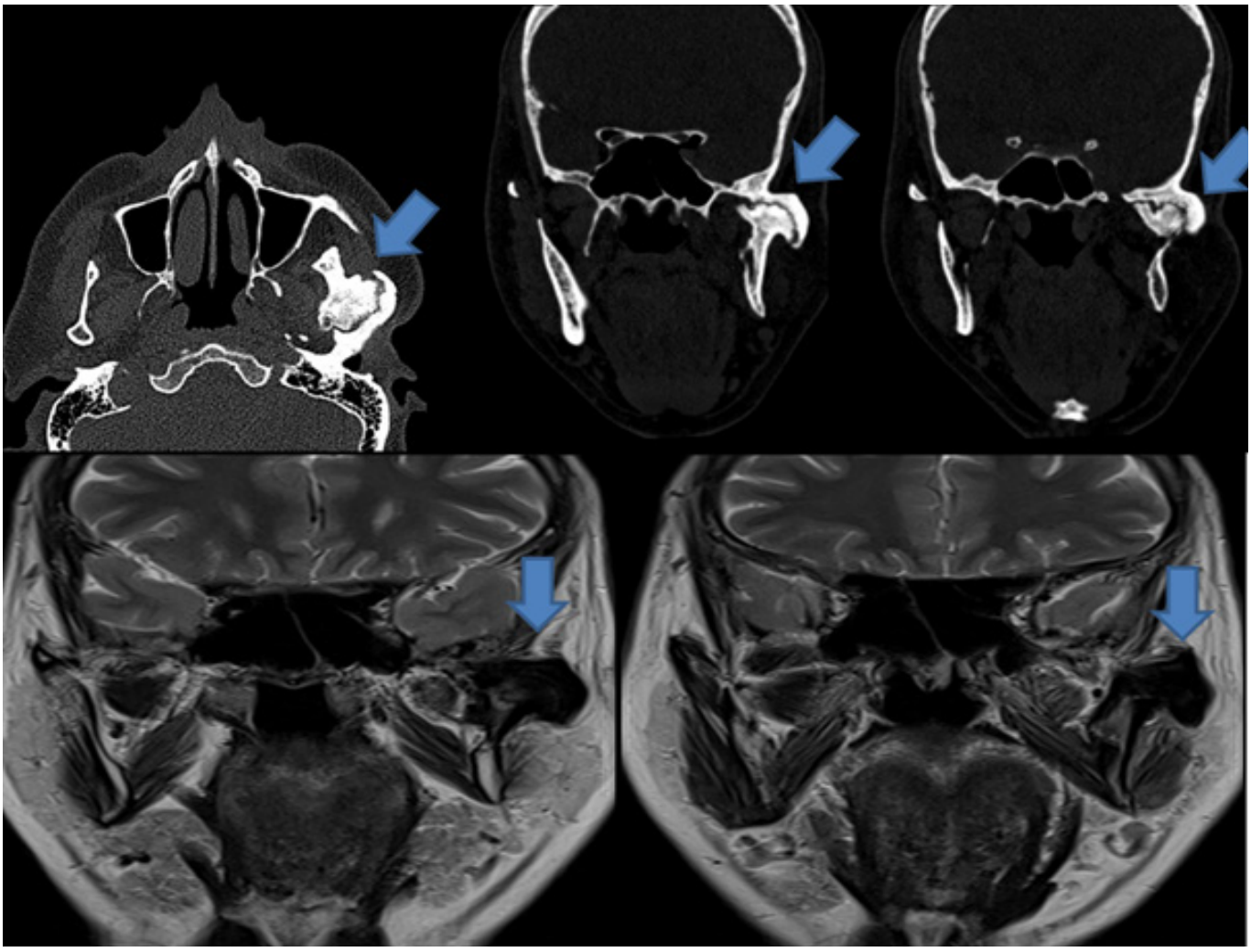

Figure. Ankylosis of the left temporomandibular joint, expansion of the joints, irregularities on the face of joint, new bone formation, sclerosis, and deformity in the bone structures involved were observed.

DISCUSSION

There are several classification methods in which TMJD are categorized (8-11). Of these, the Wilkes classification has been used as the unofficial standard classification for TMJ surgeons worldwide for many years. The simplicity of the stages identified and the increase in the level of disease at each stage made this classification feasible (3,10). However, considering that there are some deficiencies in the scope of these classifications, Dimitroulis developed a new surgical classification in 2013 that includes all TMJ-specific disorders that can be applied to future studies on TMJ surgery. This classification developed by Dimitroulis addresses the TMJD more extensively, and the classification not only identifies the clinical and radiological features of each category, but also shows the degree of surgical intervention (9). As we thought it would enable us to establish a clear communication between radiologists and surgeons and to guide surgeons more accurately. In this way, we reported our case based on this classification and received positive feedback from surgeons. In this classification, TMJD are divided into 5 categories that increase in parallel with the severity of the disease.

According to this classification, the categories have the following characteristics radiologically;

Category 1: This category corresponds to the normal TMJ. Patients present with pain complaints, but physical examination and radiological imaging are normal.

Category 2: There are minor changes in the joint in this category. MRI may have mild disc displacement, an increase or decrease in joint fluid as an indicator of inflammation.

Category 3: Includes moderate changes. Non-reductive disc displacement is seen in MRI. Mild disc contour deformity and condyle dislocation or fracture can be seen. Long-term cases may be affected by synovial chondromatosis and TMJ internal derangement.

Category 4: Includes severe TMJ changes. CT scans may show radiological signs of early changes in condylar morphology, such as loss or thinning of cartilage layer and osteophyte, small subcondral cysts, condyle head straightening, and beak type deformities. MRI can show severely degenerated, displaced and deformed joint disc, and sometimes disc perforation.

Category 5: Catastrophic changes occur. Irregular joint surface and large subchondral cysts are seen on CT scans. Although it is difficult to visualize because of irregular and deformed condyle, highly degenerated disc can be seen on MRI. In cases where joint pain is absent or tolerable, the patient may experience TMJ osteoarthrosis, or in rare cases, TMJ ankylosis or tumor. Our case falls into this category in a way that leaves no doubt due to the advanced changes and ankylosis described in TMJ (9).

CONCLUSION

We recommend that this new classification which we have started to use in our reports, and which we think may be effective in forming a common language among the physicians in the description of the disease and guide the treatment correctly, should be kept in mind by radiologists whose evaluating TMJ.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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

REFERENCES

1. Kahn J, Tallents RH, Katzberg RW, Ross ME, Murphy WC. Prevalence of dental occlusal variables and intraarticular temporomandibular disorders: molar relationship, lateral guidance, and nonworking side contacts. J Prosthet Dent 1999; 82: 410-5.
2. Katzberg RW, Tallents RH. Normal and abnormal temporomandibular joint disc and posterior attachment as depicted by magnetic resonance imaging in symptomatic and asymptomatic subjects. J Oral Maxillofac Surg 2005; 63: 1155-61.
3. Murphy MK, MacBarb RF, Wong ME, Athanasiou KA. Temporomandibular disorders: a review of etiology, clinical management, and tissue engineering strategies. Int J Oral Maxillofac Implants 2013; 28: e393-e414.
4. Young AL. Internal derangements of the temporomandibular joint: A review of the anatomy, diagnosis, and management. J Indian Prosthodont Soc 2015; 15: 2-7.
5. Dimitroulis G. The role of surgery in the management of disorders of the temporomandibular joint: a critical review of the literature. Part 2. Int J Oral Maxillofac Surg 2005; 34: 231-7.
6. Dimitroulis G. The role of surgery in the management of disorders of the Temporomandibular Joint: a critical review of the literature. Part 1. Int J Oral Maxillofac Surg 2005; 34: 107-13.
7. Dolwick MF, Dimitroulis G. Is there a role for temporomandibular joint surgery? Br J Oral Maxillofac Surg 1994; 32: 307-13.
8. Anderson GC, Gonzalez YM, Ohrbach R, Truelove EL, Sommers E, Look JO, et al. The Research Diagnostic Criteria for Temporomandibular Disorders. VI: future directions. J Orofac Pain 2010; 24: 79-88.
9. Dimitroulis G. A new surgical classification for temporomandibular joint disorders. Int J Oral Maxillofac Surg 2013; 42: 218-22.
10. Wilkes CH. Internal derangements of the temporomandibular joint. Pathological variations. Arch Otolaryngol Head Neck Surg 1989; 115: 469-77.
11. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992; 6: 301-55.

Case Report/Olgu Sunumu

HEALTH SCIENCES
MEDICINE

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A rare congenital anomaly of mediastinal vascular structures; isolated retroaortic left brachiocephalic vein

Mediastinal vasküler yapıların nadir bir konjenital anomalisi; izole retroaortik sol brakiosefalik ven

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ABSTRACT

Retroaortic left brachiocephalic vein (RALBV) is a rare condition and frequently accompanies congenital heart diseases. Isolated retroaortic left brachiocephalic vein anomaly is extremely rare. We emphasized the importance of the embryology and anatomy of the isolated RALBV anomaly and revealed the need to be assessed before the intervention. A 55-year-old man who underwent lobectomy due to lung adenocarcinoma. The patient had no known cardiac anomaly or heart disease. There was an oval-shaped structure reported as enlarged lymph node in the preaortic area on previous non-contrast CT. In the contrast-enhanced thorax computed tomography, it was seen that the structure previously described as lymph node was the left brachiocephalic vein, which showed a retroaortic course and was opacified with contrast material. In conclusion, isolated RALBV is an extremely rare anomaly. Due to the increasing numbers of cross-sectional exams, this phenomenon should be recognized and reported. Physcians should be notified before the radiological interventional procedures or thoracic surgery. Additionally, it is necessary to be careful since the treatment and follow-up of malignant diseases might be affected by misinterpretations.

Keywords: Computed tomography, isolated retroaortic left brachiocephalic vein, lung adenocarcinoma

ÖZ

Retroaortik sol brakiosefalik ven (RALBV) nadir bir durumdur ve sıklıkla doğumsal kalp hastalıklarına eşlik eder. İzole RALBV anomalisinin embriyoloji ve anatomisinin önemini bilinmeli ve müdahale öncesinde akılda tutulması gerekmektedir.Akciğer adenokarsinomu nedeniyle lobektomi yapılan 55 yaşında erkek hasta. Hastanın bilinen kalp anomalisi veya kalp hastalığı yoktu. Daha önceki kontrastsız BT'de preaortik alanda büyümüş lenf nodu olarak bildirilen oval şekilli bir yapı vardı. Hastaya yapılan kontrastlı toraks bilgisayarlı tomografisinde daha önce lenf nodu olarak tanımlanan yapının, retroaortik seyir gösteren ve kontrast madde ile opasifiye olan sol brakiyosefalik ven olduğu görüldü.Sonuç olarak izole RALBV oldukça nadir görülen bir anomalidir. Kesitsel incelemelerin artması nedeniyle bu anomali bilinmeli ve rapor edilmelidir. Radyolojik girişimsel prosedürler ve göğüs ameliyatları öncesinde dikkatli olunmalıdır. Ayrıca yanlış yorumlar malign hastalıkların tedavisini ve takibini etkileyebileceğinden dikkatli olmak gerekmektedir.

Anahtar Kelimeler: Bilgisayarlı tomografi, izole retroaortik sol brakiosefalik ven, akciğer adenokanseri

INTRODUCTION

The left retroaortic brachiocephalic vein is formed by the union of the subclavian vein and the internal jugular vein. This structure then passes anterior to the supraaortic branches of the aortic arch and joins with the right brachiocephalic vein to form the superior vena cava. Retroaortic left brachiocephalic vein is a rare condition and frequently accompanies congenital heart diseases. Isolated retroaortic left brachiocephalic vein anomaly is extremely rare (1).

CASE REPORT

A 55-year-old male patient, who had a history of lobectomy due to lung adenocarcinoma, was admitted to the radiology department for routine follow-up. The patient had no known cardiac anomaly or heart disease. There was an oval-shaped structure that was reported as an enlarged lymph node in the preaortic area on non-contrast CT, previously performed in an external center (**Figure 1**). Contrast-enhanced thorax and abdomen computed tomography was performed on the patient.

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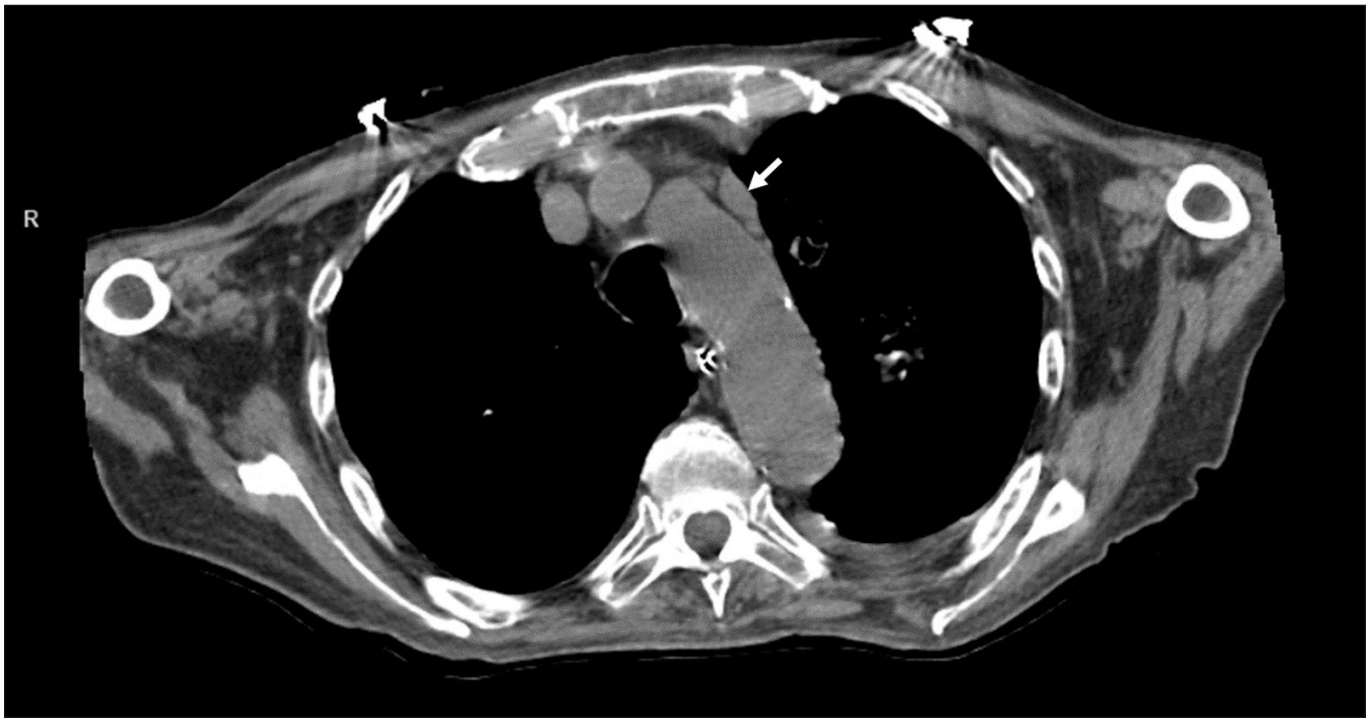

Figure 1. RALBV (arrow) observed anterior to the anterior left of the aortic arch on an axial non-contrast CT scan was misinterpreted as mediastinal LAP.

CT parameters were as follows: 2×192×0.6 mm slice collimation using z-axis flying focal spot technique; 0.25 s gantry rotation time; temporal resolution of 66 ms and an isotropic resolution of 0.3 mm. Automated tube voltage were used according to the patient's size. Images were acquired from the thoracic inlet to the pelvis. 100 ml iodinated contrast medium (iohexol, iodine content 350 mg/mL; Omnipaque TM, GE Healthcare) was intravenously administered via the cubital vein. After contrast medium injection, 30 cc saline solution injected. The flow rate of contrast and saline was 2 mL/s.

During the routine follow-up of the patient, we performed the contrast-enhanced CT examination.

The left brachiocephalic vein with a retroaortic course and opacification with contrast agent has been shown to be the structure previously defined as oval shaped. (**Figure 2-3**).

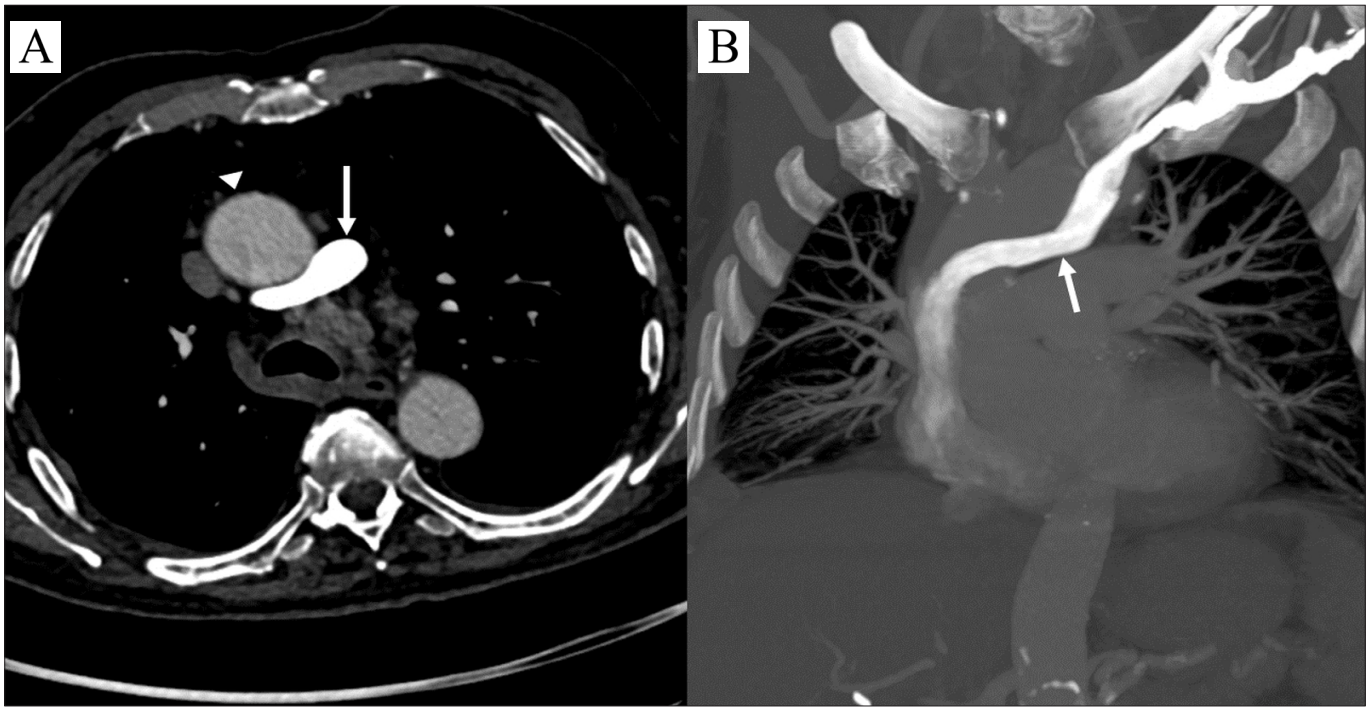

Figure 2. Post-contrast axial CT (a) and coronal MIP (b) images show contrast agent administration from the left arm. It shows that the left brachiocephalic vein (arrow) passes from the posterior of the ascending aorta (arrowhead) to the right half of the mediastinum.

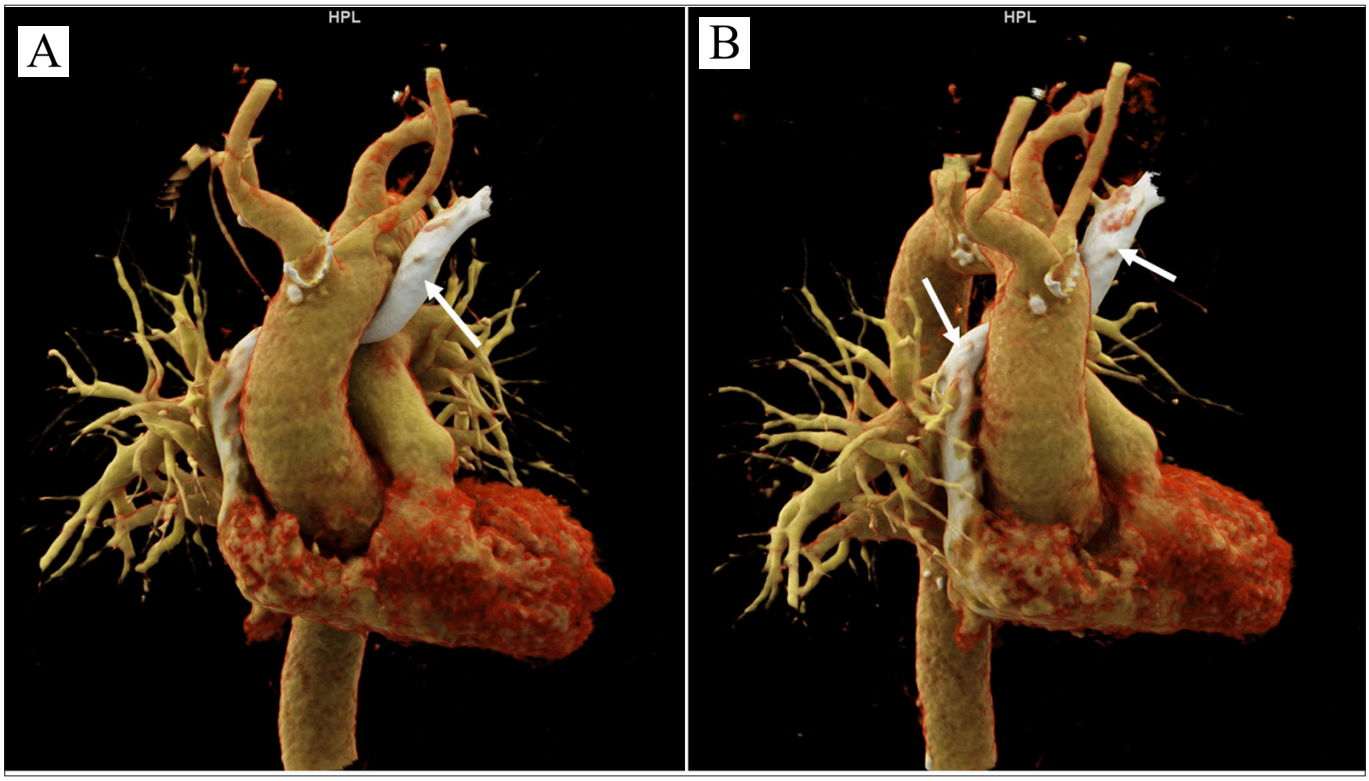

Figure 3. The reformatted volume rendering technique (VRT) images show a retroaortic left brachiocephalic vein (arrow)

DISCUSSION

Retroaortic left brachiocephalic vein is an extremely rare vascular anomaly, often accompanied by congenital heart disease. It frequently accompanies with other congenital heart diseases such as tetralogy of fallot and right aortic arch, pulmonary venous return anomaly, aortic coarctation, right atrial isomerism, atrial septal defect and ventricular septal defect (2-4). In a retrospective study conducted on 1812 cases by Chen et al. (4) covering an 8-year period, RALBV abnormalities were found in 27 cases. They found the incidence to be approximately 1.7% in patients with congenital heart disease. In other studies, in the literature, this rate was found to be approximately 0.55-0.57 (5,6).

Isolated RALBV anomaly that does not accompany with any other congenital cardiac anomaly is extremely rare. Nagashima et al. (7) found only one isolated RALBV anomaly without congenital heart anomaly in a study of 4805 cases. In other studies, in the literature, isolated RALBV anomaly not accompanying congenital heart disease was found to be approximately 0.02% (8).

The mechanism of RALBV formation is not yet clear. During normal embryological development, the right-left anterior and posterior cardinal veins merge to form the right and left common cardinal veins. The anterior cardinal veins extend superiorly on both sides and join with the internal jugular vein and subclavian vein. In the following period, most of the left anterior cardinal vein disappears and merges with transverse anastomotic channels. It will then merge with the right common cardinal vein to form the superior vena cava. The left common cardinal vein forms the coronary sinus, and the remaining part of the left anterior cardinal vein forms the oblique vein of the marshal (4,9). It is thought that the absence of fusion in transverse anastomotic ducts and formation of alternative anastomoses play a role in the formation of RALBV anomaly (4,10).

Detection of isolated RALBV anomaly is clinically very important. With the widespread use of cross-sectional examinations, it is necessary to be careful since isolated RALBV anomaly can be seen even in cases without any congenital cardiac anomaly. Additionally, since it frequently accompanies with CHD, the presence of other cardiac anomalies should be investigated in detail in cases with RALBV anomaly. Isolated RALBV can be reported as an enlarged lymph node in non-contrast CT examinations (11). As in our case, this situation is critical in guiding the follow-up and treatment of malignant diseases such as lung adenocarcinoma. In addition, if this variation is not known beforehand, it may cause technical difficulties during cardiothoracic surgeries, left-sided venous interventional procedures such as central venous catheterization, and cardiological interventional procedures such as pacemaker placement.

CONCLUSIONS

Isolated RALBV is an extremely rare anomaly. Due to the increasing numbers of cross-sectional exams, this phenomenon should be recognized and reported. One should be alert before radiological interventional procedures and thoracic surgeries. Additionally, it is necessary to be careful since the treatment and follow-up of malignant diseases might be affected by misinterpretations.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Status of Peer-review: Externally peer-reviewed.

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

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

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

REFERENCES

1. Srinivasan S, Kannivelu A, Ali SZ, See PL. Isolated retroaortic left innominate vein in an adult without cardiac or aortic anomalies. Indian J Radiol Imaging. 2013; 23: 308-9.
2. Kulkarni S, Jain S, Kasar P, Garekar S, Joshi S. Retroaortic left innominate vein-Incidence, association with congenital heart defects, embryology, and clinical significance. Ann Pediatr Cardiol 2008; 1: 139-41.
3. Bartoli JM, Chagnaud C, Moulin G, Di Stefano-Louineau D, Bory M, Kasbarian M. Pseudocoarctation of the aorta associated with retro-aortic left brachiocephalic vein: a case report. Surg Radiol Anat 1990; 12: 307-9.
4. Chen SJ, Liu KL, Chen HY, et al. Anomalous brachiocephalic vein: CT, embryology, and clinical implications. AJR Am J Roentgenol 2005; 184: 1235-40.
5. Choi JY, Jung MJ, Kim YH, Noh CI, Yun YS. Anomalous subaortic position of the brachiocephalic vein (innominate vein): an echocardiographic study. Br Heart J 1990; 64: 385-7.
6. Curtil A, Tronc F, Champsaur G, et al. The left retro-aortic brachiocephalic vein: morphologic data and diagnostic ultrasound in 27 cases. Surg Radiol Anat 1999; 21: 251-4.
7. Nagashima M, Shikata F, Okamura T, et al. Anomalous subaortic left brachiocephalic vein in surgical cases and literature review. Clin Anat 2010; 23: 950-5.
8. Takada Y, Narimatsu A, Kohno A, et al. Anomalous left brachiocephalic vein: CT findings. J Comput Assist Tomogr 1992; 16: 893-6.
9. Ko SF, Huang CC, Ng SH, et al. Imaging of the brachiocephalic vein. AJR Am J Roentgenol 2008; 191: 897-907.
10. Kim SH, Chung JW, Im JG, Choi YW, Choe YH, Han MC. Subaortic left innominate vein: radiologic findings and consideration of embryogenesis. J Thorac Imaging 1999; 14: 142-6.
11. Chern MS, Ko JS, Tsai A, Wu MH, Teng MM, Chang CY. Aberrant left brachiocephalic vein: CT imaging findings and embryologic correlation. Eur Radiol 1999; 9: 1835-9.

Case Report/Olgu Sunumu

HEALTH SCIENCES
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A rare case of adamantinoma in tibia and radiological features

Nadir bir tibia'da adamantinoma olgusu, radyolojik özellikleri

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ABSTRACT

Adamantinoma is a rare low grade primary malignant bone tumor usually found in the diaphysis of the tibia. The tumor is locally aggressive and can metastasize. As it is resistant to chemotherapy and radiotherapy, the main treatment is total excision of the lesion with wide surgical margins. Although it is difficult to distinguish from other bone lesions (such as osteofibrous dysplasia) radiologically, there are some helpful features. With this presentation of a typical case, we hope to draw the attention of radiologists to this lesion.

Keywords: Adamantinoma, tibia, bone neoplasms, radiology, MRI, osteofibrous dysplasia

ÖZ

Adamantinoma, nadir görülen düşük dereceli primer malign kemik tümörüdür ve genellikle tibia diyafizinde bulunur. Tümör lokal olarak agresiftir ve metastaz yapabilir. Kemoterapi ve radyoterapiye dirençli olduğu için asıl tedavi lezyonun geniş cerrahi sınırlarla total eksizyonudur. Radyolojik olarak diğer kemik lezyonlarından (osteofibröz displazi gibi) ayırt etmek zor olsa da bazı ayırt edici özellikleri vardır. Tipik bir vakanın bu sunumu ile radyologların dikkatini bu lezyona çekmeyi umuyoruz.

Anahtar Kelimeler: Adamantinoma, tibia, kemik neoplazmları, radyoloji, MRG, osteofibröz displazi

INTRODUCTION

Adamantinoma is a rare low grade primary malignant bone tumor. The Greek word 'adamantinos'means 'very hard'. It was first observed in ulna in 1900 by C. Maier (1,2). It was named as "primary adamantinoma of the tibia" by Fischer in 1913 because of its histological resemblance to the jaw ameloblastoma (3,6). The tumor is usually located in the diaphysis of tibia especially in 2'nd and 3'rd decades, mildly more frequently in males. Patients present to the physician with a complaint of mild pain that has been going on for years and a swelling that gradually becomes apparent. Sometimes the complaint may be a pathological fracture (4). In this article, we aimed to share the magnetic resonance imaging (MRI) and radiographic findings of this rare entity.

CASE

A 28 year old male patient admitted orthopedics and traumatology department with pain on left leg. There was a painful contour deformity on left tibia in physical examination. The patient had no other known diseases. Laboratory findings were within normal limits. Direct radiography showed a translucent lesion in the left tibia diaphyseal region, which was located in the anterior cortex with sclerotic margin (**Figure 1**). MRI revealed a mass lesion in the anterior diaphyseal section of the left tibia, that caused destruction in cortical bone. The lesion had an axial diameter of 28x17 mm with craniocaudal extension of 70 mm, extending into the tibialis anterior muscle. Significant contrast enhancement was observed in the lesion (**Figure 2**). There was also an increase in

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signal intensity from proton density to T2 sequences, and with cystic area showing a hyperintense fluid-like signal (**Figure 3,4**). No signal suppression in the lesion was observed on the fat saturation sequences. It was recommended to excise the lesion in terms of possible malignant lesion due to the exophytic extension of the bone, causing obvious destruction in the bone. A biopsy was performed and histology revealed features typical of epithelial and osteofibrous components of adamantinoma. Metastasis were not observed in other imaging techniques. The lesion was resected with a margin of normal bone by the surgeon.

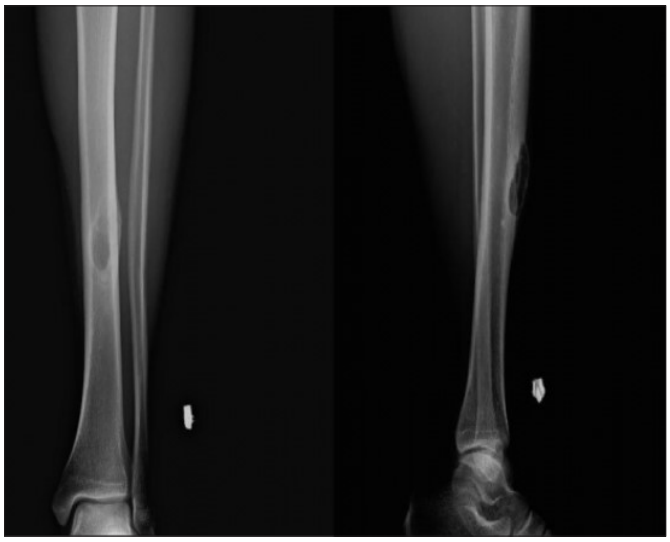

Figure 1. Anteroposterior and lateral radiographs of the left tibia and fibula demonstrate an osteolytic lesion is primarily cortical based and has a well-defined sclerotic margin on its inner aspect. Note the narrow zone of transition, which correlates with the indolent nature of the lesion.

DISCUSSION

Adamantinoma is locally aggressive tumors with slow progression and metastasis potential (2,4,7,8). Since it is not sensitive to chemotherapy and radiotherapy, the treatment is the carefully removing of the lesion with a wide surgical margin (9). Inadequate surgical procedures significantly increase the risk of local recurrence and lung metastasis (5,10-13). Therefore, preoperative imaging and staging are important for appropriate treatment. Evaluation with only radiographic findings may make the actual size of the tumor smaller than it is. MRI is the preferred imaging technique for staging musculoskeletal tumors due to its high soft tissue contrast resolution and its ability to perform multiplanar imaging (9).

Some features of the tumor such as its classic location and characteristic appearance are findings that help radiological diagnosis. In general, as in our patient, multiloculated radiolucent lesions are seen in the tibia in the form of central or eccentric localized, sclerotic limited appearance and osteolytic lesions with slightly large, sharp or insufficiently circumscribed. The lesion may be surrounded by a prominent sclerotic border that indicates slow growth (5,12). Although diaphysis is the most common location, rarely metaphyseal extension or isolated metaphyseal involvement can be seen. When metaphyseal involvement occurs, it becomes difficult to make a diagnosis since other tumors with metaphyseal location are also included in the differential diagnosis (2). Tumors involving the anterior tibial cortex, peripheral sclerosis and tumors with well-defined lesions including septation, may have multifocal involvement in the same bone. These multifocal radiolucencies surrounded by

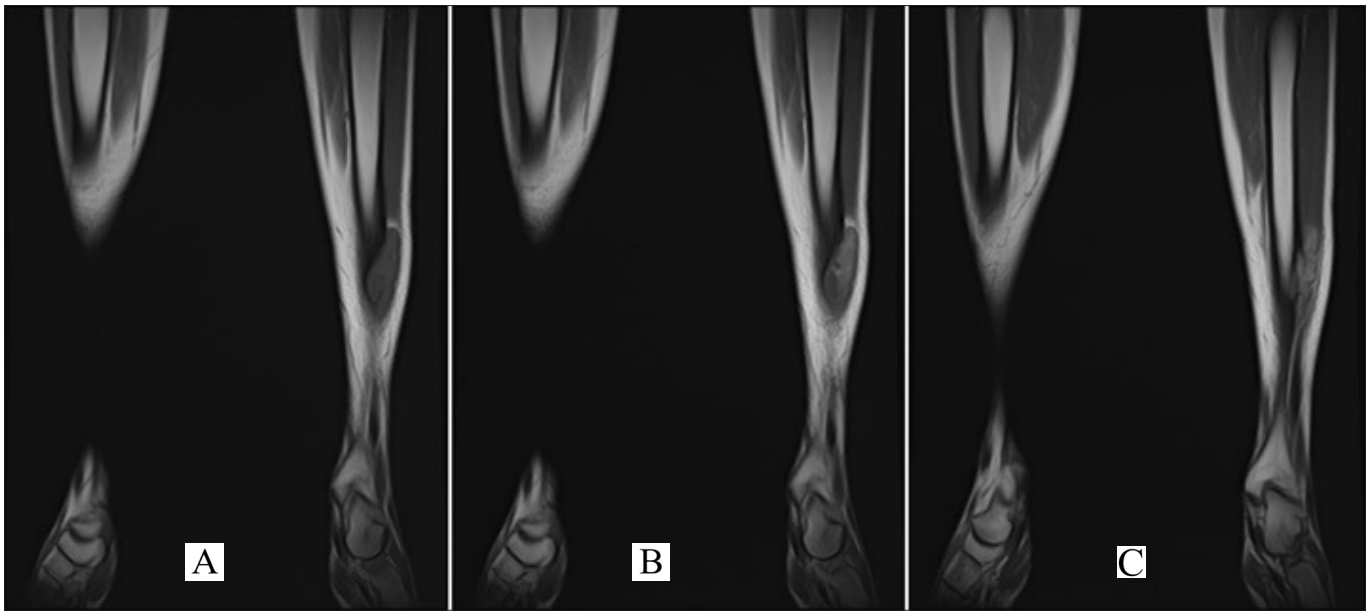

Figure 2. (a) Coronal T1-weighted image reveals anterior of tibia presence of tumor with intermediate signal intensity showing soft-tissue extension. (b-c) Coronal T1-weighted image obtained after administration of contrast medium shows enhancement, cortical destruction and soft-tissue extension.

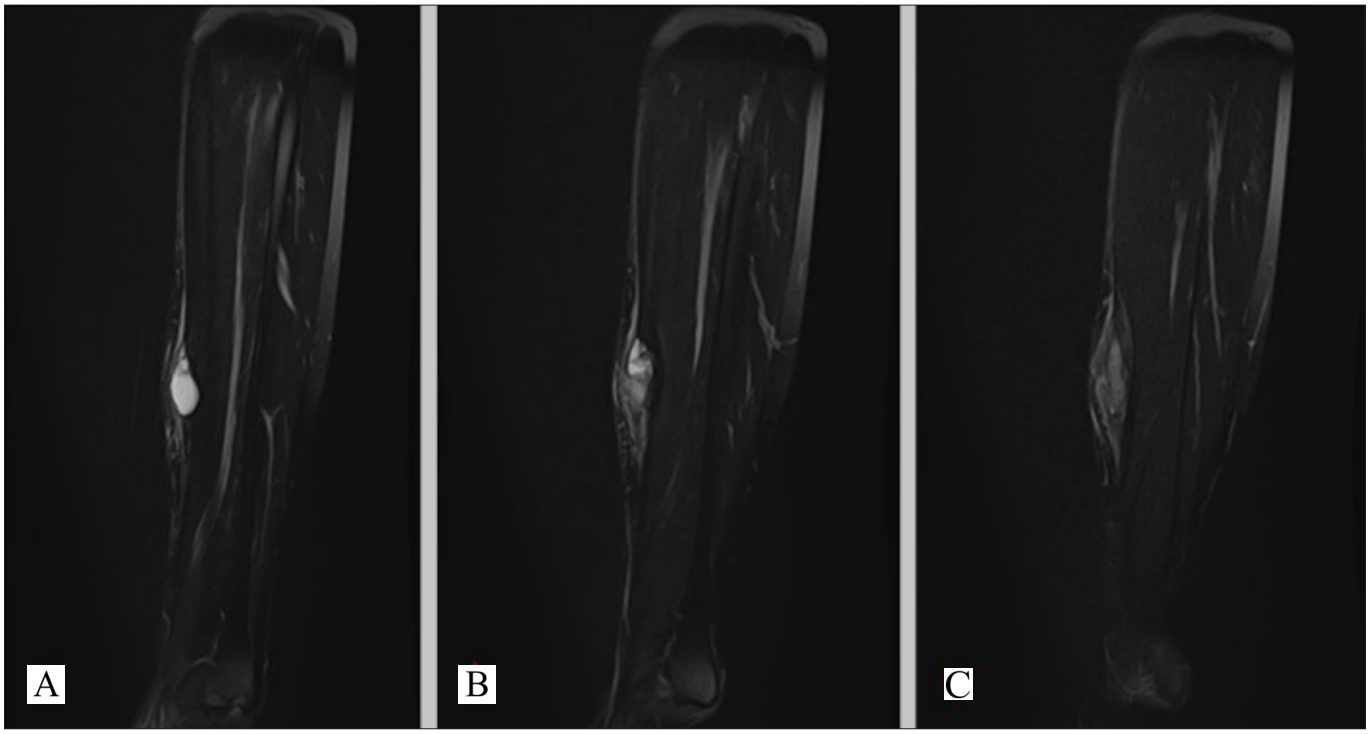

Figure 3. Cystic areas showing a hyperintense fluid-like signal in the sagittal T2-weighted images

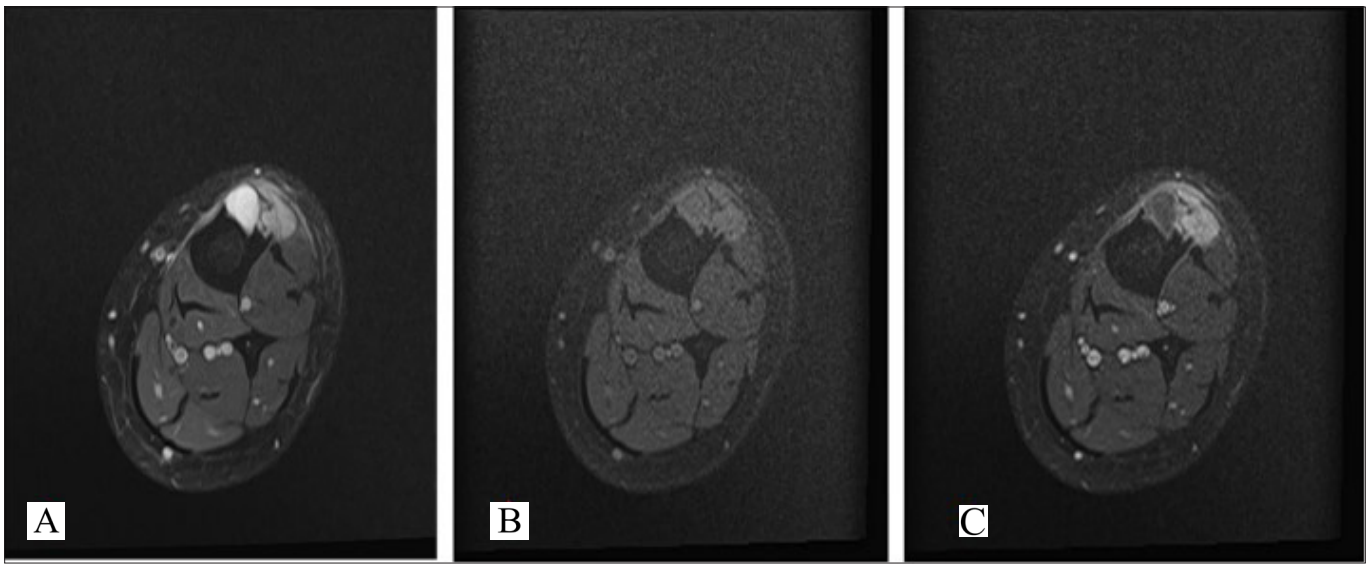

Figure 4. (a) Axial proton density imaging shows a lesion with a cystic component. (b) On axial T1-weighted fat saturated section, an intermediate signal intensity lesion with soft tissue extension destructing the anterior bone cortex was seen. (c) On axial T1-weighted images with fat-selective presaturation after contrast medium administration, lesions show intense enhancement and are well demarcated. The cystic compartment does not show enhancement.

ring-shaped densities form the characteristic "soap bubble" appearance (5). The lesion is usually located intracortically, but in some cases, there may be cortex destruction and involvement in extra cortical soft tissues. Different degrees of periost reaction can be seen (5,11).

Radiologically, the differential diagnosis of adamantinoma should include osteofibrous dysplasia and fibrous dysplasia. In direct radiographs, "soap bubble appearance" can be observed both in osteofibrous dysplasia and differentiated adamantinoma (6).

Although it is difficult to distinguish between osteofibrous dysplasia and fibrous dysplasia from adamantinoma, there are some helpful features. Osteofibrous dysplasia involve the bone cortex without medullary involvement and has a ground-glass appearance (5). Fibrous dysplasia presents with a homogeneous low signal intensity in T1- and T2-weighted images because of its histological composition of mainly fibrous material (6). On the other hand, the appearance of single or multiple nodular lesions with frontal cortex involvement located in the diaphysis and extending into the bone

marrow approaches the diagnosis of adamantinoma (5). Adamantinoma shows a more heterogeneous pattern with cystic areas (high signal intensity in T2), sometimes with hemorrhagic content (high signal intensity in T1), surrounded by a fibrous mass (low signal in all sequences) (6). Other lesions that should be kept in mind in the differential diagnosis including angiosarcoma, hemangioendothelioma, aneurrysmal bone cyst, giant cell tumor, chondrosarcoma, nonossifying fibromas, epithelial metastasis (2).

Although computed tomography (CT) can show bone cortex involvement and soft tissue extension, it cannot clearly show the intraosseous extension of the lesion. CT is often used routinely to screen for lung metastases.

MRI plays a critical role in demonstrating extension of intramedullary and soft tissue, distant cortical foci and tumor-free margins. It is seen in low signal intensity in T1-weighted images and high signal intensity in T2-weighted images. Because these appearances are also typical of most tumors, these findings are nonspecific (2). Nuclear imaging methods can be used also in the evaluation of adamantinoma (14).

CONCLUSION

The main treatment in adamantinoma is total excision of the lesion with wide surgical margins. Evaluation of the true size of the lesion and the soft tissue component in the preoperative period is important in the success of the surgical treatment. As a result, the possibility of local recurrence-residual tumor tissue and distant metastasis is reduced in the postoperative period. MRI is the most important imaging technique in cases like our case due to its high soft tissue contrast resolution and its success in showing the true limits of the tumor to guide surgical treatment correctly.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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REFERENCES

1. Maier C. Ein primäres myelogenes Plattenepithelcarcinom der Ulna. Bruns'Beitr Klin Chir 1900; 26: 533.
2. Jain D, Jain VK, Vasishta RK, Ranjan P, Kumar Y. Adamantinoma: A clinicopathological review and update. Diagnostic Pathol 2008; 3: 8.
3. Fisher B. Primary adamantinoma of the tibia. Z Pathol 1913; 12: 422-41.
4. Moon NF. Adamantinoma of the appendicular skeleton a statistical review of reported cases and inclusion of 10 new cases. Clin Orthop Relat Res (1976-2007) 1965; 43: 189-214.
5. Kahn LB. Adamantinoma, osteofibrous dysplasia and differentiated adamantinoma. Skeletal Radiol. 2003; 32: 245-58.
6. Judmaier W, Peer S, Krejzi T, Dessl A, Kühberger R. MR findings in tibial adamantinoma: a case report. Acta Radiologica 1998; 39: 276-8.
7. Chen J, Zhang J. Adamantinoma filling the medullary space of the tibia: A case report. Radiol Case Rep 2019: 14: 1330–3.
8. Mirra J. Adamantinoma and osteofibrous dysplasia. Bone Tumors. Clinical, Radiologic, and Pathologic Correlations 1989: 1217-31.
9. Özger H, Alphan B. Management of rare, malignant bone tumors: diagnosis and treatment of adamantinoma and chordoma. TOTBİD Derg 2014; 13: 252–9.
10. Keeney GL, Unni KK, Beabout JW, Pritchard DJ. Adamantinoma of long bones. a clinicopathologic study of 85 cases. Cancer 1989; 64: 730-7.
11. Van Rijn R, Bras J, Schaap G, van den Berg H, Maas M. Adamantinoma in childhood: report of six cases and review of the literature. Pediatr Radiol 2006; 36: 1068-74.
12. Khan MH, Darji R, Rao U, McGough R. Leg pain and swelling in a 22-year-old man. Clin Orthop Relat Res 2006; 448: 259-66.
13. Hazelbag HM, Taminiau AH, Fleuren GJ, Hogendoorn PC. Adamantinoma of the long bones. A clinicopathological study of thirty-two patients with emphasis on histological subtype, precursor lesion, and biological behavior. J Bone Joint Surg Am 1994; 76: 1482-99.
14. Devaney K. Dahlin's Bone Tumors. General Aspects and Data on 11,087 Cases. Am J Surg Pathol 1996; 20: 1298.

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ABBREVIATION OF JOURNAL NAME

J Heatlh Sci Med/JHSM

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WHAT SHOULD BE INDICATED BEFORE THE RESOURCES

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Status of Peer-review: Externally peer-reviewed.

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

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

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Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Excerpt from the book, which is the only author and editor;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams & Wilkins; 1996: 46-60.

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Schulz JE, Parran T Jr.: Principles of identification and intervention. In: Principles of Addicton Medicine, Graem AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams & Wilkins; 1998: 1-10.

If the editor is also the author of the chapter in the book;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag; 1988: 45-67.

Excerpt from PhD/Undergraduate Thesis;

Kilic C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

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Joos S, Musselmann B, Szecsenyi J. Integration of complementary and alternative medicine into the family market in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi: 10.1093/ecam/nep019).

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YAYIN KURALLARI, YAYIN POLİTİKASI, GENEL İLKELER VE GÖNDERME KURALLARI

YAZARLARA BİLGİ

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BİLİMSEL VE ETİK SORUMLULUK

Journal of Health Sciences and Medicine (JHSM)'in yayın ve yayın süreçleri, Dünya Tıbbi Editörler Derneği (World Association of Medical Editors (**WAME**)), Yayın Etiği Komitesi (Committee on Publication Ethics (**COPE**)), Uluslararası Tıbbi Dergi Editörleri Konseyi (International Council of Medical Journal Editors (**ICMJE**)), Bilim Editörleri Konseyi (Council of Science Editors (**CSE**)), Avrupa Bilim Editörleri Birliği (**EASE**) ve Ulusal Bilgi Standartları Organizasyonu (National Information Standards Organization (NISO)) kurallarına uygun olarak şekillendirilmiştir. Dergi, Bilimsel Yayıncılıkta Şeffaflık ve En İyi Uygulama İlkeleri'ne (Principles of Transparency and Best Practice in Scholarly Publishing (**doaj.org/bestpractice**)) uygundur.

Klinik araştırma makalelerinin protokolü Etik Komitesi tarafından onaylanmış olmalıdır. İnsanlar üzerinde yapılan tüm çalışmalarda "**Gereç ve Yöntem**" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın **Helsinki İlkeler Deklarasyonu**'na (**https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/**) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır. Çalışmaya dahil edilen tüm kişilerin **Bilgilendirilmiş Onam Formu'**nu imzaladığı metin içinde belirtilmelidir. **Journal of Health Sciences and Medicine (JHSM)'**e gönderilen makalelerdeki çalışmaların **Helsinki İlkeler Deklarasyonu'**na uygun olarak yapıldığı, kurumsal etik ve yasal izinlerin alındığı varsayılacak ve bu konuda sorumluluk kabul edilmeyecektir. Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntem bölümünde hayvan haklarını **Guide for the Care and Use of Laboratory Animals** (**https://www.nap.edu/catalog/5140/guide-for-the-care-and-use-of-laboratory-animals**) prensipleri doğrultusunda koruduklarını, çalışmalarında ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır. Olgu sunumlarında hastanın kimliğinin ortaya çıkmasına bakılmaksızın hastalardan "Bilgilendirilmiş rıza" alınmalıdır. Makalede Etik Kurul Onayı alınması gerekli ise; alınan belge makale ile birlikte gönderilmelidir. Makale yazarlar tarafından **akademik intihal önleme programı**ndan geçirilmelidir. Makalenin etik kurallara uygunluğu yazarların sorumluluğundadır.

Tüm makale başvuruları intihal araştırılması için taranmalı ve sonrasında dergi sistemine yüklenmelidir. İntihal, atıf manipülasyonu ve gerçek olmayan verilerden şüphelenilmesi veya araştırmaların kötüye kullanılması durumunda, yayın kurulu **COPE** yönergelerine uygun olarak hareket eder. Bakınız: **Guidance from the Committee on Publication Ethics** (**COPE**).

Yazar olarak listelenen her bireyin **Uluslararası Tıp Dergisi Editörleri Komitesi** (**ICMJE-www.icmje.org**) tarafından önerilen yazarlık kriterlerini karşılaması gerekir. **ICMJE** yazarlığın aşağıdaki 4 kritere dayanmasını önerir: (1) Çalışmanın tasarımı, verilerin elde edilmesi, analizi veya yorumlanması(2) Dergiye gönderilecek kopyanın hazırlanması veya bu kopyanın içeriğini bilimsel olarak etkileyecek ve ileriye götürecek şekilde katkı sağlanması (3) Yayımlanacak kopyanın son onayı (4) Çalışmanın tüm bölümleri hakkında bilgi sahibi olma ve tüm bölümleri hakkında sorumluluğu alma.

Bir yazar, yaptığı çalışmanın bölümlerinden sorumlu olmanın yanı sıra, çalışmanın diğer belirli bölümlerinden hangi ortak yazarların sorumlu olduğunu bilmeli ayrıca yazarlar, ortak yazarlarının katkılarının bütünlüğüne güvenmelidir. Yazar olarak atananların tümü yazarlık için dört kriteri de karşılamalı ve dört kriteri karşılayanlar yazar olarak tanımlanmalıdır. Dört kriterin tümünü karşılamayanlara makalenin başlık sayfasında teşekkür edilmelidir. Yayın kurulu yazarlık şartlarını karşılamayan bir kişinin yazar olarak eklendiğinden şüphe ederse yazı daha fazla incelenmeksizin reddedilecektir.

Journal of Health Sciences and Medicine (JHSM)'e gönderilen bir çalışma için bireylerden veya kurumlardan alınan mali hibeler veya diğer destekler Editör Kurulu'na bildirilmelidir. Potansiyel bir çıkar çatışmasını bildirmek için, **ICMJE Potansiyel Çıkar Çatışması Bildirim Formu**, katkıda bulunan tüm yazarlar tarafından imzalanmalı ve gönderilmelidir. Editörlerin, yazarların veya hakemlerin çıkar çatışması olasılığı, derginin Editör Kurulu tarafından **COPE** ve **ICMJE** yönergeleri kapsamında çözümlenecektir. Derginin Editör Kurulu, tüm itiraz durumlarını **COPE** kılavuzları kapsamında ele almaktadır. Bu gibi durumlarda, yazarların itirazları ile ilgili olarak yazı işleri bürosu ile doğrudan temasa geçmeleri gerekmektedir. Gerektiğinde, dergi içinde çözülemeyen olayları çözmek için bir kamu denetçisi atanabilir. Baş editör itiraz durumlarında karar alma sürecinde alınacak kararlarla ilgili nihai otoritedir. Yazarlar, dergiye bir makale gönderirken, yazıların telif haklarını **Journal of Health Sciences and Medicine (JHSM)**'e devretmiş olmayı kabul ederler. Yazı yayımlanmamak üzere reddedilirse veya herhangi bir sebepten geri çekilirse telif hakkı yazarlara geri verilir.Şekiller, tablolar veya diğer basılı materyaller de dahil olmak üzere basılı ve elektronik formatta daha önce yayımlanmış içerik kullanılıyorsa yazarlar telif hakları sahiplerinden gerekli izinleri almalıdır. Bu konudaki hukuki, finansal ve cezai yükümlülükler yazarlara aittir. **Journal of Health Sciences and Medicine (JHSM)** 'de yayımlanan makalelerde belirtilen ifade veya görüşler, editörlerin, yayın kurulunun veya yayıncının görüşlerini yansıtmaz; editörler, yayın kurulu ve yayıncı bu tür materyaller için herhangi bir sorumluluk veya yükümlülük kabul etmez. Yayınlanan içerikle ilgili nihai sorumluluk yazarlara aittir.

MAKALE "BAŞKA BİR YERDE YAYIMLANMAMIŞTIR" İBARESİ

Her yazar makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, editöre sunum sayfasında belirtmelidirler. Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir. Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal, vb.) yazarlara aittir.

YAYIN HAKKI DEVİR FORMU

Telif Hakkı Devir Formu (https://dergipark.org.tr/tr/journal/2316/file/3808/download) linkinden temin edilebilir. Makalenin ana dilinde (makalenin dili İngilizce ise, İngilizce olmalıdır, makalenin dili Türkçe ise, Türkçe olmalıdır) doldurulmalı, makale (https://dergipark.org.tr/tr/journal/2316/submission/step/manuscript/new) adresi üzerinden yüklenirken on-line olarak gönderilmelidir. 1976 Copyright Act'e göre, yayımlanmak üzere kabul edilen yazıların her türlü yayın hakkı yayıncıya aittir.

YAZIM DİLİ KONTROLÜ

Derginin yayın dili **Türkçe** ve **İngilizce**'dir, makaleler hem Türkçe hem de İngilizce olarak kabul edilmektedir. Türkçe yazılan yazılarda düzgün bir Türkçe kullanımı önemlidir. Bu nedenle Türk Dil Kurumu'nun Türkçe sözlüğü veya www.tdk.org.tr adresi ayrıca Türk tıbbi derneklerinin kendi branşlarına ait terimler sözlüğü esas alınmalıdır. İngilizce makaleler ve İngilizce Abstract gönderilmeden önce profesyonel bir dil uzmanı tarafından kontrol edilmelidir. Yazıdaki yazım ve gramer hataları içerik değişmeyecek şekilde İngilizce dil danışmanımız ve redaksiyon komitemiz tarafından düzeltilmektedir.

İSTATİSTİK DEĞERLENDİRMESİ

Tüm prospektif, deneysel ve retrospektif araştırma makaleleri istatistik yönünden (gerekirse istatistik uzmanı tarafından) değerlendirilmeli ve uygun plan, analiz ve raporlama ile belirtilmelidir.

YAYIMA KABUL EDİLMESİ

Editör ve hakemlerin uygunluk vermesi sonrası makalenin gönderim tarihi esas alınarak yayım sırasına alınır. Her yazı için bir **Doi** numarası alınır.

MAKALE YAZIM KURALLARI

Yazılar Microsoft Word programı ile çift satır aralıklı ve başlık yazıları (Makale Adı, Öz, Abstract, Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Kaynaklar vs.) 12 punto olarak, makalenin diğer kısımları 11 punto olacak şekilde, her sayfanın iki yanında ve alt ve üst kısmında 2,5 cm boşluk bırakılarak yazılmalıdır. Yazı stili Times New Roman olmalıdır. "System International" (SI) unitler kullanılmalıdır. Şekil, tablo ve grafikler metin içinde refere edilmelidir. Kısaltmalar, kelimenin ilk geçtiği yerde parantez içinde verilmelidir. Türkçe makalelerde %50 bitişik yazılmalı, aynı şekilde İngilizcelerde de 50% bitişik olmalıdır. Türkçe'de ondalık sayılarda virgül kullanılmalı (55,78) İngilizce yazılarda nokta (55.78) kullanılmalıdır. Derleme 4000, araştırma makalesi 2500, olgu sunumu 1500, editöre mektup 500 kelimeyi geçmemelidir. Öz sayfasından itibaren sayfalar numaralandırılmalıdır.

Yazının Bölümleri

1. Editöre Sunum Sayfası

Journal of Health Sciences and Medicine (JHSM)'de yayımlanmak üzere değerlendirilmesi isteğinin belirtildiği, makalenin sorumlu yazarı tarafından dergi editörüne hitaben gönderdiği yazıdır. Bu kısımda makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığı ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığı, "**Maddi Destek ve Çıkar İlişkisi**" durumu, dil ve istatistik kontrolünün yapıldığı belirtilmelidir.

2. Başlık Sayfası

Sayfa başında gönderilen makalenin kategorisi belirtilmedir (klinik analiz, araştırma makalesi, deneysel çalışma, olgu sunumu, derleme vs). Tüm yazarların ad ve soyadları yazıldıktan sonra üst simge ile 1'den itibaren numaralandırılıp, çalıştıkları kurum, klinik, şehir ve ülke yazar isimleri altına eklenmelidir. Başlık sayfasında her yazarın **Orcid no** bilgisi, **e-posta** adresi olmalıdır. Bu sayfada Sorumlu Yazar belirtilmeli isim, açık adres, telefon ve e-posta bilgileri eklenmelidir (Dergimizin formatı gereği adres bilgileri, kurumları makale dili Türkçe ise Türkçe olarak, İngilizce ise İngilizce olarak belirtilmelidir). Kongrelerde sunulan Sözlü veya Poster bildiriler başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmelidir.

3. Makale Dosyası

Yazar ve kurum isimleri bulunmamalıdır, bu bilgiler sadece başlık sayfasında olmalıdır.

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemeli, Türkçe ve İngilizce olarak yazılmalıdır. Öz: Türkçe ve İngilizce (Abstract) yazılmalıdır. Araştırma makalelerinde Öz; Amaç, Gereç, Yöntem, Bulgular ve Sonuç bölümlerine ayrılmalı ve 400 kelimeyi geçmemelidir. Derleme, olgu sunumları ve benzerlerinde Öz; kısa ve tek paragraflık olmalı, derlemelerde 300, olgu sunumlarında 250 kelimeyi geçmemelidir.

Anahtar Kelimeler: Türkçe Öz'ün ve İngilizce Abstract'ın sonlarında bulunmalıdır. En az 3 en fazla 6 adet yazılmalıdır. Kelimeler birbirlerinden noktalı virgül ile ayrılmalıdır. İngilizce Anahtar Kelimeler (Keywords) "**Medical Subject Headings (MESH)**"e uygun (www.nlm.nih.gov/mesh/MBrowser.html) olarak verilmelidir. Türkçe Anahtar Kelimeler "Türkiye Bilim Terimleri'ne uygun olarak verilmelidir (www.bilimterimleri.com). Bulunamaması durumunda bire bir Türkçe tercümesi verilmelidir.

Şekil, Fotoğraf, Tablo ve Grafikler: Metin içinde geçtiği yerlerde ilgili cümlenin sonunda belirtilmeli, metin içine yerleştirilmemeli, kaynaklardan sonra metin sonuna eklenmelidir. Kullanılan kısaltmalar altındaki açıklamada belirtilmelidir. Daha önce basılmış şekil, resim, tablo ve grafik kullanılmış ise yazılı izin alınmalıdır ve bu izin açıklama olarak şekil, resim, tablo ve grafik açıklamasında belirtilmelidir. Makale yazarlar tarafından akademik intihal önleme programından geçirilmelidir. Resim/fotoğraf jpeg ve en az 300 dpi çözünürlükte olmalıdır.

Metin Bölümleri: Yayımlanmak üzere gönderilecek yazı örnekleri şu şekildedir.

Editöriyel Yorum/Tartışma: Yayınlanan orijinal araştırma makaleleri ile ilgili, araştırmanın yazarları dışındaki, o konunun uzmanı tarafından değerlendirilmesidir. Dergide makalelerden önce yayımlanır.

Araştırma Makalesi: Prospektif-retrospektif ve her türlü deneysel çalışmalar yayımlanabilmektedir. Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Sonuç olarak düzenlenmelidir. Öz (yaklaşık 200-250 kelime; amaç, gereç ve yöntem, bulgular ve sonuç bölümlerinden oluşan Türkçe ve İngilizce), Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Sonuç, Teşekkür, Kaynaklar.

Derleme: Davet edilen yazarlar tarafından veya doğrudan hazırlanabilir. Tıbbi özellik gösteren her türlü konu için son tıp literatürünü de içine alacak şekilde hazırlanabilir. Öz (yaklaşık 200-250 kelime, bölümsüz, Türkçe ve İngilizce), konu ile ilgili Başlıklar, Kaynaklar.

Olgu Sunumu: Tanı ve tedavide farklılık gösteren veya nadir görülen makalelerdir. Yeterli sayıda fotoğraflarla ve şemalarla desteklenmiş olmalıdır. Öz (yaklaşık 100-150 kelime; bölümsüz; Türkçe ve İngilizce), Giriş, Olgu sunumu, Tartışma, Sonuç olarak düzenlenmelidir.

Editöre Mektup: Dergide son bir yıl içinde yayımlanan makaleler ile ilgili okuyucuların değişik görüş, tecrübe ve sorularını içeren en fazla 500 kelimelik yazılardır. Başlık ve Öz bölümleri yoktur. Kaynak sayısı 5 ile sınırlıdır. Hangi makaleye (sayı, tarih verilerek) ithaf olunduğu belirtilmeli ve sonunda yazarın ismi, kurumu, adresi bulunmalıdır. Mektuba cevap, editör veya makalenin yazar(lar)ı tarafından, yine dergide yayımlanarak verilir.

Eğitim: Derginin kapsamı içinde güncel konularda okuyucuya mesaj veren son klinik ve laboratuvar uygulamaların da desteklediği bilimsel makalelerdir. Öz (yaklaşık 200-250 kelime; bölümsüz; Türkçe ve İngilizce), konu ile ilgili Başlıklar, Kaynaklar.

Kitap Değerlendirmeleri: Derginin kapsamı içinde güncel değeri olan ulusal veya uluslararası kabul görmüş kitapların değerlendirmeleridir.

KAYNAKALRDAN HEMEN ÖNCE BELIRTILMESI GEREKENLER

ETİK BEYANLAR

Etik Kurul Onayı (Eğer gerkeiyorsa): "Çalışma için …….. Etik Kurulu'ndan .....tarih ve ..... sayı /karar no ile etik kurul onayı alınmıştır." ifadesiyle yazarlar tarafından belirtilmelidir.

Aydınlatılmış Onam: Bu çalışmaya katılan hasta(lar)dan yazılı onam alınmıştır (Olgu sunumlarında ve kişilerle yapılan prospektif çalışmalarda mutlaka olmalıdır. Eğer çalışma retrospektif ise: "Aydınlatılmış Onam: Çalışma retrospektif olarak dizayn edildiği için hastalardan aydınlatılmış onam alınmamıştır." ifadesiyle yazarlar tarafından belirtilmelidir.

Hakem Değerlendirme Süreci: "Harici çift kör hakem değerlendirmesi" ifadesiyle yazarlar tarafından belirtilmelidir.

Çıkar Çatışması: "Yazarlar bu çalışmada herhangi bir çıkara dayalı ilişki olmadığını beyan etmişlerdir." ifadesiyle yazarlar tarafından belirtilmelidir.

Finansal Destek: "Yazarlar bu çalışmada finansal destek almadıklarını beyan etmişlerdir" ifadesiyle yazarlar tarafından belirtilmelidir.

Yazar Katkıları: "Yazarların tümü; makalenin tasarımına, yürütülmesine, analizine katıldığını ve son sürümünü onayladıklarını beyan etmişlerdir." ifadesiyle yazarlar tarafından belirtilmelidir.

Teşekkür Yazısı: Varsa kaynaklardan önce yazılmalıdır.

Kaynaklar: Kaynaklar makalede geliş sırasına göre yazılmalıdır. Kaynaktaki yazar sayısı 6 veya daha az ise tüm yazarlar (soyadı ve adının ilk harfi olacak şekilde olmalı, yazar isimleri birbirinden virgül ile ayırılmalı) belirtilmeli, 7 veya daha fazla ise ilk 3 isim yazılıp ve ark. ("et al") eklenmeli, makale ismi (Tümce şeklinde sadece cümlenin ilk harfi ve özel isimlerin ilk harfi büyük olacak), kısa dergi adı, yıl, cilt, kısa sayfa no (15-8. şeklinde olacak, 15-18 olmayacak) eklenmeli ve noktalama işaretleri arasında birer boşluk bırakılmalıdır. Kaynak yazımı için kullanılan format Index Medicus'ta belirtilen şekilde olmalıdır (www. icmje.org). Kaynak listesinde yalnızca yayınlanmış ya da yayınlanması kabul edilmiş veya Doi numarası almış çalışmalar yer almalıdır. Dergi kısaltmaları **Cumulated Index Medicus**'ta kullanılan stile uymalıdır (http://www2.bg.am.poznan.pl/czasopisma/medicus.php?lang=eng.). Kaynak sayısının araştırma makalelerinde 40, derlemelerde 60, olgu sunumlarında 20, editöre mektupta 10 ile sınırlandırılmasına özen gösterilmelidir. Kaynaklar metinde cümle sonunda nokta işaretinden hemen önce parantez kullanılarak belirtilmelidir. Örneğin (4,5). Kaynakların doğruluğundan yazar(lar) sorumludur. Yerli ve yabancı kaynakların sentezine önem verilmelidir.

4. Şekil, Grafik, Resim ve Tablo Başlıkları

Başlıklar kaynaklardan sonra yazılmalıdır. Her biri ayrı bir görüntü dosyası (en az 300 dpi çözünürlükte, jpg) olarak gönderilmelidir.

Makalenin basıma kabulünden sonra Dizginin ilk düzeltme nüshası sorumlu yazara e-posta yoluyla gönderilecektir. Bu metinde sadece yazım hataları düzeltilecek, ekleme çıkartma yapılmayacaktır. Sorumlu yazar düzeltmeleri 2 gün içinde bir dosya halinde e-posta ile yayın idare merkezine bildirecektir.

Kaynak Yazım Örnekleri

Dergilerden yapılan alıntı;

Cesur S, Aslan T, Hoca NT, Çimen F, Tarhan G, Çifci A. Clinical importance of serum neopterin level in patients with pulmonary tuberculosis. Int J Mycobacteriol 2014; 3: 15-8 (15-18 değil).

Kitaptan yapılan alıntı;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Tek yazar ve editörü olan kitaptan alıntı;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams&Wilkins; 1996: 46-60.

Çoklu yazar ve editörü olan kitaptan alıntı;

Schulz JE, Parran T Jr: Principles of identification and intervention. In:Principles of Addicton Medicine, Graham AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams&Wilkins; 1998: 1-10.

Eğer editör aynı zamanda kitap içinde bölüm yazarı ise;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag; 1988: 45-67.

Doktora/lisans tezinden alıntı;

Kılıç C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Bir internet sitesinden alıntı;

Sitenin adı, URL adresi, yazar adları, erişim tarihi detaylı olarak verilmelidir.

Doi numarası vermek;

Joos S, Musselmann B, Szecsenyi J. Integration of complementary and alternative medicine into family prac- tice in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi:10.1093/ecam/nep019).

Diğer referans stilleri için "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References" sayfasını ziyaret ediniz.

"Bu çalışmanın içindeki materyalin tamamı ya da bir kısmının daha önce herhangi bir yerde yayımlanmadığını ve halihazırda da yayın için başka bir yerde değerlendirilmede olmadığını beyan ederim." Bu 400 kelimeye kadar olan özler hariç, sempozyumlar, bilgi aktarımları, kitaplar, davet üzerine yazılan makaleler, elektronik formatta gönderimler ve her türden ön bildirileri içerir.

Sponsorluk Beyanı

Yazarlar aşağıda belirtilen alanlarda, varsa çalışmaya sponsorluk edenlerin rollerini beyan etmelidirler:

1. Çalışmanın dizaynı 2. Veri toplanması, analizi ve sonuçların yorumlanması 3. Raporun yazılması

KONTROL LİSTESİ

Kontrol listesindekiler eksiksiz yapılmalıdır.

Makalede mutlaka olması gerekenler;

—Editöre Sunum Sayfası

—Başlık Sayfası

- Etik Durum,
- "Çıkar Çatışması Durumu" belirtir cümle,
- Orcid numaraları ve yazar bilgileri bu sayfada olmalıdır.

—Ana Metin

—Telif Hakkı Devri Formu

1. **Editöre Sunum Sayfası:** Sorumlu Yazar tarafından editöre hitaben yazılmış olmalıdır. Telefon ve E-posta eklenmelidir. Gönderilen makalenin adı, kısa adı, "Daha önceden yayımlanmamış, şu an herhangi bir dergiye değerlendirilmek üzere gönderilmemiştir ve yazarların kendi orijinal çalışmasıdır" ibaresi, "Çıkar Çatışması Beyanı" içermelidir.
2. **Başlık sayfası:** Türkçe ve İngilizce Makale başlıkları/Kısa başlıklar, Yazarlar ve Kurumları, Sorumlu Yazar posta adresi ve telefon, tüm yazarların **Orcid no** (2019 yılından itibaren zorunludur) ve **E-posta** adresleri. **Başlıkta özel isimler ve ilk harf dışında küçük harf kullanılmalıdır**.
3. **Makalenin Ana Metin sayfaları:** Türkçe ve İngilizce Makale Başlıkları/Kısa Başlıklar, Türkçe ve İngilizce Öz/Abstract ve Anahtar Kelimeler/Keywords, Makale Metni, Kaynaklar, Tablo ve Şekil Başlıkları, Tablolar. **Bu sayfada yazar isimleri, kurum bilgileri olmayacaktır.**
4. **Yazı tipi:** Başlıklarda "Times New Roman" ve 12 punto olmalı, makalenin diğer kısımlarında 11 punto, çift boşluklu satır arası ve tüm alanlarda 2,5 cm girinti ayarıyla yazılmalıdır.
5. **Öz/Abstract:** Türkçe özet **ÖZ** ile başlamalı; "**Giriş/Amaç, Gereç ve Yöntem, Bulgular ve Sonuç**" kısımlarını içermelidir. İngilizce özet **ABSTRACT** başlığıyla başlamalı "**Introduction/Aim, Material and Method, Findings/Results, Conclusion**" kısımlarını içermelidir.
6. **Anahtar Kelimeler/Keywords:** Türkçe Öz kısmının altına "**Anahtar Kelimeler**", İngilizce "Abstract" kısmının altında "**Keywords**" (birleşik) halde eklenmelidir. Anahtar kelimeler en az 3, en çok 6 kelime/sözcük olmalı, birbirlerinden virgülle ayırılmalı ve MeSH'e uygun olmalıdır.
7. **G**ereç ve Yöntem kısmında **Etik Kurul Onayı** alındığı (Alındığı yer, tarih, etik kurul no olacak şekilde yazılması önerilir) belirtilmelidir. Etik Kurul Onayı gerektirmeyen makalelerde Kurum Onayı/İzni alındığı (Çıkar Çatışması olmaması için) belirtilmelidir. İlgili belgeler talep edildiğinde gönderilmelidir. Etik problemlerde sorumluluğun yazar(lar)da olduğu unutulmamalıdır.
8. **T**artışmada istatiksel terimler (p, r, α gibi) **kullanılmamalıdır.**
9. **"Maddi Destek/Çıkar Çatışması Durumu"** kaynakçadan önce belirtilmeli, "***Teşekkür Yazısı***" varsa kaynakçadan önce yazılmalıdır.
10. **Kaynak Gösterimi;** yazım kurallarında detaylı anlatıldığı gibi olmalıdır. Derginin sayı numarası "(2)" parantez içinde olacak şekilde bizim kaynakça gösterimimizde **bulunmamaktadır.** Altı yazara kadar yazarı olan makalelerde bütün yazarların adı yazılmalı (Soyadı ve Adının ilk harfi olacak şekilde), yedi ve daha üstü yazarlı makalelerde ilk üç yazar, et al (ve ark.) şeklinde kaynak gösterilmelidir. Makalenin adı Tümce kullanımı şeklinde (**özel isimler ve ilk harf dışında küçük harf kullanılmalıdır**) olmalıdır. **Derginin kısa adı verilmelidir.** Dergi adından sonraki noktalama işaretleri arasında birer boşluk bırakılmalıdır.
11. **T**ablo, Şekil ve Resimler ayrı bir başlık altında kaynakçadan sonra yerleştirilmelidir. **Şekil/Resim** (En az 300 dpi çözünürlükte, **jpeg** dosyası olmalıdır) ve **Tablo**lar ayrı bir veya daha fazla dosya halinde gönderilmelidir.
12. **Telif Hakkı Devri Formu:** Makalenin asıl dilinde doldurulmalıdır. Tüm yazarlar tarafından imzalanmalıdır. Tüm yazarların imzasının olmadığı durumlarda **Sorumlu Yazar** tüm yazarlar adına sorumluluğu alarak imzalayabilir.