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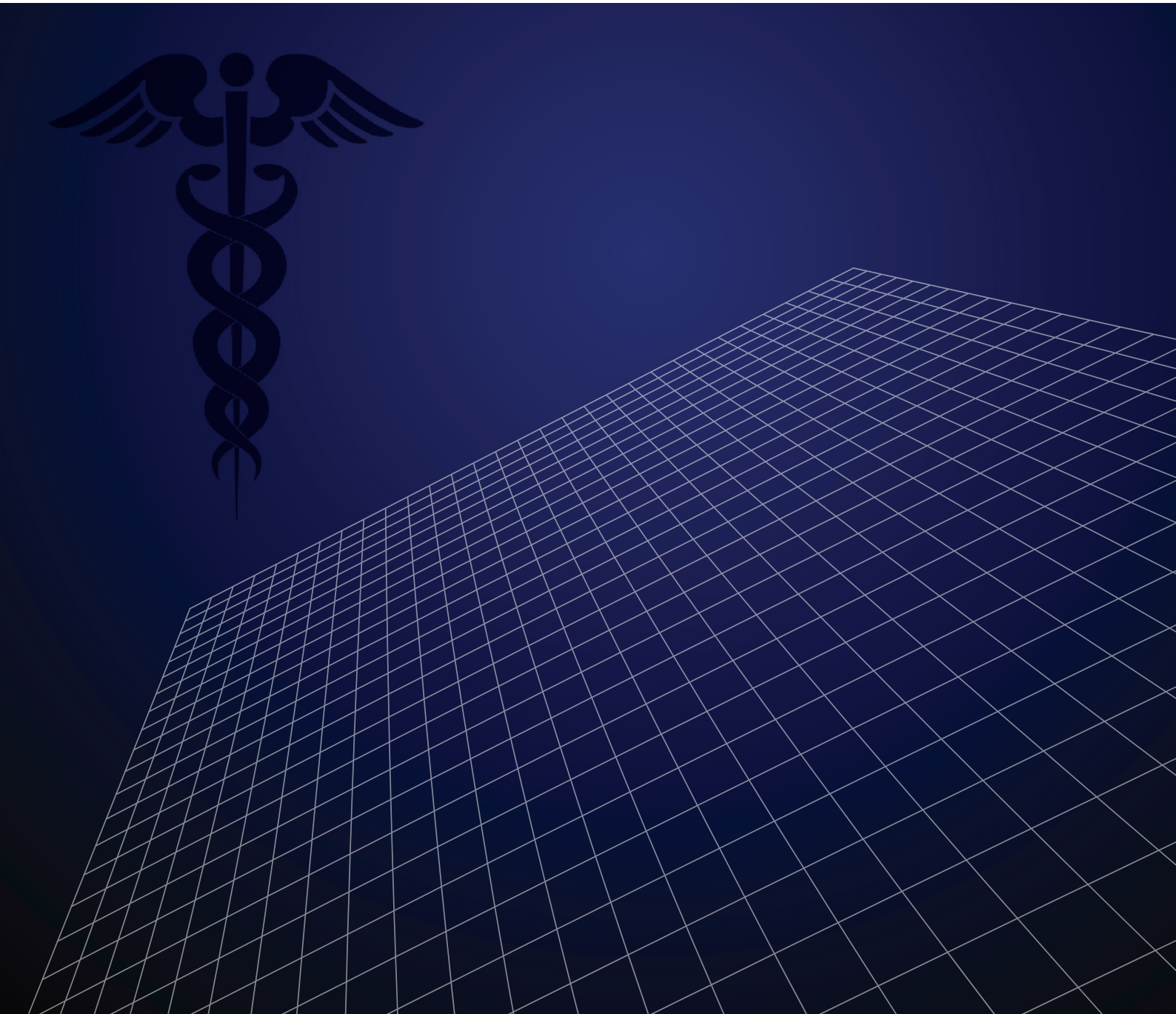

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Research Article

The effects of physical workload on cervical sagittal balance in surgeons

Cerrahlarda fiziksel iş yükünün servikal sagittal dengeye etkisi

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ABSTRACT

Aim: Surgeons are exposed to a variety of occupational risks, including work-related musculoskeletal disorders. Occupational necessities such as repetitive movements and long-term inappropriate posture in surgeons may be the cause of neck pain. This study evaluated the cervical sagittal balance parameters of the surgeons.

Material and Methods: This cross-sectional study included 57 patients with work-related neck pain between 2016 and 2019.T1S and Cobb angle were measured using magnetic resonance imaging. Personal characteristics of the participants, such as age, body mass index, height, and weight were obtained by a questionnaire filled in at the time of application.

Results: Fifty-seven participants were included in the study. Of these, 13 were neurosurgeons, 13 were otolaryngology surgeons, 12 were general surgeons, 11 were plastic surgeons, and 8 were cardiovascular surgeons.The mean age of the surgeons were 38.7 ± 6.44 yearsand the mean VAS of the surgeons were 5.12± 0.73. The mean T1S was 23.2 ° ± 7.95 ° and the mean Cobb angle was 12.3° ± 7.99° In the neurosurgeons, the mean T1S was 22.2 ° ± 11.18 ° and the mean Cobb angle was 8.4 ° ± 5.91 °. Among all surgical branches, neurosurgeons had the lowest mean values in both T1s and cobb angle measurements.

Coclusion: The physical workload of surgeons in their daily routines causes the cervical sagittal balance to deteriorate, suggesting that surgeons are in the high-risk group for occupational musculoskeletal diseases.

Key words: Neck pain, Cervical spine, T1 slope, cervical lordosis, surgeon

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ÖZ

Amaç: Cerrahlar, işle ilgili kas-iskelet sistemi bozuklukları da dahil olmak üzere çeşitli mesleki risklere maruz kalmaktadır. Cerrahlarda tekrarlayan hareketler ve uzun süreli uygunsuz duruş gibi mesleki gereklilikler sonucu boyun ağrıları görülebilmektedir. Boyun ağrıları nedenleri arasında servikal sagittal denge parametrelerinin önemli bir yeri vardır. Bu çalışmada cerrahların servikal sagittal denge parametrelerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu kesitsel çalışmaya 2016-2019 yılları arasında işle ilgili boyun ağrısı olan 57 hasta dahil edildi. Manyetik rezonans görüntüleme kullanılarak T1S ve Cobb açısı ölçüldü. Katılımcıların yaş, vücut kitle indeksi, boy, kilo gibi kişisel özellikleri başvuru sırasında doldurulan anket ile elde edildi.

Bulgular: Çalışmaya elli yedi katılımcı dahil edildi. Bunların 13'ü beyin cerrahı, 13'ü kulak burun boğaz cerrahı, 12'si genel cerrah, 11'i plastik cerrah ve 8'i kalp ve damar cerrahıydı. Cerrahların ortalama yaşı 38,7 ± 6,44 yıl ve ortalama VAS'ı 5,12± 0,73 idi. Ortalama T1S 23,2° ± 7,95° ve ortalama Cobb açısı 12,3° ± 7,99° idi. Beyin cerrahlarında ortalama T1S 22,2° ± 11,18° ve ortalama Cobb açısı 8,4° ± 5,91° idi. Tüm cerrahi branşlar içinde hem T1 hem de cobb açısı ölçümlerinde beyin ve sinir cerrahları en düşük ortalamaya sahipti.

Sonuç: Cerrahların günlük rutin iş yükü, servikal sagittal dengenin bozulmasına neden olmakta, bu da cerrahların mesleki kas-iskelet sistemi hastalıkları açısından yüksek risk grubunda olduğunu düşündürmektedir.

Anahtar Kelimeler: Boyun ağrısı, Servikal omurga, T1 eğimi, servikal lordoz, Cerrah

Introduction

Neck pain has become a major health problem in modern society, vand this is likely to be associated with adverse working conditions. The National Institute of Occupational Health (NIOSH) in the United States reported a relationship between the static load on the neck-shoulder muscle system; recurrent arm and hand movements; recurrent movements involving the same muscle groups with neck pain(1). In addition to physical risk factors in the work environment, it has been shown that working in negative psychosocial environments also may cause occupational neck pain(2, 3).

Heavy physical work with lifting, static muscular loading and inappropriatework positions are important risk factors for the development of occupational musculoskeletal diseases (4, 5). Surgeons are exposed to various physical and emotional risks during the day, although they are included in the white-collar employee group. It is stated that activities due to occupational necessity such as repetitive movements and long-term inappropriate posture in surgeons may be the cause of neck pain (6, 7).

In most of the studies that evaluated risk factors related to occupation, self-administered questionnaire was used. However, the evaluation of the effects of working conditions of occupational groups on the musculoskeletal system with radiological parameters allows us to obtain more objective data. Previous studies have reported that spinal sagittal irregularity and spinal degeneration are closely related to clinical symptoms (8). The cervical sagittal balance is related to the T1 slope and T1 slope which is highly correlated with other cervical parameters and plays an important role in the cervical sagittal alignment (9, 10). In patients with higher T1 slope, the risk of end plate damage and disc degeneration increases, and more cervical lordosis and energy expenditure is needed to maintain the horizontal balance (11). In addition, decreased segmental or global cervical lordosis is associated with degenerative changes of the cervical spine and is a cause of neck pain (12). Therefore, we think that these radiological parameters are appropriate to evaluate the effects of long-term biomechanical imbalance.

The aim of this study is to evaluate the cervical sagittal balance and spinal degeneration parameters of the among surgeons.

Material and Methods

Study Design and Population

Before starting this study, approval was obtained from the Ethics Committee of Ahi Evran University Faculty of Medicine and informed consent was acquired from all patients who were willing to participate in the study before the data was received. This cross-sectional study includes the surgeons with neck pain between 2016 and 2019. Neck pain and disability scales were filled, and cervical MRI was performed to all patients at the time of application. Inclusion criteria; Surgeons between ages 20-50 with neck pain, with or without neurological

symptoms and, a weekly operation time of ≥30 hours / week for at least two years, were included. Exclusion criteria: trauma, rheumatoid arthritis, spine tumors, patients with a history of cervical spine surgery.The study group includes neurosurgeons, ear nose throat surgeons, cardiovascular surgeons, general surgeons and plastic surgeons. The patient's informed consent was obtained from every participant.

Data Collection

Personal characteristics of the participants such as age, body mass index, height, smoking habits and marital status were obtained by a questionnaire filled in at the time of application. As a part of their clinical evaluation, the patients' clinical profiles were assessed using standardized questionnaires. Neck pain was evaluated using the visual analog scale. Neck pain was evaluated using the visual analog scale.

MRIs were performed in the radiology department of our hospital independent of the study, using the patient in the supine position.All images were obtained using the same imaging system. The standard hospital protocol for the cervical spine was used for each patient in the MRI unit. Cobb angle and T1S measurements were measured simultaneously by two spinal surgeons using the hospital imaging software system. Measurements made from mid-sagittal line. T1S is defined as the angle between the line drawn parallel to the upper end plate of T1 and the line drawn in the horizontal plane. The Cobb angle (sagittal lordosis) was measured as the angle between the parallel line to the lower end plate of C2 and the parallel line drawn to the lower end plate of the C7. Disc degeneration assessment between C2 and C7 was performed using Miyazaki's grading system22) and sagittal MRI images.

Statistical analysis was performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013). Descriptive statistics were presented using mean and Standard deviation for normally distributed variables and median (and minimum-maximum) for the non-normally distributed variables. Non-parametric statistical methods were used for values with skewed distribution. For comparison of two non-normally distributed groups Mann Whitney U test was used. Statistical significance was accepted when two-sided p value was lower than 0.05.

Results

Fifty-seven participants were included in the study. Of these, 13 were neurosurgeons, 13 were otolaryngology surgeons, 12 were general surgeons, 11 were plastic surgeons, and 8 were cardiovascular surgeons.The mean age of the surgeons were 38.7 ± 6.44 yearsand the mean VAS of the surgeons were 5.12± 0.73. The demographic data of the subgroups are presented in Table 1.

When the surgeons' weekly surgical operation times were evaluated, the average weekly operation time of neurosurgeons was > 40 hours, while the average weekly operation times of cardiovascular surgeon, otolaryngology surgeons, general surgeons and plastic surgeons were found to be <40 hours. There was no statistically significant difference between the surgical branches in terms of personal characteristics such as body mass index, height, weight.

The mean T1S was 23.2 ° ± 7.95 ° (range, 9 ° - 40 °) and the mean Cobb angle was 12.3° ± 7.99° (range, 2 ° - 29 °). Radiological measurements of all surgical branches are summarized in Table 2.

In the neurosurgeons, the mean T1S was 22.2 ° ± 11.18 ° (range, 9 ° - 40 °) and the mean Cobb angle was 8.4 ° ± 5.91 ° (range, 3 ° - 21 °). Among all surgical branches, neurosurgeons had the lowest mean values in both T1s and cobb angle measurements (Table

Table1. The demographic data of the according to surgical branches.

Variable	Neurosurgeons	Cardiovascular surgeon	General surgeon	ENT surgeon	Plastic surgeon	p value
Age (yr)	38.8±5.97	39.1±4.79	39.5±5.36	34.4±6.66	42.5±6.93	0.797
VAS	5.2±0.83	5.3±0.71	5.1±0.67	4.9±0.76	5.2±0.75	0.875
Weight (kg)	75.8±8.08	74.9±3.23	73.3±6.42	75.5±8.86	73.9±10.15	0.919
Height (cm)	170.8±5.81	173.7±3.81	169.9±7.39	168.2±8.47	167.9±6.31	0.177
BMI (kg/m2)	25.9±1.71	24.8±1.29	25.4±1.29	26.7±2.37	26.2±3.07	0.916

Abbreviations: ENT: Ear, nose and throat

Table 2. T1s and Cobb angle measurements according to surgical branches

Variable	Total study population	neurosurgeons	Cardiovascular surgeon	General surgeon	ENT surgeon	Plastic Surgeon
T1 slope (°)	23.1±8.05	22.2±11.18	23.5±7.6	21.8±6.17	23.8±8.44	24.1±6.34
Cervical lordosis (°)	12.3±7.99	8.4±5.91	11.1±9.34	12.3±8.8	14.9±6.46	14.6±9.13

Abbreviations: ENT: Ear, nose and throat

Table 3. Comparison between neurosurgeons and other surgical branches			
Variable	Neurosurgeons	Others	p
Age (yr)	38.8±5.97	38.5±6.59	0.779
VAS	5.2±0.83	5.09±0.71	0.718
T1 slope (°)	22.2±11.18	23.3±7.02	0.818
Cervical lordosis (°)	8.4±5.91	13.5±8.20	0.046

Discussion

In this study, cervical spine alignment measurements and segmental disc degeneration rates of surgeonswith neck pain were compared. When evaluating occupational musculoskeletal diseases, most of the time questionnaire was used. This situation may affect the results of the study, depending on many factors (high quantitative demands, low social support, and low influence at work). However, musculoskeletal diseases are known to recur with intervals(13, 14). There may be some changes at intensity of complaints even in the same individual who is evaluated at two different times. Therefore, we think that the examination of radiological images is more valuable than questionnaire studies in order to evaluate the effects of physical workload and working in adverse psychosocially environments on musculoskeletal diseases.

The cervical sagittal balance defines how the cervical spine is positioned in the sagittal plane. In many studies conducted about this subject, the deterioration of cervical sagittal balance has been reported to cause headache, neck pain and poor quality of life(15, 16, 17, 18).Deterioration of the cervical spine balance changes the load distribution and momentum between the vertebrae and causes degeneration in the segment that is exposed to the maximum load(19). T1 slope is a useful parameter for evaluating sagittal balance(20, 21). Yang et al. reported that patients with low T1 slope less than 25 ° had a higher degree of degeneration independent from age and gender and T1 slope less than 25 ° is a potential risk factor for cervical spondylosis development(22). In addition, high T1 slope causes patients to spend more energy on the posterior neck muscles to maintain horizontal view and horizontal balance(20). This causes the muscles to become tired more easily and cause pain. Therefore, surgeons who need long-term flexion and rotation of the neck, have higher risk for neck pain. In the present study, the mean T1S values of all surgical branches included in the study were found to be <25 (Table 2). These results suggest that surgeons have risk of occupational neck pain.

Loss of the cervical lordosis causes an increase in the length and tension of the posterior spinal muscles(23). The tension in these muscles is thought to cause neck pain or cervicogenic headache(24).McAviney et al. evaluated 277 patients with or without neck pain and reported that hypo-lordosis (cervical angle ≤20 °) was associated with neck pain(15). Therefore, in our study, we used the Cobb angle to evaluate the occupational neck pain. The mean Cobb angle was 12.3 ° ± 7.99 ° in the surgeons. These results suggest that surgeons may have loss of cervical lordosis and related neck pain complaints. In addition, when surgeons are evaluated among themselves, neurosurgeons are shown to have worse Cobb angle measurements than other surgical groups, since neurosurgeons have both longer weekly operation times than others and use auxiliary equipment (microscope or loop) in all surgeries (Table 3).

It is known that neck is the most affected body region during surgical operations(25). Equipment widely used by surgeons such as microscopes, endoscopes and loupes cause a significant increase in the load on the cervical spine(26). In addition, inappropriate working conditions such as prolonged standing inappropriate posture and neck flexion, are known to increase the risk of developing neck pain(27, 28, 29, 30). The results of our study also showed that surgeons had almost the same risk for occupational neck pain.

Study limitations

This study has several limitations. The first one is that there are small number of patients due to specificity ofjob groups and age categories. Second one is asymptomatic individuals from both groups were not taken into evaluation. Since the evaluation of asymptomatic individuals in our study was not performed, the relationship between the radiological parameters and clinical symptoms could not be clearly evaluated.

Conclusion

The physical workload of surgeons in their daily routines causes the cervical sagittal balance to deteriorate, suggesting that surgeons are in the high-risk group for occupational musculoskeletal diseases.

Conflict of Interest

No conflict of interest was declared by the authors. In addition, no financial support was received for this study.

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Research Article

The relationship between single gene polymorphism and response to cisplatin and 5-FU treatment in patients with head and neck cancer

Baş boyun kanserli hastalarda tek gen polimorfizmi ile sisplatin ve 5-FU tedavisine yanıt arasındaki ilişki

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Abstract

Aim: Head and neck cancers are the sixth most common type of cancer worldwide. The treatment process of head and neck cancers is classified as chemotherapy or chemoradiotherapy. In this study, the relationship of ERCC1, XRCC1 and MTHFR genes with treatment response was investigated.

Material and Methods: In the study, 5 ml of blood was collected from the patients to investigate single nucleotide polymorphism, DNA was isolated and investigated by pyrosequencing method.

Results: Patients were evaluated according to RECIST criteria; head and neck computed tomography scans were performed before treatment (4 weeks) and after every three cycles. The overall response rate (RR) was 10 (25%) PD, 7 (17.5%) SD, 9 (22.5%) PR, and 14 (35%) CR. Of the patients who presented with at least one polymorphic variant, four had PD, 3 had SD, 3 had PR and 1 had CR.

Conclusion: In this study, the clinical behaviour of a group of head and neck carcinoma patients was retrospectively evaluated for association with three single nucleotide polymorphisms. These included C8092A in the ERCC1 gene, G28152A in the XRCC1 gene, and C677T and A1298C in the MTHFR gene.

Keywords: Head and neck cancer, SNP, cisplatine, 5-FU

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Öz

Amaç: Baş ve boyun kanserleri dünya çapında en sık görülen altıncı kanser türüdür. Baş ve boyun kanserlerinin tedavi süreci kemoterapi veya kemoradyoterapi olarak sınıflandırılır. Bu çalışmada ERCC1, XRCC1 ve MTHFR genlerinin tedavi ile yanıt ilişkisi araştırıldı.

Gereç ve Yöntemler: Çalışmada tek nükleotid polimorfizmini araştırmak amacıyla hastalardan 5 ml kan alınarak DNA izole edildi ve pirosequencing yöntemiyle araştırıldı.

Bulgular: Hastalar RECIST kriterlerine göre değerlendirildi; tedaviden önce (4 hafta) ve her üç siklustan sonra baş ve boyun bilgisayarlı tomografi taramaları yapıldı. Genel yanıt oranı (RR) 10 (%25) PD, 7 (%17,5) SD, 9 (%22,5) PR ve 14 (%35) CR idi. En az bir polimorfik varyantı olan hastaların dördünde PD, 3'ünde SD, 3'ünde PR ve 1'inde CR vardı.

Sonuçlar: Bu çalışmada bir grup baş boyun karsinomu hastasının klinik davranışı, üç tek nükleotid polimorfizmi ile ilişki açısından retrospektif olarak değerlendirildi. Bunlar arasında ERCC1 geninde C8092A, XRCC1 geninde G28152A ve MTHFR geninde C677T ve A1298C yer alıyordu.

Anahtar Kelimeler: Baş ve boyun kanseri, SNP, cisplatin, 5-FU

Introduction

Head and neck squamous cell carcinoma (HNSCC) generally affect the mouth, lips, nose, sinuses, larynx, and throat. It is the sixth most common cancer worldwide. In men and women, squamous cell carcinoma (SCC) represents 2% and 4%, respectively (1). Chemotherapy, radiotherapy and surgical intervention are used in the treatment of squamous cell carcinoma as well as other cancers. While surgery generally is used to cure SCC (2). Chemotherapy is the most frequently employed to treat patients with advanced or recurring oral SCC (OSCC). The overall 5-year survival rate of patients with advanced HNSCC is still as low as 25% despite improvements in the rate of early detection, multi-drug therapies, and surgical interventions over the past 30 years. The development of drug resistance in patients often leads to treatment failure. The studies indicate that over 90% of cancer patient fatalities and morbidities are attributed to drug resistance (3).

Cisplatin, also known as cis-dichlorodiamine platinum, belongs to the platinum-based antineoplastic drug family. Cisplatin has anti-cancer abilities and is a non-specific antineoplastic drug. It interacts with the purine base of DNA, causing DNA damage and thus the death of cancer cells. While 80-90% of patients initially respond positively to cisplatin treatment, some tumour cells become resistant to cisplatin due to tumour heterogeneity. This resistant is 2 times higher in women than in men (4). 5-Fluorouracil (5-FU) is a cytotoxic chemotherapy agent used to treat various cancers including breast, lung, head and neck, stomach and colon cancers. 5-FU primarily inhibits the enzyme thymidylate synthase, preventing the thymidine production needed for DNA synthesis, acting as an antimetabolite to stop cell growth. In addition, 5-FU transform into 5-fluorouridine triphosphate, which penetrates the RNA structure to prevent the production of tumour RNA (5).

X-ray Repair Cross-complementing 1 (XRCC1) is a fundamental gene within the base excision repair (BER) pathway. The substitution of guanine with adenine at position 28152 (G28152A) in exon 10 of the XRCC1 gene results in a substitution of arginine with glutamine at codon 399 (Arg399Gln). This amino acid change causes a decrease in DNA repair capability (6). Glutathione S-transferases play a critical role in the cell's defence system. These phase II detoxification enzymes are responsible for detoxifying several chemotherapeutic drugs, including platinum. The A313G in exon 5 single nucleotide polymorphism, which causes alterations in amino acid is the most prevalent in GSTP1 (6). The C8092A polymorphism in the Excision Repair Cross-Complementing 1(ERCC1) is a single change in DNA nucleotide sequence which replaces cytosine with adenine. Studies indicate that the genotype variant causes decreased enzymatic activity. Furthermore, it is located on the 3' untranslated region of the ERCC1 gene, involved in the translational repression of ERCC1 mRNA and it affects ERCC1 mRNA stability (7). The ERCC1 C8092A polymorphism has supported to predict the overall survival for some cancer patients (8). The T19007C polymorphism, which is synonymous and occurs at codon 118 (converting the common codon usage AAC to an infrequent one, AAT - both coding for asparagine), has been suggested to impair

ERCC1 translation and affects the response to chemotherapy (9). Methylenetetrahydrofolate reductase (MTHFR) exhibits various polymorphisms on chromosome 1p. Among them, the C677T (Ala to Val) and A1298C (Glu to Ala) single nucleotide polymorphisms (SNPs) are the two most frequently associated with altered enzyme activity. The C677T gene polymorphism cause a thermolabile enzyme. TT and CT genotypes experience a reduction in enzyme activity of approximately 70% and 35%, respectively. The A1298C gene polymorphism leads to decreased enzyme activity, although not to the same degree as the C677T gene polymorphism (10-11).

This study uses the basic principles and methods of evidence-based medicine to evaluate the efficacy of platinum and 5-FU-based chemotherapy in head and neck cancer cases of polymorphisms in the XRCC1, ERCC1 and MTHFR gene in the Turkish population. This study is expected to lay the foundation for future investigations into the correlation between platinum-5-FU drug efficacy and gene polymorphisms of XRCC1, ERCC1, and MTHFR.

Material and Methods

Forty volunteer patients with head and neck cancer who were followed up in Pamukkale University Faculty of Medicine, Medical Oncology Outpatient Clinic were included in our study. Approval was obtained from Pamukkale University Non-Interventional Ethics Committee. Informed consent forms were obtained from the participating patients. Patients received cisplatin and 5-FU-based chemotherapy in the first line after diagnosis, and a 3-week treatment regimen was applied. Response was evaluated according to RECIST criteria, with computed tomography scans of the head and neck performed prior to treatment (at 4 weeks), after every three cycles, and after treatment completion (at 4 weeks). 5ml of whole blood was collected from the patients. DNA isolation from the collected whole blood was obtained using qiagen miniBlood kit (Cat no: 51106 Düsseldorf Germany). Single gene variation was analysed from the obtained DNA using pyrosequencing system. Patient data were obtained from patient files. Statistical analysis was performed with SPSS-17 package programme. The results were evaluated at 95% confidence interval. $P<0.05$ was considered statistically significant. Categoric variables with more than two categories were by SPSS for the Cox analysis.

Results

Patient characteristics and clinical outcomes.

Forty patients were identified between 2008 and 2012 (Table I). The median age was 61.2 years and 75% were male. The oral cavity was the most common primary site (40%). All patients were classified as locally advanced. All patients were treated with cisplatin and 5-FU.

Table 1 Characteristics of the Patients With Head and Neck and of the Treatments Administered (N 40)

Characteristic	No of patients	%
Age		
Median	61,2	
Range	40-78	
Sex		
Female	10	25
Male	30	75
Tumor location		
Oral Cavite	16	40
Oropharynx	12	30
Hypopharynx	4	10
Larynx	4	10
Tongue	2	5
Nasopharynx	2	5
Smoking history		
Never	8	20
Current	32	80

Allele Frequencies

The frequencies of the various gene polymorphisms are shown in Table 2. As a result of the six-gene polymorphism, no patient had common polymorphisms for all genes. Ten patients had two or more polymorphic homozygous variants. Twenty-seven patients had two or more heterozygous genes. No statistically significant association was observed between the presence of simultaneous gene polymorphisms.

Table 2. Allele Frequencies of the Indicated Gene Variants in the Patients with Head and Neck

	Common Homozygotes		Heterozygotes		Polymorhic Homozygotes	
Gene Variant	No	%	No	%	No	%
ERCC1 C8062A	24	60	13	32.5	3	7.5
ERCC1 T19007C	13	32.5	14	35	13	32.5
XRCC1 G28152A	24	60	13	32.5	3	7.5
GSTP1 A313G	13	32.5	25	62.5	2	2.5
MTHFR C677T	20	50	17	42.5	3	7.5
MTHFR A1298C	18	45	13	32.5	9	22.5

Correlation With Clinical Response

After 12 months of follow-up (range, 4 to 12 months; median, 8 months), response/survival data were available for all. At the end of the experiment, 36 patients (90%) were alive, 10 (25%) were alive but progression, and 4 (10%) had died. The overall response rate (RR) was 10 (25%) PD, 7 (17.5%) SD, 9 (22.5%) PR,

and 14 (35%) CR. The results of the analysis of the response rate by genotype are shown in Table 3. Of the patients who presented with at least one polymorphic variant, 4 had PD, 3 had SD, 3 had PR and 1 had CR (P.021).The treatment response analysis indicates that per additional polymorphic variant, the probability of experiencing PD was 2.14 times greater than that of SD (P .048). Furthermore, per additional variant, PD was respectively 2.28 and 1.05 times more likely than PR (P.036) .

Table 3. Response to Treatment of the Advanced Patients with Head and Neck According to Their Genotypes

	Progressive Disease		Stable Disease		Partial Response		Complete Response		p
Gene Variant	No	%	No	%	No	%	No	%	value
ERCC1 8062									0.049
C/C	4	16.6	2	8.4	6	25	12	50	
C/A	4	30.8	4	30.8	3	23	2	15,4	
A/A	2	66.7	1	33.3					
ERCC1 19007									0.052
T/T	2	14.3	3	21.5	4	28.5	5	35.7	
T/C	4	30.8	1	7.7	3	23	5	38.5	
C/C	4	30.8	3	23	2	15.4	4	30.8	
XRCC1									0.042
G/G	5	20.8	3	12.5	4	16.7	12	50	
G/A	3	23	3	23	5	38.5	2	15.5	
A/A	2	66.7	1	33.3					
GSTP1									0.058
A/A	3	23	4	31	3	23	3	23	
A/G	6	24	2	8	6	24	11	44	
G/G	1	50	1	50					
MTHFR 677									0.047
C/C	4	20	2	10	5	25	9	45	
C/T	4	23.5	4	23.5	4	23.5	5	29.5	
T/T	2	66.7	1	33.3					
MTFR 1298									0.040
A/A	4	22.2	2	11.1	4	22.2	8	44.5	
A/C	3	23	3	23	2	15.5	5	38.5	
C/C	3	33.3	2	22.3	3	33.3	1	11.1	

Discussion

Although many polymorphisms in genes involved in the DNA repair mechanism have been identified, their effects on the biological process have not been clearly explained. Researchers have focused on to explain the function of SNPs in genes implicated in NER/BER in response to chemotherapy based on cisplatin recently. The papers have been reported that ERCC1 C8092A mutation is linked to poor clinical outcomes in patients suffering from stages IIIA-IV lung cancer who have been treated with platinum-based combination therapy (12). Researchers showed that the compound mutation effects of the C8092A and T19007C genotypes act as an independent prognostic factor in T4 breast cancer patients (8). Vaezi et al. reported, that the C8092A polymorphism in the ERCC1 gene is a risk prognostic factor in head and neck cancers (13). Castro et al. (2010) showed that T19007C SNP in the ERCC1 gene has no effect on overall survival, on the contrary to literature including esophageal cancer, colorectal cancer, ovarian cancer and non-small cell lung cancer patients. When we analyzed in terms of treatment response relationship, T19007C polymorphism in ERCC1 gene was not found to be statistically significant and C8092A polymorphism was found to be statistically significant. When we evaluated our results, we found that correlated with the literature.

Genetic polymorphisms in the GSTP1 and XRCC1 genes have been shown to be associated with chemosensitivity and clinical outcomes when evaluated in their single and combined forms (6). In other study, Zhou et al. found statistically significant association of G28152A polymorphism in XRCC1 gene and A313G polymorphism in GSTP1 gene with the treatment response of lung cancer patients. In the meta-analysis of Vaezi et al., it was reported that the G28152A polymorphism in

the XRCC1 gene was associated with response to treatment in the Chinese population but not in the Caucasian race (6). Furthermore, NSCLC patients treated with platinum-based regimens and possessing G28152A polymorphism in the XRCC1 gene exhibit a low objective response rate (14). In our study, G28152A polymorphism in XRCC1 gene was found to be statistically significant in relation to treatment response, and this results are consistent with studies in Chinese and Caucasian populations. Although the A313G polymorphism in GSTP1 gene were significant in the Chinese population, the significant results were not found in our study. So we have thought that it may be due to ethnic origin.

MTHFR serves as a critical enzyme in the 5-FU metabolic process, and its enzyme activity can be diminished due to the MTHFR C677T and A1298C polymorphisms. As a result, there may be a strong link between the MTHFR C677T and A1298C polymorphisms and the effectiveness of 5-FU therapy (15). Some studies have reported a significant association between the C677T genetic variant and increased tumor response rates to 5-FU-based therapy. The A1298C allele has been linked to an increased risk of severe adverse events or poor survival after 5-FU-based chemotherapy (10). In our study, we have found that C677T and A1298C polymorphisms in MTHFR gene was association with increased tumor response rates.

In this study, five single nucleotide polymorphisms, C8092A and T19007C, in ERCC1 gene, G28152A in XRCC1 gene, A313G in GSTP1 gene and C677T and A1298C, in MTHFR gene were retrospectively evaluated for their association with the clinical behavior in a group of head and neck carcinoma patients of West Anatolia, receiving platinum and 5-FU-based chemotherapy. We have demonstrated that this five genotypes have a role as independent prognostic factors for a more favorable clinical outcome in this subset of patients. According to our results, A313G polymorphism in GSTP1 gene and T19007C polymorphism in ERCC1 gene were not found significant. This study that investigate the relationship between single nucleotide polymorphism and response to treatment in head and neck cancers is the first. However, this study is limited in terms of the number of patients.

Conflict of interest

The authors declare that they have no conflict of interest.

Financing

This study did not receive any funding.

Ethic

In this retrospective study, national and international ethical rules were complied with. This study approved Pamukkale University Ethic Committee with number of E-60116787-020-408595.

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Araştırma Makalesi

Acil servise başvuran yaşlı hastalarda eritrosit dağılım genişliği ile hastane içi mortalitesi arasındaki ilişki

The correlation between red cell dustribution width and in-hospital mortality in elderly patients applied to the emergency services

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Öz

Amaç: Eritrosit dağılım genişliği tam kan sayımı incelemesinde kullanılan bir parametredir. Son çalışmalar, kırmızı kan hücresi dağılımının, birçok hastalıkta mortalitede klinik olarak anlamlı prediktif değerde artan mortalite ile ilişkili olduğunu göstermektedir. Hastaneden taburcu olan hastaların eritrosit dağılım değerleri ile hastaneye yatan hastaların RDW düzeylerini karşılaştırdık ve hastane içi mortalite ile ilişkisi olup olmadığını araştırdık.

Gereç ve Yöntemler: Bu çalışma acil serviste yapılmış kesitsel retrospektif bir çalışmadır. Dışlama kriterlerini karşılamayan toplam 843 kişi (435 çalışma(eski) grubu ve 408 kontrol grubu) çalışmaya dahil edildi. Eritrosit dağılım değerleri çalışma ve kontrol gruplarına göre değerlendirildi.

Bulgular: Çalışma(eski) grubunda kırmızı kan hücresi dağılımının ortalama değeri 16.03 olarak bulundu. Kontrol grubunda ortalama eritrosit dağılımı değeri 14,67 bulundu. Mann Whitney U testi ile karşılaştırıldığında çalışma(eski) grubunda kırmızı kan hücre dağılım değerinin kontrol grubuna göre anlamlı olarak arttığı ve mortalite ile ilişkili olduğu gösterildi ($p < 0.05$).

Sonuç: Ortalama kırmızı kan hücresi dağılım seviyeleri, kontrol grubu ile karşılaştırıldığında hastaneden ayrılan hastalarda anlamlı olarak daha yüksekti. Yüksek kırmızı kan hücresi dağılım değerinin, mortalite için öngörü değeri olduğu gösterilmiştir.

Anahtar Kelimeler: Acil Servis, Mortalite, Eritorsit Dağılım Genişliği

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Abstract

Aim: Red blood cell distribution width is a parameter used to in the whole blood count examination. Recent studies suggest that red blood cell distribution is associated with increased mortality in clinically significantpredictive value in mortality in many diseases. We compared the red blood cell distribution values of the patients who were discharged from the hospital and the RDW levels of the patients who were hospitalized and investigated whether they were associated with in-hospital mortality

Material and Methods: This study is a cross-sectional, retrospective study performed in the emergency department. A total of 843 people (435 study(ex) group and 408 control group) who did not meet the exclusion criteria were included in the study. Red blood cell distribution values were evaluated according to the study and control groups.

Results: The mean value of red blood cell distribution in the study(ex) group was found to be 16.03. In the control group, the mean value of red blood cell distribution was found to be 14.67. When compared with Mann Whitney U test, it was shown that red blood cell distribution value increased significantly in the study(ex) group compared to the control group and was associated with mortality ($p < 0.05$)

Conclusions: The mean red blood cell distribution levels were significantly higher in ex-hospital patients compared to the control group. The high red blood cell distribution value has been shown to be a predictive value for mortality.

Keywords: Emergency Medicine, RDW, Mortality

Giriş

Eritrosit dağılım genişliği (RDW), tam kan sayımında dolaşımdaki eritrositlerin hacim değişkenliğini ölçmek için kullanılan bir parametredir. RDW, farklı anemi türlerinin tanısına yardımcı olmak için bir test olarak kullanılır ve eritrosit hacminin ortalama eritrosit hacmine göre standart sapması değerinin 100 ile çarpılması sonucu hesaplanır. Son araştırmalar, RDW'nin klinik olarak anlamlı kardiyovasküler hastalık, inme, septik şok, bakteriyemi, diabetes mellitus (DM), karaciğer hastalığı, pankreatit, kalp yetmezliği (CHF) ve toplum kökenli pnömoni ile ilişkili olduğunu göstermiştir (1-12). Orta yaşlı ve yaşlı popülasyonda RDW ile mortalite arasındaki ilişkiyi araştıran çalışmalarda, yüksek RDW'nin malnütrisyon ve anemisi olmayan hastalarda yüksek mortalite ile ilişkili olduğu gösterilmiştir (7,8). RDW ile mortalite arasındaki ilişkinin altında yatan mekanizma tam olarak anlaşılamamakla birlikte, yüksek RDW'nin inflamasyon, doku hipoperfüzyonu, oksidatif stres veya böbrek yetmezliği gibi devam eden bir hastalık süreci ile ilişkili olduğu düşünülmektedir (13). Çalışmalar, RDW'nin mortalite açısından önemli bir prediktif değere sahip olduğunu göstermiştir, ancak acil servise başvuran yaşlı hastalarda RDW'nin prognostik değeri ile ilgili çalışmalar henüz yeterli değildir. Çalışmamızda hastaneden taburcu olan hastaların RDW değerleri ile yatan hastaların RDW değerlerini karşılaştırdık ve hastane içi mortalite ile ilişkisi olup olmadığını araştırdık.

Gereç ve Yöntemler

Bu çalışma, İzmir Katip Çelebi Üniversitesi Atatürk Eğitim ve Araştırma Hastanesi acil servisinde yapılan kesitsel, retrospektif bir çalışmadır. Örneklem sayısı bakımından 01/01/2017-31/12/2017 tarihlerinde hastanemize başvuran yaklaşık 250 bin hasta evren ve n=Nt2 olarak kabul edilmiştir. Örnek büyüklüğü p.q / d2 (N-1) + t2p.q formülü kullanılarak 383 olarak hesaplanmıştır. Çalışma (eski) grubu, 01/01/2017-31/12/2017 tarihleri arasında hastanemiz acil servisine başvuran 65 yaş ve üstü 795 hastadan oluşturuldu. Kontrol grubu 2017 yılında hastanemize başvuran ve şifa ile taburcu edilen 65 yaş ve üstü 800 hastadan oluşturuldu.

Dışlama kriterlerini karşılamayan toplam 843 kişi (435 çalışma grubu (exitus hastalar) (ÇG) ve 408 kontrol grubu (KG)) çalışmaya dahil edildi. Etik kurul onayı alındıktan sonra çalışmaya başlandı ve Helsinki Bildirgesi'ne uygun olarak çalışma yürütüldü.

Dahil edilme kriterleri

SG, 01.01.2017-31.12.2017 tarihleri arasında acil servise herhangi bir tıbbi sorunla başvuran ve hastane bünyesinde exitus olan 65 yaş ve üstü hastalardan oluşturuldu.

KG, 2017 yılında acil servise başvuran ve şifa ile taburcu edilen 65 yaş ve üstü ilk 800 hastadan oluşturuldu.

Hariç tutma kriterleri

Çalışma için tespit edilen hastalar içinden aşağıdaki hastalar çalışma dışı bırakıldı:

- 65 yaş altı hastalar,
- Lösemi, miyelodisplastik sendrom, miyeloproliferatif hastalık, miyelofibroz veya agranülositoz gibi hematolojik durumları olan hastalar
- Başka bir hastaneden sevk edilen kişiler,

• Son 10 (on) gün içinde hastaneden taburcu olma öyküsü olan hastalar,

• HIV+ hastalar, travma hastaları,

• Hastaneye geldiklerinde eski sevgilisi olanlar,

• Tedavi sürecinin bitmesini beklemeden acil servisten izinsiz ayrılanlar,

• Acil servis takibinde kan testi yapılmadan taburcu edildi,

• Dünya Sağlık Örgütü tanımına göre derin anemi tanımına uyan ve kan transfüzyonuna ihtiyaç duyan hastalar,

• Polikliniğe başvuran ve hastanede hayatını kaybedenler (Figür 1).

Bu çalışmada hastalardan alınan hemogram testindeki RDW değerleri kaydedildi ve hastanemiz biyokimya laboratuvarında RDW değerleri için referans aralığı %11-16 olarak kullanılmaktaydı. Hastaların yaş, cinsiyet, kanser, DM, koroner arter hastalığı (KAH), KKY, serebrovasküler hastalık (KVH), kronik böbrek yetmezliği (KBY), kronik obstrüktif akciğer hastalığı (KOAH) gibi eşlik eden hastalıklar da hastaların tıbbi kayıtlarından kaydedildi. Hastaların laboratuvar verileri olarak RDW, lökosit, hemoglobin, nötrofil, lenfosit, MCV, üre ve kreatin değerleri kaydedildi. RDW değerleri ÇG ve KG'ye göre değerlendirildi.

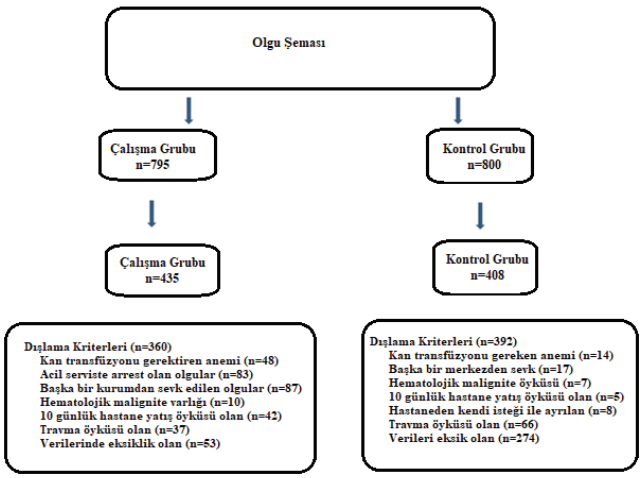

Figure 1. Figürde ÇG'de ve KG'da dışlama kriterleri olan olgu sayıları belirtildi.

İstatistiksel analiz

Hastalardan toplanan veriler MS Office Excel programına girildi. Elde edilen verilerin istatistiksel analizinde SPSS (Statistical Package for the Social Sciences) 22.0 paket programı kullanıldı. Kategorik değişkenler "n" ve "%" ve ferkans değerleri, yüzde ve ortalama ± standart sapma (SD) ile birlikte verildi. Sürekli sayısal değişkenlerin normal dağılıma uyup uymadığını analiz etmek için Kolmogorov-Smirnov yöntemi kullanıldı. Değişkenler normal dağılım göstermediğinden parametrik olmayan verilerin karşılaştırılmasında Mann Whitney U testi kullanıldı.

P değerinin 0,05'ten küçük olması istatistiksel olarak anlamlı kabul edildi.

Sonuç

ÇG'deki 435 hastanın %53,3'ü (n=203) erkek ve %46,7'si (n=203) kadındı. KG'daki 408 hastanın da 183'ü erkek (%44,9), 225'i (%55,1) kadındı. Çalışma ve kontrol grupları arasında cinsiyet açısından istatistiksel olarak anlamlı fark yoktu (p> 0,05).

ÇG ortalama yaşı 78.64 idi. Yaş dağılımına göre gruplandırıldığında ise 65-74 yaş grubunda 145 kişi (%33,3), 75-84 yaş grubunda 186 kişi (%42,8), 85 ve üzeri yaş grubunda 104 kişi (%23,9) bulunmaktadır.

KG'deki olguların yaş ortalaması 75,11 olarak hesaplandı. Yaş dağılımına göre gruplandırıldığında ise 65-74 yaş grubunda 207 kişi (%50,7), 75-84 yaş grubunda 156 kişi (%38,2), 85 ve üzeri yaş grubunda 45 kişi (%11) bulunmaktadır. ÇG ve KG arasında yaş ortalamaları açısından istatistiksel olarak anlamlı fark yoktu. (p> 0,05)

ÇG'nin ortalama RDW değeri 16.03 olarak bulundu. KG'de ortalama RDW değeri 14,67 bulundu. Mann Whitney U testi ile karşılaştırıldığında ÇG'de RDW değerinin KG'ye göre anlamlı olarak arttığı ve mortalite ile ilişkili olduğu gösterildi (p <0.001) (Tablo 1).

Tablo 1. ÇG ve KG olgularının RDW ortalamalarının karşılaştırılması

Gruplar	n	X	Mann Whitney U Test			
			Sıra Ort.	U	z	p
ÇG	435	16,03	497,04	56098,5	-9,241	<0,001
KG	408	14,67	342,00			

RDW değerleri en yüksek çeyrekte olan hastalar incelendiğinde 53'ünün KG'den, 158'inin ÇG'den olduğu gösterildi. En düşük çeyrekte olan hastaların RDW düzeyi incelendiğinde ise tam tersi bir durum olduğu, bunların 150'sinin KG'den, 62'sinin ise ÇG'den olduğu gösterildi (Tablo 2).

Tablo 2. ÇG ve KG olgularında en düşük ve en yüksek çeyreklikteki RDW değer karşılaştırması

Gruplar	RDW (En yüksek çeyreklik) n (%)	RDW (En düşük çeyreklik) n (%)
ÇG	158 (%74)	62 (%29)
KG	53 (%26)	150 (%71)

Çalışma ve kontrol gruplarının ortalama RDW değerleri yaş gruplarına göre sınıflandırıldı ve birbirleri ile karşılaştırıldı. Buna göre çalışma(eski) grubunun ortalama RDW değeri 65-74 yaş grubunda 16,24, kontrol grubunda ise ortalama RDW değeri 14,58 olarak bulunmuştur. İstatistiksel olarak karşılaştırıldığında çalışma(eski) grubunda ortalama RDW

değerinin anlamlı olarak arttığı ve mortalite ile ilişkili olduğu gösterildi. 75-84 yaş grubu dikkate alındığında çalışma(eski) grubunda ortalama RDW değeri 16,04, kontrol grubunda ortalama RDW değeri 14,78 olarak bulundu. ortalama RDW değerinin çalışma(eski) grupta önemli ölçüde arttığını ve mortalite ile ilişkili olduğunu göstermiştir. Son olarak 85 yaş ve üstü yaş grubu dikkate alındığında çalışma(ex) grubundaki ortalama RDW değeri 15,71 olarak bulunurken, kontrol grubundaki ortalama RDW değeri 14,73 olarak gösterilmiştir. İstatistiksel olarak karşılaştırıldığında çalışma(eski) grubunda ortalama RDW değerinin anlamlı olarak arttığı ve mortalite ile ilişkili olduğu gösterildi (Tablo 3).

RDW ortalama değerleri, kanser, DM, hipertansiyon (HT), KAH, KKY, KOAH gibi komorbid hastalıkları öyküsü olan ÇG'de, KG'ye göre anlamlı olarak yüksek bulundu Komorbid hastalık varlığında ortalama RDW değerleri karşılaştırıldığında, ÇG'nin ortalama RDW değerinin malignite, DM, HT, KAH, KKY, KOAH komorbid hastalık varlığında anlamlı olarak arttığı ve mortalite ile ilişkili olduğu gösterildi (p <0,05) (Tablo 3).

Tablo 3. ÇG ve KG olgularının yaş dağılımlarına ve komorbid hastalıklara göre RDW ortalamalarının karşılaştırılması

Yaş	Grup	n	X	Ortalama Aralık	Mann Whitney U Test U	Z	p
65-74 yıl	ÇG	145	16,24	211,19	9977,00	-5,355	,000
	KG	207	14,58	152,20			
75-84 yıl	ÇG	186	16,04	198,65	9457,50	-5,547	,000
	KG	156	14,78	139,13			
>85 yıl	ÇG	104	15,71	84,61	1341,00	-4,132	,000
		45	14,73	52,80			
Komorbid Hastalık							
Malignite	ÇG	88	17,14	79,16	1085,50	-4,539	,000
	KG	47	15,26	47,10			
DM	ÇG	123	16,24	139,61	4845,50	-4,372	,000
	KG	117	14,79	100,41			
HT	ÇG	231	15,99	270,87	17124,50	-6,543	,000
	KG	229	14,72	189,78			
KAH	ÇG	131	15,58	128,77	4615,50	-3,637	,000
	KG	98	14,58	96,60			
KKY	ÇG	88	16,55	82,03	1713,00	-3,219	,001
	KG	57	15,15	59,05			
KBY	ÇG	73	16,26	50,10	649,50	-1,355	,175
	KG	22	15,12	41,02			
SVH	ÇG	63	15,47	47,31	799,50	-0,710	,478
	KG	28	15,14	43,05			
KOAH	ÇG	57	16,99	66,26	1011,00	-3,240	,001
	KG	55	15,51	46,38			

ÇG: Çalışma grubu; KG: Kontrol grubu; DM: Diabetes Mellitüs; HT: Hipertansiyon; KAH: Koroner arter hastalığı; KKY: Konjestif kalp yetmezliği; KBY: Kronik böbrek yetmezliği; SVH: Serebrovasküler hastalık; KOAH: Kronik obstrüktif akciğer hastalığı

ÇG olgularında, tam kan sayımının diğer parametreleri olan nötrofil-lenfosit oranı (NLO) ve trombosit-lenfosit oranı (PLO) ortalamalarının da yine RDW ortalama değerleri gibi, KG'den anlamlı yüksekti. Bu üç değer karşılaştırıldığında en anlamlı sonucun NLR ile elde edildi (p <0.001). PLO diğer iki parametreden daha az anlamlı bulundu (p = 0.014) (Tablo 4).

Tablo 4. ÇG ve KG olgularının NLO, PLO ve RDW değerlerinin karşılaştırılması

Parametre	Grup	n	Mann Whitney U Test Ortalama Aralık	U	Z	p
			497,04	56098,50	9,241	,000*
	KG	408	342,00			
NLO	ÇG	435	499,60	54982,50	-9,555	,000**
	KG	408	339,26			
PLO	ÇG	435	441,91	80079,00	-2,451	,014
		408	400,77			

*=2,4505E-20, **=1,2398E-21

Tartışma

RDW'nin artması ile mortalite ve morbidite arasındaki fizyolojik mekanizma halen tam olarak anlaşılamamıştır. Ancak klinik çalışmalar, çeşitli hasta popülasyonlarında artmış RDW ile patofizyolojik süreçler arasında ilişki olduğunu göstermektedir (14,15). RDW değerinin inflamasyon, doku hipoperfüzyonu, oksidatif stres veya böbrek yetmezliği gibi devam eden bir hastalık sürecinin varlığı ile ilişkili olduğu düşünülmektedir (13).

Altmış beş yaş ve üzeri 36.226 hastayla yapılan bir çalışmada, İlk başvuruda ve sonraki 3. ayda RDW değerleri ölçülmüş ve bu hastalarda tüm nedenlere bağlı 10 yıllık ölümler incelenmiştir. Bu olgularda RDW değeri 16,6 üzerinde olan hastaların altında olan hastalardan tüm nedenlere bağlı mortalite 2.3 daha fazla risk altında olduğu gösterilmiştir (16). NHANES III çalışmasına dayanan bir başka yayında, SVH ve DM tanıları olmayan 20 yaş ve üzeri 15.460 bireyden oluşan bir popülasyon çalışılmıştır (17). RDW değerlerinin en yüksek ve en düşük olduğu çeyrekler karşılaştırıldığında, RDW'nin tüm nedenlere bağlı ölümlerde hem erkekler hem de kadınlar için ölüm riskinin önemli bir belirleyicisi olduğu gösterilmiştir (17). Çalışmamızda, ÇG'ye 435 olgu ve KG'ye 408 olgu dahil edilmiş olup, ÇG'deki ortalama RDW değeri 16,03 olarak bulunmuştur. KG'deki ortalama RDW değeri ise 14,67 bulundu. Literatürdeki yayınlara benzer olarak ÇG'deki RDW ortalama değeri KG'den yüksek bulunmuş ve yüksek RDW değerinin mortalite ile ilişkili olduğu görülmüştür. Yine RDW değerleri yüksekten düşüğe doğru sıralanırsa, en yüksek çeyrekte RDW değerine sahip olanların %74'ünün eksitus olgular olduğu ve en düşük çeyrekte RDW değerine sahip olanların ise sadece

%29'unun eksitus olgular olduğu görülmektedir. RDW'nin birçok hastalıkta mortaliteyi tahmin etmede anlamlı prediktif değere sahip olduğu görüldü (1-6, 9-12).

Arbel ve ark. yaptıkları bir çalışmada, İsrail'deki bir toplum sağlığı merkezindeki RDW değerlerini gözden geçirmiştir. Bu çalışmada, 40 yaş ve üzeri 225.006 hastanın RDW değerleri ile tüm nedenlere bağlı mortalite ve kardiyovasküler morbidite riski arasındaki ilişkiyi 5 yıllık bir süreçte incelenmiştir ve çalışma popülasyonu farklı RDW değerlerine göre sınıflandırılmıştır. Bu çalışmada; RDW değeri>%17 olan popülasyonda tüm nedenlere bağlı ölüm riski, RDW değeri <%13 olan popülasyona göre erkeklerde 4,6 kat, kadınlarda 3,3 kat daha fazla olduğu bulunmuştur (18).

Artmış RDW'nin, kardiyovasküler hastalık, inme, septik şok, bakteriyemi ve toplum kökenli pnömoni kliniği olan olgularda artmış mortalite riski ile ilişkili olduğu gösterilmiştir (1-6). Yakın tarihli bir başka çalışmalarda, RDW'nin kalp yetmezliği olan hasta popülasyonunda prognostik önemi vardır ve orta yaşlı ve yaşlı popülasyonda RDW ile mortalite arasındaki bağlantıyı göstermiştir. Yine Patel ve ark. aynı çalışmada, malnütrisyonu ve anemisi olmayan hastalarda da RDW'nin yüksek mortalite ile ilişkili olduğu gösterilmiştir (7-8).

Retrospektif yapılan bir vaka kontrol çalışmasında, Spell ve ark., sigmoidoskopisi normal olan 494 hastada RDW değişikliklerini inceledi. Beş yıllık süreçte izlenen bu hastaların 225'ine (%46) kolorektal kanser tanısı konmuştur (19). Ortalama RDW değerleri kolorektal kanserli grupta diğerlerine göre daha yüksekti. Ayrıca RDW değerleri hem sağ kolorektal kanserli hem de sol kolorektal kanserli hastalarda anlamlı olarak yüksek bulundu (19).

Baicus ve ark. ikinci basamak bir üniversite hastanesinde istemsiz kilo kaybı ile hastaneye başvuran ardışık 253 hasta üzerinde çalışmıştır (20). Bu hastaların 61'ine (%24) malignite tanısı kondu ve kanser hastalarında ortalama RDW değerleri daha yüksek bulundu (%14,6 veya %15,1 p=0,022). Koma ve ark. akciğer kanseri tanısı alan 332 hastanın verilerini retrospektif olarak inceledi ve bu çalışmada, yüksek RDW değerlerinin komorbiditeden bağımsız olarak kanser ile ilişkili olduğu bulunmuştur (21).

Arbel ve ark. RDW değeri >%17 olan bireylerde, RDW değeri <%13 olan bireylere göre DM insidansının daha yüksek olduğunu göstermiştir (18). Chen ve meslektaşları, Tayvanlı bir nüfus üzerinde yaptıkları çalışmada zıt sonuçlar elde ettiler. RDW değeri en yüksek çeyrekte olan bireylerde, RDW değeri en düşük çeyrekte olan bireylere göre DM prevalansı daha düşük bulunmuştur (8).

Tanindi ve ark. (22) hipertansif hastalarda ortalama RDW değerinin prehipertansif ve normal gruplara göre anlamlı olarak yüksek olduğunu bulmuşlardır. Bilal ve ark. (23), 100 hasta üzerinde yaptıkları kesitsel çalışmada HT hastalarında ortalama RDW değerinin arttığını ve HT hastalarında düzenli olarak RDW değerinin kontrol edilmesi gerektiğini belirtmişlerdir.

Osadnik ve ark. stabil KAH tanısıyla PKG yapılan ve bu hastaları ortalama 2,5 yıl takip eden ardışık 2550 hastada RDW değerlerini ölçmüşlerdir (15). RDW değerleri tüm hasta gruplarında mortalite ile anlamlı korelasyon gösterdi. Çetin ve ark. KAH şüphesi olan ve KAG uygulanan 296 hasta üzerinde kesitsel ve gözlemsel bir çalışma yapmış ve kesin KAH tanısı olan bireylerde KAH olmayan hastalara göre RDW değerlerinin anlamlı olarak arttığını göstermiştir (24).

Wang ve ark. başvuru sırasında AKS tanısı alan ardışık 1654 hastada RDW değerini ölçmüştür. Artmış RDW değerlerinin, tekrarlayan enfarktüs, 1 ay içinde kalp yetmezliği gelişmesi riski ve 1 aylık mortalite ile ilişkili olduğu gösterilmiştir (25).

Lappe ve ark. 1489 KAH hastasını incelemiş ve 8,4-15,2 yıllık periyodu takip etmiştir. Yapılan analizde, RDW'nin tüm nedenlere bağlı ölümlerin önemli bir belirleyicisi olduğu gösterilmiştir (26). Tonelli ve ark. 4111 MI vakasında ölçülen RDW değerleri inceledi ve olgular ortalama 59,7 ay takip edildi. RDW değerlerinin, yeni başlayan kalp yetmezliği de dahil olmak üzere tüm end organ hasarı durumlarında anlamlı olarak yüksek olduğu bulunmuştur (10).

Çalışmamızda kanser, DM, HT, KAH, KKY, KOAH gibi komorbid hastalıkların varlığında ÇG'de ortalama RDW değeri KG'ye göre anlamlı olarak artmış ve mortalite ile ilişkilendirilmiştir.

Solak ve ark. evre 1'den evre 5'e kadar sınıflandırılan 367 KBY hastasında RDW değerlerini inceledi (27). Bu çalışmada RDW değerlerinin 1. evreden 5. evreye yükseldiği gösterildi. Ayrıca RDW değerleri ile glomerüler filtrasyon hızı değerleri arasında anlamlı ve ters bir korelasyon vardı.

Mucsi ve arkadaşları böbrek nakli yapılan ve 3 yıl takip edilen 723 hastanın RDW değerlerini ölçmüştür (28). Çalışmada RDW değerinde %1 artış olduğu ve 3 yıllık mortalite riskinde anlamlı artış olduğu gösterildi.

Çalışmamızda iki gruptaki KBY tanısı alan hastalar karşılaştırıldığında çalışma(eski) grubundaki ortalama RDW değerinin kontrol grubuna göre sayısal olarak arttığı ancak istatistiksel olarak anlamlı fark göstermediği gösterildi (p=0,175).).

Ramirez - Moreno ve ark. ilk kez iskemik inmeli 224 kişinin kesitsel çalışmasını bulmuştur (29). Çalışmamızda her iki grupta

KVH öyküsü olan hastalar karşılaştırıldığında çalışma(eski) grubundaki ortalama RDW değerinin kontrol grubuna göre sayısal olarak arttığı ancak istatistiksel olarak anlamlı fark göstermediği gösterildi (p=0,478).).

Ortalama RDW değerleri, yeni tanıtılan diğer hematolojik parametrelerle karşılaştırıldı; Kara ve ark., laringeal kanser tanısı konulan ve ekarte edilen hastalarda LLO, PLO ve RDW gibi hematolojik parametrelerin prognostik rolünü belirlemek için çalıştıkları bu hastalarda RDW ve PLO düzeylerinin anlamlı olarak arttığını bulmuşlardır. NLR düzeyinde anlamlı artış yoktu (30).

Eksitus olgularda RDW, NLR ve PLO ortalamalarının anlamlı olarak arttığı gösterilmiştir. En anlamlı artış NLO'da (p <0.001) gösterilmişken, PLO diğer iki belirteçten daha az anlamlıydı (p=0.014). Literatürü incelediğimizde çalışmamızı destekleyen birçok sonucun elde edildiğini görebiliriz.

Çalışmamızda eksitus olgularda yaşayan olgularla karşılaştırıldığında RDW'nin anlamlı olarak yüksek olduğu görülmüştür.

Sonuç

RDW'nin mortalite üzerindeki etkisine ilişkin literatür ve diğer hematolojik belirteçlerle karşılaştırmalı literatür sınırlıdır. Çalışmamız, yüksek RDW değerinin yaşlı hastalarda mortalite için prediktif bir değer olduğunu ve bu parametrenin yaşlı hastalarda kullanılabileceğini göstermiştir, ancak daha fazla merkezi ve daha geniş popülasyonu kapsayan daha fazla araştırmaya ihtiyaç vardır.

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Research Article

Work-related musculoskeletal disorders and ergonomics among gynecologists

Jinekologlarda işe bağlı kas-iskelet hastalıkları ve ergonomi

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Abstract

Aim: Work-related musculoskeletal disorders (WRMSD) have been a prevalent health issue among gynecologists. The current nationwide survey aimed to establish the prevalence and predictors of pain and WRMSD among gynecologists in Turkey, as well as their influence on family, social, and professional life.

Material and Methods: The current prospective descriptive study was conducted as a national survey including gynecologists operating as a specialist for at least two years in a tertiary hospital with more than 500 beds.

Results: The survey was completed by 286 (131 female) respondents out of a total of 390 participants. The locations of pain were as follows: neck (49.3%), upper back (49.3%), lower back (44.4%), shoulder (43.49%), hand/fingers (34.8%), thumb (11.2%), wrist (21.9%), hip (17.3%), knee (26.8%), and foot (17.8%). 58.7% of the gynecologists discovered at least one diagnosis of WRMD. Female surgeons were at threefold risk of upper back pain (β: 3.546 (%95 confidence interval (CI), 1.304-9.645; p=0.013), and at least two regions of pain (β: 3.847; CI:1.241-11.928; p=0.020). Left dominant hand increased risk of pain in the elbow (β:11.360, CI: 2.721-47.422; p=0.001), hip (β:1.155, CI: 1.004-1.283; p=0.045), and pain in the more than two regions (β:6.786, CI: 1.246-36.967, p=0.027). Exercise hours per week were found a protective factor for upper back pain and pain in more than two regions (β:1.198, CI:1.005-1.355, p=0.013; β:1.286, CI: 1.088-1.441, p=0.007).

Conclusion: WRMSD are potentially affecting the gynecologist's quality of life, income and professional life. Future research can be conducted to increase awareness and prevention from WRMSD among gynecologists.

Keywords: work related musuloskeletal disorders, pain, gynecologist, ergonomics, operation

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Öz

Amaç: İşe bağlı kas-iskelet hastalıkları (İBKİH), jinekologlarda sık görülen halk sağlığı sorunudur. Ulusal anket çalışmasında Turkiye'deki jinekologlarda İBKİH ve ağrı sıklığı ve prediktif faktörleri araştırılarak bunun jinekologların aile, sosyal ve iş hayatı üzerine etkisini belirlemek amaçlanmıştır.

Gereç ve Yöntemler: Prospektif tanımlayıcı anket çalışmasına Turkiye'de 500 yataktan fazla kapasitesi olan üçüncü basamak hastanelerinde çalışan ve en az 2 yıllık uzman olan jinekologlar çalışmaya dahil edilmiştir.

Bulgular: Çalışmaya katılan 390 jinekoloji uzmanının 286'sı (131 kadın) çalışmayı tamamladı.Ağrı lokalizasyon sıklıkları sırasıyla şöyledir: %49,3 boyun, %49,3 % sırt, %44,4 bel, %43,49 omuz, %34,8 el/ el parmakları, %26,8 diz, %21,9 el bileği, %17,3 kalça, %17,8 ayak ve %11,2 başparmak. %11,2 başparmak. Katılımcıların %58,7'sinde en az bir İBKİH tanısı mevcuttu. Kadın cinsiyeti sırt ağrısı (β: 3.546 (%95 confidence interval (CI), 1.304-9.645; p=0.013) ve en az iki bölgede ağrı riskini (β: 3.847; CI:1.241-11.928; p=0.020) üç kat arttırmakta idi. Sol el hakimiyeti olan jinekologlarda dirsek (β:11.360, CI: 2.721-47.422; p=0.001), kalça (β:1.155, CI: 1.004-1.283; p=0.045)ve en az iki bölgede ağrı riski (β:6.786, CI: 1.246-36.967, p=0.027) artmaktaydı. Haftalık egzersiz saati arttıkça sırt ağrısı ve en az iki bölgede ağrı sıklığı azalmaktaydı. (β:1.198, CI:1.005-1.355, p=0.013; β:1.286, CI: 1.088-1.441, p=0.007).

Sonuç: Jinekologların yaşam kalitesi, iş hayatı ve geliri iş hayatına bağlı kas iskelet hastalıklarından etkilenmektedir. Bu konuda farkındalık ve korunmak için yeni çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: işe bağlı kas iskelet hastalıkları, ağrı, jinekolog, ergonomi, cerrahi operasyon

Introduction

For decades, work-related musculoskeletal disorders (WRMSD) have been a prevalent health issue among surgeons(1). Repetitive strain injuries can cause damage to the muscles, nerves, and/or joints of surgeons and typically affect the spine, wrist, and hands (2-4). In addition to causing chronic pain, these injuries can have negative socioeconomic effects, a negative impact on the quality of life of the of life, and a negative influence on job satisfaction and productivity (5-8).

Every time a gynecologist performs surgery, whether it be laparoscopic or open, they run the chance of developing WRMSD. The researchers explored the musculoskeletal problems that gynecologists from across the world report (7-13). Unfortunately, these studies had several limitations, including a lack of demographic data, comparative operation methodologies, small sample sizes, and a lack of treatment modalities statistics (5-13). The prevalence of musculoskeletal complaints among surgeons appeared to be primarily due to a lack of awareness and the adoption of ergonomic guidelines (9-13). To our knowledge, only one study dealing with ergonomics among Turkish gynecological laparoscopists has been found (9).

The current nationwide survey aimed to establish the prevalence of pain and WRMSD among gynecologists in Turkey, as well as their influence on family, social, and professional life. To highlight new modalities in ergonomics and the working environment for surgeons, the secondary goals included identifying the predictors of WRMSD and pain.

Material and Methods

Study Participants and Design: Previous survey data were utilized to calculate the sample size for the study (5,7,9,10). A gynecologist operating as a specialist for at least two years in a tertiary hospital with more than 500 beds was required to participate in the survey nationwide. About 5000 gynecologists make up the group, and they come from 51 different Turkish cities, uniformly portraying Turkey. The OpenEpi® sample calculation used a universe of 5000 people, a frequency of musculoskeletal conditions of 85%, a confidence interval of 95%, a goal power of 80%, and a target population of 135 people (14). The local ethics committee (KAEK/2021.09.210) approved this cross-sectional study, which was conducted in accordance with the Declaration of Helsinki. The eligibility requirements were as follows: 1) at least two years of experience as a gynecological specialist in a tertiary hospital, and 2) the absence of clinically diagnosed inflammatory musculoskeletal disorders. Participation was voluntary in the search. Participants who agreed to take part in the study and met the inclusion criteria were required to peruse and sign a written consent form.

Process for Creating and Implementing the Survey: The survey was designed and implemented using the Google Forms Survey Platform by researchers with ten years of experience in gynecology (HT, NAV, NK), public health (MGG), and algology

(SAT). In our institution, pilot testing was conducted with 10 gynecologists; however, their results were not included in our analysis. Emails were sent to 4789 physicians. The survey was completed by 286 respondents out of a total of 390 participants. As part of the survey, written informed consent was obtained from participants.

Survey Form: The survey questions have been built on a comprehensive review of the prior literature (5-13). a) demographics b) operating characteristics c) musculoskeletal pain for a year d) Experience with WRMSD and its diagnosis/ treatment e) Effects of the pain on practice, family, and social life, as well as an awareness of ergonomics. The first component of the questionnaire inquired about the surgeon's characteristics (age, gender, height and weight, dominant hand, glove number, smoking, sleep, and physical activity habits) and years of experience. The second section asked about the duration of operations, benign versus malignant cases, the patient's body mass index (BMI), and the annual number of surgeries. The third- and fourth-part questions were about WMSD and were adapted from a Nordic musculoskeletal questionnaire that was verified in Turkish (Cronbach alfa: 0.78) by Kahraman et al (15). The participant was asked if he or she had pain in the neck/shoulder/elbow/ wrist–hand/upper back/lower back/hip/knee/ankle–foot over the previous 12 months. The participant was then required to respond to questions about the pain's duration, treatment, and impact on daily life and professional life. In addition, we asked the respondent how he or she dealt with the discomfort during the surgery, such as by taking a break, adjusting the monitor position or equipment, or by taking painkillers. The participants were then asked if they had been diagnosed with WRMSD or received treatment for it since their residency.

Statistical Analysis

We performed the statistical analysis with the Statistical Package for Social Sciences (SPSS 23.0 IBM SPSS Inc., Chicago, IL) program. The distribution of the variables was examined using the visual (histogram and probability graphs) and Shapiro-Wilk method, and it was found to fit the non-parametric distribution. Demographic data were presented as numbers with percentage (%) and median with (median with 25.-75. percentile). To determine the statistical difference between paired nominal/categorical data we used Mc-Nemar Test. We used Pearson Chi-Square test or Fisher's Exact test for nominal/categorical data. The Mann-Whitney U test was used to compare the quantitative values of two independent groups. We used binomial regression for determining the factors affect single or multiple pain regions. When creating the model, we used variables that only had statistical differences with pain more than two zones. We tested the model structure with each factor's presence and absence to evade multi-collinearity. And, we used correlation tests with regression variables to control any confounding factors. Statistical significance of p-value accepted as $p<0.05$ at a 95% confidence interval.

Results

Sociodemographic Factors of Participants: Our survey included 286 (131 female) surgeons. The participants' median age was 39.50 (33-62) years, and their mean BMI was 25.35. Most participants were right-handed and wore glove size 7.5 (n = 107). More than fifty percent of the individuals (n=154, %53.8) regularly exercised. The median number of years of experience was 10 (2-40). Most of the surgeons (183/286) mainly conducted open surgery. More benign cases were made annually, according to surgeons (n:223,78%). Many of the surgical patients were either overweight or Type 1 obese. In either open surgery (n:139, %48.6) or laparoscopy (n:117,40.9%), almost half of the participants said that only nurses helped them. Most surgeons favored trocar ipsilateral in laparoscopy (n:207, 75.8%) and were told that the size of the equipment in the operating room was standard (n:256, 89.5%). Most of the participants (n:196, 68.5%) were neither aware of nor educated on ergonomics. The participants' sociodemographic characteristics and surgical experiences are detailed in Table 1.

Pain During/After Surgery: Prevalence and Effects on The Life:Most respondents reported feeling pain in at least one body region. Eleven subjects (3.9%) reported no pain. The locations of pain were as follows: neck (49.3%), upper back (49.3%), lower back (44.4%), shoulder (43.49%), hand/fingers (34.8%), thumb (11.2%), wrist (21.9%), hip (17.3%), knee (26.8%), and foot (17.8%) (Table 1). When asked when they felt pain, 132 of them (46.7%) said after the surgery was over, 35 of them (12.4%) had pain all the time, and 65 of them (23%) said their pain started during the surgery and lasted all day. Most of the participants' pain-relieving maneuvers during surgery involved changing their position (59%%) or the table height (25%) for the patient. Forty percent of respondents neglected the pain during the surgery. Over fifty-five percent of participants received medical treatment for their pain. One-third of the participants received physical rehabilitation

Table 1. Sociodemographic Characteristics of Participants	
Participants	286
Sex (female/total (n, %))	131/286 (54.2)
Age (years) (median with min-max)	39 (28-65)
Height (cm) (median with min-max)	172.0 (150.0-192.0)
Weight (kg) (median with min-max)	75 (44-108)
Body mass index (kg/m2) (mean with standard deviation)	25.35 (±3.70)
Experience (years) (median with min-max) / (median with 25.-75. percentile)	10 (2-40)
Dominant hand (right/total (n, %)	266/286 (93.0)
Glove size no (median with min-max)	7.5 (6-9)
Smoking (active/total (n, %)	83 (29.0)
Exercise regularly (yes/total (n, %)	154 (53.8)
How many hours do you exercise in a week (median with min-max)	3 (1-20)
How many hours do you sleep? (median with min-max)	6 (1-9)
Surgeries: laparoscopy more Open more equal open and laparoscopy	 36 183 67
Number of surgeries in a year (median with min-max)	100 (20-400)
Duration of surgeries (hours) (median with min-max)	2 (1-7)
Surgery type:(n, %) more benign case more malignant case equal	 223 (78.0) 43 (15.0) 20 (7.0)
Body mass index of patients (n, %) normal overweight tip 1 obesity tip 2 obesity morbid obesity	 18 (6.3) 138 (48.3) 101 (35.3) 29 (10.1) 0 (0)
Assistance during surgery:(n, %) Resident, fellow and nurse Resident and nurse Fellow and nurse Only nurse	 50 (17.5) 77 (26.9) 20 (7.0) 139 (48.6)
Equipment size(n, %) standart too small too big	 256 (89.5) 8 (2.8) 22 (7.7)
Awareness about ergonomy in the theater: (n, %) No From residency from congress during profficiency By myself	 196 (68.5) 21 (7.3) 43 (15.0) 1 (0.3) 44 (15.4)
Prevalance of pain regions (n, %) Neck Shoulder Elbow Hand-fingers Thumb Wrist Lower Back Hip Knee Foot	 136 (52.7) 109 (42.7) 26 (9.6) 94 (34.8) 30 (11.2) 59 (21.9) 120 (44.4) 47 (17.3) 72 (26.7) 47 (17.4)

treatment. Fifteen of the respondents had a surgical intervention to alleviate their pain. 7.7% of the participants took a sick day for pain relief. Limitation of movement (49.3%), posture discomfort (44.1%), decrease in patience (34.6%), sleep disorders (32.2%), and decrease in surgery performance (23.8%), anger/irritability (24.1%), concentration deficiency (18.2%), unwillingness in the education of gynecology (teach or learn; 15%), decrease in relationship with family and friends (26.2%), and limitation for hobbies (23.1%) were the most frequently reported effects of pain.

WRMSD Diagnosis and Treatment: Respondents were questioned on the diagnosis and treatment of WRMSD. 58.7% (n = 168) of the gynecologists discovered at least one diagnosis. Myofascial pain/strain/spasm was the most frequently diagnosed (27.6%) and treated (22.0%) condition. Myofascial pain was associated with female sex, smoking, shorter height, more benign cases, and more open surgeries per year (p=0.009, p=0.019, p=0.036, p0.01, respectively). Participants reported lumbar disc herniation/spondylosis at a rate of 21.3%, and 46 of them received treatment. Age (p=0.001), the experience of more than ten years (p=0.001), and the frequency of laparoscopies performed annually (p=0.048) were all associated with lumber disc herniation/spondylosis. Cervical disk herniation/spondylosis was seen in 17.5% of the surgeons, with 38 of them receiving treatment. There was a correlation between cervical disk herniation/spondylosis and age (p=0.007) and more than ten years of experience (p=0.005). The additional WRMSDs mentioned by respondents included lateral epicondylitis (15.7%), shoulder impingement/bursitis/tendinitis (12.9%), carpal tunnel syndrome (7.3%), and cubital tunnel syndrome (7.0%). All these WRMSDs were examined in Table 2.

Risk Analysis of Pain Regions: Logistic regression was used to examine the effect of sex on pain in each region and more than two regions (Table 3-4). Female surgeons were at threefold risk of upper back pain (: 3.546 (%95 confidence interval (CI), 1.304-9.645; p=0.013), and at least two regions of pain (: 3.847; CI:1.241-11.928; p=0.020). Left dominant hand increased risk of pain in the elbow (:11.360, CI: 2.721-47.422; p=0.001), hip (:1.155, CI: 1.004-1.283; p=0.045), and pain in the more than two regions (:6.786, CI: 1.246-36.967, p=0.027). Exercise hours per week were found a protective factor for upper back pain and pain in more than two regions (:1.198, CI:1.005-1.355, p=0.013; :1.286, CI: 1.088-1.441, p=0.007).

Discussion

This is, to the best of our knowledge, the first survey of WRMSD among gynecologists in Turkey, and 58 percent have reported having suffered at least one injury. Being in line with the literature, such a high percentage is alarming (5-10).

The most often reported diagnoses were myofascial pain and lumbar/cervical disk herniation/spondylosis. Myofascial discomfort was correlated with female sex, smoking, shorter height, more benign cases, and more annual surgeries. Spondylosis was associated with age, years of gynecological experience, and number of surgeries per year.

Neck, back, shoulder, hand, and finger pain were common among the respondents. When asked when they were aware of the pain, most of them said after the surgery was completed. During the operation, the participants generally adjusted the table height or their position to ease the pain. The pain experienced during the surgery was overlooked by nearly half of the respondents. More than half of the participants received medical therapy for their pain, as well as physical rehabilitation. The most frequently reported effects of pain were mobility restriction, distress with posture, a decrease in tolerance, sleep disorders, and a decline in surgical performance. The risk variables for pain following surgery were the left dominant hand and the female sex. More hours of exercise per week were found to be a protective factor for pain.

A high rate of WRMSD among gynecologists has previously been observed in various parts of the world, similar to the findings of our study. According to reports, 53% of people in Australia and New Zealand sustained at least one injury (10). In research from China, Europe, and North America (4-9) higher rates of WRMSD, such 85-90%, were discovered.

Previous research has demonstrated a high prevalence of work-related musculoskeletal injuries, including degenerative spinal disease (17%), rotator cuff pathology (18%), and degenerative lumbar spine disease (19%). The neck, arm, shoulder, and back are the most commonly affected areas of their high risk of work-related musculoskeletal discomfort (11-12). As predicted our findings were consistent with previous research.

Previous studies have suggested that women have a higher prevalence of musculoskeletal disorders than males, despite the fact that a limited number of female surgeons participated in these studies (6-10). Our study included nearly fifty percent female respondents. We showed that female sex is a significant risk factor when evaluating muscle pain and disease. We hypothesized that female surgeons may be at a disadvantage in terms of ergonomics in the operating room due to their short height and weaker upper-body strength. Furthermore,

Table 2. Characteristics of Work Related Musculoskeletal Disorders

	Myofacial pain	Carpal tunnel syndrome	Cubital tunnel syndrome	Lateral epicondilitis	Rotatuar cuff syndrome/ tendinitis/burcitis	Cervical disk herniation/spondilitis	Lomber disk herniation/spondilitis	Priformis syndrome	Thumb arthritis
Total (+/total) (n/%)	78 (27.6)	21 (7.3)	20 (7.0)	45 (15.7)	37 (12.9)	50 (17.5)	61 (21.3)	26 (9.1)	33 (11.5)
Got treatment	63 (22.0)	15 (5.2)	12 (4.2)	34 (11.9)	33 (11.5)	38 (13.3)	46 (16.1)	21 (7.3)	23 (8.0)
Sex									
Male (+) (n,%)	33 (21.3)	1 (0.6)	7 (4.5)	24 (15.5)	16 (10.3)	21 (13.5)	33 (21.3)	11 (7.1)	16 (10.3)
Female (+) (n,%)	46 (35.1)	20 (15.3)	13 (9.9)	21 (16.0)	21 (16.0)	29 (22.1)	28 (21.4)	15 (11.5)	17 (13.0)
p:	.009*	<.001*	.074	.899	.152	.057	.986	.202	.484
Age (n=286)									
- (median with 25.-75. percentile)	40 (36-45)	40 (35.5-45)	39 (35-45)	39 (35-45)	39 (35-44)	39 (35-45)	39 (35-44.5)	39 (35-45)	39 (35-45)
+ (median with 25.-75. percentile)	39 (35-46)	39 (35-45)	50 (43.5-57)	42 (37.5-54)	48 (43-58)	42.5 (37.75-55)	43 (37-55)	43 (39-50.5)	40 (37.5-49)
p**	.314	.866	<.001	.019	<.001	.007	.001	.008	.065
Weight (kg) (n=286)									
- (median with 25.-75. percentile)	75 (65-87)	76 (65-88)	75 (66-87.25)	75 (65-87)	75 (65.5-87)	75 (65.25-87)	75 (64.5-87)	75 (65-86.75)	75 (65-86)
+ (median with 25.-75. percentile)	71 (63-87)	68 (63.5-73)	64.5 (56.5-70)	70 (65-83.5)	70 (59-81)	70 (60-86)	74 (66-86.5)	69 (65.00-87.75)	73 (63.5-90)
p**	.400	.013	.001	.241	.031	.201	.766	.594	.708
Height (cm) (n=286)									
- (median with 25.-75. percentile)	174 (167-180)	173 (167-180)	172 (167-180)	172 (166.5-180)	172 (167-180)	172 (167-180)	172 (166.5-180)	172 (167-180)	172 (167-180)
+ (median with 25.-75. percentile)	170 (165-178)	165 (161-170)	170 (160-180)	170 (167.5-180)	170 (161-180)	172 (164.5-180)	172 (167-180)	170 (162.25-177.25)	172 (165.5-180)
p**	.036	<.001	.465	.803	.758	.984	.334	.272	.988
Surgical experience (years) (n=286)									
- (median with 25.-75. percentile)	10 (6-15)	10 (5.5-15)	10 (5-14.5)	10 (5-15)	9 (5-13)	10 (5-14.75)	10 (5-13.5)	10 (5-15)	10 (5-15)
+ (median with 25.-75. percentile)	10 (5-16)	9 (5-20)	20 (11.25-30)	12 (7-26)	20 (15-30)	12 (8.75-25)	13 (6.5-26)	14 (11-25)	13 (9-21.5)
p**	.518	.622	<.001	.009	<.001	.005	.001	<.001	.005

Table 3. Factors compared with pain regions (2 regions at least)

		pain more than two zone		
		None (n %**)	Exists (n %**)	p value*
Sex (n=266)	Female	24 (19.7)	98 (80.3)	.001
	Male	55 (38.2)	89 (61.8)	
Dominant hand (n=266)	Right	77 (31.3)	169 (68.7)	.045
	Left	2 (10.0)	18 (90.0)	
Smoking (n=266)	No	22 (27.8)	57 (72.2)	.668
	Yes	57 (30.5)	130 (69.5)	
Exercise (n=266)	No	47 (33.3)	94 (66.7)	.168
	Yes	32 (25.6)	93 (74.4)	
Surgery frequency (n=266)	Open	51 (29.7)	121 (70.3)	.839
	Laparoscopic	20 (31.7)	43 (68.3)	
	Equal	8 (25.8)	23 (74.2)	
Surgery pathology (n=266)	More benign	62 (30.0)	145 (70.0)	.979
	More malign	12 (29.3)	29 (70.7)	
	Equal	5 (27.8)	13 (72.2)	
Patient body mass index (n=266)	Normal	6 (35.3)	11 (64.7)	.827
	Overweight	39 (30.2)	90 (69.8)	
	Obese	34 (28.3)	86 (71.7)	
Ergonomics education (n=253)	No	51 (28.2)	130 (71.8)	.305
	Yes	25 (34.7)	47 (65.3)	
		(n) Median (25.-75. percentile)	(n) Median (25.-75. percentile)	
Age		n=79 40 (35-45)	n=187 39 (35-45)	.842
Surgical glove size		n=79 7.5 (7-7.5)	n=187 7 (6.5-7.5)	<.001
Exercise hours		n=46 4 (2-5)	n=95 2 (2-3)	.001
Sleep hours		n=79 7 (6-7)	n=187 6 (6-7)	.292
Surgical experience years		n=79 10 (5-15)	n=187 10 (5-15)	.695
Surgery count per year		n=79 100 (50-240)	n=187 100 (60-200)	.423
Surgeon Body mass index		n=79 26.12 (24.11-28.08)	n=187 25.35 (22.23-27.47)	.034

surgical instruments are typically designed for the larger male hand (13). The female sex, however, continued to be a risk factor even after these were adjusted. It could be because our culture has given female physicians in the family more responsibility, which makes them feel more stressed out. Or it's possible that male surgeons were unaware of their complaints or unwilling to acknowledge they had physical complaints.

Left-handedness was discovered to be a risk factor in the current study. Individuals who are left-handed confront difficulties with surgical training, equipment, and operating room efficiency. Lee et al. (16) assert that the training environment is less appropriate for left-handed trainees and not conducive to the development of proficient surgical skills. However, according to a recent study of orthopedists, left-handed surgeons have a larger percentage of ambidexterity and ambidexterity was found to be more advantageous in the operating room (17). It is possible that the influence of hand dominance on ergonomics and surgical skills varies by subspecialty; therefore, additional research is required.

Limitation

One of the study's strengths is its altered population. Capturing a variety of ergonomic experiences was enabled by the inclusion of multiple devices. The detailed questions regarding working conditions, pain regions, pain treatment methods, sick

Table 4. Risk Factor Analysis of Musculoskeletal Pain					
Factors included in test (Enter Method) 1. Sex (male-female) 2. Dominant hand (right/left) 3. Exercise hours per week 4. Surgeon's BMI 5. Surgical glove size	Singe Regions	Factors	p value	Exp (B)	95% CI
	Neck	None significant			
	Shoulder	None significant			
	Upper back	Female	.013	3.546	1.304-9.645
		Exercise hours per week (protective-reversed exp (B))	.045	1.198	1.005-1.355
	Elbow	Left dominant	.001	11.360	2.721-47.422
	Hand-fingers	None significant			
	Thumb	None significant			
	Wrist	Left dominant	.017	4.542	1.310-15.742
	Lower Back	None significant			
	Hip	Left dominant	.013	5.721	1.441-22.706
		Surgeon BMI (protective-reversed exp (B))	.045	1.155	1.004-1.283
	Knee	None significant			
	Feet	None significant			
	Multiple Regions				
	At least two regions	Female	.020	3.847	1.241-11.928
		Left dominant	.027	6.786	1.246-36.967
		Surgeon BMI	.643	1.033	.901-1.183
		Surgical glove size	.479	.695	.257-1.892
		Exercise hours (protective-reversed exp (B))	.007	1.286	1.088-1.441

leave, the effects of pain on the surgeon's life, the ergonomics of the operating room, and the surgeon's lifestyle are an additional strength of the study. The limitations of the study include a limited sample size, nonresponse, and the inherent self-selection bias of survey-based study designs. We lacked the use of objective measurements like electromyography. This study also does not address whether ergonomic interventions have reduced any of the reported complaints.

Conclusion

The objective of the study was to determine the prevalence and predictive factors of WRMSD in gynecologists. More than half of the gynecologists experienced WRMSD severe enough to effect familial, professional and social life, which was the most striking finding of the analysis.

In conclusion, female surgeon sex and left-handed dominance are related with significantly elevated risks of physical pain when doing surgery. It should be emphasized that exercise is linked to a protective component.

WRMSD are potentially affecting the surgeon's quality of life, income and professional life. Future research can be conducted to increase awreness and prevention from WRMSD among gynecologists.

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Availability of Data and Materials: The Data and materials are available from the corresponding author upon reasonable request and are subject to ethical review.

Authors' Contributions

HT: design of the work; acquisition, analysis, and interpretation of data; drafting and substantial review of the manuscript, review of the manuscript

SAT, design of the work; acquisition, analysis, and interpretation of data, review of the manuscript

AV: acquisition, analysis, and interpretation of data; drafting and substantial review of the manuscript, review of the manuscript

MGG: design of the work; acquisition and interpretation of data; drafting and substantial review of the manuscript; review of the manuscript

NÇ: design of the work; drafting and substantial review of the manuscript; review of the manuscript

All authors approved the final version of the paper to be published.

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Research Article

Evaluation of patient satisfaction in Ankara traıning and research hospital family medicine polyclinics

Ankara Eğitim ve Araştırma Hastanesi aile hekimliği polikliniklerinde hasta memnuniyetinin değerlendirilmesi

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Abstract

Aim: By determining the patient satisfaction levels and revealing the affecting factors, it can be provided to provide more qualified health services. In this study, it was aimed to determine patient satisfaction in our family medicine outpatient clinics.

Material and Methods: 270 volunteer adult patients over the age of 18 were included in the study. A questionnaire questioning the sociodemographic characteristics and habitual status of the patients and the Outpatient Satisfaction Scale were administered to the participants during the face-to-face interview.

Results: 78 (28.88%) of the participants were male, 192 (71.11%) were female, and the mean age was 41.72±15.0 years. It was observed that 94.07% of the participants wanted to come back to the family medicine outpatient clinic, and 95.92% recommended it. The mean scale score of all participants was found to be 111.25±27.67. There was no statistically significant difference between the participants' total and sub-dimension scores of scale and age, gender, and marital status (p>0.05). The "General satisfaction" scores of the participants whose education level was elementary school were found to be higher (p=0.044). Scale total scores of the participants whose occupational status was unemployed were found to be higher (p=0.035).

Conclusion: It has been observed that patient satisfaction is affected by sociodemographic characteristics such as education level and occupational group. We think that the factors positively affecting patient satisfaction are a correct patient-physician relationship and good communication skills.

Keywords: Patient satisfaction; Family Practice; outpatient clinic

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Öz

Amaç: Hasta memnuniyet düzeylerinin belirlenmesi ve etkileyen faktörlerin ortaya konması ile daha nitelikli sağlık hizmet sunulması sağlanabilir. Bu çalışmada, aile hekimliği polikliniklerimizdeki hasta memnuniyetini saptamak amaçlanmıştır.

Gereç ve Yöntemler: 18 yaş üstü 270 gönüllü erişkin hasta çalışmaya dâhil edildi. Hastaların sosyodemografik özelliklerini, alışkanlık durumlarını sorgulayan bir anket ve Ayaktan Hasta Memnuniyet Ölçeği katılımcılara yüz yüze görüşme esnasında uygulandı.

Bulgular: Katılımcıların 78 (%28.88)'u erkek, 192 (%71.11)'i kadın ve yaş ortalaması 41.72±15 yıl idi. Katılımcıların %94.07'inin aile hekimliği polikliniğine tekrar gelmek istediği, %95.92'sinin tavsiye ettiği gözlenmiştir. Tüm katılımcıların ölçek ortalama puanı 111.25±27.67 olarak bulundu. Katılımcıların ölçek toplam ve alt boyut puanları ile yaş, cinsiyet, medeni durum arasında istatistiksel olarak anlamlı bir farklılık saptanmadı (p>0.05). Katılımcıların eğitim durumu lise altı olanların "Genel memnuniyet" puanları daha yüksek bulundu (p=0.044). Katılımcıların mesleki durumu çalışmıyor olanların ölçek toplam puanları daha yüksek bulundu (p=0.035).

Sonuç: Hasta memnuniyetinin eğitim düzeyi, meslek grubu gibi sosyodemografik verilere göre değiştiği görülmüştür. Hasta memnuniyetini olumlu etkileyen faktörlerin doğru bir hasta-hekim ilişkisi ve iyi iletişim becerileri olduğunu düşünmekteyiz.

Anahtar Kelimeler: Hasta memnuniyeti; Aile Hekimliği; poliklinik

Introduction

The first person to be in contact with the patient and provide health care is the family physician. It is the first medical contact point in the health system and acts as an inter-unit coordinator. The family physician takes responsibility in all matters related to health, including the community, family and social life of patients [1].

Family physicians treat people with the society in which they live; they evaluate independently without distinction of age, gender, disease and considers health services holistically. The family physician feels responsible for all aspects of the patient's health and meets all the patient's health-related needs [2].

Patient satisfaction is a basic criterion that shows at what level the patient's wishes are met. It is the level of satisfaction that patients feel between what they expect from the hospital and what they find. It is the evaluation of the health service, provided by the patient. In health services, patient satisfaction is seen as a kind of quality assessment indicator. The increase in the value given to patient satisfaction is attributed to the reflection of customer behaviors that emerged in the 1970s on the health sector and the increase in patients' demands for the quality of health services. As a result of the evaluation of the factors related to patient satisfaction, supporting the factors that increase the satisfaction and eliminating the factors that reduce it contributes positively to the prognosis of the patients and the efficiency of the treatment of the patients is increased. In this way, a patient-centered approach is adopted [3].

With the increase in the level of education in the society, individuals emerge who criticize the service provided. The main concept that reveals the effectiveness, efficiency and quality of the health service is patient satisfaction. Determining what patients are sufficiently satisfied with and what they complain about increases the quality of health care and leads to changes in line with the expectations of the patients [4].

It has been revealed that the satisfaction level of the patients receiving treatment service is affected by factors such as monthly household income, age, education level, marital status, having a child and gender [5]. Situations where patients' expectations cannot be met trigger many problems such as patient dissatisfaction and non-compliance with treatment [6].

The healthcare industry is becoming increasingly competitive. Measuring, evaluating and improving the quality of services provides significant benefits in terms of meeting and exceeding patient expectations. The competition is increasing due to the increase in private health centers, and the ability of health institutions to establish and maintain superiority in such an environment enables a customer-oriented system, based on patient satisfaction to begin to form [7].

In this study, it was aimed to determine the sociodemographic characteristics and clinical factors affecting the satisfaction of the patients who applied to the Ankara Training and Research Hospital Family Medicine outpatient clinics.

Material and Methods

The research is a prospective, observational and analytical type of study. It was carried out between 13.01.2022 and 13.04.2022 in Ankara Training and Research Hospital Family Medicine Outpatient Clinics. The study was approved by the local ethics committee of Ankara Training and Research Hospital (date 12.01.2022- no 21-831). The study was carried out in accordance with the Declaration of Helsinki Principles (www.wma.net/e/policy/b3.htm). All people included in the study signed the informed consent form.

There are approximately 20,000 people aged 18 and over who applied to the Family Medicine Outpatient clinics of our hospital within 3 months. The sample size was calculated as 268 people at the 90% confidence level in the calculation made by taking the population 20,000, the confidence interval 95%, and the margin of error 5%. A total of 270 people were included in our study. Individuals over the age of 18 who applied to Ankara Training and Research Hospital Family Medicine Outpatient clinics for any reason and agreed to participate in the study and signed the informed consent form were included in the study. Those who were illiterate, had communication disabilities, were followed up for a psychiatric illness or dementia were not included in the study. A questionnaire consisting of questions about the patient's socio-demographic characteristics (age, gender, marital status, educational status, etc.), smoking, alcohol use and frequency was applied by the researcher.

In order to evaluate the satisfaction of the patients, the Outpatient Satisfaction Scale (OSS) was applied. OSS consists of 5 sub-dimensions (5-point Likert-type-strongly disagree, disagree, undecided, agree, strongly agree) and a total of 29 questions. Sub-dimensions are appointment (items 1,2,3,4,5), effective examination (items 6,7,8,9,10,11,12,13,14,15,16,17,18), employee attitude (19,20,21 items), waiting time and counseling (22,23,24 items), general satisfaction (25,26,27,28,29 items). As the score of the total and sub-dimensions of the scale increases, patient satisfaction also increases. Scores of the total and sub-dimensions of the scale were “strongly disagree” between 1-1.79 points, “disagree” between 1.80-2.59 points, “undecided” between 2.60-3.39 points, between 3.40-4.19 points "I agree", between 4.20-5 points "I totally agree" is evaluated. The validity and reliability study of the scale was carried out by Kaya and Maımaıt in 2018 [8].

Statistical analysis

SPSS 25.0 package program was used for data analysis in the study. Descriptive data on the sociodemographic information of the participants were shown as frequency (n and %) tables. Continuous variables were given as mean±standard deviation.

When the continuous data of the study were examined in terms of normality assumptions, it was determined that it showed normal distribution both because the number of samples was over 200 and because the Skewness and Kurtosis values were in the ± 3.29 threshold range. Therefore, in order to determine whether there was a significant difference between the total and sub-dimension scores of the outpatient satisfaction scale, the sociodemographic data of the participants, and various variables, the Independent Samples T test, one of the parametric tests, and the One-Way ANOVA test for the variables with 3 or more groups were applied. In case of significant difference between groups, Sidak test, one of the post-hoc tests, was used to determine between which groups the significance was.

Results

78 (28.9%) of the participants were male, 192 (71.1%) were female, and the mean age was 41.72±15 years. The frequency distribution of the participants' sociodemographic data is shown in Table 1.

It was observed that 94.07% of the participants wanted to come back to the family medicine outpatient clinic, and 95.92% recommended it. The answers received in the inquiry about the hospital process and experiences of the participants are shown in Table 2.

It was determined that 108 (40%) of the participants never smoked, 186 (68.88%) did not use alcohol, and 54 (20%) had moderate alcohol consumption.

The mean OSS score of all participants was found to be 111.25±27.67. Statistics related to the results obtained from the scale and sub-dimension scores are given in Table 3.

There was no statistically significant difference between the participants' total and sub-dimension scores of OSS and age, gender, and marital status ($p>0.05$).

The "General satisfaction" scores of the participants whose education level is below high school were found to be higher. According to the results of the sidak post-hoc analysis, a statistically significant difference was found between elementary school and high school ($p=0.044$), and between elementary school and university ($p=0.024$) (Table 4).

Table 1. Sociodemographic Data of Participants (n=270)

		n or Median (min-max)	% or mean±SD
Age (years)		41.0 (18.0-75.0)	41.72±15,47
	18-45	158	58.5
	46-65	93	34.4
	>65	19	7.0
Gender	Male	78	28.9
	Female	192	71.1
Marital status	Married	134	49.6
	Single	109	40.4
	Divorced	27	10.0
Educational Status	Elemantary school	19	7.0
	High school	55	20.4
	University	196	72.6
Occupation	Unemployed	112	41.5
	White Collar	134	49.6
	Blue Collar	24	8.9
Income perception	More income than expense	40	14.8
	Income equals expense	157	58.1
	Income less than expenses	73	27.0
Chronic disease	Yes	101	37.4
	No	169	62.6

Min=Minimum, Max=Maximum, SD=Standart Deviation

Table 2. Participants' Experiences with the Hospital Process

		n (min-max)	% Mean±SD
Mode of transportation to the hospital	Public transport	76	28.13
	Private vehicle	85	31.55
	Other	109	40.47
Number of visits to the Family Medicine Outpatient Clinics		2.0 (1.0-30.0)	3.80±4.15
Would you like to come to the Family Medicine Outpatient Clinic again?	Yes	254	94.07
	No	16	5.93
Would you recommend?	Yes	259	95.92
	No	11	4.18
I usually come to write a prescription	Yes	107	39.61
	No	163	60.49
I usually come for Inspection	Yes	224	82.96
	No	46	17.04
I usually come for tests and examinations	Yes	234	86.75
	No	36	13.35
I usually come for my chronic illness follow-up	Yes	84	31.12
	No	186	68.98
If you have the chance to go to another hospital, would you still prefer to come here?	Yes	225	83.34
	No	45	16.76
Is it easy to reach the center?	Yes	259	95.91
	No	11	4.19
Was the inspection time sufficient?	Yes	249	92.27
	No	21	7.83
I feel safe with the doctor	Yes	265	98.12
	No	5	1.98
I am usually examined within 15 minutes	Yes	234	86.76
	No	36	13.34
I can comfortably ask questions during the examination.	Yes	263	97.46
	No	7	2.64

Min=Minimum, Max=Maximum, SD=Standart deviation

Table 3. Statistics of Scores from the Outpatient Satisfaction Scale (OSS) and Sub-dimensions

	n	Min	Max	Mean	SD
Outpatient Satisfaction Scale (OSS) Total	270	29.00	145.00	111.25	27.67
Appointment	270	5.00	25.00	18.31	5.65
Effective Examination	270	13.00	65.00	51.90	13.42
Employee Attitude	270	3.00	15.00	12.07	3.24
Waiting time and Counseling	270	3.00	15.00	10.82	3.22
General Satisfaction	270	5.00	25.00	18.14	5.35

N=Number, Min=Minimum, Max=Maximum, SD=Standart deviation

Table 4. Comparison of Participants' Scale and Sub-Dimensional Scores in terms of Educational Status

	Groups	n	Mean±SD	F	p	Post-Hoc
Outpatient Satisfaction Scale Total	1)Elementary	19	122.63±19.47	1.877	0.155	-
	2)High school	55	108.65±27.83			
	3)University	196	110.89±28.15			
Appointment	1)Elementary	19	20.26±5.15	1.754	0.175	-
	2)High school	55	17.47±5.73			
	3)University	196	18.36±5.66			
Effective Examination	1)Elementary	19	55.63±9.69	0.902	0.407	-
	2)High school	55	50.85±14.19			
	3)University	196	51.84±13.51			
Employee Attitude	1)Elementary	19	13.26±1.76	1.440	0.239	-
	2)High school	55	11.85±2.95			
	3)University	196	12.02±3.42			
Waiting time and Counseling	1)Elementary	19	12.16±2.14	1.797	0.168	-
	2)High school	55	10.62±3.15			
	3)University	196	10.75±3.32			
General Satisfaction	1)Elementary	19	21.32±3.22	3.661	0.027	1>2 1>3
	2)High school	55	17.85±5.74			
	3)University	196	17.92±5.33			

F=One Way ANOVA, Post-Hoc=Sidak, p<0.05

OSS total scores of the participants whose occupational status was unemployed were found to be higher (p=0.035). "Effective examination" scores, one of the sub-dimensions of OSS, were found to be higher in those with blue-collar occupational status (p=0.040). A statistically significant difference was found between the "General satisfaction" scores, which is one of the sub-dimensions of OSS, and their professional status (p=0.005). The "General satisfaction" scores of those whose occupational status is unemployed were found to be higher than the other occupational subgroups (p=0.005) (Tablo 5).

There was no statistically significant difference between the participants' total and sub-dimension scores of OSS and the presence of chronic disease (p>0.05). There was no statistically significant difference between the participants' total and sub-dimension scores of SME and their re-admission to the outpatient clinic (p>0.05).

There was no statistically significant difference between the participants' OSS total and sub-dimension scores and the response to the question "If you had the chance to go to another hospital, would you still prefer to come here" (p>0.05) (Table 6).

Participants who answered yes to the question "I feel safe with the doctor" had higher "general satisfaction" scores (p=0.045) (Table 7).

Table 5. Comparison of Participants' Scale and Sub-Dimensional Scores in Terms of Occupational Status

	Groups	n	Mean±SD	F	p	Post-Hoc
Outpatient Satisfaction Scale Total	1)Unemployed	112	114.97±24.11	3.391	0.035	-
	2)White collar	134	106.96±30.03			
	3)Blue collar	24	117.96±26.80			
Appointment	1) Unemployed	112	18.46±5.64	0.803	0.449	-
	2)White collar	134	17.98±5.70			
	3)Blue collar	24	19.50±5.50			
Effective Examination	1) Unemployed	112	53.77±11.68	3.252	0.040	-
	2)White collar	134	49.84±14.70			
	3)Blue collar	24	54.75±12.23			
Employee Attitude	1) Unemployed	112	12.41±2.77	2.554	0.080	-
	2)White collar	134	11.64±3.66			
	3)Blue collar	24	12.88±2.56			
Waiting time and Counseling	1) Unemployed	112	11.09±3.05	2.788	0.063	-
	2)White collar	134	10.41±3.35			
	3)Blue collar	24	11.88±3.05			
General Satisfaction	1) Unemployed	112	19.24±4.61	5.441	0.005	1>2
	2)White collar	134	17.08±5.59			
	3)Blue collar	24	18.96±6.22			

F=One Way ANOVA, Post-Hoc=Sidak, p<0.05

Table 6. Comparison of the Scale and Sub-Dimensional Scores of the Participants in terms of the Question "If You Had the Chance to Go to Another Hospital, Would You Still Prefer to Come Here"

	Groups	n	Mean±SD	t	p
Outpatient Satisfaction Scale Total	Yes	225	111.43±27.81	0.228	0.820
	No	45	110.40±27.29		
Appointment	Yes	225	18.44±5.65	0.813	0.417
	No	45	17.69±5.69		
Effective Examination	Yes	225	51.76±13.6	-0.415	0.678
	No	45	52.67±12.61		
Employee Attitude	Yes	225	12.15±3.16	0.864	0.388
	No	45	11.69±3.64		
Waiting time and Counseling	Yes	225	10.88±3.21	0.657	0.512
	No	45	10.53±3.34		
General satisfaction	Yes	225	18.21±5.28	0.442	0.659
	No	45	17.82±5.73		

t=Independent Samples Test, p<0.05

Discussion

In this study, it was observed that patient satisfaction varies according to sociodemographic data such as education level and occupational group. It was observed that patient satisfaction did not change according to other factors such as age, gender, marital status. Generally, the satisfaction of those who felt safe with the doctor was found to be high.

A significant difference was found between the general satisfaction scores of the sub-dimensions of OSS and the educational status. It was observed that as the level of education increased, the level of satisfaction decreased. Similarly, while there is a study showing that the level of education increases as patient satisfaction decreases [9]. There are also studies that could not find a relationship between education level and patient satisfaction [10,11]. The reason why people with a high level of education cannot fully meet their expectations from health services may be that they could not meet the expectations due to the unique methods of health care. The underlying reason why those with low education levels are more satisfied may be the satisfaction of being able to access health services.

Table 7. Comparison of the Scale and Sub-Dimensional Scores of the Participants in terms of the Variable "I Feel Safe With the Doctor"

	Groups	n	Mean±SD	t	p
Outpatient Satisfaction Scale Total	Yes	265	111.59±27.52	1.427	0.155
	No	5	93.80±33.60		
Appointment	Yes	265	18.34±5.67	0.524	0.601
	No	5	17.00±4.85		
Effective Examination	Yes	265	52.06±13.4	1.399	0.163
	No	5	43.6±13.24		
Employee Attitude	Yes	265	12.09±3.22	0.605	0.547
	No	5	11.20±4.92		
Waiting time and Counseling	Yes	265	10.86±3.17	0.932	0.120
	No	5	8.60±5.41		
General satisfaction	Yes	265	18.23±5.27	2.012	0.045
	No	5	13.4±8.05		

t=Independent Samples Test, p<0.05

In this study, the effective examination scores of the blue-collar and unemployed workers were found to be higher than the white-collar group. In the literature, there are studies that found a relationship between the occupational group and patient satisfaction [12,13], and there are also those that could not find a relationship [10,11,14]. This can be explained by the high rate of occupational similarity in the patients participating in this study. In our study, the fact that the unemployed people are more satisfied can be explained by the low level of expectation and the respect and gratitude shown to having a profession.

In our study, no significant difference was found in terms of patient satisfaction between those who answered yes to the question "would you still prefer to come here if you had the chance to go to another hospital" and those who answered no. Most of the patients reported that they preferred to come back to our hospital. However, it has been reported in the literature that patient satisfaction in private hospitals is higher than in public hospitals, and that patients would prefer a private hospital if they had the chance to go to another hospital [15,16]. It is thought that this preference is due to the fact that doctors, nurses and other health personnel can spare more time. The high level of satisfaction in our hospital may be due to the fact that the population around our hospital is not at the socioeconomic level to choose a private hospital.

The "general satisfaction" scores of those who answered "yes" to another question "I feel safe with the doctor" were found to be significantly higher. The high level of trust in doctors and health personnel increases satisfaction. Paying attention to patient privacy, ensuring that they are examined in a safe environment, and informing patients in a good way provide a sense of trust in patients. In our study, 98.12% of people answered "yes" to this question and this shows us that there is an environment of trust in our polyclinics. The study of Öztürk et al. is another study showing that as the environment of trust increases, the level of satisfaction increases [17].

Conclusion

It has been observed that patient satisfaction is affected by sociodemographic characteristics such as education level and occupational group. Generally, the satisfaction of those who felt safe with the doctor was found to be high. We think that the factors affecting patient satisfaction are correct patient-physician relationship and good communication skills.

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Scientific responsibility statement

All authors declared that they have participated in the research sufficiently to share responsibility for its content:

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Research Article

Negative impact of COVID-19 pandemia on gastric cancer surgery: Real-life data

COVİD-19 pandemisinin mide kanser cerrahisi üzerine olumsuz etkisi: gerçek yaşam verileri

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Abstract

Aim: In the Coronavirus disease 2019 (COVID-19) pandemic, the primary aim has been social isolation to control the spread of the virus. During this period, the surgery of cancer patients may have been interrupted due to the change in working conditions in hospitals and the postponement of elective surgeries. In this study, the effect of the pandemic on the clinical and surgical characteristics of patients operated for gastric cancer (GC) was investigated.

Material and Methods: Patients who were operated for GC in the general surgery clinic of our hospital between 1 June 2019 and 15 January 2021 and were followed up in the intensive care unit (ICU) during post-operative period were included in the study. Operative patients in the first 9 months of the pandemic (AP) were compared with patients who were operated for GC in the 9 months before the pandemic (BP) by performing a propensity score match analysis. The clinical features, diagnostic methods, surgical characteristics, whether they received neoadjuvant treatment or not, pathological stages at the time of operation,tumor node metastasis (TNM) stage, time from symptom onset to diagnosis, time from diagnosis to operation, post-operative complications, length of hospital stay, and costs were compared.

Results: A total of 55 patients (21 (38.2%) female and 34 (61.8%) male) with a mean age of 65.1±10.7 years and a mean American Society of Anesthesiologists (ASA) score of 2.5±0.5 were included in the study. Twenty-eight (50.9%) of them were operated on BP and 27 (49.1%) were operated on AP. Abdominal pain (89.3% vs 44.4%; p=0.005) and nausea-vomiting (57.1% vs. 18.5%; p=0.010) were more common in the BP group as admission symtoms. The time from symptom onset to cancer diagnosis was longer in AP group (87.5±78.2 vs 175.9±71.2 days; p<0.005). There were more patients receiving neoadjuvant therapy in AP group (44.4% vs 10.7%; p= 0.015); however, the time from neoadjuvant therapy to operation was similar (57.3±34.8 vs 62.8±55.5 days; p=0.441). Considering the pathological TNM stages, the number of stage 3B patients was higher in AP group (33.3% vs. 7.1%; p=0.04). The hospitalization period of the entire study group was 11.4±4.7 days; length of stay in the ICU was 4.7±2.0 days; the median total cost was 11,244.0 TL(The Turkish Lira) [9,443-15,202 TL]; there was no difference between the groups (p>0.05).

Conclusion: In our cohort, COVID-19 pandemic did not make any difference in factors such as diagnostic methods, operation types, surgical complications, length of hospital stay and cost on GC surgery. More patients were referred to neoadjuvant therapy during the pandemic. The pandemic may have led to disease progression as it prolonged the time from symptom onset to diagnosis.

Keywords: COVID-19 pandemic, gastric cancer, neoadjuvant treatment

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Öz

Amaç: Coronavirüs hastalığı 2019 (COVID-19) salgınında öncelikli amaç, virüsün yayılmasını kontrol altına almak için sosyal izolasyon olmuştur. Bu dönemde hastanelerdeki çalışma koşullarının değişmesi ve elektif ameliyatların ertelenmesi nedeniyle kanser hastalarının ameliyatlarına ara verilmiş olabilir. Bu çalışmada pandeminin mide kanseri nedeniyle ameliyat edilen hastaların klinik ve cerrahi özelliklerine etkisi araştırıldı.

Gereç ve Yöntemler: Hastanemiz genel cerrahi kliniğinde 1 Haziran 2019-15 Ocak 2021 tarihleri arasında mide kanseri nedeniyle ameliyat edilen ve ameliyat sonrası dönemde yoğun bakım ünitesinde (YBÜ) takip edilen hastalar çalışmaya dahil edildi. Mide kanseri nedeniyle, pandeminin ilk 9 ayında ameliyat olan hastalar (AP), eğilim skoru eşleşme analizi yapılarak pandemiden önceki 9 ayda ameliyat edilen hastalarla (BP) karşılaştırıldı. Klinik özellikler, tanı yöntemleri, cerrahi özellikler, neoadjuvan tedavi alıp almadıkları, operasyon anındaki patolojik evreleri, tümör lenf nodu metastazı (TNM) evresi, semptom başlangıcından tanıya kadar geçen süre, tanıdan operasyona kadar geçen süre, operasyon sonrası komplikasyonlar, hastanede kalış süresi ve maliyetler karşılaştırıldı.

Bulgular: Yaş ortalaması 65,1±10,7 yıl ve Amerikan Anestezistler Derneği (ASA) skoru ortalaması 2,5±0,5 olan 21 (%38,2) kadın ve 34 (%61,8) erkek olmak üzere toplam 55 hasta çalışmaya dahil edildi. Bunlardan 28'i (%50,9) pandemi öncesi, 27'si (%49,1) pandemi içerisinde ile ameliyat edildi. Başvuru semptomları olarak karın ağrısı (%89,3 vs %44,4; p=0,005) ve bulantı-kusma (%57,1 vs. %18,5; p=0,010) BP grubunda daha sık görüldü. Semptom başlangıcından kanser tanısına kadar geçen süre AP grubunda daha uzundu (87,5±78,2 vs 175,9±71,2 gün; p<0,005). AP grubunda neoadjuvan tedavi alan hasta sayısı daha fazlaydı (%44,4 vs %10,7; p= 0,015); ancak neoadjuvan tedaviden operasyona kadar geçen süre benzerdi (57,3±34,8 vs 62,8±55,5 gün; p=0,441). Patolojik TNM evreleri dikkate alındığında evre 3B hasta sayısı AP grubunda daha fazlaydı (%33,3 vs %7,1; p=0,04). Çalışma grubunun tamamının hastanede kalış süresi ortalama 11,4±4,7 gündü; Yoğun bakımda kalış süresi 4,7±2,0 gün; ortalama toplam maliyet 11.244,0 TL(Türk Lirası) [9.443-15.202 TL]; gruplar arasında fark yoktu (p>0,05).

Sonuç: Kohortumuzda COVİD-19 salgını tanı yöntemleri, ameliyat türleri, cerrahi komplikasyonlar, hastanede kalış süresi ve mide kanseri ameliyatı maliyeti gibi faktörlerde herhangi bir farklılık yaratmadı. Pandemi sırasında daha fazla hasta neoadjuvan tedaviye yönlendirildi. Pandemi, semptomların başlangıcından tanıya kadar geçen süreyi uzattığı için hastalığın ilerlemesine yol açmış olabilir.

Anahtar Kelimeler: COVİD-19 pandemisi, mide kanseri, neoadjuvan tedavi

Introduction

Gastric cancer (GC) is an important cause of mortality and morbidity worldwide. There are more than one million new cases and approximately 769,000 deaths (one in 13 deaths globally) in 2020 [1] . It ranks 5th worldwide in terms of cancer incidence and 4th in terms of cancer-related mortality [1] .

The Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which started in December 2019 in Wuhan, China and was declared a pandemic by the World Health Organization on March 11, 2020. It has turned into a major pandemic all over the world and has been going on for 2.5 years. As of June 6, 2022, 530,266,292 people have been infected all over the world and 6,299,364 people have died all over the world [2] . With the decisions taken by the Turkish Ministry of Health at the beginning of the pandemis in our country, it was primarily aimed to prevent the spread of this contagious pandemic, with social isolation and closures, hospital elective outpatient clinic applications were reduced and elective surgical procedures were banned for a while in order to reduce the number of affected people. In this period, the surgery of cancer diseases may have been interrupted due to the change in working conditions in hospitals and the postponement of elective surgeries. Some centers have identified cancers that can be safely delayed for several months to manage cancer and have recommended neoadjuvant therapies as an alternative therapy [3] .

Our aim in this study was to investigate the effect of the pandemic on gastric cancer surgery in our center by comparing the patients who were operated for gastric cancer before the pandemic and in the first 9 months of the pandemic.

Material and Methods

Patients who were operated for GC in the general surgery clinic of University of Health Sciences, Ankara Dışkapı Yıldırım Beyazıt Research and Education Hospital between 1 June 2019 - 14 March 2020 [before pandemic (BP)] and 15 March 2020 - 1 December 2020 [after pandemic (AP)] and were followed up in the intensive care unit (ICU) in the post-operative period were included in the study. Considering the date of 14 March 2020, when the pandemic was declared in our country and the precautions were started, the patients who were operated during AP due to GC in the first 9 months of the pandemic were compared with patients who were operated before BP for GC in 9 months by performing a propensity score match analysis . Demographic characteristics of patients (age, gender), American Society of Anesthesiologist (ASA) scores, Charlson comorbidity index, admission symptoms (weight loss, abdominal pain, nausea-vomiting, malaise, melena, dysphagia), diagnostic methods (endoskopic, surgical), surgical characteristics (type, duration, emergency or elective), whether they received neoadjuvant therapy, tumor-node-metastasis (TNM) stages, pathological tumor stages at the time of operation, time from symptom onset to diagnosis, time from diagnosis to operation, whether pre-operative thorax computed tomography (CT) was taken, post-operative complications, length of hospital stay, duration of ICU stay, blood product requirement in the operation, serum carcinoembryonic antigen (CEA), alpha feto protein (AFP), carbohydrate antigen 19-9 (CA 19-9), hemoglobin level, kidney function tests, liver function tests, glucose value and patient costs were compared.

TNM classification made by the International Union for Cancer Control (UICC) and the American Joint Cancer Committee (AJCC) was used as the staging system.

For our study, research approval was obtained from Turkish Ministry of Health and The study was approved by the institutional ethics committee.

Statistical analysis

IBM SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) was used for data analysis in our study. The patients who were operated during AP were matched with the patients who were operated during BP with the propensity score match analysis. Continuous variables were expressed as mean±standard deviation or median (min-max), and categorical data were expressed as numbers and percentages. Normality analyzes of continuous variables were performed using the Kolmogorov-Smirnov goodness-of-fit test. Because the data did not fit into the normal distribution, AP and BP comparisons were made with the Wilcoxon Ordered Signs Test. Chi-square test was used to compare categorical data. Statistical significance level was considered as $p<0.05$.

Results

A total of 55 patients, 21 (38.2%) female and 34 (61.8%) male, with a mean age of 65.1±10.7 years and a mean ASA score of 2.5±0.5 were included in the study. Twenty-eight (50.9%) of them were operated on during BP and 27 (49.1%) were operated on AP. The median Charlson comorbidity index was 2 [1-4] and all patients had at least one comorbidity; 24 (43.6%) patients had at least 2 or more comorbidities. The most common comorbidities were hypertension with 32.7% and diabetes mellitus with 14.5%. Hypertension (48.1% vs 17.9%; p=0.017) and coronary artery disease (22.2% vs 3.6%; p=0.045) were more common in patients in AP group. The most common symptoms at presentation were weight loss with 72.7%, abdominal pain with 67.3%, nausea and vomiting with 38.2% and melena with 10.9%. Three (5.5%) patients presented with dysphagia. In BP group, abdominal pain (89.3% vs 44.4%; p=0.010), nausea-vomiting (57.1% vs 18.5%; p=0.005) and weight loss (89.3% vs. 55%), 6; p=0.005) was more frequent. There was no difference in terms melena and other symptoms (p>0.05). There was no difference between the BP group and AP group in terms of age, gender, ASA, and comorbidities (p>0.005) (Table 1).

The time from symptom onset to diagnosis was statistically significantly longer in the AP group (87.5±78.2 vs 175.9±71.2 days; p<0.005). Out of 98.1% of patients were diagnosed endoscopically; 90.9% of them were operated under elective conditions. A total of 15 (27.3%) patients received neoadjuvant therapy. The number of patients who received neoadjuvant treatment was significantly higher in AP group (44.4% vs 10.7%; p=0.015). Laparoscopic GC surgery is rarely performed in our center in AP. Almost all of the patients were operated with conventional surgery (92.9% vs 100%; p=0.368). There was no difference between BP and AP for diagnosis method and operation planning . The hospitalization duration of the all study group was 11.4±4.7 days; length of stay in the ICU was 4.7±2.0 days; the median total cost was 11,244.0 TL (Turkish Lira) [9,443-15,202 TL]; there was no difference between the groups (p>0.05) (Table 1).

Table 1. Comparison of the general characteristics o participants between the study groups

Features	All Study Group (N=55,%)	Before Pandemic Group (N=28,%)	After Pandemic Group (N=27,%)	p
Age (years) (Mean±SD)	65.1±10.7	65.5±9.4	64.8±12.2	0.816*
Gender		0.458		
Female	21 (38.2)	10 (35.7)	11 (40.7)	>0.05**
Male	34 (61.8)	18 (64.3)	16 (59.3)	>0.05**
ASA (Mean±SD)	2.5±0.5	2.5±0.8	2.6±0.6	0.544**
Charlson comorbidity index (median)[25-75]	2 [1-4]	2 [2-4]	2 [1-4]	0.257**
Comorbodities				
Hypertension	18 (32.7)	5 (17.9)	13 (48.1)	0.017**
Diabetes mellitus	8 (14.5)	6 (21.4)	2 (7.4)	0.137**
Arrhythmia	3 (5.5)	0 (0)	3 (11.1)	0.111**
Coronary artery disease	7 (12.7)	1 (3.6)	6 (22.2)	0.045**
Chronic obstructive pulmonary disease	1 (1.8)	0 (0)	1 (3.7)	0.491**
Presenting Symptoms				
Abdominal Pain	37 (67.3)	25 (89.3)	12 (44.4)	0.010**
Nausea-Vomiting	21 (38.2)	16 (57.1)	5 (18.5)	0.005**
Weight Loss	40 (72.7)	25 (89.3)	15 (55.6)	0.005**
Weakness	16 (29.1)	6 (21.4)	10 (37.0)	0.164**
Melena	6 (10.9)	5 (17.9)	1 (16.7)	0.105**
Time From Symptom Onset To Diagnosis (days) (Mean±SD)		87.5±78.2	175.9±71.2	<0.005**
Diagnostic Method	0.368**			
Endoscopical	54 (98.1)	27 (96.4)	27 (100)	-
Surgical	1 (1.8)	1 (3.6)	0 (0)	-
Surgery Plan	0.187**			
Urgent	5 (9.1)	4 (14.3)	1 (3.7)	>0.05**
Elective	50 (90.9)	24 (85.7)	26 (96.3)	>0.05**
Neoadjuvant Therapy	5 (27.3)	3 (10.7)	12 (44.4)	0.015**
Type Of Surgery				
Open Surgery	53 (96.4)	26 (92.9)	27 (100)	>0.05**
Laparoscopic Surgery	2 (3.6)	2 (7.1)	0 (0)	>0.05**
Duration Of Hospitalization İn Intensive Care (days) (Mean±SD)	4.7±2.0	5.5±2.4	3.8±0.6	0.507*
Total Length Of Hospitalization (days) (Mean±SD)	11.4±4.7	12.7±2.3	10.0±0.5	0.263*
Total Cost (TL)[Median 25-75 Percentil]	11,244 [9,443-15,220]	17,056.75±3.493.21	11,795.71±556.683	0.437*

SD:Standart deviaiton, ASA: American Society of Anesthesiologists, TL:Turkish Lira
*T test, **Chi-square test

The time from neoadjuvant therapy to operation was similar (57.3±34.8 vs 62.8±55.5 days; p=0.441). Considering the surgery performed, total gastrectomy (TG) and D2 lymph node dissection (LND) were performed in 40 (72.7%) patients. Distal gastrectomy and D2 LND were performed in one (1.8%) patient. Combined organ resection (splenectomy, colon resection, cholecystectomy, etc.) was performed at a higher rate in AP group (44.4% vs 25.0%; p=0.019). The operation times of the two groups were similar (211.9±13.7 vs 177.8±13.8 min; p=0.085). A total of 10 (18.2%) patients required blood product replacement during the operation. There was no difference in terms of blood product requirement in BP and AP groups (p=0.389). Considering the pathological TNM stages, the number of stage 3B patients was higher in AP group (33.3% vs. 7.1%; p=0.04). Pathological N3 was higher in AP group (40.7% vs 23.1%; p=0.031). Post-operative complications were encountered in a total of 19 (34.5%) patients. Of these, 2 (3.6%) bleeding, 8 (14.5%) post-operative respiratory failure, 2 (3.6%) pulmonary embolism, 4 (7.3%) wound infection, and 3 of them (5.5%) were anastomotic leakage. There was no difference in terms of post-operative complications in of BP and AP groups (p>0.05) (Table 2).

Table 2. Compaison of the Operative Characteristics of the Participans Between te Study Groups			
Features	Before Pandemic Group (N=28,%)	After Pandemic Group (N=27,%)	p
Time to operation after neoadjuvant therapy (days) (Mean±SD)	57.3±34.8	62.8±55.5	0.441*
Surgery performed			
TG+D2 LND	21 (75.0)	19 (70.4)	0.467**
Distal gastrectomy+D2 LND	1 (3.6)	0 (0)	0.509**
TG+D2 LND+Cholecystectomy	2 (7.1)	1 (3.7)	0.514**
TG+D2 LND+Segmentary colon resection	1 (3.6)	1 (3.7)	0.745**
TG+ D2 LND+Splenectomy	3 (10.7)	2 (7.4)	0.518**
TG+D2 LND+Splenectomy+Cholecystectomy	0 (0)	1 (3.7)	0.491**
TG+ D2 LND+Liver metastatectomy	0 (0)	2 (7.4)	0.111**
TG+ D2 LND+Metastatectomy+Cholecytectomy	0 (0)	1 (3.7)	0.491**
Combined organ resection	7 (25.0)	12 (44.4)	0.019**
Operation time (minutes) (Mean±SD)	211.9±13.7	177.8±13.8	0.085*
Blood product requirement	6 (21.4)	4 (14.8)	0.389**
Pathological TNM Stage			
Stage 1A	3 (10.7)	6 (22.2)	>0.05**
Stage 1B	0 (0)	1 (3.7)	>0.05**
Stage 2A	3 (10.7)	3 (11.1)	>0.05**
Stage 2B	3 (10.7)	2 (7.4)	>0.05**
Stage 3A	8 (28.6)	4 (14.8)	>0.05**
Stage 3B	2 (7.1)	9 (33.3)	0.034**
Stage 3C	5 (17.9)	0 (0)	>0.05**
Stage 4A	4 (14.3)	2 (7.4)	>0.05**
Pathological Stages			
T Stage			
1A	2 (7.1)	1 (3.7)	0.514**
1B	1 (3.6)	0 (0)	0.509**
2	2 (7.1)	3 (11.1)	0.482**
3A	5 (17.9)	6 (22.2)	0.473**
3B	5 (17.9)	4 (14.8)	0.524**
4A	12 (42.9)	13 (48.1)	0.451**
N Stage			
N0	7 (25)	7 (25.9)	0.591**
N1	6 (21.4)	5 (18.5)	0.527**
N3	9 (23.1)	11 (40.7)	0.031**
M Stage			
MA	1 (3.6)	4 (14.8)	0.164**
Post-operative Complications			
Bleeding	1 (3.6)	1 (3.7)	0.745**
Respiratory failure/pneumonia	4 (14.3)	4 (14.8)	0.626**
Pulmonary embolism	1 (3.6)	1 (3.7)	0.745**
Wound infection	2 (7.1)	2 (7.4)	0.681**
Anastomotic Leakage	2 (7.1)	1(3.7)	0.514**
SD: Standard deviation, TG: Total gastrectomy, LND: Lymph node dissection, T: Tumor, N: Node, M: Metastasis *T test **Chi-square test			

In the pre-operative period, thorax CT was performed in 44 (80%) patients. The majority of them were in AP group. Three (5.5%) patients were reoperated. The reason for the operation was anastomotic leakage in 1 (1.8%) patient, deep wound infection in 1 (1.8%) patient, and bleeding in 1 (1.8%) patient.

When the laboratory findings and tumor markers of the patients were evaluated, no difference was found between the two groups in the period of BP and AP (p>0.05) (Table 3).

Table 3. Comparison of Laboratory Findings of the Participants Between the Study Groups

Features	Before Pandemic Group (N=28,%)	After Pandemic Group (N=27,%)	p
Hg (gr/dl)*	11.5±2.9	11.9±2.3	0.285***
Creatinine (mg/dl)*	0.9±0.3	0.8±0.2	0.364***
Glucose (mg/dl)*	106.0±22.2	105.5±29.9	0.364***
AST (U/L)**	17 [9-102]	16 [8-187]	0.731***
ALT (U/L)**	13.5 [6-97]	17.8 [6-111]	0.395***
CEA (µg/L)*	8.5±15.4	9.6±17.7	0.364***
AFP (ng/ml)*	3.6±3.0	3.3±1.9	0.459***
CA 19-9 (U/ml)**	11.4 [0.8-545.5]	11.1 [1-1584]	0.286***

*Mean±standard deviation; **Median [25-75 percentil], AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CEA: Carcinoembryonic antigen, AFP: Alpha feto protein, CA 19-9: Cancer antigen 19-9
****Mann Whitney U Testi

In the postoperative period, repetitive COVID-19 real-time polymerase chain reaction (RT-PCR) was performed on upper respiratory tract samples from six patients with suspected COVID-19. No positive results were obtained.

Discussion

In our study, the COVID-19 pandemic did not make any difference on GC surgery on the diagnostic methods, operation types, surgical complications, length of hospital and ICU stay, and cost. However, patients who were operated in AP period were more symptomatic. More patients were referred to neoadjuvant therapy during the pandemic. In addition, the number of patients operated for TNM stage 3B GC and combined organ resection was higher in AP period.

The diagnosis of GC is mostly made by gastroscopy (endoscopy). The number of GC screenings has decreased during the COVID-19 pandemic. In 2020, the number of gastroscopies in Italy decreased by 53.6% compared to 2019, and by 57% in the Netherlands [4, 5] . There is a linear model relationship between the number of endoscopies performed and diagnosed gastric cancers. In the case of a 20% reduction in endoscopy, the average number of GC diagnoses per week was reduced by 54.1% [6]. This shows that there has been a decrease in the diagnosis of GC owing to the pandemic. Another study showed that hospital admissions decreased during the pandemic and patients wanted to receive health services such as video interviews[7]. As shown in our study, the COVID-19 pandemic caused a prolongation of the time from symptom onset to diagnosis and more symptomatic hospital admissions. The reason for the high number of advanced stage patients in AP group may be the delay in diagnosis. In the study of Li et al . [8] , the pandemic; showed that, it caused delay in admission of symptomatic patients to the hospital and a prolongation of the time from diagnosis to surgery.

Patients with locally advanced GC may be initially referred for neoadjuvant chemotherapy. Four weeks after the end of neoadjuvant treatment, patients were evaluated for suitability for surgery. Studies on neoadjuvant chemotherapy for gastric cancer demonstrated that a waiting period of more than 6 weeks before surgery can improve the rate of complete response, with no effect on prognosis [9] . This seems to have led to a tendency to neoadjuvant therapy as an alternative treatment option during the pandemic. In one study, treatment was delayed in 12% of patients with gastric cancer, and the treatment modality was changed to chemotherapy or immunotherapy in 20% of patients [7]. In our study, the number of patients who received neoadjuvant therapy was significantly higher in the AP group. This can be attributed to the avoidance of postoperative complications due to the COVID-19 pandemic, interrupting elective surgeries, or seeking alternative treatment to surgery..

In one study, it was concluded that by taking the necessary precautions, strict cancer treatment can be performed without delay, as stated in the usual guidelines, and this has no effect on mortality [10]. In our study, no positive

diagnostic test for COVID-19 was detected in any patient with suspected COVID-19 during the AP period. These results support the continuation of cancer treatment without disruption. Similar to our study Gocayev et al. [11] found that there were no significant differences in the duration of hospitalization, postoperative complications, and blood product requirements for BP and AP. In the study of Li et al. [8] they found that the postoperative hospital stay was longer and the total hospitalization cost increased in the AP period. However, in our study, no difference was observed between the two groups in terms of length of hospital stay and cost.

Conclusion

As a result, in our study, the time from symptom onset to diagnosis was prolonged in patients with gastric cancer during the pandemic period. This may have caused the patients to be more symptomatic at the time of presentation and disease progression while waiting for surgery. We think that this may be due to reasons such as PCR tests, decreased endoscopic procedures, and the reluctance of patients to visit the hospital during the pandemic. To avoid complications related to the COVID-19 pandemic after surgical treatment, patients may have been referred to neoadjuvant therapy as an alternative.

Ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board of University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital (reference no.: 106/23) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Conflict of Interest

The authors have no conflict of interest to declare.

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Research Article

Hemoptysis in adult patients: Etiology, recurrence and risk of mortality

Erişkin hastalarda hemoptizi: Etyoloji, rekürrens ve mortalite riski

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Abstract

Aim: The etiology of hemoptysis varies according to population differences, time, geographical region, and diagnostic tests used. The aim of this study is to investigate the etiological causes, recurrence and mortality risk of hemoptysis in a university hospital.

Material and Methods: The data of 391 patients who applied to our hospital with hemoptysis between June 2011 and February 2022 were analyzed using the hospital electronic file system. Demographic characteristics, smoking information, radiological findings and related diagnoses of the patients were recorded. The obtained data were analyzed.

Results: A total of 391 patients, including 229 males and 162 females, were included in the study. The mean age of all patients was 54.5±20.0 years. Pneumonia (49.7%), lung cancer (21%), pulmonary embolism (17.8%) were the most common causes of hemoptysis. 48.5% of our cases had idiopathic hemoptysis. There was no difference between men and women in terms of diagnoses related to hemoptysis (p=0.937). The mean hemoptysis recurrence rate was 10.2% and the recurrence time was 375 days (min:6-max:2886) in all patients. The overall mortality rate was 6%. In the correlation analysis, only the length of stay in the first hemoptysis was found to be associated with mortality (p<0.05).

Conclusion: In our study; the overall mortality rate was 6%, and the risk of recurrence and mortality was high, and the risk of recurrence was higher in patients using anticoagulants or antiaggregants and in patients with lung cancer.

Keywords: Hemoptysis, etiology, recurrence, mortality

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Öz

Amaç: Hemoptizinin etiyolojisi, popülasyon farklılıklarına, zamana, coğrafi bölgeye, kullanılan tanısal testlere göre değişmektedir. Bu çalışmanın amacı bir üniversite hastanesinde hemoptizinin etyolojik nedenlerini, rekürrens ve mortalite riskini araştırmaktır.

Gereç ve Yöntemler: Hastanemize Haziran 2011-Şubat 2022 tarihleri arasında hemoptizi nedeniyle başvuran 391 hastanın verileri hastane elektronik dosya sisteminden faydalanılarak incelendi. Hastaların demografik özellikleri, sigara kullanım bilgileri, radyolojik bulguları, ilişkili tanıları kaydedildi. Elde edilen veriler analiz edildi.

Bulgular: Çalışmaya 229 erkek 162 kadın olmak üzere 391 hasta dahil edildi. Tüm hastaların yaş ortalaması 54.5±20.0 idi. Pnömoni (%49.7), akciğer kanseri (%21), pulmoner emboli (%17.8) en sık hemoptizi nedenleriydi. Olgularımızın %48.5'i idiopatik hemoptiziydi. Hemoptiziyle ilişkili tanılar açısından kadın-erkek arasında farklılık saptanmadı (p=0.937). Tüm hastalarda ortalama hemoptizi rekkürrens oranı %10.2, rekürrens süresi 375 gün (min:6-max:2886) bulundu. Genel mortalite oranı %6 olup, Korelasyon analizinde sadece ilk hemoptizde yatış süresinin mortalite ile ilişkisi bulundu (p<0.05).

Sonuç: Çalışmamızda; genel mortalite oranı %6 bulunmuş olup, rekürrens ve mortalite riskinin yüksek olduğu, antikoagülan ya da antiagregan kullanan hastalarda ve akciğer kanseri tanılı hastalarda rekürrens riskinin daha yüksek olduğu görüldü.

Anahtar Kelimeler: Hemoptizi, etyoloji, rekürrens, mortalite

Introduction

Hemoptysis is expectoration of bleeding from the tracheobronchial tree or lung parenchyma. The annual incidence of hemoptysis is 0.1% in outpatients and 0.2% in inpatients. It is a potentially life-threatening medical emergency and carries a high risk of death (1). The etiology of hemoptysis varies according to differences in patient population, time, geographical region, and diagnostic tests used. Lung cancer, pulmonary embolism and bronchiectasis are the leading causes of hemoptysis. The predominant cause of hemoptysis has changed from tuberculosis and bronchiectasis to lung cancer (2). Chest radiography is recommended as the initial diagnostic test in hemodynamically stable patients with hemoptysis. Bronchoscopy is recommended after computed tomography in patients with massive hemoptysis, abnormal radiographic findings, and risk factors for malignancy despite normal radiographic findings (3,4,5).

The aim of this study is to investigate the demographic and etiological characteristics, recurrence risk, recurrence time and mortality rate of patients admitted to our hospital with hemoptysis.

Materal and Methods

The data of 391 patients admitted to our hospital between June 2011 and February 2022 due to hemoptysis, were analyzed using the hospital electronic file system. Patients over the age of 18 were included in the study. Patients with missing file data were excluded from the study. The patients' demographic characteristics, smoking status, radiological findings and related diagnoses were recorded. The collected data were analyzed. The amount of hemoptysis was determined as <30 ml/day mild, 30-100 ml/day moderate, 100-600 ml/day severe, and >600 ml/day massive. Except for the first episode of hemoptysis, recurrent episodes at least 30 days apart were considered as recurrent hemoptysis (6).

Statistical analysis

Nominal and ordinal data were defined by frequency analysis, measurement data were defined by mean and standard deviation values. Fischer's Exact and Chi-Square Similarity Ratio tests were used for difference analysis of nominal and ordinal data. Before the difference analysis of the measurement data, Kolmogorov Smirnov analysis was performed for normality test. Mann-Whitney U test was used for the difference in measurement data between groups, as all measurement data did not fit the normal distribution. In relational screening analysis, Spearman's rho correlation was used for univariate analysis and Binary Logistic Regression analysis was used for multivariate analysis. All analyzes were performed in SPSS 17.0 for Windows software, at 95% confidence interval and 0.05 significance level.

Results

A total of 391 patients, comprising 229 males and 162 females, were included in the study. The mean age of all patients was 54.5±20.0 years (Table 1). Atelectasis (22.8%), nodule (20.9%), and emphysematous changes (13.3%) were the most common tomography findings (Table 2). There was no difference between males and females in terms of tomography

findings (p=0.214). Pneumonia (49.7%), lung cancer (21%), pulmonary embolism (17.8%) were the most common causes of hemoptysis (Table 3). There was no difference between males and females in terms of diagnoses related to hemoptysis (p=0.937). The observed recurrence rate of hemoptysis in all patients was 10.2%. Mean hemoptysis recurrence time was 375 days (min:6-max:2886). In the patient population we examined, massive hemoptysis was observed in 35 (8.95%) patients. Among the patients with massive hemoptysis, 10 patients were diagnosed with lung cancer (2.55%), 11 with pneumonia (2.81%), 8 with bronchiectasis (1.53%), 3 with pulmonary embolism (0.76%), 1 with anticoagulant use (0.25%), 1 with endometriosis (0.25%), and 1 (0.25%) with active tuberculosis. Twenty-four (6.1%) of these patients were lost. In our study, the mortality rate in massive hemoptysis was found to be 68.57%. Therapeutic bronchoscopy was performed in 1 patient (0.25%), bronchial artery embolization in 3 patients (0.76%), and surgical treatment in 17 (4.3%) patients.

Table 1. Demographic data of patients

Age	n:391	54.5±20.0
Gender n(%)		
Male	229	(58.6)
Female	162	(41.4)
Smoking n(%)		
Quit smoking	80	(20.5)
Never smoked	160	(40.9)
Active smoker	140	(35.8)
Thorax computed tomography n(%)	263	(67.3)
Diagnostic Bronchoscopy n(%)	88	(22.5)
Hemoptysis Recurrence n(%)	40	(10.2)
Hospital Mortality n(%)	24	(6.1)

Table 2. Thorax computed tomography findings

Thorax computed-tomography findings	n	%
Atelectasis	60	22.8
Nodule	55	20.9
Emphysematous changes	35	13.3
Ground glass	28	10.6
Bronchiectasis	28	10.6
Consolidation	23	8.7
Solid mass	19	7.2
Peribronchial infiltration	15	5.7
Cavity	9	3.4
Pulmonary artery dilatation	6	2.2
Tuberculosis sequelae	5	1.9
Aneurysm	2	0.7
Fungus ball	1	0.3

Table 3: Hemoptysis-related diagnoses

Hemoptysis-related diagnoses	n	%
Pneumonia	78	49.7
Lung cancer	33	21
Pulmonary embolism	28	17.8
Use of anticoagulant or antiaggregant	14	8.9
Bronchiectasis	12	7.6
Bronchitis	10	6.4
Active lung tuberculosis	4	2.5
Vascular malformation	4	2.5
Pulmonary edema	4	2.5
Bronchial benign tumor	1	0.6
Endometriosis	1	0.6
Aspergillosis	1	0.6

In the group with hospital mortality, cavity, a thoracic computed tomography finding, was more common (12.5% vs. 1.6%) (p<0.05). Among the diagnoses associated with hemoptysis, lung cancer (33.3% vs. 7.1%) and pneumonia (45.8% vs. 18.3%) were more common in the group with hospital mortality, and the differences between the groups were statistically significant (p<0.05). The mean hospital stay at first hemoptysis was higher in the group with hospital mortality (p<0.05). Moreover, the distribution of all demographic, clinical, thoracic computed tomography and hemolysis-related diagnoses examined in the study in terms of mortality was not statistically significant (Table 4).

Spearman's rho correlation analysis results demonstrated that, there was a significant and positive correlation between the first hemoptysis and hospital mortality and length of stay (r=0.394; p<0.01), cavity (r=0.174; p<0.01), tuberculosis sequelae (r=0.103; p<0.05), bronchial artery embolization (r=0.100; p<0.05), surgical treatment for hemoptysis (r=0.102; p<0.05), lung cancer (r=0.224; p<0.01), pneumonia (r=0.166; p<0.01), and endometriosis (r=0.198; p<0.01) (Table 5).

Among the variables that were significantly correlated in the correlation analysis, there was a statistically significant difference between the groups with and without mortality only in terms of length of stay at first hemoptysis (B=0.097; p<0.05). The contributions of cavity, bronchial artery embolization, surgery, lung cancer, pneumonia and endometriosis parameters in multivariate analysis were not statistically significant (p>0.05) (Table 6).

According to the ROC analysis results regarding the diagnostic value of the length of stay in the first hemoptysis on hospital mortality, the diagnostic value of the length of stay in the first hemoptysis was found to be 85.3% (Area Under Curve (AUC)= 0.853; p<0.01). When the cut-off value of 14.5 days of hospitalization in the first hemoptysis was taken, the sensitivity and specificity of hospital mortality were found to be 85.7% and 86.8%, respectively (Figure 1).

Table 4. Distribution of some clinical, radiological and hemoptysis-related findings according to mortality groups and results of difference analysis

	Hospital Mortality		p
	None (n=367)	Yes (n=24)	
Gender n (%)			
Male	218 (59.4)	11 (45.8)	0.137[a]
Female	149 (40.6)	13 (54.2)	
Average age ± SS	54.25±20.11	58.08±17.57	0.412[b]
Hospital unit n (%)			
Policlinic	273 (74.4)	14 (58.3)	0.231[c]
Inpatient service	93 (25.3)	10 (41.7)	
Intensive care unit	1 (0.3)	-	
Thorax computed tomography n (%)	248 (67.6)	15 (62.5)	0.379[a]
Thorax computed tomography findings n (%)			
Bronchiectasis	25 (6.8)	1 (4.2)	0.514[a]
Cavity	6 (1.6)	3 (12.5)	0.013[a]
Solid mass	16 (4.4)	3 (12.5)	0.103[a]
Consolidation	21 (5.7)	2 (8.3)	0.420[a]
Ground-glass	28 (7.6)	-	0.159[a]
Nodule	52 (14.2)	3 (12.5)	0.556[a]
Fungus	1 (0.3)	-	0.939[a]
Aneurysm	2 (0.5)	-	0.881[a]
Tuberculosis sequelae	7 (1.9)	2 (8.3)	0.100[a]
Emphysematous changes	31 (8.4)	4 (16.7)	0.157[a]
Pulmonary artery dilatation	6 (1.6)	-	0.682[a]
Atelectasis	56 (15.3)	4 (16.7)	0.518[a]
Peribronchial infiltration	15 (4.1)	-	0.380[a]
Diagnostic bronchoscopy n (%)	82 (22.3)	6 (25.0)	0.464[a]
Therapeutic bronchoscopy n(%)	1 (0.3)	-	0.939[a]
Bronchial artery embolization n (%)	2 (0.5)	1 (4.2)	0.173[a]
Surgery n (%)	14 (3.8)	3 (12.5)	0.078[a]
Hemoptysis-related diagnoses n (%)			
Lung cancer	26 (7.1)	8 (33.3)	0.000[a]
Bronchitis	11 (3.0)	-	0.494[a]
Pneumonia	67 (18.3)	11 (45.8)	0.003[a]
Aspergillosis	1 (0.3)	-	0.939[a]
Active pulmonary tuberculosis	3 (0.8)	1 (4.2)	0.225[a]
Bronchiectasis/Cystic fibrosis	11 (3.0)	1 (4.2)	0.538[a]
Vascular malformation	4 (1.1)	-	0.775[a]
Anticoagulant-antiaggregant use	13 (3.5)	1 (4.2)	0.594[a]
Pulmonary edema	4 (1.1)	-	0.775[a]
Pulmonary embolism	25 (6.8)	3 (12.5)	0.242[a]
Systemic disease	21 (5.7)	-	0.255[a]
Bronchial benign tumor	1 (0.3)	-	0.939[a]
Endometriosis	-	1 (4.2)	0.061[a]
Recurrence n (%)	38 (10.4)	2 (8.3)	0.546[a]
Smoking n (%)			
None	156 (42.5)	15 (62.5)	
Quit Smoking	76 (20.7)	4 (16.7)	0.143[c]
Active smoker	135 (36.8)	5 (20.8)	
Length of stay at first hemoptysis (mean) ± SS	8.25±10.13	23.57±12.25	0.001[b]
Time to recurrence (mean)± SS	375.90±576.57	366.50±94.04	0.412[b]

a. Fischer's Exact Test, b. Mann Whitney U Test, c. Likelihood Ratio, SS: Standard Deviation.

Table 5. Spearman's rho correlation analysis results for the relationship between hospital mortality and some clinical, radiological and hemoptysis-related findings

Hospital Mortality	r	p
Gender	0.066	0.192
Age	0.041	0.413
Hospital unit	0.087	0.087
Length of stay in first hemoptysis	0.394**	0.002
Thorax computed tomography	-0.026	0.609
Bronchiectasis	-0.025	0.615
Cavity	0.174**	0.001
Solid mass	0.091	0.073
Consolidation	0.027	0.599
Ground-glass	-0.071	0.161
Nodule	-0.012	0.820
Fungus ball	-0.013	0.799
Aneurysm	-0.018	0.718
Tuberculosis sequelae	0.103*	0.042
Emphysematous changes	0.069	0.173
Pulmonary artery dilatation	-0.032	0.529
Atelectasis	0.009	0.853
Peribronchial infiltration	-0.051	0.314
Diagnostic bronchoscopy	0.015	0.763
Therapeutic bronchoscopy	-0.013	0.799
Bronchial artery embolization	0.100*	0.049
Surgical	0.102*	0.043
Lung cancer	0.224**	0.000
Bronchitis	-0.044	0.391
Pneumonia	0.166**	0.001
Aspergillosis	-0.013	0.799
Active pulmonary tuberculosis	0.080	0.115
Bronchiectasis Cystic fibrosis	0.016	0.748
Vascular malformation	-0.026	0.608
Anticoagulant- antiaggregant use	0.008	0.874
Pulmonary edema	-0.026	0.608
Pulmonary embolism	0.053	0.296
Systemic disease	-0.061	0.229
Bronchial benign tumor	-0.013	0.799
Endometriosis	0.198**	0.000
Recurrence	-0.016	0.752
Time to recurrence	0.144	0.371

*p<0.05 **p<0.01

Discussion

Of all hemoptysis cases, 50% remain cryptogenic, with the most common causes that can be detected listed as airway infections (bronchitis, pneumonia, lung abscess) (22%), bronchial carcinoma or metastases (17.4%), bronchiectasis/ cystic fibrosis (6.8%), pulmonary cardiovascular causes such as edema, mitral stenosis (4.2%), pulmonary artery embolism (2.6%), tuberculosis (2.7%), anticoagulant or antiaggregant use (3.5%). In Western countries, the average age is 62, and

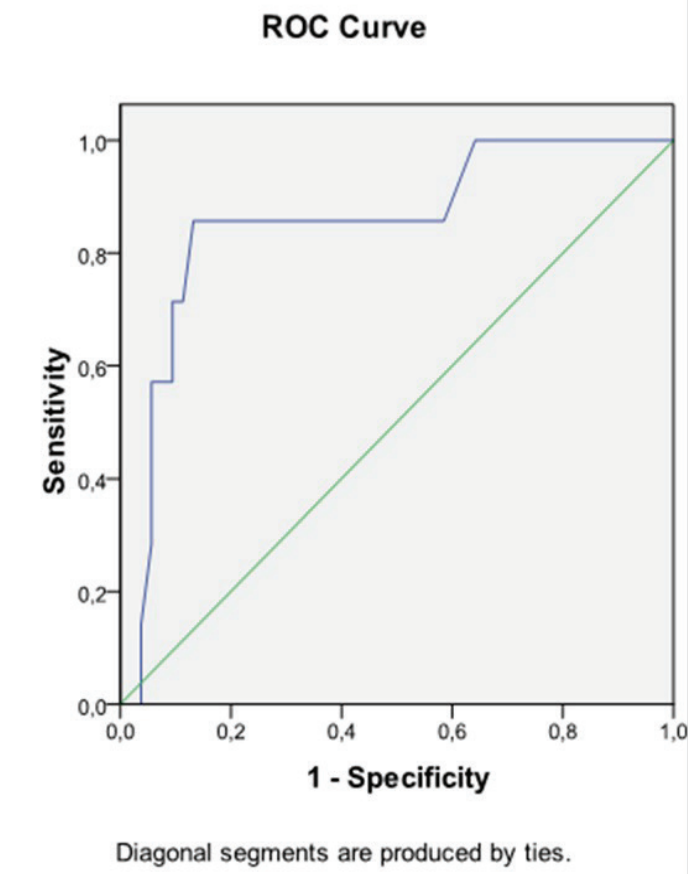

Figure 1. ROC analysis results on the diagnostic value of length of stay at first hemoptysis on hospital mortality.

In our study, male cases presenting with hemoptysis were more common, and pneumonia (49.7%), lung cancer (21%), pulmonary embolism (17.8%), use of anticoagulants (8.9%), and bronchiectasis (7.6%) were the most common causes. The reason why pneumonia is more common in etiology and has a higher mortality is that our hospital is a solid organ and hematological transplant center, and a reference hospital for solid and hematological malignancies. Community and hospital-acquired resistant viral, bacterial and fungal pneumonias are common in our hospital. In a study by Fidan et al. in 2002, lung cancer was the leading cause of hemoptysis (34.3%), followed by bronchiectasis (25.0%), tuberculosis (17.6%), pneumonia (10.2%), and pulmonary embolism (4.6%). Most of the lung cancer patients were male (p=0.002) (6). In our study, no gender difference was observed in terms of lung cancer, which may be due to the increased incidence of lung cancer in the female population over the years. Lung cancer mortality is higher in men than in women, but the size of this difference continues to decrease due to the higher incidence of lung cancer in women and increases in mortality (7,8,9).

Table 6. Binary logistic regression analysis results among parameters with significant correlation with hospital mortality

	B	S.E.	Wald	df	p	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
Length of stay in first hemoptysis	0.097	0.046	4.476	1	0.034	1.102	1.007	1.205
Cavity(1)	-42.312	31663.892	0.000	1	0.999	0.000	0.000	.
Bronchial artery embolization(1)	-3.043	44471.720	0.000	1	1.000		0.000	.
Surgery(1)	19.231	19033.107	0.000	1	0.999	2.248E8	.000	.
Lung cancer(1)	-3.386	2.080	2.651	1	0.103	0.034	0.001	1.994
Pneumonia(1)	-2.174	1.765	1.517	1	0.218	0.114	0.004	3.617
Endometriosis(1)	-25.055	40192.957	0.000	1	1.000	0.000	0.000	.
Constant	51.239	65065.736	0.000	1	0.999	1.790E22		

-2 Log likelihood: 21.499; Cox & Snell R^2: 0.304; Nagelkerke R^2: 0.592.

In the study of Özgül et al., the most common etiology in hemoptysis patients was tuberculosis (43.8%), followed by lung cancer (21.7%) and chronic bronchitis (5.5%) (10). In the study of Ünsal et al., the most common causes of hemoptysis were bronchiectasis (22.4%), lung cancer (18.9%), active tuberculosis (11.2%) and inactive tuberculosis (10.5%) (11).

In Uzun et al's prospective cohort, lung cancer (53.3%), pulmonary embolism (23.1%) and bronchiectasis (23.1%) were the main causes of hemoptysis, consistent with our study. This study is the first to show that pulmonary embolism is the leading cause of hemoptysis. In our study, pulmonary embolism was found to be the cause of hemoptysis with a high rate and supports this study (2).

In our study, tuberculosis as the cause of hemoptysis was seen at a lower rate (2.5%) compared to other studies. After the effective tuberculosis control programs implemented in our country, the registered tuberculosis incidence has decreased by an average of 5% annually for the last 10 years. In 2005, a total of 20,535 tuberculosis patients were registered and the incidence was 29.4 per hundred thousand, while it was 14.6 per hundred thousand in 2017 (12). We thought that this change in the incidence of tuberculosis was the reason why the tuberculosis rates observed in our study were lower than in other studies conducted in our country. Widespread use of antibiotics and advances in radiological methods used in the diagnosis of lung malignancies have led to changes in the etiology of hemoptysis. In the study published by Lee et al. in 2000, bronchiectasis was found to be the most common cause of hemoptysis (13). In previous studies in our country, hemoptysis due to bronchiectasis was observed at higher rates compared to our study (2,6,10,11).

However, despite advanced diagnostic methods, the cause of hemoptysis cannot be determined in most patients (50%) with hemoptysis (4). In our case, 48.5% of our cases were idiopathic hemoptysis.

Bleeding localization and hemoptysis can be detected in 33-82% and 35-50% of the cases, respectively, by chest X-ray, in 70-100% and 60-77%, respectively, by computed tomography, in 73-93% and 2.5-8%, respectively, by bronchoscopy (1). Computed tomography (CT) was used in 67.3% of our cases. It has been reported that up to 10% of pulmonary malignancies in patients with hemoptysis can remain hidden on chest X-ray and 96% of them can be detected by CT (13). In our cases, diagnostic bronchoscopy was performed in 22.5% of the patients. There are publications reporting that CT is superior to bronchoscopy in showing the centre of bleeding (14). Bronchial artery embolization (BAE), performed in 3 of our patients, is a minimally invasive procedure that has become the preferred treatment for recurrent and massive hemoptysis. When performed by an experienced operator with sufficient technical equipment, clinical success, defined as cessation of bleeding within 24 hours after BAE or in same-admission, can reach 75-98%, but the recurrence rate of bleeding varies between 1 and 27% (15). Surgery was performed in 17 of the patients enrolled in our study due to massive hemoptysis. Although lung resection is associated with high morbidity and mortality rates in the treatment of massive hemoptysis, it is the only permanent curative method when necessary (16). Recurrence was observed in 10.2% of our cases. Recurrence of hemoptysis is common (47%) even following embolization in hemoptysis and is associated with high mortality (17). In our study, recurrence was not found to be associated with mortality.

In a study from our country, lung cancer was shown to be the most common cause of recurrent hemoptysis (18). Fidan et al. revealed that the most common etiology in recurrent hemoptysis is bronchiectasis (6). In our study, the most common recurrence risk was seen in patients with lung cancer diagnosis and use of anticoagulant/antiaggregant. In a study evaluating long-term prognostic outcomes in patients with hemoptysis, bronchiectasis was found to be associated with an increased risk of recurrence (19). Fidan et al and Ryuge et al also found bronchiectasis to be the most common diagnosis in recurrent hemoptysis (6,20). Tobacco smoke and its bronchopulmonary inflammatory consequences constitute an etiology for bronchial bleeding, regardless of the severity of the underlying disease (21). Although it was not associated with hemoptysis mortality in our study, 56% of the patients presenting with hemoptysis had a history of smoking.

In our study, the overall mortality rate was 6%, and it was shown that there was a statistically significant and positive relationship between hospital mortality and length of stay at first hemoptysis, cavity, tuberculosis sequelae, bronchial artery embolization, surgery status, lung cancer, pneumonia and endometriosis. However, in the correlation analysis, only the length of stay in the first hemoptysis was found to be associated with mortality. Mondoni et al. reported that the overall mortality rate was 13.7%, increased from 18.1% to 31% after a one-year follow-up, and lung malignancy was the main determinant of mortality (19). Mortality rates are 50-100% in patients with massive hemoptysis treated conservatively (1). Massive hemoptysis is the expectoration of 600 mL of blood over 24 hours, usually in an adult. Massive hemoptysis was observed in 8.9% of the patient population we examined. Most of the patients with massive hemoptysis consisted of patients diagnosed with lung cancer, pneumonia and bronchiectasis. The etiologies of massive hemoptysis vary greatly according to demographic characteristics. Malignancy, bronchiectasis and chronic infection are the most common causes in adults (22). In our study, the mortality rate due to massive hemoptysis was 68.57%, which is consistent with the literature (1,22).

Conclusion

In our study, it was observed that the risk of recurrence and mortality in hemoptysis is high, it can recur even after a long time, and the risk of recurrence is higher in patients using anticoagulants or antiaggregants and in patients with lung cancer diagnosis. Patients and physicians should be careful and cautious in terms of hemoptysis-associated mortality, morbidity and recurrence risk.

Conflict of Interest and Source of Funding

The authors declare that there is no conflict of interest.

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Ethics Committee Approval

Ethics committee approval was obtained from Baskent University Medicine and Health Sciences Research Committee. (Ethics committee No:KA22/14 – Date:11.01.2022).

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Research Article

Mechanical aortic valve replacement in children

Çocuklarda mekanik aort kapak replasmanı

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Abstract

Aim: Aortic stenosis is a congenital heart disease characterized by the narrowing of the aortic valve, the valve that regulates blood flow from the heart's left ventricle to the aorta. While aortic stenosis can affect individuals of all ages, including children, it poses unique challenges in pediatric patients. The severity of aortic stenosis in children can vary widely, ranging from mild to severe, and may present with symptoms such as chest pain, fatigue, and shortness of breath. If left untreated, aortic stenosis can lead to significant complications and negatively impact a child's overall health and quality of life.

Material and methods: Between February 2019 and June 2023, 38 patients were operated due to aortic valve pathologies in our hospital. Aortic valve repair was performed in 11 of these patients, and aortic valve replacement was performed in 27 patients. Patients' age, gender, body weight, aortic valve pathology, etiology of aortic valve pathology (congenital, rheumatic, infective endocarditis), presence of Marfan Syndrome, previous operation history, aortic annulus diameter, type of valve used, valve size, type of root enlargement if performed, cardiopulmonary bypass duration, cross-clamp duration, duration of intensive care unit stay, duration of ward stay, inotrope requirement, duration of inotrope use, mechanical ventilation duration, volume of drainage and mortality were retrospectively searched from patient files and hospital database.

Results: The median age of the patients was 12.96±3.38 (IQR=11.00-16.00) years, their weights ranged between 43.81±14.21 kilograms. Eight patients were female (29.6%) and 19 patients were male. (70.4%) The diagnosis was aortic stenosis in 8 patients (29.6%), aortic insuffiency in 9 patients (33.3%) and both aortic stenosis and insuffiency in 10 patients.(37%) The aortic annulus diameters of the patients were 21.59±4.64 mm. Anterior or posterior root enlargement was performed in 11 patients (40.7%) due to narrow aortic annulus. The Nick procedure was applied to 7 patients (63.6%), the Manoughian procedure to 2 patients (18.2%), and the Konno procedure to 2 patients (18.2%). Considering the mechanical aortic valve dimensions used in the patients, 5 patients had size 19 prosthetic aortic valve (18.5%), 8 patients had size 21 prosthetic aortic valve (29.6%), 8 patients had size 23 prosthetic aortic valve (29.6%), and 6 patients had size 25 prosthetic aortic valve (22.2%) were used. Mortality was observed in 3 patients.(11.1%) Causes of mortality can be listed as low cardiac output, neurological events and sepsis.

Conclusion: The ultimate goal is to ensure that children who undergo aortic valve replacement can lead healthy and fulfilling lives. By continually refining our approaches and learning from each case, we can make significant strides in the treatment of aortic valve issues in children and offer them the best possible outcomes.

Aortic valve replacement in children requires a multidisciplinary approach, with a focus not just on the surgical procedure itself but also on long-term management and support. With ongoing advancements and a collaborative mindset, we can continue to improve the care provided to these young patients and help them thrive.

Keywords: aortic valve replacement, aortic stenosis, aortic regurgitation, aortic root enlargement

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Öz

Amaç: Aort darlığı, kalbin sol ventrikülünden aorta kan akışını düzenleyen kapak olan aort kapağının daralması ile karakterize doğuştan bir kalp hastalığıdır. Aort darlığı çocuklar da dahil olmak üzere her yaştan bireyi etkileyebilirken, pediatrik hastalarda benzersiz zorluklar ortaya çıkarır. Çocuklarda aort darlığının şiddeti, hafif ile şiddetli arasında geniş ölçüde değişebilir ve göğüs ağrısı, yorgunluk ve nefes darlığı gibi semptomlarla kendini gösterebilir. Aort darlığı tedavi edilmezse önemli komplikasyonlara yol açabilir ve çocuğun genel sağlığını ve yaşam kalitesini olumsuz etkileyebilir.

Gereç ve Yöntemler: Şubat 2019-Haziran 2023 tarihleri arasında hastanemizde aort kapak patolojileri nedeniyle 38 hasta ameliyat edildi. 11 hastaya aort kapak tamiri, 27 hastaya aort kapak replasmanı yapıldı. Hastaların yaşı, cinsiyeti, vücut ağırlığı, aort kapağı patolojisi, aort kapağı patolojisinin etiyolojisi (konjenital, romatizmal, enfektif endokardit), Marfan Sendromu varlığı, geçirilmiş ameliyat öyküsü, aort anulus çapı, kullanılan kapak tipi, kapak boyutu, yapıldıysa aortik kök genişletme prosedürü, kardiyopulmoner baypas süresi, kros klemp süresi, yoğun bakımda kalış süresi, serviste kalış süresi, inotrop gereksinimi, inotrop kullanım süresi, mekanik ventilasyon süresi, drenaj miktarı, revizyon gereksinimi ve mortalite retrospektif olarak hasta dosyalarından ve hastane veri tabanından tarandı.

Bulgular: Hastaların medyan yaşı 12,96±3,38 (IQR=11,00-16,00) yıl olup, ağırlıkları 43,81±14,21 kg arasında değişmekteydi. Sekiz hasta (%29.6) kadın, 19 hasta erkekti(%70.4). 8 hastada (%29.6) aort darlığı, 9 hastada (%33.3) aort yetmezliği ve 10 hastada (%37) hem aort darlığı hem de yetmezlik tanısı kondu. Hastaların aort anulus çapları 21,59±4,64 milimetre idi. 11 hastada (%40.7) dar aort anulus nedeniyle anterior veya posterior kök genişletmesi yapıldı. 7 hastaya Nick (%63.6), 2 hastaya Manoughian (%18.2) ve 2 hastaya Konno (%18.2) prosedürü uygulandı. Hastalarda kullanılan mekanik aort kapak ölçülerine bakıldığında 5 hastada 19 numara protez aort kapağı (%18.5), 8 hastada 21 numara protez aort kapağı (%29.6), 8 hastada 23 numara protez aort kapağı (%29.6), 6 hastada ise 25 numara protez aort kapağı (%22.2) kullanıldı. Mortalite 3 hastada (%11.1) görüldü Mortalite nedenleri düşük kardiyak output, nörolojik olaylar ve sepsis olarak sıralanabilir.

Tartışma: Nihai hedef, aort kapağı replasmanı yapılan çocukların sağlıklı ve tatmin edici bir yaşam sürdürebilmelerini sağlamaktır. Yaklaşımlarımızı sürekli iyileştirerek ve her vakadan öğrenerek, çocuklarda aort kapağı sorunlarının tedavisinde önemli adımlar atabilir ve onlara mümkün olan en iyi sonuçları sunabiliriz.

Sonuç: Çocuklarda aort kapak replasmanı, sadece cerrahi prosedürün kendisine değil, aynı zamanda uzun vadeli yönetim ve desteğe odaklanan multidisipliner bir yaklaşım gerektirir. Devam eden ilerlemeler ve işbirlikçi bir zihniyetle, bu genç hastalara sağlanan bakımı iyileştirmeye ve gelişmelerine yardımcı olmaya devam edebiliriz.

Anahtar Kelimeler: Aortik kapak replasmanı, Aort darlığı, Aort yetmezliği, Aortik kök genişletme

Introduction

Aortic stenosis is a congenital heart disease characterized by the narrowing of the aortic valve, the valve that regulates blood flow from the heart's left ventricle to the aorta. While aortic stenosis can affect individuals of all ages, including children, it poses unique challenges in pediatric patients. The severity of aortic stenosis in children can vary widely, ranging from mild to severe, and may present with symptoms such as chest pain, fatigue, and shortness of breath. If left untreated, aortic stenosis can lead to significant complications and negatively impact a child's overall health and quality of life.

Aortic valve replacement (AVR) is a surgical procedure commonly employed to treat severe cases of aortic stenosis in children. The primary goal of AVR is to relieve the obstruction and restore normal blood flow through the aortic valve. Over the years, advancements in medical technology and surgical techniques have significantly improved the outcomes of aortic valve replacement in children, leading to better long-term prognosis and enhanced quality of life.

Despite the promising results in aortic valve repair, AVR is needed in severely deformed valves secondary to repetitive interventions and repairs.[1] Although mechanical valves are also available in small numbers, they can still be used from certain age group patients.[2] These mechanical prostheses are not suitable for use in infants and young children. In these patients, aortic root enlargement methods can be used in the presence of narrow aortic annulus. Posterior root enlargement methods can be listed as Nick and Manoughian. Anterior root enlargement method is Konno procedure.[3]

With these methods, it may be possible to use larger prostheses. The use of mechanical prosthesis also reveals the need for lifelong anticoagulant use. Anticoagulant use in children is a very complicated issue.

In addition, a female patient needs adjustment due to pregnancy in the following periods. Valve deformation that develops after biological valve replacement is quite rapid in children compared to adults. This is caused by an increased immunological response and increased calcium metabolism in young patients.

Although aortic homografts are a suitable alternative for aortic root reconstruction in the pediatric population, difficulties in obtaining homografts limit this use.[4]

In our study, we examined the results of patients who underwent AVR due to aortic valve pathologies. By elucidating the current knowledge and advancements in this field, this paper aims to contribute to the existing body of literature and provide valuable insights for clinicians, researchers, and families seeking comprehensive information on aortic stenosis and aortic valve replacement in children.

Materıal and Methods

Between February 2019 and June 2023, 38 patients were operated due to aortic valve pathologies in our hospital. Aortic valve repair was performed in 11 of these patients, and AVR was performed in 27 patients. All patients who were younger than 18 years of age at the time of the operation and who had undergone prosthetic AVR were included in the study. Patients who were older than 18 years of age at the time of the operation and who had more than one valve replacement were excluded from the study.

Patients' age, gender, body weight, aortic valve pathology, etiology of aortic valve pathology (congenital, rheumatic, infective endocarditis), presence of Marfan Syndrome, previous operation history, aortic annulus diameter, type of valve used, valve size, type of root enlargement if performed, cardiopulmonary bypass (CPB) duration, cross-clamp (CC) duration, duration of intensive care unit (ICU) stay, duration of ward stay, inotrope requirement, duration of inotrope use, mechanical ventilation duration, amount of drainage , need of revision and mortality were retrospectively searched from patient files and hospital database.

Warfarin sodium and enoxaparin were given as anticoagulants to all patients who underwent mechanical valve replacement. The international ratio (INR) target was kept between 2.0-3.0. In this process, patients and families were given warfarin sodium use training, and patients were called for follow-up at close intervals in the first 6 months to assess compliance.

Early mortality is the mortality that develops within the first month after the operation. Mortality was also controlled from the national health screening system in addition to the hospital database.

The follow-up period was calculated as the time between the operation date and the last hospital admission.

Operative Procedure: All patients were operated with median sternotomy and CPB at 28 degrees hypothermia. In all patients, del-Nido cardioplegia was administered antegradely via an aortic root needle and by direct coronary perfusion from the coronary ostia after aortotomy. All aortic valves were mounted in the annular position with individual plegitic sutures. Aortic root enlargement was performed in 11 patients to implant larger valves. The type of root enlargement performed was the Nick procedure in 7 patients, the Manoughian procedure in 2 patients, and the Konno procedure in 2 patients.

Statistical Analysis

Continuous data are presented as Mean ± SD, Median (IQR), whereas categorical data are presented as frequency (n) and percentage (%). Normality was tested using the Shapiro–Wilk test. All statistical analyses were performed using IBM SPSS (Statistical Package for the Social Sciences) Statistics ver.25.

Results

The median age of the patients was 12.96±3.38 (IQR=11.00-16.00) years, their weights ranged between 43.81±14.21 kilograms. Eight patients were female (29.6%) and 19 patients were male.(70.4%) The diagnosis was aortic stenosis in 8 patients (29.6%) and aortic insuffiency in 9 patients (33.3%) and both aortic stenosis and insuffiency in 10 patients(37%).

Considering the etiology of aortic valve pathology, rheumatic valve disease was observed in 5 patients (18.5%), congenital valve disease was observed in 19 patients (70.4%), and infective endocarditis was observed in 3 patients (11.1%). When congenital valve pathologies were examined, bicuspid aortic valve was seen in 16 patients (84.2%), while other etiologies were subaortic membrane, opera transposition of great arteries and truncus arteriosus, and a total of 3 patients (15.9%). 4 patients had Marfan syndrome (14.8%). Fifteen patients (55.6%) were patients who had undergone previous cardiac surgery and were reoperated.

The aortic annulus diameters of the patients were 21.59±4.64 milimeters. Anterior or posterior root enlargement was performed in 11 patients (40.7%) due to narrow aortic annulus. The Nick (63.6%) procedure was applied to 7 patients, the Manoughian (18.2%) procedure to 2 patients, and the Konno procedure (18.2%) to 2 patients.

Considering the mechanical aortic valve dimensions used in the patients, 5 patients had size 19 prosthetic aortic valve

(18.5%), 8 patients had size 21 prosthetic aortic valve (29.6%), 8 patients had size 23 prosthetic aortic valve (29.6%), and 6 patients had size 25 prosthetic aortic valve. (22.2%) were used.

All patients were operated under CPB and the Mean CPB time was 155.37±56.05 minutes, CC time was 107.78±43.65 minutes. Inotropic support was started in all patients after CPB. Depending on the hemodynamic status of the patients, inotropes continued during the intensive care period. The duration of inotrope use was 64.81±96.07 (IQR=16.00-48.00) minutes.

The follow-up period of the patients on mechanical ventilator was 67.70±148.27 hours. Patients who continued to have hemodynamic instability and could not wean from CPB or needed CPB again after the surgery were transferred to the intensive care unit under extracorporeal membrane oxigenarator(ECMO) support. In patients who could leave ECMO according to hemodynamic status, weaning was performed at the bedside in the ICU. The patients who needed ECMO were 2 (7.4). Three patients (11.1%) were re-operated on the first day after surgery due to bleeding. The drainage volume of the patients in the first 24 hours was measured as 646.30±245.31 mililiters.

Mortality was observed in 3 patients (11.1%) Causes of mortality can be listed as low cardiac output, neurological events and sepsis.

The patients were followed up in the pediatric cardiovascular surgery intensive care unit after AVR surgery. The patients were taken to the ward after a few days. The hospitalization period in the pediatric CVS ICU was 5.00±6.89 days, and the hospitalization period in the ward was 10.30±7.05 days. The follow-up period of the patients was 15.04±16.99 (IQR=1-28) days.

Discussion

AVR in children is quite a complex procedure. It involves replacing a damaged or malfunctioning aortic valve with a prosthetic valve. It's often necessary when the aortic valve doesn't function properly, leading to conditions such as aortic stenosis or regurgitation. However, performing this surgery in children poses unique challenges compared to adults. One of the primary challenges is selecting the appropriate prosthetic valve for children. Children's hearts are still growing, which means that a valve that is initially well-fitted may become too small over time. Surgeons need to consider the child's age, size, and expected growth to choose a valve that can accommodate their future needs [5,6].

Additionally, the age of the child plays a significant role in the decision-making process. Infants and young children require specialized care due to their smaller anatomy and higher surgical risks. Sometimes, aortic valve repair may be attempted before considering replacement, particularly in cases where the valve structure can be preserved [7].

Aortic valve repair is an excellent alternative when possible because it preserves the patient's own valve tissue, minimizing the need for long-term anticoagulation therapy. However, repair isn't always feasible, especially in severe cases or when the valve damage is extensive [8].

Another critical aspect is the timing of the surgery. In some cases, AVR in children is performed as an emergency procedure due to severe symptoms or life-threatening complications. However, when possible, surgeons may choose to delay the surgery to allow the child to grow, minimizing the need for multiple surgeries as they age [9].

Post-operative care is crucial in ensuring the success of the procedure. Children may require close monitoring in the intensive care unit and may need to be on various medications to manage pain, prevent infections, and regulate heart function. Cardiac rehabilitation and follow-up visits are also essential to monitor the child's progress and ensure proper healing. Long-term outcomes and quality of life are also important considerations [10].

While AVR can greatly improve a child's condition and quality of life, it's crucial to remember that prosthetic valves have limited durability. Children may require additional surgeries or interventions as they grow to replace the valve as they outgrow the initial implant.This situation highlights the importance of comprehensive follow-up care, including regular echocardiograms, to assess the function of the prosthetic valve and monitor any potential complications. Close collaboration between cardiologists, surgeons, and the child's family is essential to ensure the best long-term outcomes [11].

In recent years, there have been advancements in the field of AVR in children. Minimally invasive techniques and the development of newer prosthetic valves have improved outcomes and reduced the invasiveness of the procedure. Ongoing research aims to further refine surgical techniques and develop more durable and growth-friendly prosthetic valves for children [12].

However, lifelong anticoagulant use is required in prosthetic valve replacement. There are handicaps in the use of anticoagulants in children. These can be listed as increased

risk of bleeding, difficult dose adjustment, monitoring requirements, limited data on safety and efficacy, potential interaction with other medications, lifestyle restrictions and psychological impact [13].

The field of pediatric cardiac surgery is continuously evolving, and with advancements in medical technology, we can provide better outcomes for children with aortic valve issues. Collaborative efforts between surgeons, researchers, and healthcare professionals are vital to improving the surgical techniques and long-term care for these young patients

Conclusion

In conclusion, the ultimate goal is to ensure that children who undergo aortic valve replacement can lead healthy and fulfilling lives. By continually refining our approaches and learning from each case, we can make significant strides in the treatment of aortic valve issues in children and offer them the best possible outcomes.

Aortic valve replacement in children requires a multidisciplinary approach, with a focus not just on the surgical procedure itself but also on long-term management and support. With ongoing advancements and a collaborative mindset, we can continue to improve the care provided to these young patients and help them thrive.

Ethical Approval

The Ankara Bilkent City Hospital Clinical Researches Ethics Committee, (No: E2-23-3988, Date: 25/04/2023) has authorized all techniques used in this work. The authors declare that they adhered to the ethical norms of the 1975 Helsinki Declaration, as revised in 2008.

Conflict of Interest

The authors declare no conflict of interest.

Disclosure

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Araştırma Makalesi

Şiddetli pankreatiti öngörmede yeni biyobelirteç; Sistemik immün-inflamasyon indeksi

New biomarker to predict severe pancreatitis; Systemic ımmuno-inflammation

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Öz

Amaç: Akut pankreatit (AP), pankreasta sıklıkla peripankreatik dokuları, bazen de uzak dokuları tutan akut inflamatuar bir süreçtir. Şiddetli akut pankreatiti(ŞAP) öngörmede kolay, hızlı ve ucuz biyobelirteçleri tanımlamak bir ihtiyaçtır. Birçok çalışmada da SII anlamlı bir inflamasyon öngörücüsü olarak gösterilmiştir. Bu çalışmada SII'ın ŞAP'ı öngörmede prediktif değerini ortaya koymayı amaçladık.

Gereç ve Yöntemler: Bu retrospektif çalışma Ankara Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu'nun 12.09.2022 tarihli 146/08 karar numaralı onayı ile yapıldı. Çalışmaya hastanemizde akut pankreatit ile yatarak tedavi görmüş 131 hasta dahil edildi. SII'ın ŞAP'ı öngörmede prediktif değeri karşılaştırmalı analiz ve ROC analizi ile değerlendirildi.

Bulgular: Çalışmaya 59'u(%45) kadın 72'si(%55) erkek toplam 131 hasta dahil edildi. Bunların 95'i(%72,5) HAP ile 36'sı(%22,5) ŞAP ile takip edilen hastalardı. HAP grubuna göre serviste yatış süresi ve yoğun bakımda yatış süresi anlamlı olarak yüksekti($p<0,01$). İki grup karşılaştırıldığında SII değerleri ŞAP grubunda anlamlı olarak daha yüksek saptandı ($p<0,01$). Yapılan ROC analizinde; SII ≥ 1660,36 için istatistiksel anlamlı bir değer elde edildi ($p<0,001$). Serum SII ≥ 1660,36 kesim değeri için; duyarlılık %72,2; özgüllük %91,6; pozitif prediktif değeri %76; negatif prediktif değeri ise %90 bulundu. Eğri altındaki alan (EAA) değeri 0,89 ve standart hatası 0,029 olarak saptandı ($p=0,001$).

Sonuç: Bu çalışma, SII değeri 1660,36'dan yüksek olan AP hastalarının ŞAP olma olasılığının daha yüksek olduğunu göstermiştir. SII, herhangi bir nedenle akut inflamasyonun tetiklediği otoinflamatuar kaskadın bir belirtecidir. Acil servise başvuran ve acil servise başvuruda hesaplandığında AP tanısı alan hastaların klinik sonuçlarını tahmin etmek için faydalı bir skorlama sistemi olabilir.

Anahtar kelimeler: pankreatit; SII; sistemik İmmün-inflamasyon indeksi

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Abstract

Aim: Acute pancreatitis (AP) is an acute inflammation of the pancreas that affects cells, peripancreatic tissues, and sometimes distant tissues. It can range from mild forms needing observation to severe forms with multiple organ failure and death. Thus, there is a need for simple, fast, and affordable biomarkers to predict acute diary pancreatitis. The SII can predict inflammation. This study aimed to assess the SII's predictive value for severe acute pancreatitis (SAP).

Material and Methods: This retrospective study, approved by Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital's Ethics Committee (decision 146/08, 12.09.2022), involved 131 patients over 18 hospitalized with acute pancreatitis. The SII's predictive value for SAP was evaluated using comparative and ROC analyses.

Results: The study included 131 patients 72.5% were followed up with HAP and 22.5% with SAP. Length of stay in the ward and ICU was significantly higher in the HAP group ($p<0.01$). The SII values of the SAP group were significantly higher than the other group ($p<0.01$). ROC analysis showed that SII ≥ 1660.36 was a reliable biomarker for SAP ($p<0.001$). For this cutoff value, sensitivity was 72.2%, specificity 91.6%, positive predictive value 76%, and negative predictive value 90%. AUC was 0.89 (SE=0.029, p=0.001).

Conclusion: The study revealed that acute pancreatitis (AP) patients with a systemic immune-inflammation index (SII) over 1660.36 were more prone to severe acute pancreatitis (SAP). The SII, indicative of acute inflammation, can help predict clinical outcomes for AP patients admitted to the emergency department.

Keywords: pancreatitis, SII, systemic Immuno-inflammation index

Giriş

Akut pankreatit (AP), pankreasta sıklıkla peripankreatik dokuları, bazen de uzak dokuları tutan akut inflamatuar bir süreçtir. Sadece pankreası etkileyen hafif lokal formlardan ölümle sonuçlanabilecek çoklu organ yetmezliği olan ciddi formlara kadar geniş yelpazede klinik tablo ile karşımıza çıkan önemli bir hastalıktır. Akut pankreatitin altında yatan başlıca patolojik süreçler pankreas dokusunun inflamasyonu, ödemi ve nekrozunun yanı sıra ekstrapankreatik organların inflamasyonu ve yaralanmasıdır. AP insidansı her iki cinsiyette eşit oranlara sahiptir ve sıklık 5–35/100.000 arasında değişmektedir[1]. Etiyolojide safra kesesi taşı, alkol, hipertrigliseridemi, endoskopik retrograd kolanjiopankretografi, genetik yatkınlık, bazı ilaçlar yer almaktadır. En sık safra kesesi taşı ve alkol ile ilişkilidir[2].

Akut pankreatitli hastalarda genel mortalite yaklaşık% 5'tir[3]. Nekrotizan pankreatitli hastalarda mortalite, nekrozun az olduğu interstisyel pankreatitli hastalara kıyasla daha yüksektir (sırasıyla yaklaşık% 17 ve% 3). Nekrotizan pankreatitli hastalar arasında, enfekte nekrozlu hastalarda mortalite, steril nekrozu olanlara göre daha fazladır (sırasıyla yaklaşık % 30 ve % 12). Akut pankreatitteki ölümlerin yaklaşık yarısı hastalığın ilk 2 haftasında meydana gelir ve genellikle organ yetmezliğine atfedilir. Ölümlerin geri kalanı bu aralıktan haftalar ila aylar sonra meydana gelir ve ölüm genellikle enfekte nekroz veya steril nekrozun komplikasyonları ile ilişkili organ yetmezliği ile ilgilidir[4]. Mortaliteyi azaltma hedefiyle şiddetli akut pankreatiti hafif akut pankreatitten ayırmak için erken ve kolay tanı göstergelerini tanımlamaya ihtiyaç vardır.

En son 2012 de revize edilmiş olan Atlanta sınıflandırma sistemi, akut pankreatiti şiddetine bağlı olarak hafif, orta ve şiddetli olarak ayırır. Atlanta sınıflandırma sistemi; organ yetmezliği ve lokal veya sistemik komplikasyonların varlığı ya da yokluğu, kalıcı ya da geçici olması ve komplikasyonların süresini göz önünde bulundurur[5].

Klinik, laboratuvar ve radyolojik risk faktörlerine, çeşitli şiddet derecelendirme sistemlerine ve serum belirteçlerine dayalı olarak AP'nin şiddetini tahmin etmek için çok sayıda tahmin modeli geliştirilmiştir. Bunların bir kısmı hastaların triyajına yardımcı olmak için başvuru sırasında yapılabilirken, diğerleri ancak ilk 48 ila 72 saat veya sonrasında elde edilebilir. Pek çok skorlama sistemi bildirilmiştir ancak hiçbirinin mükemmel olduğu kanıtlanmamıştır. Kullanılan başlıca skorlama sistemleri ranson kriterleri, Akut Fizyoloji ve Kronik Sağlık Muayenesi (APACHE) II skoru, sistemik inflamatuar yanıt sendromu skoru, BISAP skoru, Balthazar skorudur. Haricen serum C-reaktif protein(CRP), hematokrit, BUN, kreatinin gibi laboratuvar değerleri de şiddetle ilişkilendirilmiştir[6]. Hastaları gruplandırmak için yararlı olsalar da, hiçbiri yatak başında belirli bir hastada AP'nin ciddiyetini tahmin etmede yüksek doğruluğa sahip değildir. Birçok skorlama sisteminin(örn. Ranson, Glasgow) tamamlanması 48 saat sürer, yalnızca bir kez kullanılabilir ve yüksek derecede duyarlılık ve özgüllüğe sahip değildir.

Akut şiddetli pankreatiti öngörmede kolay, hızlı ve ucuz biyobelirteçleri tanımlamak bir ihtiyaçtır. Sistemik immün inflamasyon indeksi (SII), biyobelirteç olarak sadece tam kan sayımında bakılabilen nötrofil (N), lenfosit (L) ve trombosit (P) sayılarına dayalı olarak(NxP/L) hesaplanır. İnflamasyonla seyreden bilinen hastalıklarla(kanser, inme vb.) SII indeksinin ilişkisi araştırmacılar tarafından çokça sorgulanmış ve ilgi görmüştür. Birçok çalışmada da SII anlamlı bir inflamasyon öngörücüsü olarak gösterilmiştir[7-11]. Pankreatit şiddetini öngörmede nötrofil / lenfosit oranı (NLR) ve trombosit / lenfosit oranı (PLR) gibi inflamatuar hücrelerin sayıları kullanılarak bir formülle hesaplanan sistemik inflamasyon skorları da kullanılmıştır[12]. Bu çalışma, SII'nin akut pankreatitin şiddetini tahmin etmek için etkili bir biyobelirteç olup olmadığını araştırmayı amaçlamıştır.

Gereç ve Yöntemler

Bu retrospektif çalışma Ankara Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu'nun 12.09.2022 tarihli 146/08 karar numaralı onayı ile 1964 Helsinki deklarasyonuna uygun olarak yapıldı. Çalışmaya 30.06.2015-30.06.2021tarihleri arasında hastanemizde akut pankreatit tanısı ile yatarak tedavi görmüş 18 yaş üstü 131 hasta bilgilendirilmiş onam alınarak dahil edildi. Kanser tanısı olan, iskemik inme öyküsü olan haricen otoimmün ve inflamatuar hastalık öyküsü olan toplam 16 hasta çalışma dışı bırakıldı. Hastalar Atlanta kriterlerine göre hafif akut pankreatit(HAP) olanlar bir grup(n:95,%72,5) , orta derecede şiddetli ve şiddetli akut pankreatit olanlar(ŞAP) diğer grup(n:36,%27,5) olmak üzere 2 gruba ayrıldı. Hastaların klinik ve demografik özellikleri ve ilk yatışındaki laboratuvar sonuçları dosyalarından elde edilerek kaydedildi. Yaş, cinsiyet, pankreatit etiyolojisi, yoğun bakım yatış süresi, servis yatış süresi, serum glukoz, wbc, nötrofil, lenfosit, kreatinin, albümin, hemoglobin, INR, GGT, amilaz, lipaz, CRP, ALT, LDH, kalsiyum, laktat, platelet ve NLR, PLR ve SII indeksi ile iki grup arasındaki ilişki incelendi.

Akut pankreatit, epigastrik ağrı, yüksek amilaz-lipaz seviyeleri (normalin üst sınırından en az üç kat daha fazla) ve bilgisayar-tomografi taramasından kontrol edilen pankreas inflamasyonu dahil olmak üzere klinik, laboratuvar ve radyolojik muayene sonuçları kullanılarak teşhis edildi. SII skoru nötrofil ve platelet sayıları çarpılıp lenfosit sayısına bölünerek elde edildi.

İstatistiksel Analiz

Sürekli değişkenler ortalama ± standart sapma, median (min-max); kategorik veriler sayı ve yüzde şeklinde ifade edildi. Sürekli değişkenlerin normallik analizleri Kolmogorov-Smirnov Uyum İyiliği Testi ile yapıldı. Veriler normal dağılıma uyduğu durumlarda iki grup arasındaki analizlerde T testi, uymadığı durumlarda ise Mann Whitney U Testi kullanıldı. Üç ve daha fazla grup arasındaki karşılaştırmalar Kruskal Wallis Testi ile yapıldı. Analizler IBM SPSS versiyon 20.0 (IBM Corporation, Armonk, NY, USA) ile yapıldı. İstatistiksel anlamlılık düzeyi p<0,05 olarak ele alındı. SII skorları, Receiver Operating Characteristics (ROC) eğrisi analizi ile incelendi. Anlamlı sınır değerlerinin varlığında bu sınırların senstivite, spesifite, pozitif ve negatif prediktif değerleri hesaplandı. Tip 1 hata düzeyinin %5'in altında olduğu durumlar testin tanısal değerinin istatistiksel olarak anlamlı olduğu şeklinde yorumlandı.

Bulgular

Çalışmaya yaş ortalaması 56,42±17,11 olan 59'u(%45) kadın 72'si(%55) erkek toplam 131 hasta dahil edildi. Bunların 95'i(%72,5) HAP ile 36'sı(%22,5) ŞAP ile takip edilen hastalardı. Her iki grupta da en sık sebep safra kesesi taşları olarak görüldü(n:103, %78). ŞAP grubunda HAP grubuna göre serviste yatış süresi ve yoğun bakımda yatış süresi anlamlı olarak yüksekti(p<0,01)(Tablo 1).

Tablo 1: Hastaların bazı klinik ve demografik özellikleri

	HAP(n=95)	ŞAP(n=36)	p
Yaş (yıl) (Ort±Ss)	52,53±17.01	66,69±12,67	0,04*
Cinsiyet (n,%) Erkek Kadın	 56(%59) 39(%41)	 16(%44) 20(%56)	0,136**
AP Etiyolojisi(n,%) Biliyer Alkolik Hipertriglisemiye sekonder Hiperkalsemiye sekonder İlaca bağlı	 75(%78,9) 10(%10,5) 7(%7,4) 2(%2,1) 1(%1,1)	 28(%77,8) 4(%11,1) 2(%5,6) 0(%0) 2(%5,6)	0,529***
Yoğun bakım yatış süresi(gün) (Ort±Ss)	0±0	0,41±1.84	<0,01*
Servis yatış süresi(gün) (Ort±Ss)	8,5±4,37	11,75±7,79	<0,01*

*T testi, ** Ki kare testi, ***Fisher'ın Kesin testi
HAP: Hafis akut pankreatit, ŞAP: Şiddetli akut pankreatit, AP: Akut pankreatit

Laboratuvar bulgularına bakıldığında serum glukoz, beyaz hücre sayısı(WBC), kreatinin, C-reaktif protein (CRP), laktat, nötrofil sayısı ve LDH değeri ŞAP grubunda MAP grubuna göre anlamlı olarak yüksek saptandı. (p<0.01). Aynı şekilde PLR, NLR ve SII değerleri ŞAP grubunda anlamlı olarak daha yüksek saptandı. (p<0.01). Lenfosit sayısı ve serum albümin ise ŞAP

grubunda HAP grubuna göre anlamlı olarak düşük saptandı. (p<0.01). Hemoglobin, INR, alkalen fosfataz(ALP), gama–glutamil transferaz (GGT), amilaz, lipaz, alanin aminotransferaz (ALT), kalsiyum ve platelet değerlerinde iki grup arasında anlamlı fark saptanmadı (Tablo 2).

Akut pankreatit şiddetini göstermeyi tayin etmek için SII'ın prediktif değerini göstermek için ROC eğrisi oluşturuldu. ŞAP'ı öngörmede SII değerinin bir biyobelirteç olarak kullanılıp kullanılamayacağına yönelik olarak yapılan ROC analizinde; SII ≥ 1660,36 için istatistiksel anlamlı bir değer elde edildi (p<0,001). Akut pankreatit hastalarında serum SII ≥ 1660,36 kesim değeri için; duyarlılık %72,2; özgüllük %91,6; pozitif prediktif değeri %76; negatif prediktif değeri ise %90 bulundu. Eğri altındaki alan (EAA) değeri 0,89 ve standart hatası 0,029 olarak saptandı (p=0,001). (Tablo 3, Şekil 1).

Tablo 2: Hastaların laboratuvar verileri

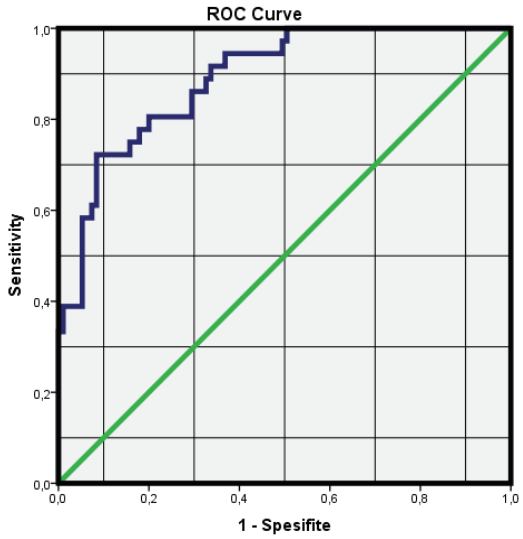
	HAP(n=95)	ŞAP(n=36)	p
Glukoz[median (min-max)]	121(70-384)	178(87-716)	<0,01*
WBC[median (min-max)]	9,7(4,6-20,1)	13,2(5,3-22,7)	<0,01*
Kreatinin[median (min-max)]	0,87	0,97	<0,01*
Albumin[median (min-max)]	3,6	3,2	<0,01*
Hemoglobin[median (min-max)]	13,9	14,4	0,327*
INR[median (min-max)]	1	1	0,829*
ALP[median (min-max)]	118	119,5	0,494*
GGT[median (min-max)]	177,5	214	0,251*
AMİLAZ[median (min-max)]	1207	1236	0,355*
LİPAZ[median (min-max)]	2909	2897	0,747*
CRP[median (min-max)]	22,2	60	<0,01*
ALT[median (min-max)]	105	136,5	0,546*
LDH[median (min-max)]	207,5	264	<0,01*
Kalsiyum[median (min-max)]	9,6	9,4	0,080*
Laktat[median (min-max)]	1,6	3	<0,01*
Nötrofil[median (min-max)]	7	9,55	<0,01*
Lenfosit[median (min-max)]	1,8	1,15	<0,01*
Platelet[median (min-max)]	231(116-486)	252(135-455)	0,249*
PLR[median (min-max)]	130,9(22,05-430)	224,2(112,5-1010)	<0,01*
NLR[median (min-max)]	3,88(0,62-14,56)	8,69(3,19-40,8)	<0,01*
SII[median (min-max)]	1002(27,57-2634,56)	2057,4(1001,1-12444)	<0,01*

*Mann Whitney U Testi
** SII: sistemik immün-inflamasyon indeksi; ALT:alanin aminotransferaz; GGT: gama-glutamil transferaz; ALP: alkalen fosfataz; WBC: beyaz kan hücresi; PLR: trombosit-lenfosit oranı; NLR: nötrofil-lenfosit oranı, CRP; C reaktif protein; INR: international normalised ratio

Tablo 3: Şiddetli akut pankreatiti öngörmek için SII değeri için EAA ve eşik değerleri

	Tanısal test						ROC Eğrisi		p
	Kesim değeri	Senstivite	Spesifite	PPD	NPD	EAA	Standart hata	%95 GA	
SII	≥ 1660,36	72,2	91,6	76	90	0,89	0,029	0,832-0,948	<0,001**

* PPD: Pozitif prediktif değer, NPD: Negatif prediktif değer, EAA: Eğri altındaki alan, GA: Güven aralığı, SII: sistemik immün-inflamasyon indeksi
** ROC Curve Analiz testi



Şekil 1: Akut pankreatitin ciddiyetini belirlemede SII'ın performansını değerlendirmek için ROC eğrisi analizi.

Tartışma

Bu çalışma akut pankreatitin şiddetini öngörmede SII'ın prediktif değerini göstermek amacıyla yapıldı. SII, inflamasyon ve immün yanıtı gösteren, son yıllarda ilgi görmüş, basit ve ucuz hesaplanabilen bir indekstir. İlk olarak 2014 yılında Hu ve ark. [13] hepatoselüler karsinom için küratif rezeksiyondan sonra hastaların prognozunu tahmin etmek için SII adını verdikleri bir gösterge geliştirdi. SII, litre başına periferik kan trombositlerinin, nötrofillerin ve lenfositlerin preoperatif sayımlarından hesaplandı. Daha sonra birçok çalışma kanser hastalarında ve inflamasyonla seyreden hastalıklarda SII skorunu konu aldı.

Şiddetli akut pankreatit, pankreas ve pankreas dışı nekroz gelişimi, bunların müteakip enfeksiyonu ve çoklu sistem organ yetmezliği nedeniyle yüksek morbidite ve mortalite ile ilişkilidir[14]. ŞAP'ın teşhisi klinik tabloya, laboratuvar testlerine ve görüntüleme sonuçlarına dayanır. Hangi hastaların ciddi bir klinik seyir izleyeceğini ve hangi hastaların majör fizyolojik hasar olmadan iyileşebileceğini öngörmek amacıyla fiziksel ve radyolojik skorlama sistemleri geliştirilmiştir. Ancak akut pankreatit karmaşık bir hastalıktır; Birkaç kriterin varlığına rağmen, sonraki seyrini tahmin etmek kolay değildir çünkü çoğu kez aynı başlangıç klinik ve radyolojik skorları olan hastalarda hastalığın klinik seyri değişkenlik gösterebilir. Hastalığın ciddiyetinin doğru ve tek tip olarak kabul edilen tanımlarının olmaması ve AP'nin yaygın olarak karşılaşılan komplikasyonları nedeniyle hastalığı değerlendirmek zordur. Bu sebeple klinisyenler şiddeti öngörmede mükemmel yöntemi hep aramıştır.

AP'nin ciddiyetini sınıflandırmaya yardımcı olan çeşitli puanlama sistemleri (Ranson, APACHE II, SOFA, BISOP, vb.) vardır. Hastanın hastaneye yatışında Ranson skoru veya hastalık şiddeti için APACHE II kriterleri kullanılarak objektif olarak değerlendirilebilen AP'nin şiddeti; AP seyri sırasında, atağın başlangıcından sonraki 48 saat içinde 3 veya daha fazla Ranson kriteri gözlenirse veya hastalığın seyri sırasında herhangi bir zamanda 9 veya daha fazla APACHE II kriteri gözlenirse hastalık şiddetli olarak kabul edilir. Bunların yanında AP şiddetini öngörmede kullanılan tomografi ve laboratuvar değerlerinin kullanıldığı birtakım değerlendirme teknikleri de mevcuttur[15].

İnflamasyonun pankreatit oluşumunda ve gelişiminde rol oynadığı iyi bilinmektedir. Şiddetli akut pankreatitin erken döneminde, immünsüpresyon, bağırsak mukozal bariyer disfonksiyonunun neden olduğu kompleks inflamasyon ve enfeksiyonda rol oynayabilir. Bir çalışma, hasarlı hücreler, nötrofiller ve reaktif oksijen türleri arasındaki çapraz iletişimin, pankreatit sürecini sinerjik olarak teşvik ettiğini göstermiştir. Trombositler, akut pankreatitin sistemik inflamatuar sürecine doğrudan katılır, böylece derhal kemik iliği yanıtı ile telafi edilen tüketime yol açar. Uzun yıllar boyunca, nötrofillerin ŞAP patolojisine katkılarının geleneksel olarak inflamasyona eşlik eden kemokin ve sitokin kaskadlarını içerdiği düşünülüyordu. Bu nedenle, nötrofiller, makrofajlar, lenfositler ve plazma hücreleri de dahil olmak üzere bu inflamatuar hücrelere dayanan skorlar ve göstergeler, akut pankreatitte immünolojik dengeyi yansıtmak için kullanılmıştır[11].

Bu çalışma, SII değeri 1660,36'dan yüksek olan AP hastalarının ŞAP olma olasılığının daha yüksek olduğunu göstermiştir (duyarlılık =% 72,2, özgüllük =% 91,6 ve EAA = 0.89). Yapılan benzer bir çalışmada da SII'ın ŞAP'ı öngörmede diğer kullanılan PLR NLR gibi skorlara göre daha iyi olduğu sonucuna varılmıştır[11]. Bizim çalışmamızda da bu çalışmayla korele bir sonuç ortaya çıktı.

Ranson kriterleri AP şiddetinin öngörmede en sık kullanılan değerlendirme yöntemidir. Ancak skor elde etmek için hasta yatışından sonra 48 saat geçmiş olması gereklidir. Bunla karşılaştırıldığında SII hasta yatışında bakılan tam kan sayımında bakılabilecek ek tetkik gerektirmeyen kolay ucuz ve hızlı bir değerlendirme yöntemidir.

Sonuç

SII, herhangi bir nedenle akut inflamasyonun tetiklediği otoinflamatuar kaskadın bir belirtecidir. Acil servise başvuran ve acil servise başvuruda hesaplandığında AP tanısı alan hastaların klinik sonuçlarını tahmin etmek için faydalı bir skorlama sistemi olabilir.

Bu çalışmanın tek merkezli retrospektif bir çalışma olması ana kısıtlarından biridir. SII, belirli alt gruplar oluşturularak, yaş sınıflaması yapılarak ve komorbiditeler göz önüne alınarak daha geniş ve ulusal serilerde incelenirse ŞAP'ı öngörmede hızlı, ucuz ve kolay bir biyobelirteç olarak kullanılacaktır.

Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların herhangi bir çıkar dayalı ilişkisi yoktur.

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Research Article

Effect of music intervention on anxiety levels in cancer patients receiving radiotherapy

Kanser hastalarında radyoterapi sırasında müzik dinlemenin anksiyete seviyelerine etkisi

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Abstract

Aim: Diagnosis and treatment of malignancies may cause distress in patients. Complementary treatments like music intervention to relieve anxiety of cancer patients is a new paradigm. We aimed to evaluate the effect of music intervention on anxiety in patients undergoing radiotherapy.

Material and Methods: One hundred patients who received radiotherapy with curative intent were included in the study. Patients were divided into music intervention and control groups. Each group consisted of 50 patients but three patients from the music intervention group and 2 patients from the control group were excluded from the analysis because they could not completely fill in the questionnaires. In music intervention group patients selected the type of music they desired to listen freely during radiotherapy. Music intervention was not used in the control group during radiotherapy. Anxiety levels were evaluated with STAI-I and BAI questionnaires after the first session of radiotherapy in both groups. STAI-II was implemented before radiotherapy

Results: Forty-eight patients in the control and 47 patients in the music intervention group were included in the analyses. The mean STAI-I scores after radiotherapy were 42.1 ± 11.1 and 29.9 ± 6.7 in the control and music intervention groups, respectively with a statistically significant intergroup difference (p=0.000). The mean BAI scores after RT were 19.96 ± 6.3 and 13.3 ± 3.1 in the control and music intervention groups, respectively with a statistically significant difference. (p=0.000).

Conclusion: Music intervention during radiotherapy sessions may be effective on reducing the radiotherapy-related anxiety in cancer patients.

Keywords: Cancer, Anxiety, Music interventions, Radiotherapy

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Öz

Amaç: Kanser tanı ve tedavisi hastalarda kaygıya neden olabilmektedir. Kanserli hastaların kaygılarını azaltmak için müzik müdahalesi gibi tamamlayıcı tedaviler güncel yaklaşımlardır. Bu çalışmada Radyoterapi alan hastalarda müzik müdahalesinin kaygı üzerine etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Küratif amaçlı radyoterapi alan 100 hasta çalışmaya dahil edildi. Hastalar müzik müdahale ve kontrol gruplarına ayrıldı. Her grup 50 hastadan oluşmakta ancak müzik müdahale grubundan 3, kontrol grubundan 2 hasta anketleri tamamlayamadıklarından analize dahil edilmediler. Müzik müdahale grubundaki hastalar radyoterapi sırasında dinleyecekleri müzik türünü kendileri seçtiler. Kontrol grubuna radyoterapi sırasında müzik dinletilmedi. Her iki grupta ilk radyoterapi uygulaması sonrası kaygı düzeyleri STAI-I ve BAI anketleri ile değerlendirildi.

Bulgular: Kontrol grubunda 48 hasta ve müzik grubunda 47 hasta analiz edildi. Radyoterapi sonrası ortalama STAI-I skorları kontrol ve müzik gruplarında sırasıyla 42.1 ± 11.1 ve 29.9 ± 6.7 olarak bulundu ve istatistiksel olarak farklılık vardı (p=0.000). Radyoterapi sonrası ortalama BAI skorları kontrol ve müzik gruplarında sırasıyla 19.96 ± 6.3 and 13.3 ± 3.1 olarak bulundu ve istatistiksel olarak farklılık vardı (p=0.000).

Sonuç: Radyoterapi sırasında müzik dinlemek kanser hastalarında kaygıyı azaltmada etkili olabilmektedir.

Anahtar Kelimeler: kanser, kaygı, müzik müdahaleleri, radyoterapi

Introduction

Cancer is one of the most common cause of death worldwide and the incidence of cancer is rapidly increasing [1]. Radiotherapy (RT) plays an essential role in the treatment of cancer patients and nearly 50% of cancer patients receive radiotherapy during their disease process [2]. Cancer and cancer treatment cause psycological distress which reduces the quality of life in patients. In cancer patients, radiotherapy increases the level of anxiety and depression [3]. Besides the reduced quality of life cancer-related anxiety is associated with decreased overall survival. As cancer treatment-related anxiety significantly reduces the quality of life and survival, various therapeutic interventions are being used to reduce this stress including music intervention [4]. In a study patient distress related to RT was found to be a prognostic factor associated with decreased survival [5]. As a clinical model of psychotherapy, music therapy is being applied to a wide range of populations in the healthcare system [6]. Various music intervention activities are involved in the treatment of cancer related anxiety. Music intervention is an effective and non-invasive method in the treatment of the fear of hospital and the stress that patients experience due to the stage of their disease [7].

Music intervention reduces anxiety and improves the quality of life in cancer patients [8,9]. Music has an effect on cingulo-frontal cortex. Cingulo-frontal cortex is activated by the music interventions which decrease the anxiety and pain [10]. The activation of cingulo-frontal cortex by music intervention is observed on functional magnetic resonance imaging of brain [11]. Music therapy decreases pain and anxiety which are related to invasive procedures like colonoscopy, bronchoscopy and cystoscopy. As easily applied and effective assessment tools, State-Trait Anxiety Inventory (STAI) and Visual Analogue Scales are being used to measure the anxiety and pain felt by the patients during these procedures [12-16]

As the patient anxiety is an important issue related with quality of life and the survival and music intervention was observed to be effective in reducing anxiety in many medical procedures, we conducted this observational survey study to analyse the effect of music intervention on anxiety experienced during radiotherapy.

Material and Methods

This is a single-center observational survey study evaluating the music interventions on anxiety related to RT in cancer patients who received curative RT between June 1, 2022 and September 15, 2022. This study included 100 patients with cancer diagnosis who received curative RT. Patients willing to participate in the study voluntarily, were informed about all aspects of the study. The participants were informed that, that was a survey study and their treatment schedule or treatment results would not be affected by this study. All participants signed the informed consent form of the study before answering the questionnaires. Patients older than 18 years of age with sufficient literacy and cognitive level to respond to a written questionnaire in Turkish language, and those receiving curative radiotherapy were included in

the study. Patients receiving anti-anxiety or anti-depressant drugs, palliative radiotherapy, cases with hearing loss, and radiotherapy history were excluded from the study

After the approval of the institutional ethical board (date: May 25, 2022; decision no: 2022-05/1861) patients were divided into control group (n=50) and music intervention (n=50) groups. Three patients from the music intervention and 2 patients from the control group excluded from the study because they did not fill in the questionnaires completely. All patients received standard curative radiotherapy doses required for their cancer type and stage; and standard treatment schedules were not altered. The patients of the music intervention group music with headphones during the radiotherapy session.

Three questionnaires were used in the study;

1) Demographic-Clinical Data Questionnaire: A demographic and clinical data questionnaire developed by researchers consisting of information about age, educational level, diagnosis, blood pressure, and heart rate was used to evaluate the demographic and clinical data of participants. The participants filled the demographic part of the questionnaire. Clinical data was filled by the investigator doctor. Additionally, blood pressures and heart rates before and after the radiotherapy session were measured by an investigator doctor and written on this form.

2) The State-Trait Anxiety Inventory (STAI): STAI questionnaire has two sections that evaluate state and trait anxiety, with 20 questions in each section. The scale's adaptation to Turkish, validity and reliability studies were carried out by Öner and Le Comte. The emotions or behaviors expressed in the state anxiety inventory items are answered by marking one of the options none, a little, a lot, and entirely, according to the degree of intensity. The scores obtained on the state anxiety scale theoretically vary between 20 and 80 points. In the evaluation of the scale, it is accepted that those who score below 36 do not have anxiety, those who score between 37 and 42 have mild anxiety, and those who score 42 and above have high anxiety [17].

3) Beck Anxiety Inventory (BAI): BAI is an anxiety inventory focusing on anxiety's somatic symptoms, consisting of 21 questions. Responses range from 0 (not at all) to 3 (severely). Evaluation is made by summing the scores. The results according to total scores are like this; 0–9, normal or no anxiety; 10–18, mild to moderate anxiety; 19–29, moderate to severe anxiety; and 30–63, severe anxiety [18].

The demographic-Clinical Data questionnaire and STAI-II was answered only before the radiotherapy section (the blood pressure and heart rate were measured before and after the session). All participants answered STAI-I and BAI questionnaires after the first radiotherapy session. Questionnaires were administered to all participants under the supervision of the investigator doctor. Questionnaires were administered to the patients participating in the study at different times, thus preventing patients from interacting with each other. In order not to cause bias, the patients in the control group were not given any information about listening to music.

In music intervention group patients selected the music freely without being tied to a specific list. Investigator doctors conducted an interview with patients to decide the type of music to listen to the music group. During this interview; the patient was asked what kind of music he/she likes, the patient-specific music list was created together with the patient. During the RT session, patients in music group listened their specific music list created in the interview with noise cancelling headphones to minimize the ambient noise of treatment room. All patients were watched from the camera on the treatment console during the treatment.

The aim of this study was to evaluate the effect of music interventions on radiotherapy anxiety. The primary endpoint was to evaluate the anxiety levels of participants. Secondary endpoints were physiological functions such as blood pressure and heart rate that may be related to anxiety.

Statistical Analysis

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 25.0, IBM Corporation, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to analyze normal distri¬bution of data. All measurements are expressed as means with standard deviations, medians, and minimum and maximum values. We compared blood pressures, heart rates, STAI score and BAI score between music and control group by using paired sample t test for normally distributed data and Mann Whitney U for nonnormally distributed data. P values <0.05 were statistically significant.

Results

We randomized 100 cancer patients and included 95 patients receiving curative radiotherapy in this study. Patient characteristics were resulted in table 1.

The primary endpoint was to evaluate the anxiety levels and the secondary endpoints were the vital signs related like blood pressure and heart rate to anxiety. The baseline vital signs

and STAI-II scores of patients were not statistically different. Baseline results of the patients were summarized in table 2.

Vital signs of the patients (systolic and diastolic blood pressure, heart rate) after RT decreased statistically significant in music group. Before RT systolic blood pressure of the patients were 125.52 ± 9.3; and 125.43 ± 8.3 in control group and music group respectively (p=0.877). Before RT diastolic blood pressure of the patients were 80.73 ± 6.1 and 80.21 ± 5.9 in control group and music group respectively (p=0.562). After RT systolic blood pressure of the patients were 138.85 ± 10.8 and 126.730 ± 12.7 in control group and music group respectively (p=0.000). After RT diastolic blood pressure of the patients were 87.60 ± 12.16 and 83.19 ± 11.3 in control group and music group respectively (p=0.061).

The heart rate of the patients after RT were 75.9 ± 7.3 and 70.68 ± 7.7 in control group and music group, respectively (p=0.001).

The mean STAI-I scores after RT were 42.1 ± 11.1 and 29.9 ± 6.7 in control group and music group respectively. This difference between the groups was statistically significant (p=0.000). The mean BAI scores after RT 19.96 ± 6.3 and 13.3 ± 3.1 in control group and music group respectively. This difference between the groups was statistically significant (p=0.000). Results were summarized in table 3.

Table 1: Characteristics of Patients

		All Patients N = 95	Control Group N = 48	Music Group N = 47
Mean Age (y)(range)		65.54 (52-81)	66.1 (52-81)	64.94 (59-74)
Gender	Male	41	19	22
	Female	54	29	25
Disease Site	Lung	29	14	15
	Prostate	13	7	6
	Breast	15	8	7
	GIS	19	8	11
	Head and Neck	9	5	4
	Other	10	6	4

Table 2: Patients baseline clinical characteristics

Parameters	All Patients N = 95 Mean± SD (range)	Control Group N = 48 Mean± SD (range)	Music Group N = 47 Mean± SD (range)	P value	Statistical Test
Before RT					
SBP (mm Hg)	125.47 ± 8.8 (105-140)	125.52 ± 9.3 (105-140)	125.43 ± 8.3 (105-140)	0.877	Mann-Whitney Test
DBP (mm Hg)	80.47 ± 6 (65-90)	80.73 ± 6.1 (65-90)	80.21 ± 5.9 (65-90)	0.562	Mann-Whitney Test
Heart Rate (b.p.m)	68.79 ± 6.4 (50-80)	68 ± 6.7 (50-80)	69.60 ± 6 (57-80)	0.237	Mann-Whitney Test
STAI-II Score	46.40 ± 5.7 (34-59)	45.33 ± 6.9 (34-59)	47.49 ± 4 (41-59)	0.174	Mann-Whitney Test

Abbreviations: RT: Radiotherapy; Min: minute; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; b.p.m: Beats Per Minute; STAI: State-Trait Anxiety Inventory;

Table 3: Patients' post-radiotherapy clinical characteristics

Parameters	All Patients N = 95 Mean± SD (range)	Control Group N = 48 Mean± SD (range)	Music Group N = 47 Mean± SD (range)	P value	Statistical Test
After RT					
SBP (mm Hg)	132.84 ± 13.2 (105-160)	138.85 ± 10.8 (120-160)	126.70 ± 12.7 (105-150)	0.000	Mann-Whitney Test
DBP (mm Hg)	85.42 ± 11.9 (60-115)	87.60 ± 12.16 (65-115)	83.19 ± 11.3 (60-115)	0.061	Mann-Whitney Test
Heart Rate (b.p.m)	73.32 ± 7.9 (50-89)	75.9 ± 7.3 (62-89)	70.68 ± 7.7 (50-88)	0.001	T- Test
STAI-I Score	36.08 ± 11 (20-62)	42.1 ± 11.1 (20-62)	29.9 ± 6.7 (20-54)	0.000	Mann-Whitney Test
BAI Score	16.71 ± 6 (9-33)	19.96 ± 6.3 (10-33)	13.3 ± 3.1 (9-22)	0.000	Mann-Whitney Test

Abbreviations: RT: Radiotherapy; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; b.p.m: Beats Per Minute; STAI: State-Trait Anxiety Inventory; BAI: Beck Anxiety Inventory

Discussion

With the increasing evidence that music intervention which is easily applicable, tolerable and low-cost it is started to be used in the treatment of symptoms such as anxiety and pain related to primary treatment of the patients. Anxiety is a serious problem in cancer patients in the diagnosis and treatment process so we conducted this study to evaluate the effect of listening to music on radiotherapy anxiety.

In a study Elith et al complemantary treatments like music, aromatherapy and guided imagery were found to reduce the anxiety in head and neck cancer patients who were immobilised for radiotherapy. STAI-I inventory was used in the study and the anxiety levels were reduced by complemantary treatments [19]. In our study only music therapy was used to be able to evaluate the effect of only one complemantary treatment method. In a study, in which the effect of listening to music before RT simulation on anxiety was evaluated. It was reported that there was a strong decrease in state anxiety levels for the music therapy cohort with an average post-simulation change effect of 8,2 units ($p<0.0001$), while state anxiety actually increased in the no music therapy cohort, with a mean change effect of -1.2 units [20]. In our study, we obtained that the STAI-I scores were lower in the group listening to music during RT.

Chen et al. aimed to analyze the effects of music intervention on anxiety reduction before RT in oncology patients by using STAI and vital signs. The mean change of pre- and post-test STAI scores in both the music group and the control group showed a significant decrease from baseline post test (all $p < 0.005$). In vital signs, music therapy decreased systolic blood pressure and heart rate ($p<0.005$) [21]. When vital signs were evaluated in our study, it was observed that diastolic blood pressure, systolic blood pressure and heart rate decreased statistically in favor of the music group. In a study of O'Steen et al the effect of patient self-selected music on radiotherapy anxiety was evaluated. They observed that music decreases the radiotherapy anxiety but could not reach a statistically significant result. In our study music was selected by the participants also, and we observed a statistically significant decrease in anxiety levels [22]. In the O'Steen et al's study all participants were women, in our study the group was heterogeneous in the terms of gender, this could effect the radiotherapy anxiety levels of the patients. In recent music studies the kind of music was chosen either by the researcher or by the participant. Preferred music by the participant may be more related to reduced anxiety than the preferred music by the researcher [23,24]. In our study partipicants in music group listened the music they preferred and the anxiety decreased by this music intervention.

This study have some limitations. The present study only performed music intervention once in participating subjects prior to radiotherapy, and collected only one set of pre- and post intervention measurements of the STAI scales and vital signs rather than repeating either music therapy or measurements, that is, no test was conducted immediately after the intervention. Anxiety levels were not measured during or after radiotherapy to evaluate duration of effects.

Conclusion

We obtained that music interventions reduces the anxiety levels of cancer patients receiving radiotherapy. So music intervention which is a therapy method with low-cost and without side effects could be recommended as a standart procedure in radiotherapy clinics to reduce the anxiety and related problems of cancer patients but more studies with more patient numbers should be designed.

Conflict of Interest

The authors have no conflicts of interest to declare.

Financial Disclosure

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Research Article

Does using atezolizumab with more combination chemotherapy prolong survival in small cell lung cancer?

Küçük hücreli akciğer kanserinde daha fazla kombine kemoterapi ile atezolizumab kullanımı sağkalımı uzatır mı?

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Abstract

Aim: For nearly 50 years, the standard first-line treatment for small cell lung cancer (SCLC) has been platinum-based chemotherapy combined with etoposide regimen. The use of atezolizumab in combination with chemotherapy in the first-line treatment of extensive-stage SCLC has recently been shown to improve survival in a randomized trial. Patients with SCLC not treated with immunotherapy received standard 6 cycles of platinum-based chemotherapy with the most effective survival results, whereas in the randomized trial of atezolizumab, standard 4 cycles of chemotherapy were administered. This retrospective study aims to present real-life data of atezolizumab combined with 6 cycles of chemotherapy in the first-line treatment of extensive-stage SCLC.

Material and Methods: The study included patients diagnosed with disseminated SCLC in our clinic who received a minimum of 6 cycles of treatment with carboplatin-etoposide plus atezolizumab in the first-line induction phase. Patients who completed the induction phase received atezolizumab 1200 mg every 3 weeks in the maintenance phase. Patients who received less than 6 cycles of chemotherapy combined with atezolizumab in the induction phase and patients with missing laboratory data were excluded from the study. Characteristics of the patients, treatments administered, response rates and survival data were analyzed. Kaplan-Meier test was used to determine survival data and the effects of metastasis sites were analyzed using log-rank test.

Results: Twenty-four patients fulfilling the criteria were included. The median age was 64 years and two thirds had comorbid disease. The median number of chemotherapy cycles was 6 (6-12) and atezolizumab cycles was 8 (6-54). After a median follow-up of 9.4 months, the median progression-free survival (PFS) and overall survival (OS) were 9.5 months (95% CI 0.0-25.8) and 30.1 months (95% CI 3.26-57.004), respectively. The overall response rate was 87.5%. There was no significant difference between the number of metastatic sites (p = 0.77) and OS. Grade 3 side effects were observed in more than half of the patients. The most common side effects were hematological toxicities, and all toxicities were manageable.

Conclusion: These real-life data confirm the efficacy and safety of atezolizumab combined with at least six cycles of chemotherapy in the induction phase in the first-line treatment of extensive-stage SCLC.

Keywords: Atezolizumab, cancer, chemotherapy, immunotherapy, lung

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Öz

Amaç: Küçük hücreli akciğer kanserinde (KHAK) yaklaşık 50 yıldır standart birinci basamak tedavi platin bazlı kemoterapi ile kombine etoposid rejimidir. Atezolizumabın yaygın evre KHAK birinci basamak tedavisinde kemoterapi ile kombine kullanımı yakın zamandan sağkalımı iyileştirdiği randomize bir çalışmada gösterilmiştir. Immunoterapi tedavisi uygulanmayan KHAK'li hastalara standart 6 kür platin bazlı kemoterapi uygulanarak en etkili sağkalım sonuçlarına ulaşılırken, atezolizumabın randomize çalışmasında standart 4 kür kemoterapi uygulanmıştır. Bu retrospektif çalışma, yaygın evre KHAK birinci basamak tedavisinde 6 kür kemoterapi ile kombine atezolizumabın gerçek yaşam verilerini sunmayı amaçlamaktadır.

Gereçler ve Yöntemler: Çalışmaya kliniğimizdeki yaygın evre KHAK tanılı ve birinci basamak indüksiyon fazında karboplatin-etoposid artı atezolizumab ile kombine minimum 6 siklus tedavi alan hastalar dahil edildi. İndüksiyon fazı tamamlanan hastalara idame fazında atezolizumab 1200 mg 3 haftada bir uygulandı. İndüksiyon fazında 6 siklus atezolizumab ile kombine kemoterapiden az tedavi alan hastalar ile laboratuvar verileri eksik olan hastalar çalışma dışı bırakıldı. Hastaların özellikleri, uygulanan tedaviler ve tedaviye yanıt oranları ile sağ kalım verileri incelendi. Sağkalımı verilerini belirlemek için Kaplan-Meier testi kullanıldı ve metastaz bölgelerinin etkileri log-rank testi kullanılarak analiz edildi.

Bulgular: Kriterleri karşılayan 24 hasta dahil edildi. Ortanca yaş 64 idi ve üçte ikisinde komorbid hastalık vardı. Medyan kemoterapi döngüsü sayısı 6 (6-12) ve atezolizumab döngüsü 8 (6-54) idi. Medyan 9,4 aylık takipten sonra medyan progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) sırasıyla 9.5 ay (%95 GA 0.0-25.8) ve 30,1 aydı (%95 GA 3.26-57.004). Genel yanıt oranı %87.5 idi. Metastatik bölge sayısı ($p = 0.77$) ile OS arasında anlamlı bir fark bulunamadı. Hastaların yarısından fazlasında derece 3 yan etki gözlendi. En sık yan etkiler hematolojikdi ve toksisiteler yönetilebilirdi.

Sonuç: Bu gerçek yaşam verileri, yaygın evre KHAK birinci basamak tedavisinde indüksiyon fazında en az altı siklus kemoterapi ile kombine atezolizumab etkiliğini ve güvenliliğini doğrulamaktadır.

Anahtar Kelimeler: Atezolizumab, kanser, kemoterapi, immünoterapi, akciğer

Introduction

Lung cancer is the leading cause of cancer death. According to its biology, treatment and prognosis, it is divided into 2 classes by the World Health Organization: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). SCLC accounts for approximately 15% of all lung cancer cases. The disease is classified into two stages: limited and extensive. Small Cell Lung Cancer is a chemotherapy (CT) sensitive cancer, but differs from other types of lung cancer due to its rapid doubling time and early development of extensive disease. Approximately two thirds of patients have diffuse stage disease at the time of diagnosis and the number of early-stage patients eligible for multimodality treatment is quite low.1,2

The median life expectancy in SCLC without treatment is 2-4 months after diagnosis and 6-12 months with treatment. The overall 5-year survival rate is around 5-10%. Compared to non-small cell lung cancer, treatment options are fewer and prognosis is worse. The standard first-line treatment for nearly 50 years has been a regimen of etoposide combined with platinum-based CT. Although this treatment has a rapid response rate, the median progression-free survival (PFS) is 5.5 months and the median overall survival (OS) is 10 months, because when the disease is refractory to first-line platinum combination therapy, subsequent-line therapies are not effective enough.3-5

Atezolizumab, a monoclonal antibody against programmed cell death ligand 1 (PD-L1), has become an important part of treatment in most types of cancer in recent years. Immunotherapy agents had antitumor activity in SCLC, but did not provide a survival advantage after first-line CT. However, combining PD-1/PD-L1 pathway inhibitors with CT in first-line treatment improved overall survival in patients with extensive-stage SCLC.6-8 In SCLC immunotherapy studies, first durvalumab and then atezolizumab showed survival benefit when combined with CT in the first-line setting and were accepted as the preferred treatments for extensive-stage disease in the guidelines.7,9

Patients with SCLC who are not treated with immunotherapy have the most effective survival results with standard 6 cycles of platinum-based KT. In the IMpower133 trial, a survival benefit was demonstrated by adding atezolizumab to the standard 4 cycles of carboplatin-etoposide combination CT.

Although this benefit has been demonstrated in randomized controlled trials, investigation of real-life efficacy and safety is important to confirm the results and has not been extensively studied. This retrospective study aims to present real-life data of 6 cycles of CT combined with atezolizumab in the first-line treatment of extensive SCLC.

Material and Methods

Study Population and Data Collection

Patients diagnosed with extensive SCLC at the Medical Oncology Clinic of Aydın Adnan Menderes University were included in this study. Inclusion criteria were having histologically or cytologically confirmed extensive stage SCLC according to the modified version of the Veterans Administration Lung Cancer Study Group (VALSG) staging system, being 18 years of age or older, and receiving a minimum of 6 cycles of treatment combined with carboplatin-etoposide plus atezolizumab in the first-line induction phase between 01 January 2019 and 01 March 2023. The data of the patients were accessed by entering the hospital information system via computer. Demographic, clinicopathological information, response rates and survival data were recorded retrospectively.

A minimum of 6 cycles of carboplatin (area under the curve 5 mg/mL per min on day 1), etoposide (100 mg/m2 iv on days 1-3) and atezolizumab (1200 mg iv on day 1) were administered in each 21-day cycle of the induction phase. Patients who completed the induction phase received atezolizumab 1200 mg every 3 weeks in the maintenance phase until disease progression or unacceptable side effects according to RECIST criteria or the patients request to discontinue treatment. At the beginning of treatment, all patients underwent positron emission tomography-computed tomography (PET/CT) and cranial magnetic resonance imaging for systemic evaluation of the disease. PET/CT scanning was used to assess response, and thoracic computed tomography (CT) was added when necessary. Response to treatment was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). Patients who could not be evaluated for response, who received less than 6 cycles of atezolizumab combined with CT in the induction phase, and patients with missing laboratory data were excluded from the study. Treatment-related adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Ethics committee approval was obtained from Adnan Menderes University Faculty of Medicine Clinical Research Ethics Committee in accordance with the Declaration of Helsinki (Decision No: 13-2023/93).

Statistical Analysis

Continuous variables were expressed as median (minimum [min] - maximum [max]), categorical variables as frequency and corresponding percentage. Survival data were presented as PFS and OS. Progression-free survival was defined as the time between the start of atezolizumab and first disease progression or death. Overall survival was defined as the time between the initiation of atezolizumab and death or the patient's last hospital visit. Survivals were analysed by the Kaplan-Meier method and the log-rank test was used to investigate the effect of metastasis site on survival. All p values were based on a two-tailed test of significance ($p = 0.05$). Statistical analysis was performed using IBM SPSS version 22 (SPSS Inc, Chicago, Illinois) software.

Results

A total of 24 patients who fulfilled the criteria were included in the study. Twenty patients (83.3%) were male, and the median age was 64 years. Only 8.3% (n:2) of the patients had no smoking history. One third of the patients had no comorbid disease, the most common comorbidities were diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD) and hypertension (HT). All but one patient had small cell neuroendocrine carcinoma. The patient with large cell neuroendocrine carcinoma was treated as SCLC because the Ki67 index was 55%.10 Only 1 patient (4.16%) had recurrent metastatic disease, the other patients had de-novo extensive stage disease. The most common sites of metastasis were lung, bone and non-regional lymph nodes. Five patients had central nervous system (CNS) metastases. Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 45.83% and 1 in 54.16% of patients (Table 1).

In the induction phase, the median number of CT+ atezolizumab cycles was six. Following the induction phase, 70.83% received maintenance therapy and the median number of total atezolizumab cycles was eight. Nine patients (37.5%) died during follow-up. Five patients had brain metastases at diagnosis or during treatment and received cranial radiotherapy (RT). Two patients received prophylactic cranial irradiation (PCI); one received it in the initial limited phase and the other received it during the maintenance phase. A total of 9 patients received consolidative thoracic radiotherapy. One of the patients received thoracic radiotherapy only in the limited phase, while the other eight patients received thoracic radiotherapy in the maintenance phase. The objective response rate (ORR) was 87.5% and 1 patient (4.16%) had progressive disease as the best treatment response. Seven patients had complete response. Thoracal radiotherapy was performed in 71.4% (n:5) of patients with complete response (Table2).

Table 1. Demographic and clinicopathological features of the patients

		Number (n)	% Value
Age, median (min-max) (year)	64 (51-76)		
Gender (male/female)	Male	20	(83.33%)
	Female	4	(16.16%)
Comorbid Disease	DM	8	(33.33%)
	HT	6	(25%)
	CAD	4	(16.16%)
	COPD	7	(29.16%)
	No comorbidity	8	(33.33%)
Smoking Status	Smoker	22	(91.66%)
	Never smoked	2	(8.33%)
ECOG performance status score	0	11	(45.83%)
	1	13	(54.16%)
Histopathology	SCLC	23	(95.83%)
	LCNEC	1	(4.16%)
Stage at the time of diagnosis	Limited	1	(4.16%)
	Extensive	23	(95.83%)
Number of metastatic sites	1	6	(25%)
	2	10	(41.66%)
	3	6	(25%)
	4	0	
		2	(8.33%)

CAD=Coronary artery disease CAD; COPD= chronic obstructive pulmonary disease; DM=Diabetes mellitus; HT=Hypertension; LCNEC= large cell neuroendocrine carcinoma; SCLC= small cell lung cancer

Table 2. Characteristics of therapy and objective tumor responses

		Number (n)	% Value
Patients received cranial irradiation	Yes	7	(29.16%)
	No	17	(70.83%)
Patients received thoracic irradiation	Yes	9	(37.5%)
		15	(62.5%)
CT+Atezolizumab cycles, median (min-max)	6 (6-12)		
Total atezolizumab cycles, median (min-max)	8 (6-54)		
Best response	Complete response	7	(29.16%)
	Partial response	14	(58.33%)
	Stable response	2	(8.33%)
	Progressive disease	1	(4.16%)

At a median median follow-up of 9.4 months (min-max: 5.1-40.4), median PFS and OS were 9.5 months (95% CI: 0.0-25.8) and 30.1 months (95% CI: 3.26-57.004), respectively (Figure 1,2). Analysis using the log-rank test to investigate the effect of the number of metastatic sites on OS showed no significant results (p=0.77) (Figure 3).

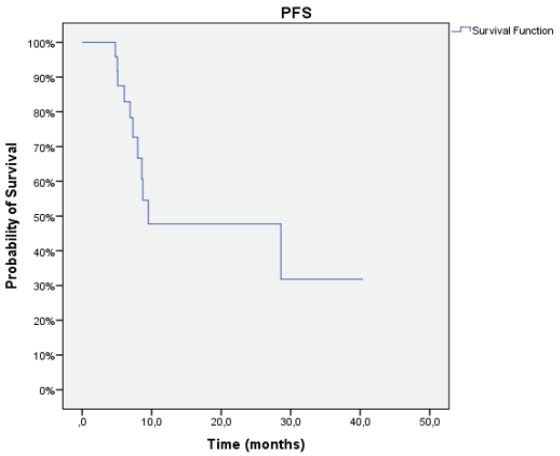

Figure 1. Progression-free survival of the patients

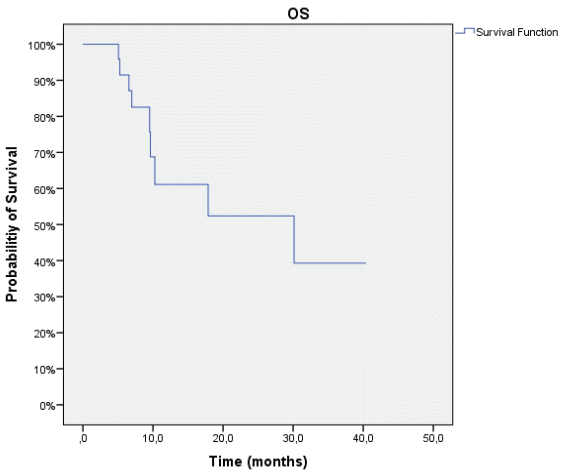

Figure 2. Overall survival of the patients

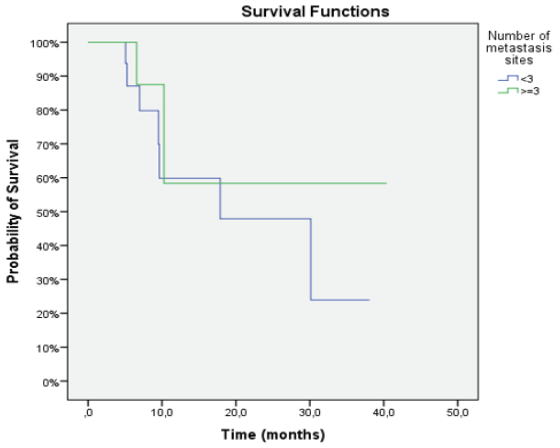

Figure 3. Overall survival by number of metastasis sites > 3, <3

Table 3. Adverse events

Event	Any Grade, n(%)	Grade 1-2, n(%)	Grade 3-4, n(%)
Anemia	19 (79.16%)	12 (50%)	7 (29.16%)
Neutropenia	21 (87.5%)	8 (33.33%)	13 (54.16%)
Thrombocytopenia	13 (54.16%)	9 (37.5%)	4 (16.16%)
Febrile Neutropenia	4 (16.16%)	------	4 (16.16%)
Fatigue	20 (83.33%)	17 (70.83%)	3 (12.5%)
Nausea	12 (50%)	11(45.83%)	1 (4.16%)
Vomiting	8 (33.33%)	8 (33.33%)	-------
Acute kidney injury	3 (12.5%)	3 (12.5%)	--------
Hepatic enzymes elevation	5 (20.83%)	5 (20.83%)	--------
Diarrhea	6 (25%)	6 (25%)	-------
Hypothyroidism	4 (16.16%)	4 (16.16%)	-------
Pneumonitis	1 (4.16%)	1 (4.16%)	-------

Discussion

This retrospective study is the first research that reported the real-life data experience of at least six cycles of CT combined with atezolizumab in the first-line treatment of extensive SCLC in a single center. Patients in our study had the same median age as in IMpower1337, but more patients had an ECOG performance of "0" and the median follow-up was approximately 4 months less. In addition, 25% (37.5% vs. 12.4%) more patients underwent thoracic RT consecutively.

In contrast to the standard median 4 cycles of CT+atzolizumab in the AB.Sahin et al. and IMpower133 studies using real-life data, the median was higher in our study. Similarly, the median number of atezolizumab cycles was similarly higher (8 cycles versus 7 cycles).7,11While the mean ORR in SCLC first-line atezolizumab plus CT studies in this literature was 61%, the ORR in our study was higher at 87.5% (ORR range: 60.2%-63.6%).7,11,12

In our retrospective study, PFS and OS were determined as 9.5 and 30.1 months, respectively. PFS and OS were higher compared to the IMpower133 study, where PFS and OS were 5.2 and 12.3 months, respectively. In another study examining patients with diffuse stage SCLC, median PFS was 6.8 months and median OS was 11.9 months with the combination of atezolizumab and CT.7,12 The most important reason for this may be that there were fewer patients. In addition, in contrast to the previous studies, the inclusion of patients who completed at least 6 cycles of CT+ atezolizumab treatment, the high number of patients with ECOG "0" performance and the fact that we mostly applied thoracic radiotherapy may be factors in the high OS.

In a meta-analysis, age (<65 versus ≥65) and ECOG-PS (0 versus ≥ 1) were found to be associated with response to immunotherapy.13 In our study, the median age of the patients was 64 years and those with ECOG-PS "0" were more common. In addition, giving full dose treatment and tolerating local treatments such as RT in patients with good performance may contribute to a higher OS.

In the phase 3 KEYNOTE-604 study in which pembrolizumab was added to CT in the first-line treatment of extensive stage SCLC, OS was better in patients with ≥3 metastatic sites in the pembrolizumab arm. In our study, no statistically significant relationship was found between the number of metastatic sites and OS. The reason for this may be that our patients were fewer compared to other studies.14

Predictive biomarkers such as PDL-1 expression and tumor mutation burden (TMB) have been investigated to determine the efficacy of immunotherapy treatment in solid tumors such as NSCLC. Although TMB has been shown to be high in SCLC, subgroup analyses of atezolizumab and durvalumab studies have shown that both PD-L1 expression and TMB have no predictive value.15,16 It is known that patients have permanent responses with immunotherapy treatments, and the number of atezolizumab cycles was 12 or more in seven of our patients. Biomarkers that can predict immunotherapy response are important both in delivering treatment to more patients and in applying more aggressive local treatments to patients with response. The need for predictive markers in cancer treatment with immunotherapy, especially progressive SCLC, continues.

In retrospective studies including atezolizumab real-life data, consolidative thoracic RT was applied to an average of 30% patients.11-12 In our study, nine patients (37.5%) received thoracic RT as consolidative treatment. Seven patients received RT in the maintenance phase and one patient received RT before disease recurrence. It has been reported that RT may increase tumor response with direct and abscopal effects in patients receiving immunotherapy treatment.17 Looking at the literature, randomized controlled trials investigating the efficacy and safety of CT plus RT combined with immunotherapy in extensive stage SCLC are lacking.

The overall safety profile in our study was similar to that of the reference studies despite fewer patients. There were no adverse events leading to treatment discontinuation or death. All patients had some degree of adverse events but they were manageable. The most common was bone marrow toxicity. All immune-mediated adverse events were low grade and manageable.

The main limitations of our study are the small number of cases, short follow-up period and retrospective design. In addition, we could not perform further subgroup analyses in patients receiving thoracic radiation. In addition, predictive biomarkers for immunotherapy such as PD-L1 and TMB were not analysed.

Conclusion

In conclusion, these real-life data confirm the efficacy and safety of maintenance atezolizumab with at least six cycles of atezolizumab plus CT in the induction phase in the first-line treatment of extensive SCLC in our small patient series. However, it is crucial to identify predictive biomarkers and clarify the use of thoracic RT. We believe that larger randomised trials with large numbers of patients and real-life data are needed to determine the ideal number of atezolizumab plus CT.

Declaration of Conflicting Interest

Author declares no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Approved by the following research ethics committee

Adnan Menderes University for Non-Invasive Clinical Research (E-53043469-050.04.04-347380, Decision No:13-2023/93).

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Availability of Data and Materi al

The data sets and data analyzed in the study are available from the corresponding author on reasonable request.

Authors Contributions

All authors have made substantial contributions to conception, design, acquisition of data; or analysis and interpretation of data; or have been involved in drafting the manuscript or revising it critically for important intellectual content.

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Araştırma Makalesi

Tek taraflı pseudoeksfolyasyon materyali olan glokomlu ve hastalıksız bireylerin, optik koherens tomografi-anjiografi cihazı ile makula değerlendirmesi

Evaluation of macula with optical coherence tomography-angiography device in glaucomatous and disease-free individuals with unilateral pseudoexfoliation material.

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Öz

Amaç: Bu çalışmanın amacı, tek taraflı psödoeksfoliasyon materyali (XFM) izlenen bireylerde, glokom geliştiği durumlarda ve gelişmediği durumlarda makula vasküler yoğunluğunun gözler arası değişimini gözlemlemektir.

Gereç ve Yöntemler: Çalışmaya, 38 adet tek taraflı psödoeksfoliasyon sendromlu (XFS) bireyin 76 gözü ve 36 adet tek taraflı psödoeksfoliasyon glokomlu (XFG) hastanın 72 gözü dahil edilmiştir. Her iki grubun XFM bulunan ve bulunmayan gözlerinin makula parametreleri optik koherens tomografi-anjiografi (OCT-A) cihazı kullanılarak incelenmiştir. Tüm makula belirteçleri ortalama karşılaştırmasına dayanan standart t testi ile değerlendirilmiştir. Aynı zamanda, her iki gruptaki XFM pozitif ve negatif olan göz grupları birbirleriyle ve gruplar arasında Kruskal-Wallis (KW) testi ile karşılaştırılmıştır.

Bulgular: Tek taraflı XFS olan grupta, gözler arası yüzeysel kapiller pleksus yoğunluğunda az sayıda anlamlı farklılık görülmüşken, tek taraflı XFG olan grupta glokomlu gözlerin lehine anlamlı düzeyde damar yoğunluğunda azalma dikkati çekmektedir. Makulanın üst ve alt yarımında (p=0,0018, p=0,0002), fovea (p=0,014), parafovea (p=0,0411), parafoveanın inferior yarımı (p=0,0126) ve temporalinde (p=0,0126) glokomlu gözlerde azalmış vasküler yoğunluk saptanmıştır. Derin kapiller pleksusta ise hem grup içi hem de gruplar arası kıyaslamalarda yüzeysel damar tabakasına göre anlamlılık azalmıştır.

Sonuç: Medikal tedaviyle kontrol altında olan glokom hastalarında makula bölgesinde özellikle yüzeysel kapiller pleksusun yoğunluğunda azalma olduğu gösterilmiştir. Ancak bu damarsal azalma, glokomu olmayan gözlerde XFM varlığında öncü belirti olarak gösterilememiştir.Anahtar kelimeler: optik koherens tomografi anjiografi, makula damar yoğunluğu, psödoeksfoliasyon glokomu

Anahtar Kelimler: Optik koherens tomografi-anjiyografi, makula damar yoğunluğu, psödoeksfoliasyon glokomu

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Abstract

Aim: The aim of this study was to observe interocular variations in macular vascular density among individuals with unilateral pseudoexfoliation material (XFM) and its association with glaucoma development.

Material and Methods: The study included a total of 76 eyes from 38 individuals with unilateral pseudoexfoliation syndrome (XFS) and 72 eyes from 36 individuals with unilateral pseudoexfoliation glaucoma (XFG). OCT-A was used to examine all macular markers in both XFM-positive and XFM-negative eyes within each group, and the data were analyzed using the standard mean comparison t-test. Furthermore, the Kruskal-Wallis test was used to compare the XFM-positive and XFM-negative eye groups between the XFS and XFG cohorts.

Results: The unilateral XFS group showed relatively infrequent significant differences in superficial capillary plexus density between the eyes. In contrast, the unilateral XFG group exhibited a significant decrease in vascular density in various macular regions, including the total macula (p=0,0004), superior and inferior hemifields (p=0,0018, p=0,0002), fovea (p=0,014), parafovea (p=0,0411), inferior half of parafovea (p=0,0126), and temporal region (p=0,0126). However, the deep capillary plexus showed decreased significance in both within-group and between-group comparisons compared to the superficial vascular layer.

Conclusion: Our findings indicate a decrease in macular capillary plexus density, particularly in the superficial region, in glaucoma cases effectively managed with medical treatment. However, this vascular decrease could not be identified as an early sign in the presence of XFM (pseudoexfoliation material), which is a significant risk factor for glaucoma.

Keywords: optic coherens tomography-angiography, macula vessel density, pseudoexfoliation glaucoma

Giriş

Glokom, retina ganglion hücrelerinin kaybıyla ve optik nöropatiyle seyreden; multifaktöryel ve ilerleyici bir hastalıktır. (1) Yükselen göz içi basıncı (GİB), glokom için gösterilmiş ana risk faktörü olmakla beraber; tek risk faktörü değildir. Yapılan çalışmalar, vasküler ve iskemik nedenlerin etyopatogenezde önemli faktörler olduğunu göstermektedir. (2,3)

Son dönmede kullanımı yaygınlaşan optik koherans tomografi-anjiografi cihazı (OCT-A), retinanın tabakalarını ve farklı segmentlerdeki damarlanmayı, kontrast madde kullanımı gerektirmeden gösterebilen non- invaziv bir görüntüleme yöntemidir. Eritrositlerin hareketliliğinin tespiti prensibiyle retina, koroid ve optik disk mikrosirkülasyonu ve nihayetinde glokomun vasküler etyopatogenezi üzerine veri sunar. (4,5) Bu veriler, glokom etyopatogenezindeki aydınlatılmamış noktalara ışık tutabilecek potansiyeli taşımaktadır.

Güncel glokom çalışmalarında hız kazanan başka bir nokta; erken glokom hasarında makula bölgesinde oluşabilecek değişikliklerdir. (6,7) Uzun bir süre boyunca, glokomun son evresine kadar makula bölgesinin korunduğu ve etkilenmediği düşünülmüştür. Ancak, son yıllarda giderek artan sayıda çalışma, erken dönem glokomda makula bölgesinde değişiklikler olduğu yönünde kanıt göstermeye başlamıştır. Güncel glokom tanı ve takibinde makuladaki hasara yönelik yapısal ve fonksiyonel testler klinik pratikte yerini almıştır.(6,7)

Glokomun vasküler etyopatogenezinin inceleme noktasında, glokom için yüklü bir risk faktörü olan psödoeksfoliasyon materyalinin (XFM) varlığı önemli bir belirleyicidir. XFM biyomikroskopik muayenede kolayca tespit edilebilen, tek taraflılık gösterebilen ve vasküler afinitesi gösterilmiş amiloid benzeri fibrogranüler yapıda birikimsel bir maddedir. XFM'nin gözde tespit edildiği durumlara psödoeksfoliasyon sendromu (XFS), XFS'ye ek olarak GİB yüksekliği ve/veya glokomatöz sinir lifi kaybı eşlik ettiği durumlara psödoeksfoliasyon glokomu (XFG) adı verilmektedir. XFM tespit edilen gözlerde %50'ye varan oranlarda XFG geliştiği ve XFG'lerin, primer açık açılı glokomlara göre çok daha agresif seyir gösterdiği gösterilmiştir. (8,9)

XFG'nin fizyopatolojisinde yaygın olarak kabul edilen görüş; trabeküler ağın XFM ile tıkanması, humör aközün dışa akımının bozulması ve nihayetinde GİB'in progresif olarak artması ve fluktuasyon göstermesidir. Ancak yapılan GİB kontrollü çalışmalar, XFG'nin GİB'in tüm değerlerinde gelişebildiğini ve agresif seyrettiğini göstermektedir. (8-11) GİB'den bağımsız olarak, glokoma yatkınlık oluşturabilecek etki mekanizmaları üzerine lamina kribrosada ve vasküler akımda bozulma olduğu yönünde literatürde pek çok çalışma bulunmaktadır. (11-16)

Biz, çalışmamızda tek taraflı XFM izlenen bireyleri, glokom gelişen ve gelişmeyenler olmak üzere 2 grupta inceledik. XFM varlığında makuladaki kalınlık ve vasküler yoğunluğun değişimini, bireylerin sağlıklı gözleriyle kıyaslayarak yorumladık ve XFM'nin maküler alandaki vasküler etkilerini ortaya koymaya çalıştık.

Gereç ve Yöntemler

Bu kesitsel çalışma, Dünya Tıp Birliği Helsinki Bildirgesi'ne uygun olarak hazırlanmış ve Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından onaylanmıştır. Katılımcıların tümünden aydınlatılmış onam alınmıştır. Tüm katılımcılar üçüncü derece sağlık kuruluşunda tanı almıştır ve takipleri sürdürülmüştür. Klinik muayene ve değerlendirmelerin tamamı, çalışmaya ait tüm prosedürler tek klinisyen tarafından gerçekleştirilmiştir (yazarın kendisi). Oftalmik muayene; en iyi düzeltilmiş görme keskinliği (EDGK), ön segmentin biyomikroskopik değerlendirmesi, Goldmann 3 aynalı lens ile açı muayenesi, 90 dioptrilik (D) lens ile fundoskopik muayene, santral kornea kalınlığı (SKK) ölçümü, Humphrey görme alanı değerlendirmesi ve OCT-A ile makula ve optik disk görüntülemesini kapsamaktadır.

Çalışmadan dışlanma koşulları; XFG dışındaki diğer tüm glokom tipleri, bilateral XFG veya XFS izlenen hastalar, fakoemülsifikasyon dışında geçirilmiş göz cerrahileri, ortam opasitesi bulunan durumlar, geçirilmiş (iskemik veya non-iskemik) optik nöropati öyküsü, optik disk anomalileri (kolobom, tilte disk, optik disk druzeni vs.), retinal vasküler hastalıklar (diabetik retinopati, hipertansif retinopati, vasküler oklüzif hastalıklar vs.), üveit, vitreoretinal ara yüzey hastalıkları, sferik veya silindirik refraktif kusurun >3D olması, vasküler disfonksiyon veya vaskülit oluşturabilen sistemik hastalıklardır.

Tüm OCT-A görüntülemeleri, pupilla dilate edilerek AngioRTVue XR (Optovue Inc., Freemount, CA) cihazının 2015.1.1.98 software versiyonuyla, tecrübeli bir teknisyen tarafından çekilmiştir. Makula bölgesinin (6x6mm2) kalınlığı, derin ve yüzeysel kapiller damar yoğunluğu (%), buna ek olarak retinal sinir lifi tabakası (RNFL) kalınlığı (µm) cihaz tarafından software'ine uygun şekilde otomatik olarak ölçülmüştür. İmajlara ait olası tüm artefaktlar (segmentasyon hataları, çekim kalitesindeki zayıflık, fiksasyona ait sorunlar, hareket artefaktları) klinisyen tarafından kontrol edilmiş, hatalı çekimler çalışmaya dahil edilmeden uygun çekim kalitesi sağlanana kadar tekrarlanmıştır. Sinyal gücü < 7/10 olan görüntüler çalışmaya dahil edilmemiştir.

Tek taraflı XFM izlenen ve çalışmaya dahil edilen bireyler 2 gruba ayrılmıştır:

Grup 1: 19 kadın ve 19 erkek olmak üzere 65,12±14,11 yaş ortalamasına sahip, tek gözlerinde XFM olup diğer gözlerinde olmayan 38 katılımcıdan oluşmaktadır. Bu gruptaki bireylerin her iki gözünde de glokom düşündüren hiçbir bulgu bulunmamıştır. Bilateral olarak optik disk görünümleri sağlıklı, GİB<21 mmHg, gözler arası simetrik RNFL ve normal görme alanı bulguları gözlemlenmiştir. Bu grup, tek taraflı XFS grubu olarak adlandırılmıştır.

Grup2: :18 kadın ve 18 erkek olmak üzere 69,00±12,11 yaş ortalamasına sahip, tek gözlerinde XFM olup, XFM mevcut olan gözde glokom bulguları (optik diskte glokomatöz çukurlaşma, tanı veya takip sürecinde en az bir kere GİB≥ 21 mmHg tespiti, gözler arası asimetrik RNFL ve XFM izlenen gözde glokomatöz RNFL kaybı, glokomla uyumlu görme alanı kaybı) gelişen 36 katılımcıdan oluşmaktadır. XFM izlenmeyen gözlerde ise tüm ölçümler normal limitlerde ve muayene bulguları tamamen sağlıklı gözlerle uyumlu olarak izlenmiştir. Bu grup, tek taraflı XFG grubu olarak tanımlanmıştır. Bu gruptaki hastaların glokomlu gözlerine topikal tedavi başlanarak takip edilmiştir. Topikal tedavi ile kontrol altına alınmayan glokom gelişmesi durumunda hastalar cerrahi planlanarak çalışmadan çıkarılmıştır.

Her iki grubun XFM olan ve olmayan gözlerinin OCT-A ile incelenen tüm makuler belirteçleri standart ortalama karşılaştırmalı t testi ile değerlendirilmiştir. Her iki gruptaki XFM pozitif ve negatif olan göz grupları birbirleriyle ve gruplar arasında Kruskal-Wallis testi ile kıyaslanmıştır. Belirtilen analizler yapılmadan önce değişkenlerin normal dağılım gösterip göstermedikleri Shapiro-Wilk, Shapiro-Franca ve çarpıklık/yığılma testleri ile kontrol edilmiştir ve normal dağılımdan anlamlı bir farklılık bulunmamıştır.

Tüm istatistiksel analizler, STATA istatistiksel analiz programının 17. versiyonuyla çalışılmıştır.

Bulgular

Bu karşılaştırmalı kesitsel çalışmada, 38 sayıda bireyin 76 sayıda gözü tek taraflı XFS (Grup 1) olarak, 36 sayıda hastanın 72 sayıda gözü tek taraflı XFG (Grup 2) olarak, Ağustos 2021 ve Nisan 2022 ayları arasında, tek bir merkezde, üçüncü derecede sağlık kurumunda değerlendirilerek çalışmaya dahil edilmiştir. 2 grubun yaşları sırasıyla 65,12±14,11 ve 69,00±12,11 olarak bulunmuştur. Grupların yaşları arasında istatistiksel olarak anlamlılık bulunmamıştır (p=0,21) Erkek/ kadın oranları da her iki grupta %50-%50 olarak bulunmuştur.

Katılımcıların klinik karakteristikleri Tablo 1'de gösterilmiştir. Tabloda izlendiği üzere Grup 1'de gözler arası klinik karakteristiklerde anlamlı fark yokken (tümünde, p > 0,05 olup spesifik p-değerleri için ilgili tabloya bakılabilir), grup 2'de glokom gelişen gözün aleyhinde anlamlı değişiklikler gözlemlenmiştir.

Tablo 2, makuladaki yüzeysel kapiller yoğunluk (%) değerlerini göstermektedir. Grup 1'de XFM izlenen gözlerin parafoveal bölgesinin inferior yarısında (p=0,049) ve nazalinde (p=0,02) anlamlı bir damarsal azalma izlenmekle birlikte; totalde ve diğer anatomik lokasyonlarda anlamlı fark bulunamamıştır (p>0.05 olup spesifik p değerleri için ilgili tabloya bakılabilir). Tek taraflı XFG'si olan grup 2'de ise gözler arası anlamlılık

belirginleşmiştir. Makulanın totali (p= 0,0004) üst ve alt yarımı (p=0,0018, p=0,0002), fovea (p=0,014), parafovea (p=0,0411) ve parafoveanın inferior yarımı (p=0,0126) ve temporalinde (p=0,0126); glokomlu gözlerin aleyhinde anlamlı düzeyde damar yoğunluğu azalması dikkati çekmektedir. Glokom izlenmeyen gözlerin (grup 1'deki bireylerin her iki gözü ve grup 2'deki bireylerin hastalıksız gözü) 3'lü Kruskal Wallis kıyaslamasında perifoveanın temporali (p=0,04) dışında anlamlı hiçbir fark izlenmezken; bu 3'lü kıyaslamaya XFG'li gözler ilave edilip 4'lü Kruskal Wallis kıyaslaması yapıldığında, her noktada istatistiksel anlamlılık gözlemlenmektedir. (p≤ 0,05 olup spesifik değerler için ilgili tabloya bakılabilir)

Tablo 3, gözlerin makuladaki derin kapiller yoğunluğunu (%) göstermektedir. Hem grup içi hem gruplar arası kıyaslamalarda anlamlılık, yüzeysel damar tabakasına göre azalmıştır. Grup 1'de perifoveanın temporali (p=0,007); grup 2'de fovea (p=0,0385) ve perifoveanın temporali (p=0,0314) dışında anlamlı fark izlenmemiştir. Glokom izlenmeyen gözlerin (grup 1'deki bireylerin her iki gözü ve grup 2'deki bireylerin hastalıksız gözü) 3'lü Kruskal Wallis kıyaslamasında perifoveanın temporali (p= 0,04); tüm gözlerin 4'lü Kruskal Wallis kıyaslamasında ise maküla totali, üst ve alt yarımı (tümünde p= 0,04), fovea (p=0,05), perifoveanın üst yarımı (p=0,05) ve perifoveanın temporali ve inferioru (p= 0,04) dışında anlamlı fark izlenmemiştir.

Tablo 1: Katılımcıların Klinik Karakteristikleri

	Tek Taraflı XFS (n=38)			Tek taraflı XFG (n=36)		
	XFM+	XFM-	p	XFM +	XFM -	p
GİB (mmHg)	16,8±2,19	16,70±1,90	0,83	18,4±2,11	16,54±2,01	0,01
SKK (µm)	548,01±22,11	543,59±23,99	0,41	530,02±20,99	535,44±22,86	0,30
EDGK (decimal)	0,84 ± 0,22	0,88 ± 0,23	0,44	0,62 ± 0,20	0,89 ± 0,24	<0,0001
Topikal ilaç (n)	0	0		2,32±1,11	0	
Lens durumu (n)						
Fakik	20	21		15	16	
Psödofakik	18	17		21	20	
RNFL kalınlığı (µm)	105,02±10,40	106,38±10,01	0,56	70,01±16,22	102,05±16,39	<0,0001
Görme alanı MD (dB)	-0,69± 0,29	-0,79 ± 0,55	0,32	-6,65±8,72	-2,15 ± 1,32	<0,0001
PSD (dB)	1,03 ± 0,62	1,10 ± 0,90	0,69	5,00±3,55	2,10 ± 1,65	<0,0001

Tablo 2: Tek taraflı XFS ve XFG'lerin Makula Yüzeysel Kapiller Yoğunlukları (%)

	Tek Taraflı XFS			Tek Taraflı XFG				
	XFM (+)	XFM (-)	p	XFM (+)	XFM (-)	p	3'lü KW	4'lü KW
Makula Totali	46,92±4,71	48,46±3,05	0,09	40,80±4,69	45,23±4,37	0,001	0,25	0,03
Superior-Hemi	46,69±4,63	48,22±2,99	0,09	41,21±4,61	45,05±4,50	0,002	0,26	0,03
İnferior-Hemi	47,17±4,89	48,70±3,20	0,11	40,44±5,12	45,38±4,45	0,001	0,44	0,03
Fovea	18,34±6,96	18,73±5,99	0,79	16,70±5,11	19,85±4,50	0,014	0,52	0,04
ParaFovea	48,60±5,17	50,30±3,78	0,11	45,02±4,53	47,49±4,63	0,041	0,09	0,03
Superior-Hemi	48,30±5,69	50,42±4,09	0,07	45,37±4,17	46,95±4,98	0,14	0,11	0,05
İnferior-Hemi	48,52±4,92	50,78±3,70	0,049	44,62±5,58	48,00±4,53	0,013	0,11	0,04
Tempo	48,29±6,10	49,59±4,85	0,31	44,74±5,39	47,68±5,18	0,035	0,40	0,05
Superior	48,70±6,34	51,00±4,65	0,08	46,16±5,03	47,28±5,53	0,36	0,09	0,05
Nasal	47,63±5,17	50,58±3,86	0,02	44,61±4,67	46,27±5,48	0,16	0,09	0,05
İnferior	48,92±5,03	50,25±4,56	0,23	44,47±6,77	48,72±4,35	0,005	0,08	0,04
Perifovea	47,69±4,81	49,00±3,09	0,16	41,03±5,04	45,55±4,74	0,001	0,33	0,02
Superior-Hemi	47,35±4,65	48,60±3,07	0,17	41,26±5,17	45,49±4,76	0,001	0,49	0,02
İnferior-Hemi	48,02±5,05	49,39±3,28	0,17	40,82±5,45	45,57±4,98	0,001	0,49	0,02
Tempo	44,70±5,67	46,36±2,68	0,11	37,13±5,74	41,84±5,16	0,002	0,04	0,02
Superior	46,53±5,14	47,88±3,89	0,20	41,04±5,42	45,33±5,11	0,003	0,30	0,02
Nasal	52,14±4,08	52,99±2,83	0,29	45,80±5,56	49,72±4,74	0,005	0,07	0,03
İnferior	48,02±5,48	48,71±3,76	0,52	40,23±5,63	45,40±5,33	0,001	0,09	0,02

Tablo 3: Tek taraflı XFS ve XFG'lerin Makula Derin Kapiller Yoğunlukları (%)								
	Tek Taraflı XFS			Tek Taraflı XFG				
	XFM (+)	XFM (-)	p	XFM (+)	XFM (-)	p	3'lü KW	4'lü KW
Makula Totali	45,64±6,74	47,42±5,68	0,22	44,78±5,23	46,46±4,17	0,13	0,38	0,04
Superior-Hemi	45,80±6,89	47,78±5,62	0,17	44,84±5,50	46,32±4,42	0,20	0,40	0,04
İnferior-Hemi	45,49±6,67	47,09±5,89	0,27	44,73±5,57	46,65±4,38	0,10	0,39	0,04
Fovea	33,60±8,71	34,17±6,82	0,75	33,25±6,61	36,57±5,48	0,039	0,42	0,05
ParaFovea	51,25±5,58	52,63±5,01	0,40	51,83±4,34	52,40±3,84	0,55	0,44	0,48
Superior-Hemi	51,15±6,08	52,87±4,69	0,17	52,17±3,94	52,62±3,42	0,60	0,30	0,28
İnferior-Hemi	51,36±5,33	52,38±5,44	0,41	51,49±5,34	52,19±4,75	0,55	0,29	0,25
Tempo	51,86±5,22	53,42±5,09	0,19	53,21±3,99	52,93±4,04	0,76	0,11	0,10
Superior	49,35±7,85	52,07±5,43	0,08	51,27±5,07	51,98±4,57	0,52	0,15	0,14
Nasal	53,57±5,06	53,35±4,82	0,85	53,60±4,45	53,80±3,69	0,83	0,80	0,78
İnferior	50,25±6,43	51,68±6,20	0,33	49,25±7,34	50,91±6,09	0,29	0,54	0,49
Perifovea	46,57±7,39	48,43±6,14	0,24	45,20±6,02	47,11±4,65	0,13	0,45	0,39
Superior-Hemi	46,63±7,44	48,44±6,10	0,25	44,80±6,46	46,56±4,82	0,18	0,10	0,05
İnferior-Hemi	46,48±7,47	48,42±6,42	0,23	45,56±6,48	47,67±5,04	0,12	0,15	0,09
Tempo	46,97±6,61	52,41±4,99	0,0007	47,12±8,33	50,84±3,99	0,031	0,04	0,04
Superior	44,77±8,34	47,29±6,83	0,15	43,65±6,03	45,40±5,79	0,20	0,10	0,09
Nasal	48,17±8,65	46,95±6,85	0,50	45,41±6,50	45,30±5,91	0,88	0,07	0,10
İnferior	45,52±7,76	47,07±7,34	0,37	44,56±6,66	46,99±5,97	0,10	0,12	0,04

Tablo 4 grup içi ve gruplar arası yapılan makula kalınlık kıyaslamasını göstermektedir. Grup 1'de XFM olup olmaması arasında hiçbir anlamlı fark yokken; grup 2'de glokom gelişen gözlerin, total makula kalınlıklarında (p=0,0022) ve üst yarımlarında (p=0,013) anlamlı düzeyde incelme tespit edilmiştir. Glokomsuz gözlerin 3'lü grup şeklinde karşılaştırmalarında hiçbir anlamlılık bulunmazken; glokomlu gözler dahil edilerek yapılan 4'lü karşılaştırmada fovea, perifovea, perifovea'nın temporal- superior ve nazali hariç; tüm noktalarda anlamlı fark görülmüştür.

Tablo 5'te yüzeysel ve Tablo 6'da ise derin kapiller damar yoğunluğu ve makula kalınlığı arasında korelasyon olup olmadığı incelenmiştir. Hem yüzeysel hem derin kapiller pleksus ve makula kalınlığı arasında görülen pozitif korelasyon; fovea bölgesinde göze çarpmaktadır. Bunun dışında da kalınlık ve damar yoğunluğu arasındaki pozitif ve negatif yönlü korelasyonlar Tablo 5 ve 6'da detaylı bir şekilde gösterilmiştir.

Tablo 4: Tek taraflı XFS ve XFG'lerin Makula Kalınlık (µm) Değerlendirmesi								
	Tek Taraflı XFS			Tek Taraflı XFG				
	XFM (+)	XFM (-)	p	XFM (+)	XFM (-)	p	3'lü KW	4'lü KW
Makula Totali	279,42±12,22	281,19±11,30	0,51	269,33±16,58	282,42±15,04	0,002	0,45	0,03
Superior-Hemi	281,35±12,17	283,04±11,33	0,52	273,46±17,47	285,00±17,51	0,013	0,42	0,03
İnferior-Hemi	277,92±12,85	279,54±11,73	0,57	268,52±18,72	275,35±13,34	0,07	0,09	0,05
Fovea	252,73±21,98	251,77±21,52	0,85	255,04±18,91	257,70±15,43	0,50	0,19	0,15
ParaFovea	319,62±15,91	320,96±12,93	0,69	313,26±19,47	320,96±15,73	0,06	0,10	0,05
Superior-Hemi	320,12±16,31	321,31±13,22	0,73	313,96±19,24	321,16±16,87	0,09	0,09	0,04
İnferior-Hemi	319,31±15,95	320,27±13,13	0,78	312,70±20,32	320,35±15,69	0,07	0,08	0,05
Tempo	311,65±15,20	312,92±13,85	0,70	306,17±19,97	312,17±16,13	0,08	0,07	0,05
Superior	323,35±16,39	324,31±13,50	0,71	314,78±20,45	323,30±18,29	0,06	0,08	0,05
Nasal	322,23±18,09	324,62±12,95	0,51	318,57±17,87	325,04±14,38	0,09	0,07	0,05
İnferior	321,65±16,56	321,69±13,69	0,99	312,78±21,56	321,08±16,49	0,06	0,09	0,03
Perifovea	278,04±12,53	278,81±11,51	0,80	269,43±19,45	275,52±14,58	0,13	0,12	0,11
Superior-Hemi	280,08±12,37	281,00±12,19	0,74	272,78±19,97	278,65±16,67	0,17	0,10	0,05
İnferior-Hemi	275,92±13,25	276,85,11,36	0,77	266,09±19,59	272,17±13,81	0,12	0,09	0,05
Tempo	267,69±12,72	268,50±12,57	0,78	258,74±19,60	265,22±14,48	0,11	0,32	0,07
Superior	278,35±12,03	279,00±11,83	0,81	270,57±20,68	276,87±18,43	0,17	0,10	0,11
Nasal	295,50±16,15	295,96±14,30	0,96	289,00±20,74	294,04±15,00	0,23	0,12	0,15
İnferior	270,40±13,09	272,15±12,14	0,55	258,41±19,16	265,70±13,82	0,06	0,09	0,02

Tablo 5: Makula Kalınlığı ve Yüzeysel Kapiller Yoğunluğu Arası Korelasyon

	Tek Taraflı XFS				Tek Taraflı XFG			
	XFM+	p	XFM-	p	XFM+	p	XFM-	p
Makula Totali	-0,084233	0,62	0,0511	0,76	0,19900	0,23	0,462	0,01
Superior-Hemi	-0,114851	0,49	-0,0804	0,62	0,09534	0,57	0,489	0,006
İnferior-Hemi	-0,025162	0,88	0,2205	0,18	0,30886	0,06	-0,093	0,58
Fovea	0,552470	0,0016	0,6179	0,0003	0,30466	0,06	-0,235	0,16
ParaFovea	-0,072889	0,66	-0,0498	0,77	0,23803	0,15	-0,251	0,13
Superior-Hemi	-0,08533	0,61	-0,1200	0,47	0,36883	0,045	-0,3042	0,06
İnferior-Hemi	-0,089061	0,69	0,0713	0,67	0,26257	0,11	-0,111	0,51
Tempo	-0,075128	0,65	-0,1636	0,33	0,45541	0,011	-0,256	0,12
uperior	-0,120901	0,47	-0,0193	0,91	0,16301	0,33	-0,350	0,05
Nasal	0,000212	0,99	-0,0241	0,89	0,45912	0,011	-0,144	0,39
İnferior	-0,113437	0,50	0,1446	0,39	0,07910	0,64	-0,088	0,60
Perifovea	-0,091683	0,58	0,1505	0,37	0,23817	0,15	-0,099	0,55
Superior-Hemi	-0,068188	0,68	0,0144	0,93	0,21093	0,20	-0,160	0,34
İnferior-Hemi	-0,085220	0,61	0,2666	0,11	0,23045	0,16	-0,060	0,72
Tempo	0,055647	0,74	0,2265	0,17	0,04659	0,78	-0,219	0,19
Superior	-0,003546	0,98	-0,0389	0,82	0,30156	0,07	-0,063	0,71
Nasal	-0,135121	0,42	0,2967	0,07	0,16566	0,32	-0,082	0,62
İnferior	-0,023656	0,89	0,0707	0,67	0,18532	0,27	0,022	0,90

Tablo 6: Makula Kalınlığı ve Derin Kapiller Yoğunluğu Arası Korelasyon

	Tek Taraflı XFS				Tek Taraflı XFG			
	XFM+	p	XFM-	p	XFM+	p	XFM-	p
Makula Totali	-0,048397	0,77	-0,1436	0,40	-0,0526	0,76	0,160	0,34
Superior-Hemi	-0,011618	0,94	-0,2418	0,14	-0,1249	0,46	0,271	0,10
İnferior-Hemi	-0,088906	0,60	-0,0088	0,96	0,24862	0,13	0,454	0,0117
Fovea	0,398372	0,0292	0,2947	0,08	0,42485	0,018	0,166	0,32
ParaFovea	-0,181588	0,28	-0,2758	0,10	0,35685	0,05	0,390	0,0327
Superior-Hemi	-0,157143	0,35	-0,3083	0,06	0,30606	0,06	0,312	0,06
İnferior-Hemi	-0,196509	0,24	-0,2088	0,21	0,30553	0,06	0,437	0,0156
Tempo	-0,280806	0,09	-0,3012	0,07	0,50018	0,005	0,201	0,23
Superior	-0,1032292	0,54	-0,2767	0,09	0,21369	0,20	0,448	0,0128
Nasal	-0,0456231	0,79	-0,2607	0,11	0,50067	0,005	0,299	0,07
İnferior	-0,2631205	0,11	-0,1567	0,35	0,11315	0,50	0,408	0,0252
Perifovea	-0,054180	0,75	-0,1469	0,38	-0,0107	0,95	0,246	0,14
Superior-Hemi	0,018472	0,91	-0,2720	0,10	-0,1083	0,52	0,111	0,51
İnferior-Hemi	-0,124417	0,46	0,0008	0,99	0,13583	0,42	0,302	0,07
Tempo	0,134776	0,42	-0,1903	0,25	-0,1037	0,54	0,272	0,10
Superior	0,068464	0,68	-0,2897	0,08	-0,0158	0,93	0,052	0,76
Nasal	-0,149101	0,35	-0,2209	0,18	0,02149	0,90	0,243	0,14
İnferior	-0,197595	0,23	0,0322	0,85	0,05297	0,75	0,253	0,13

Tartışma

Son zamanlarda yapılan çalışmalarda, glokomun erken döneminde bile makula bölgesinde değişikliklerin olabileceği fark edilmiştir. Güncel glokom tanı ve takibinde, makuladaki hasara yönelik yapısal ve fonksiyonel testler uygulamada yerini almaktadır. Biz çalışmamızda, glokom için ana risk faktörü olarak kabul edilen XFM'nin, hastalık gelişim sürecinde makulanın vasküler yapılarında öncü bulgu oluşturup oluşturmadığını anlamayı hedefledik.

Glokom etyopatogenezinde vasküler yapının rolünü inceleyen OCT-A ile yapılmış birçok çalışma literatürde mevcuttur. Bu çalışmaların bazıları yüzeysel kapiller yoğunluğun güçlü bir tanısal belirteç olduğunu belirtirken (17), diğerleri orta

seviyede olduğunu ifade etmektedir (18). Bu farklılık, makula kesitinin 3x3mm veya 6x6mm olarak ele alınmasından kaynaklanabileceği şeklinde yorumlanmaktadır (19). Çünkü makulanın glokomda en çok etkilenen bölgeleri inferotemporal ve superotemporaldir ve bu bölgeler 3x3mm'lik alanda dışında kalır, 6x6mm'de daha uygun bir şekilde görüntülenebilir. Bu nedenle çalışmamızda makulayı 6x6 mm'lik boyutta taradık.

Çalışmamızda, XFM bulunan ancak henüz glokom gelişmemiş gözlerde anlamlı vasküler bulgular gözlenmedi. İstatistiksel olarak anlamlı farklar, glokom gelişmesine bağlı olarak belirginleşti. İstatistiksel anlamlılık, yüzeysel kapiller pleksusta, derin kapiller pleksusa göre daha belirgin olarak ortaya çıktı. Sonuçlarımız bu açıdan El-Nimri ve arkadaşlarının sonuçları ile benzerlik göstermektedir (20). Chen ve arkadaşları da yüzeysel kapiller pleksus ölçümlerinin glokom açısından makula ganglion sinir kompleksi ve RNFL ölçümlerine benzer oranda tanısal değeri olduğunu belirtmektedir (17).

Glokom gelişim sonrasında (hangi alt tipi olursa olsun) makuladaki vaskülaritenin azaldığı, literatürde birçok çalışmada gösterilmiştir (17-26). Bizim çalışmamız da bunu desteklemektedir.

Çalışmamız, Paşaoğlu ve arkadaşlarının çalışmasıyla birçok noktada benzerlik göstermektedir. Paşaoğlu ve arkadaşları da tek taraflı XFS'leri incelemişler ancak bizim sonuçlarımızdan farklı olarak tek taraflı XFS'lerin makulanın yüzeysel damar tabakasının iç bölgelerinde gözler arası farklılıklar gösterdiğini belirtmişlerdir (21). Bizim çalışmamızda ise tek taraflı XFS'li bireylerin gözleri arasında ne makula kalınlıkları ne de yüzeysel kapiller pleksus yoğunluğu açısından anlamlı farklar bulunamamıştır. İki benzer çalışmanın sonuçlarındaki farklılıkların olası nedenleri, kullanılan cihazlar arasındaki farklar, makula bölgesinin farklı boyutlarda taranması ve örneklem gruplarındaki farklılıklar olabilir.

Çınar ve arkadaşlarının sonuçları ise bizim sonuçlarımıza benzerlik göstermektedir. Tek taraflı XFS olan hastalarda XFM izlenen ve izlenmeyen gözler arasında ve oluşturdukları sağlıklı kontrol grupları ile yapılan karşılaştırmalarda, yüzeysel ve derin kapiller pleksuslar arasında fark gözlenmemiştir. Çınar ve arkadaşları da bizim gibi Optovue Angio-Vue sistemi kullanarak 6x6 mm makula taraması yapmışlardır (22). Bu tartışmalı sonuçlar, makula incelemesinde boyutsal farkın sonuçlar üzerindeki potansiyel etkisini göstermektedir.

Çalışmamızın yetersizlikleri arasında, hasta sayısının kısmen az olması, kesitsel bir çalışma olması ve hastaların aksiyel uzunluğunun ölçülmemiş olması yer almaktadır. Çalışma grubundaki hastaların refraktif kusurları belirli bir aralıkta kontrollü olsa da, psödofakik hastaların katarakt ameliyatı öncesindeki ölçümleri bilinmemektedir. Psödofakik hastaların ameliyat öncesi ölçümleri 3D'nin ötesinde olabilir ve aksiyel uzunluktaki farkların makuladaki damar yoğunluğu üzerindeki etkisi göz ardı edilmiş olabilir. Ayrıca, XFM bulunmayan sağlıklı bir üçüncü kontrol grubunun çalışmaya dahil edilmesi, sağlıklı gözlerle daha doğru bir karşılaştırma sağlayabilirdi.

Sonuç

Medikal tedaviyle kontrol edilen glokom hastalarında, özellikle yüzeysel kapiller pleksusun yoğunluğunda makula bölgesinde azalmanın olduğu gösterilmiştir. Ancak, bu damarsal azalma, glokom için ana risk faktörü olan XFM varlığında öncü bir bulgu olarak gösterilememiştir. Çalışmamızın, gelecekte daha geniş hasta gruplarında OCT-A teknolojisi kullanılarak oluşturulabilecek prospektif çalışmalara öncülük ederek literatüre katkı sağlayacağını düşünüyoruz.

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Araştırma Makalesi

Bilinç Kaybı Yaşayan Hastada Epileptik Nöbet ve Senkop Ayırıcı Tanısında Kullanılabilecek Biyobelirteçler

Biomarkers That Can Be Used In The Differential Diagnosis Of Epileptic Seizure And Syncope In Patients Presenting With Loss Of Consciousness

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Öz

Amaç: Bilinç kaybı, senkop ve epileptik nöbetlerin ortak belirtisidir. Çalışmamızda acil servise bilinç kaybı ile başvuran hastalarda senkop ve epileptik nöbet ayırıcı tanısı için kullanılabilecek klinik ve biyokimyasal biyobelirteçleri belirlemek amaçlanmıştır.

Gereç ve Yöntemler: Hastanemiz acil servisine üç ay boyunca bilinç kaybı şikâyeti ile başvuran hastaların dosyaları ve laboratuvar incelemeleri (laktat, hemoglobin, nötrofil, lenfosit) sonuçları tarandı, demografik özellikleri ve eşlik eden hastalıkları kaydedildi. Elde edilen verilerin istatistiksel analizinde SofaStat (Auckland, New Zealand) programı kullanıldı.

Bulgular: Epileptik nöbet nedeniyle başvuran hastalar, senkop nedeniyle başvuranlara kıyasla daha genç hastalardı ancak cinsiyet dağılımı birbirine benzerdi. Senkop tanısı alanlarda diyabet ve hipertansiyon öyküsü daha fazlaydı. İlk kez bilinç kaybı yaşayanlara kıyasla daha önce benzer öyküsü olanlarda epilepsi olma olasılığı daha fazlaydı. Epileptik nöbet vakalarında, epizot sonrasında konfüzyon öyküsü senkop vakalarından daha fazlaydı. Epileptik nöbeti olan hastaların serum laktat düzeyi ortancası (3,3 U/L), senkop hastalarına (2,3 U/L) kıyasla anlamlı düzeyde daha yüksekti (p=0,002). Epilepsi ve senkop ayırıcı tanısı için serum laktat düzeyinde ki en iyi eşik değer; 2,5 U/L idi. Bu eşik değerin tanısal doğruluk oranı % 60,5 iken, sensitivitesi %60,2 ve spesifisitesi %62,3 idi. Kadınların hemoglobin ve hematokrit değerlerinin ortancası erkeklere kıyasla anlamlı düzeyde daha düşüktü.

Sonuç: Çalışmamızın sonuçları, serum laktat düzeylerinin bilinç kaybı hastalarında epileptik nöbet ve senkop ayırıcı tanısında önemli bir biyobelirteç olduğunu göstermektedir. Serum laktat değeri özellikle hasta ve hasta yakınlarının epizodu tarifleyemediği durumlarda değerli bilgiler sunabilir.

Anahtar Kelimeler: Epileptik Nöbet, Senkop, Laktat, Biyobelirteç

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Abstract

Aim: Loss of consciousness is a common finding of syncope and epileptic seizures. In our study, we aimed to determine the clinical and biochemical biomarkers that can be used to differentiate syncope and epileptic seizures in patients admitted to emergency departments with loss of consciousness.

Material and Methods: The files and laboratory examination results of the patients who applied to the emergency department for three months with loss of consciousness were scanned, and their demographic characteristics and accompanying disorders were derived. SofaStat (Auckland, New Zealand) program was used for statistical analysis of the obtained data.

Results: Patients presenting with epileptic seizures are younger than those presenting with syncope but the gender distribution of patients was similar. Those presenting with syncope were more likely to have a history of diabetes and hypertension. The median serum lactate level (3.3 U/L) of those presenting with epileptic seizures was significantly higher than those presenting with syncope (2.3 U/L) (p=0.002). The best cut-off level of lactate level in differentiating the epileptic seizure and syncope was 2.5 U/L. The diagnostic accuracy of this level was 60.5%, whereas the sensitivity was 60.2% and specificity was 62.3%. The median hemoglobin and hematocrit values of women were significantly lower than men.

Conclusion: The data in our study show that serum lactate levels are an important biomarker in differentiating patients presenting with epileptic seizures from those presenting with syncope. The serum lactate value can provide valuable information, in particular for the cases in whom the patient or their relatives could not describe the episode.

Keywords: Epileptic Seizure, Syncope, Lactate, Biochemical Biomarker

Giriş

Acil servise başvuran olguların yaklaşık dörtte üçünde temel başvuru nedeni; geçici bilinç kayıplarıdır [1]. Acil tedavi ve tanı için bilinç kaybında epileptik nöbet ve senkop ayırıcı tanısının hızlı bir biçimde yapılması gerekir. Senkop, serebral hipoperfüzyona ikincil olarak gözlenen ve genellikle kalıcı bir defisit yaratmayan geçici bilinç ve postural tonus kaybı olarak tanımlanır [2]. Etiyolojisinde sıklıkla hemodinamik ve kardiyovasküler nedenler yer alır. Ancak, olguların üçte birinden fazlasında altta yatan neden bulunamamaktadır [3]. Epilepsi nöbetiyle başvuran olguların aksine senkop olgularının elektroensefalografi (EEG) çekimlerinde genellikle bir anormallik izlenmez. Tedavide ise temel yaklaşım tetikleyici faktörlerden kaçınmaktır [4]. Bilinç kaybı ile başvuran olgularda senkobu destekleyen temel bulgular; postüral değişikliğe bağlı olarak gelişen ataklar, baş dönmesi/gözlerde kararma, çarpıntı, solukluk, terleme, genel güçsüzlüğü takiben gelişen bilinç kaybı ve hızlıca normale dönme olarak sıralanabilir. Bununla birlikte idrar kaçırma, dil ısırma gibi daha çok epileptik nöbetlerde görülen belirtiler senkoba da eşlik edebilir.

Epilepsi nöbetleri ise; kortekstеki anormal aşırı veya senkron nöronal aktiviteye bağlı ortaya çıkan geçici klinik bulgulardır [5]. Acil servise başvuran nöbet hastalarının bir kısmı bilinen epilepsi tanılı hastalar iken, diğer kısmını da kafa travması [6], ilaç intoksikasyonu, metabolik bozukluklar, enfeksiyonlar veya akut santral patolojiler gibi nedenlere bağlı nöbet geçiren olgular ya da ilk epileptik nöbetini geçiren vakalar oluşturur. Epilepside klinik tanı; anamnez ve hastadaki epizodun gözlenmesine dayanır. EEG en çok kullanılan yardımcı tanı yöntemdir. Ne var ki normal bir trasesinin varlığı epilepsi tanısını ekarte ettirmediğinden, ayırıcı tanıda EEG yeterince güvenilir olmayabilir [7]. Anamnezde; hastanın perinatal öyküsü, gelişme basamakları, kafa travması, merkezi sinir sistemi enfeksiyonu, ailede epilepsi öyküsünün sorgulanması önem taşımaktadır. Ayırıcı tanıda; kreatin fosfokinaz (CPK), laktat dehidrojenaz (LDH), nöron spesifik enolaz (NSE) ve prolaktin gibi laboratuvar analizleri epileptik nöbetin tespitinde yararlı bilgiler sunabilir [8,9]. Epileptik nöbetlere aritmi, bradikardi, hipotansiyon gibi kafa karışıklığına yol açan kardiyolojik semptomlar da eşlik edebilir ve tanı koymada güçlüklere neden olabilir [10,11]. Klinik pratikte epileptik nöbetlerin en sık taklitçileri; senkop ve psikojen nöbetlerdir. Ayırıcı tanıda ayrıca; geçici iskemik ataklar, auralı migren, hareket bozuklukları ve metabolik bozukluklar da düşünülmelidir [12].

Senkop ve epileptik nöbetin benzer klinik bulgularının olması nedeni ile acil servise kısa süreli bilinç kaybı ile başvuran hastalarda dikkatli bir anamnez ve nörolojik muayene gerekmektedir. Ayırıcı tanıda önerilen EEG ile NSE ve prolaktin

gibi enzim analizlerinin kullanımı acil servis pratiğinde genellikle mümkün olmamaktadır. Epileptik olmayan olayların epilepsi olarak yanlış teşhis edilmesi, uygun tedavi başlanmasını geciktirmenin yanı sıra antiepileptik ilaçların gereksiz yere reçete edilmesi sebebiyle de hastalar için ek medikal ve sosyal riskler oluşturmaktadır [13]. Anamnezin yetersiz olduğu, ilk kez ve/veya şahitli olmayan bilinç kaybı hastalarında, mevcut acil servis şartlarında bilinç kaybı hastalarına uygulanan rutin laboratuvar testleri (arteryel kan gazı, hemogram, kardiyak enzimler) ile doğru tanıya ulaşmak yeterince güvenilir ve kolay olmamaktadır. Bu nedenle çalışmamızda; acil servise bilinç kaybı ile başvuran hastalarda senkop ve epileptik nöbet ayrımı için kullanılabilecek klinik ve biyokimyasal biyo-belirteçlerin tanısal doğruluk oranlarını belirlemeyi amaçladık.

Gereç ve Yöntemler

Çalışmamız; 01 Mart 2023 ve 01 Haziran 2023 tarihleri arasında Sakarya Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi acil servisine bilinç kaybı ile başvuran hastaların verileri üzerinde retrospektif olarak yapıldı. Dahil edilme kriterleri olarak, 18 yaşından büyük olmak, acil servisimize şuurun etkilendiği bir atak ile başvurmak ve bu atağın epilepsi nöbeti ya da senkop nedeniyle gelişmesi olarak alınır iken, dahil edilmeme kriterleri ise; psikojen nöbetler, geçici iskemik ataklar, auralı migren, hareket bozuklukları, metabolik bozukluklar, acil başvuruya neden olan epizodun hasta tarafından tariflenememesi ve herhangi bir kişi tarafından da gözlenmemesi olarak alındı. Bilinç kaybı ile başvuran eski epilepsi tanılı hastalar ve vücutta kasılma, idrar inkontinansı ve/veya ağızdan köpük gelme şikayetleri eklenen veya sağlık çalışanı şahitli nöbeti olan hastalar epilepsi nöbeti olarak kabul edildi ve epilepsi grubuna dahil edildiler. Bilinç kaybı ile başvuran; gözlerde kararma, çarpıntı, vücut renginde solukluk ve/veya terleme dışında ek bir şikâyeti olmayan hastalar ise senkop grubuna dâhil edildiler.

Hastaların demografik özellikleri, hastane bilgi sistemindeki dosyalarında yer alan anamnez ve muayene notları, konsultasyon notlarındaki bilgiler, eşlik eden hastalıkları ve laboratuvar incelemeleri (laktat, hemogram, nötrofil, lenfosit sayısı) toplanarak değerlendirildi. Elde edilen verilerin istatistiksel analizinde SofaStat (Auckland, New Zealand) programı kullanıldı. Tüm analizler için $p < 0,05$ değeri istatistiksel olarak anlamlı kabul edildi. Homojen ve normal dağılıma uyan veriler parametrik testlerle, uymayan veriler ise non-parametrik testlerle değerlendirildi. İstatistiksel anlamlılık, normal dağılan veriler için bağımsız örneklem student-t testi (iki grup için) veya ANOVA (ikiden fazla grup için), ve normal dağılmayan veriler için ise Mann Whitney U testi (iki grup için) veya Kruskal-Wallis H testi (ikiden fazla grup) kullanılarak değerlendirildi. Kategorize değişkenlerin dağılımını için ise normal dağılım gösteren veriler ve normal dağılım göstermeyen verilerde sırasıyla Ki-Kare testi ve Fisher'in kesin olasılık testi kullanıldı.

Bulgular

Çalışmamıza 62'si kadın (%38,7) ve 98'i erkek (%61,3) olmak üzere 160 hasta dâhil edildi. Bu hastaların 103'ünde (%64,3) epizot epileptik nöbet olarak, 57 (%35,7) hastanınkinde ise senkop olarak değerlendirildi. Her bir hastaya dair yalnızca tek bir epizotun sonrasındaki veriler çalışmaya alındı. Epileptik nöbet hastalarının 13'ündeki (%12,6) epizotlar, kendileri ve şahit olanlar tarafından, fokal başlangıçlı olarak tariflenirken, 70 hastada (%67,9) jeneralize nöbet gözlenmişti. Yirmi hasta (%19,4) ise başlangıç kısmı net tariflenemeyen (sınıflandırlamayan) epileptik nöbetler ile başvurmuştu.

Senkop ile başvuran hastaların ortanca yaşı [70 (18-90)] epilepsi nöbeti ile başvuranlarınkine [48 (18-90)] kıyasla daha yüksekti ($p< 0,001$). Epileptik nöbet ile başvuran hastalar ile senkop ile başvuran hastalardaki cinsiyet dağılımı birbirine benzerdi ($p=0,100$). Senkop ile başvuranlarda diyabetes mellitus ve hipertansiyon öyküsü olma olasılığı daha fazlaydı. Her iki gruptaki ritm bozukluğu ve eski inme öyküsü sıklığı birbirine benzerdi (Tablo 1).

Tablo 1. Epilepsi ve senkop gruplarında komorbid hastalık öyküsü dağılımı

		Epilepsi [n(%)]	Senkop [n(%)]	p değeri#
Diyabetes Mellitus	var	14 (13,59)	11 (19,29)	0,012
	yok	89 (86,41)	46 (80,71)	
Hipertansiyon	var	22 (21,36)	32 (56,14)	< 0,001
		81 (78,64)	25 (43,86)	
Aritmi	var	5 (4,85)	2 (3,50)	0,690
	yok	98 (95,15)	55 (96,50)	
Serebrovasküler Hastalık	var	18 (17,47)	11 (19,29)	0,774
		85 (82,53)	46 (80,71)	

#Ki-kare testi

Epilepsi hastalarının daha önce benzer bir epizot ile başvurma oranı (% 62,13), senkop hastalarına kıyasla (% 5,25) daha yüksekti ($p< 0,001$). Epileptik nöbet ile başvuranlarda, epizot esnasında ağızdan köpük gelme (% 41,75), dil ısırma (% 52,42), vokalizasyon (% 15,53) ve idrar inkontinansı (% 49,51) öyküsü sıklığı, senkop ile başvuranlara kıyasla (sırasıyla % 3,50, %1,75, %1,75, % 0,0) daha fazlaydı (tüm kıyaslamalar için p<

0,001). Epileptik nöbet ile başvuranlarda, epizot sonrasında konfüzyon öyküsü sıklığı (% 79,61), senkop ile başvuranlardan (% 8,77) daha yüksekti (p< 0,001) (Tablo 2).

Tablo 2. Epilepsi ve senkop grupları arasında klinik biyobelirteçlerin dağılımı

		Epilepsi [n(%)]	Senkop [n(%)]	p değeri#
Ağızdan Köpük Gelme	var	43 (41,75)	2 (3,50)	< 0,001
	yok	60 (58,25)	55 (96,50)	
Dil Isırma	var	54 (52,42)	1 (1,75)	< 0.001
	yok	49 (47,58)	56 (98,25)	
Postiktal Konfüzyon	var	82 (79,61)	5 (8,77)	< 0,001
	yok	21 (20,39)	52 (91,23)	
Vokalizasyon	var	16 (15,53)	1 (1,75)	0,006
	yok	87 (84,47)	56 (98,25)	
İdrar İnkontinansı	var	51 (49,51)	0 (0)	< 0,001
	yok	52 (50,49)	57 (1)	

#Ki-kare testi

Epileptik nöbet nedeniyle başvuranların serum laktat düzeyi ortancası (3,3 U/L), senkop nedeniyle başvuranlara (2,3 U/L) kıyasla anlamlı düzeyde daha yüksekti (p=0,002) (Tablo 3). Serum laktat değerleri analiz edildiğinde, epilepsi ve senkop hastalarını ayırt etmek için en iyi eşik değer 2,5 U/L idi. Bu eşik değerin tanısal doğruluk oranı (diagnostic accuracy) % 60,5 iken, sensitivitesi %60,2 ve spesifisitesi %62,3 idi. Diğer laboratuvar parametrelerinde -hemoglobin, hematokrit, beyaz küre, nötrofil, lenfosit, Nötrofil/Lenfosit Oranı (NLO), platelet- her iki grup arasında anlamlı farklılık yoktu (Tablo 3).

Tablo 3. Laboratuvar değerlerinin gruplar arası dağılımı

	Epilepsi	Senkop	P değeri
Hemoglobin	12,977±2,153	12,675±1,939	0,381*
Hematokrit	41 (14,9-49,7)	38,2 (19,5-49,5)	0,273**
Laktat	3,3 (0,6-16)	2,3 (0,8-11,3)	0,002**
NLO	5,1±6,5	6,4±6,7	0,222*
Lökosit	10065±4291	10480±5043	0,582*
Nötrofil	7076±4037	7738±4745	0,352*
Lenfosit	2340±1664	2018±1226	0,202*

* Student t test, ** Mann-Whitney U testi

Kadın ve erkek hastaların epizot sıklığı benzerdi. Kadınların hemoglobin ve hematokrit değerlerinin ortancası (12,6 ±66,565 / 38,1 ±68,492) erkeklere kıyasla (13,85±89,316 / 41,2±88,097) anlamlı düzeyde daha düşüktü (sırasıyla; p=0,002 ve p=0,009). Kadınların ortanca laktat değeri [2,3 (1-16)] ile erkeklerinki [3 (0,6-16)] benzerdi (p=0,319). Diğer laboratuvar parametrelerinde (beyaz küre, nötrofil, lenfosit, NLO, platelet) kadınlar ve erkekler arasında anlamlı farklılık yoktu (tüm kıyaslamalar için p> 0,05).

Tartışma

Bilinç kaybına neden olan epileptik nöbet ve senkop, farklı etiyolojilere, tedavilere ve prognozlara sahip iki farklı klinik tablodur. Ortak semptom olan bilinç kaybı ise acil servis profesyonellerinin sıkça karşılaştığı, hızlı ve doğru karar vermeyi gerektiren bir durumdur. Acil servisin yoğunluğu, hastanın atağı tam tarif edememesi ve bilinç kaybına şahit olan bir kişinin olmaması tanıyı zorlaştırır. Bu nedenle doğru tanıya ulaşmak için ayrıntılı bir anamnez ve klinisyenin tecrübesinin yanı sıra bir takım biyobelirteçler ve objektif testlere ihtiyaç duyulmaktadır. Çalışmamızda senkop hastalarının yaş ortalaması epileptik nöbet hastalarından anlamlı şekilde yüksekti ve senkop tanısı alan hastalarda komorbid olarak hipertansiyon ve diyabetes mellitus daha fazla eşlik etmekteydi. Bu sonuçlar, acil servise bilinç kaybı ile başvuran yaşlı ve komorbid hastalığı olan vakalarda senkop olasılığının ön planda düşünülmesinin daha uygun olabileceğini göstermektedir. Genç ve eşlik eden hastalığı olmayan bilinç kaybı olgularında ise ilk olarak epileptik nöbet olasılığı düşünülmelidir. Bu bulgular, acil servis şartlarında erişkin yaş hastalarda senkop, genç yaş hastalarda ise epileptik atağa yönelik ileri tetkiklerin daha öncelikli olarak planlanmasının, tanıya erken ulaşılması açısından önemli olduğuna işaret etmektedir. Vokalizasyon, dil ısırma, ağızdan köpük gelmesi ve idrar inkontinansı hem epileptik nöbette hem de senkopta görülebilirken, bizim çalışmamızdaki senkop hastalarında idrar inkontinansı hiç görülmemiş, diğer bulgular da epileptik nöbetlere anlamlı olarak daha fazla eşlik etmiştir. Epileptik nöbet ile başvuran hastalarımızın yaklaşık yarısında idrar inkontinansı, ağızdan köpük gelme ve dil ısırması tesbit edilmiştir. Ancak çalışmamızda epileptik nöbetler için en değerli klinik biyobelirteçler; hastaların beşte dördünde var olan 'postiktal konfüzyon hali' ve beşte üçünde var olan 'daha önce benzer şikâyet ile başvuru hikâyesi' olmasıdır. Yoğun çalışan acil kliniklerinde hızlı ve doğru tanı koyabilmek için acil profesyonelleri ve konsultan hekimler tarafından bu klinik biyobelirteçleri kullanmak ayırıcı tanıya ulaşmak için güvenilir ve hızlı bir yaklaşım olabilir.

Senkop ve epileptik nöbet ayırıcı tanısında NSE, prolaktin, LDH ve CPK-BB gibi objektif biyokimyasal belirteçlerin epilepsi nöbetlerinde yükseldiği tespit edilmesine rağmen çoğu acil serviste bu markerler rutin olarak çalışılmamaktadır [8]. Genellikle, ileri tetkik olarak epileptik nöbet ve yalancı-nöbet ayırımı yapmak amacıyla hastaneye yatışı yapılan vakalarda, yatış sürecinde gözlenen epizotların hemen sonrasında alınan

kanlarda araştırılan belirteçlerdir. Acil servislerde ise hemen her bilinç kaybı vakasında rutin olarak çalışılan, arteryel kan gazı, hemogram ve kısa biyokimyasal testler ile güvenilir bir ön tanı oluşturulmaya çalışılmaktadır. Yapılan çalışmalarda epilepsi nöbetleri sırasında ve sonrasında arterial laktat seviyelerinde geçici yükselmeler gözlendiği ancak, nöbetin süresi ve tipine bağlı olarak ölçülen laktat değerleriyle ilgili bireysel farklılıklar olduğu bildirilmiştir [1,14,15,16]. İlk kez 1964 yılında Broder ve Weil tarafından şoklu hastalarda laktat seviyeleri 4 mmol/l'yi aştığında olumsuz sonuçlar gözlemlendiği ve laktatın prognostik bir belirteç olduğu bildirilmiştir [17]. Orringer ve ark. jeneralize tonik-klonik nöbetleri (GTKN) takiben ilk iki saat içinde serum laktat seviyesinin yükseldiğini bildirmiştir [18]. Benzer şekilde, Matz ve ark. olaydan sonraki 2 saat içinde ölçüldüğünde, GTKN' i senkoptan ayırmada serum laktatının yararlılığını göstermiştir [19,20].

Laktat tüm hücrelerde; kaslar (%25), deri (%25), beyin (%20), bağırsaklar (%10) ve eritrositler (%20) değişen derecelerde üretilir [21]. Epilepsi nöbetlerinde beyindeki anormal elektriksel aktivite nedeniyle oluşan kas kasılmaları esnasında hücrelerin enerji kullanımı artar ve anaerobik enerji üretimi nedeniyle laktat düzeyinde artış görülebilir. Özellikle jeneralize ve uzun süreli nöbetlerde, beyin dokusundaki oksijen ve enerji kaynaklarının azalması nedeniyle de laktat birikimi daha belirgin olabilir. Çalışmamızdaki veriler, literatür ile uyumlu olarak serum laktat düzeylerinin epileptik nöbet nedeniyle başvuran hastaları senkop nedeniyle başvuran hastalardan ayırt etmede önemli bir biyobelirteç olabileceğini göstermiştir [1,22,23].

Hosseini ve arkadaşları, toplam 388 epileptik hasta ve 306 kontrol hastası ile yaptıkları bir çalışmada, NLO ile epilepsi hastalığı arasında ilişki olduğunu ve epilepsi hastalarında NLO' nın arttığını rapor etmişlerdir [24]. Ne var ki bizim çalışmamızda bu gruplar arasında NLO ortalamalarında anlamlı farklılık saptanmadı. Bu durumun çalışmamızdaki hasta sayısı kısıtlamasından kaynaklı olabileceğini düşünmekteyiz. Epileptik nöbetlerin teşhisi için altın standart olan video EEG monitörizasyonu acil servis ortamlarında kullanılmamakta ve her hastanede bulunmamaktadır. Rutin EEG ise nöroloji poliklinikleri tarafından elektif şartlarda yapılmaktadır ve nöbetler arasında yapılan çekimlerde nonspesifik bulgular gösterebilmektedir. Bu nedenle, acil serviste epileptik nöbet tanısını doğrulamak için serum laktat seviyesi ölçümü basit ve hızlı bir yöntem olarak önerilebilir.

Sonuç

Literatürdeki yakın dönem çalışmaların sonuçlarıyla uyumlu olarak, bizim çalışmamızda da epileptik nöbet nedeniyle bilinç kaybı yaşayan olgularda ortalama laktat değerinin senkop olgularına kıyasla anlamlı olarak yüksek saptanması, laktatın ayırıcı tanıda önemli bir biyokimyasal belirteç olabileceğini göstermektedir. Özellikle hasta ve hasta yakınlarının bilinç kaybı epizodunu tarifleyemediği durumlarda değerli bilgiler sunabilir. Ayrıca, epileptik nöbet hastalarında acil profosyonelleri için hastanın daha önce benzer bir epizot ile acil servis başvurusunun olması ve post-iktal konfüzyon halinin gözlenmesi pratikte uygulanabilecek birer klinik biyobelirteçdir.

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Araştırma Makalesi

Gustave roussy immün skor operabl kolorektal kanserli hastalarda prognozu ve sağkalımı öngörebilir mi?

Can gustave roussy ımmune score predict the prognosis and survival in patients with operabl colorectal cancers?

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Öz

Amaç: Opere olan metastatik olmayan kolorektal kanserli hastalarda, tanı anında bakılan GRIm skorunun, nüks, prognoz ve sağkalım üzerine etkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çok merkezli retrospektif bir çalışma olarak planlanmış olup, toplam dört farklı merkezden veriler elde edildi. Kliniklerimizdeki hastalar 2010 yılı ile 2023 yılı tarihleri arasında tanı almış hastalardan oluşmaktadır. Gustave Roussy İmmün Skoru (GRIm-Score) belirlenmesi için hastaların operasyon öncesindeki nötrofil, lenfosit, nötrofil/lenfosit oranı (NLR) serum albümin (ALB) ve serum laktat dehidrogenaz (LDH) düzeyleri yanı sıra Kras, Braf mutasyon durumları ve CEA düzeyleri değerlendirildi. Hastalar GRIm skorlarına göre 0-1 düşük ve 2-3 yüksek olmak üzere iki gruba ayrıldı. Sonrasında hastalıksız sağkalım ve genel sağkalım analizleri yapıldı.

Bulgular: Çalışma popülasyonumuz tanıda metastatik olmayan, opere olmuş 405 kolorektal kanserli hastadan oluşmaktadır. Hastalar genel demografik verileri ve onkolojik özellikleri açısından GRIm skor düzeylerinin yüksek veya düşük olmasına göre gruplandırıldı. Yüksek GRIm-skor gurubuyla; yüksek N (Lenf Nodu) pozitifliği ve ileri TNM (T tümör boyutu, N lenf nodu ve M metastaz durumu) evresi, yüksek CEA düzeyi, RAS ve RAF mutasyonun varlığı, yüksek yaş ortalaması ve yüksek VKİ(>25) ile örtüşüyordu. Yapılan sağkalım analizlerinde kadın olmak (HR:0.53;%95CI: 0.33-0,85; p=0.010) ölüm riskini azaltırken, GRIm skorunu yüksek olması (HR:1.86;%95CI: 1.06-3.26; p=0.030) ve RAS mutasyonun olması ise (HR:2.01;%95CI: 1.14-3.54; p=0.016) ölüm riskini arttırdığı bulundu. Hastalıksız sağkalım açısından da benzer analiz yapıldığında ise CEA'nın 5 ng/ml ve üstü olması (HR:1.98;%95CI: 1.09-3,60; p=0.025), RAS mutasyonun olması (HR:2.41;%95CI: 1.56-3.74; p<0.001), nüks riskini artırdığı bulundu nüks/progresyon yerinin kemik metastazı olması ise (HR:0.42;%95CI: 0.20-0.89; p=0.024) nüks riskini azalttığı bulundu (p<0.001, -2 loglikelihood= 1102,47) olarak

Sonuç: Çalışmamızda erken evre kolorektal kanserli hastalarda bir inflamatuar ve beslenme risk puanlama sistemi olan GRIm-skor 'un başta genel sağkalım olmak üzere hastalıksız sağkalımı açısından belirleyici olduğu bulundu. Çok değişkenli analizde hastalıksız sağ kalımda GRIm-skoru' nun etkisi kaybolurken, genel sağkalım da ise diğer faktörlerden bağımız olarak etki ettiği gösterildi. Bu yönüyle GRIm-skor opere kolorektal kanserli hastalarda sağkalımı ön görmesi nedeniyle pratikte kullanışlı bir parametre olarak değerlendirilmesi önerilir.

Anahtar Kelimeler: GRIm skor, Kolorektal kanser, İnflamatuar, Hastalıksız yaşam, Genel sağ kalım

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Abstract

Aim: It was aimed to evaluate the effect of GRIm score measured at the time of diagnosis on recurrence, prognosis, and survival in patients with operated early-stage colorectal cancer.

Material and Methods: Our study was planned as a multicenter retrospective study and data were obtained from four different centers. The patients in our clinics consist of patients diagnosed between 2010 and 2023. In order to determine the Gustave Roussy Immune Score (GRIm-Score), the patients' preoperative neutrophil, lymphocyte, neutrophil/lymphocyte ratio (NLR), serum albumin (ALB) and serum lactate dehydrogenase (LDH) levels, as well as Kras, Braf mutation status and CEA levels were evaluated. The patients were divided into two groups according to their GRIm scores. Disease-free survival (DFS) and overall survival (OS) were then analyzed.

Results: Our study population consisted of 405 operated colorectal cancer patients who were not metastatic at diagnosis. Patients were grouped according to their general demographic data and oncological characteristics, whether their GRIm score levels were high or low. With a high GRIm-score; high N (Lymph Node) positivity and advanced TNM stage, high CEA level, presence of RAS and RAF mutations coincided with high mean age and high VKİ. In survival analyzes, it was found that being female decreased the risk of death, while a high GRIm score and having a RAS mutation increased the risk of death.

Conclusion: In our study, it was found that the GRIm-score, which is an inflammatory and nutritional risk scoring system in patients with early-stage colorectal cancer, is determinative in terms of disease-free survival, especially overall survival. In Çok değişkenli analysis, it was shown that while the effect of GRIm-score disappeared in DFS, it was affected independently from other factors in survival. In this respect, GRIm-score is recommended to be evaluated as a practical parameter since it predicts survival in patients with operated colorectal cancer.

Keywords: GRIm score, Colorectal cancer, Inflammatory, Disease-Free Survival, OS.

Giriş

Kolorektal kanserler tüm dünyada erkeklerde ve kadınlarda en sık görülen ilk üç kanser arasında olup, önemli bir morbidite ve mortalite sebebidir [1].

Kanser ilişkili inflamasyonun diğer birçok kanser grubunda olduğu gibi; kolorektal kanserlerde de prognoz için önemli olduğu düşünülmektedir. Literatürde son yıllarda birçok inflamatuar indeks tanımlanmış ve bunların prognozla ilişkili olabileceği düşünülmüştür [2]. Sistemik immun inflamatuar indeks, prognostik nutrisyonel indeks, aspartat aminotransferaz-lenfosit oranı indeksi gibi inflamasyonu öngördüren çeşitli indekslerdeki yüksekliklerinin; kolorektal kanserlerde olumsuz prognoz ile ilişkili olduğu gösterilmiştir [3,4].

Gustave Roussy Immun Skoru (GRIm-Score), ilk kez 2017 yılında Bigot ve ark. tarafından tanımlanmış olup, serum laktat dehidrogenez (LDH), serum albumin ve nötrofil-lenfosit oranı (NLR) baz alınarak hesaplanan ve prognozu öngürdürücü güçlü bir inflamatuar skor olarak kabul edilmiştir [5,2]. GRIm-skorun prognostik önemi, küçük hücreli dışı akciğer kanseri, küçük hücreli akciğer kanseri, özefagus skuamöz hücreli kanser, hepatoselüler karsinom gibi çeşitli kanserlerin erken ve ileri evrelerinde gösterilmiştir [6-7]. Literatürde kolorektal kanserde GRIm skoru ile prognoz ve sağkalım arasındaki ilişkiyi gösteren çalışma sayısı kısıtlı sayıda olup, çalışmamızda opere edilen metastatik olmayan kolon kanserli hastalarda, tanı anında bakılan GRIm skorunun, nüks, prognoz ve sağkalım üzerine etkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler

Çalışmamız, çok merkezli retrospektif bir çalışma olarak planlanmış olup, toplam dört farklı merkezden veriler elde edilmiştir. Çalışmamıza 18 yaş ve üzeri, patolojik olarak konfirme edilmiş, evre 1-3 ve opere olmuş kolorektal kanserli hastalar dahil edilmiştir. Hastalar 2010 ile 2023 tarihleri arasında tanı almış hastalardan oluşmaktadır. Hastaların temel demografik özelliklerine ek olarak, tümör yerleşim yeri, evre, aile öyküsü, adjuvan kemoterapi alıp almama durumları, temel laboratuvar parametreleri, nüks olup olmaması, ve son takiplerindeki son durumları ayrıntılı olarak kayıt edilmiştir. Veriler hastane veri tabanları ve hasta dosya arşivi kullanılarak kayıt altına alınmıştır. Son takip tarihi 6 aydan önce olan ve düzenli takiplerine gelmeyen hastalar çalışmamıza dahil edilmemiştir.

Gustave Roussy Immun Skoru (GRIm-Score) belirlenmesi için

hastaların operasyon öncesindeki nötrofil, lenfosit, nötrofil/lenfosit oranı (NLR) serum albümin (ALB) ve serum laktat dehidrogenaz (LDH) düzeyleri değerlendirilmiştir. GRIm skoru LDH (her merkez için normal aralıkta ise: 0 puan vs normalin üst limitinin üstünde ise: 1 puan), ALB (≥35 g/L: 0 puan vs. <35g/L: 1 puan), ve NLR (≤6: 0 puan vs. >6: 1 puan) olarak değerlendirilmiştir. Hastalar GRIm skorlarına göre iki gruba ayrılmıştır; GRIm skor düşük grup (toplam skor 0 veya 1) ve GRIm skor yüksek grup (toplam skor 2 veya 3) [5,8].

İstatistiksel Analiz

İstatistiksel analizler "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, ABD)" kullanılarak yapıldı. Tanımlayıcı istatistikler, kategorik değişkenler için n ve %, sürekli değişkenler için Mean±SD olarak sunulmuştur. Çeşitli sayısal parametre skorlarının mortaliteyi öngörmesine ait ROC Curve analizi sonuçları verilmiştir. Tanı tarihi operasyon tarihi olarak alınan hastalarda, tanıdan eğer nüks var ise nüks tarihi ya da son kontrol tarihine kadar geçen süre hastalıksız sağkalım olarak; tanıdan ölüm var ise ölüme ya da son kontrol tarihine kadar geçen süre ise genel sağkalım olarak tanımlanmıştır. Kategorik değişkenlerin karşılaştırılmasında Chi Square test yada Fisher's exact test kullanılmıştır. Çeşitli klinik parametre grupları arasında genel sağkalım ve hastalıksız sağkalım sürelerinin karşılaştırılmasında Kaplan Meier yöntemi kullanılmıştır. Son olarak ise çeşitli klinik faktörlerin ölüm ve nüks riski üzerine çok değişkenli Cox Regresyon sonuçları verilmiştir. p<0.05 istatistikçe anlamlı kabul edilmiştir.

Bulgular

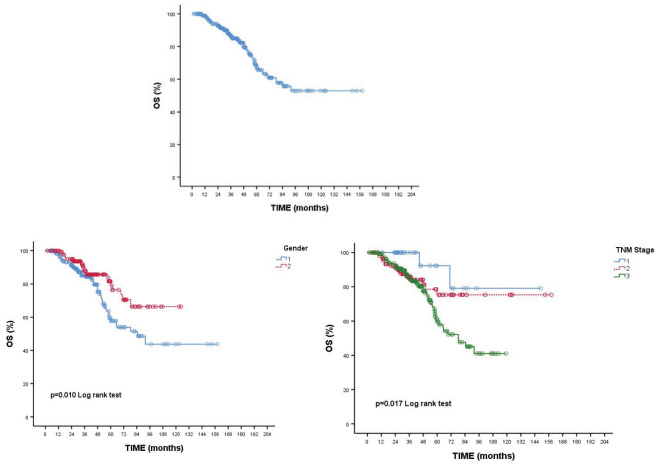
Çalışmamız, tanıda metastatik olmayan opere olmuş 405 kolorektal kanserli hastadan oluşmaktadır. %57,8'ini (n=234) erkek hastalar oluşmaktaydı. Yaş ortalamaları ise 60,41±9,91(33-81) idi. Hastalarımızın %70,9'u (n=287) kolon kanseri iken, kolon kanseri olanların çoğunluğu (%64,8'i, n=186) sol kolon kanserli hastalardan oluşuyordu. Hastaların tanı anından itibaren ortalama takip süresi 41,61±25,17 (8.4-104.5) aydı. Vücut Kitle İndeksi (VKİ) ortalaması ise 26,06±3,26 idi. Hastaların %14,6'sında (n=59) ailede kolon kanseri öyküsü mevcuttu.

Hastaların tanı anındaki TNM evrelemesi analiz edildi. T evresi olarak çoğunluk T3 evresinde olanlarda iken (%62, n=251), N evresi olarak ise N1 (%50,4, n=204) evresinde olanlar çoğunluktaydı. Bunların sonucunda da en fazla hasta sayısı evre 3 (%63, n=255) olan hasta grubundaydı. Hastalar tümör marker olan CEA ve kolon tümör mutasyonu analizi olarak RAS ve RAF mutasyon durumu açısından incelendiğinde; CEA düzeyi < 5 ng/ml olan hasta oranı %51,6 (n= 209) idi. RAS mutant hasta oranı % 16,3 (n=66) iken, BRAF mutant hasta oranı ise %3,7 (n=15) idi.

Hastaların genel demografik verileri ve onkolojik özellikleri açısından çalışmamızın ana bileşeni olan GRIm skor düzeyinin yüksek ve düşük olmasına göre gruplandırılması Tablo 1'de özetlenmiştir. Bu analize göre GRIm skorunun anlamlı olarak yüksek olduğu hastaların genel özellikleri; tanıda N evresi olarak N2, TNM evresinde evre 3, RAS ve BRAF mutant, CEA>5, yaş ortalaması ve VKi' nin yüksek, nüks ve mortalitenin olduğu hastalardı. (sırasıyla p<0,001, p<0,001, p<0,001, p=0,013, p<0,001, p=0,013, p<0,001,p<0,001, p<0,001).

Hastaların tanı anında bakılan temel laboratuvar parametrelerinin mortalite ile olan ilişkisi incelenmiştir. Bu analize göre mortalite varlığının tahminini yapmak için, albümin (p<0,001), lenfosit (p=0,042), nötrofil (p=0,003), nötrofil/lenfosit oranı (NLR) (p=0.001) ve laktat dehidrogenaz (LDH) (p<0,001) parametreleri istatistikçe anlamlı bulundu. Anlamlı bulunan bu parametreler ROC analizine konularak kesme noktaları tespit edildi. Anlamlı bulunan laboratuvar verilerin ROC analiz sonuçlarında mortaliteyi belirleme duyarlılıkları ve seçicilikleri ile birlikte değerlerin kesme noktaları Tablo 2'de belirtilmiştir.

Genel sağkalım analizleri yapıldı. Hastalarımızın medyan genel sağkalım süresine (ay) erişilemedi. 2 yıllık genel sağkalım oranı %92,7'iken 5 yıllık genel sağkalım oranı %66,6'idi. Şekil 1'de genel sağkalım grafiği gösterilmiştir.



Şekil.1 Genel sağ kalım, Cinsiyete göre sağ kalım (1=Erkek, 2=Kadın) ve TNM evrelerine göre sağ kalım grafiği

Genel sağkalım sonuçları ile anlamlı ilişki bulanan; cinsiyet, RAS mutasyon durumu ve tanıdaki CEA düzeyi sonuçlarının sağkalım süresi ile 2 ve 5 yıllık sağkalım oranları Tablo 3' te gösterilmiştir.

Tablo. 1 Sosyodemografik ve Klinik Özelliklerin GRIm skoruna göre Gruplanması

		GRIm		
	Total N=405	Düşük N=258	Yüksek N=147	p
Cinsiyet				
Erkek	234 (57,8)	157 (60,9)	77 (52,4)	0.097
Kadın	171 (42,2)	101 (39,1)	70 (47,6)	
Tümör lokalizasyonu				
Sağ kolon	101 (24,9)	67 (26)	34 (23,1)	0.067
Sol kolon	186 (45,9)	126 (48,8)	60 (40,8)	
Rektum	118 (29,1)	65 (25,2)	53 (36,1)	
Tanıda T Evresi				
T1	4 (1,0)	4 (1,6)	0 (0)	0.127
T2	55 (13,6)	38 (14,7)	17 (11,6)	
T3	251 (62,0)	163 (63,2)	88 (59,8)	
T4	95 (23,5)	53 (20,5)	42 (28,6)	
Tanıda N evresi				
N0	150 (37,0)	119 (46,1)	31 (21,1)	<0.001
N1	204 (50,4)	116 (45)	88 (59,9)	
N2	51 (12,6)	23 (8,9)	28 (19)	
TNM Evre				
1	37 (9,1)	30 (11,6)	7 (4,8)	<0.001
2	113 (27,9)	89 (34,5)	24 (16,3)	
3	255 (63,0)	139 (53,9)	116 (78,9)	
Ailede kolon kanseri				
Yok	342 (84,4)	211 (82,7)	131 (89,7)	0.058
Var	59 (14,6)	44 (17,3)	15 (10,3)	
Bilinmiyor	4 (1,0)			
RAS				
Negatif	339 (83,7)	229 (88,8)	110 (74,8)	<0.001
Mutant	66 (16,3)	29 (11,2)	37 (25,2)	
BRAF				
Negatif	390 (96,3)	253 (98,1)	137 (93,2)	0.013
Mutant	15 (3,7)	5 (1,9)	10 (6,8)	
CEA ng/ml				
<5	209 (51,6)	170 (65,9)	39 (26,5)	<0.001
≥5	196 (48,4)	88 (34,1)	108 (73,5)	
Nüks durumu				
Yok	277 (68,4)	222 (86)	55 (37,4)	<0.001
Var	128 (31,6)	36 (14)	92 (62,6)	
Mortalite				
Sağ	323 (79,8)	228 (88,4)	95 (64,6)	<0.001
Vefat	82 (20,2)	30 (11,6)	52 (35,4)	
Ortalama takip süresi	41,61±25,17	40,32±27,76	43,89±19,70	0.133
Ortalama yaş	60,41±9,91	59,56±10,81	61,91±7,92	0.013
Ortalama VKİ	26,06±3,26	25,52±3,33	27,01±2,93	<0.001

N (%): Pearsan Chi Square test, Mean±SD: Independent t test, p<0.05 istatistiksel olarak anlamlı

Tablo.2 Çeşitli Parametre Değerlerinin Mortaliteyi Ayırt Etmede Öngörücü Değerlerinin Analizi						
Değişkenler	AUC	%95 CI	Cut-off	Duyarlılık (%)	Özgüllük (%)	p
Albümin(g/L)	0.723	0.669-0.777	≤34.2	78,0	56,7	<0.001
Lenfosit(/mm3)	0.573	0.503-0.642	≤1,30	58,5	51,1	0.042
PLT(/mm3)	0.552	0.486-0.618	≥317.50	56,1	55,7	0.148
Nötrofil(/mm3)	0.606	0.547-0.666	≥5.98	58,5	56,3	0.003
NLR	0.616	0.556-0.677	≥4.15	58,5	58,2	0.001
LDH (U/L)	0.675	0.612-0.738	≥216.50	63,4	61,6	<0.001
AUC, Eğrinin altında kalan alan ; %95CI, Güven aralığı						

Tablo. 3 Hastalara ait Genel Sağkalım karşılaştırmaları				
Genel Sağkalım (ay)	Median (%95 CI)/2 ve 5 yıllık %			p
Genel	Median (%95 CI)	2 yıllık%	5 yıllık%	
	(-)	%92,7	%66,6	
Cinsiyet				
Erkek	84,50 (58,04-110,95)			0.010
Kadın	- (-)			
Tanıda T evresi				
T1	- (-)			0.004
T2	- (-)			
T3	- (-)			
T4	58,13 (44,40-71,85)			
Tanıda N evresi				
N0	- (-)			0.015
N1	78,26 (55,99-100,54)			
N2	78,36 (-)			
TNM				
1	- (-)			0.017
2	- (-)			
3	78,26 (58,12-98,40)			
RAS	Median (%95 CI)	2 yıllık%	5 yıllık%	
Negatif	-	%93,6	%75,4	<0.001
Mutant	58,13 (50,04-66,22)	%88,3	%38,8	
CEA (ng/dl) grup	Median (%95 CI)	2 yıllık%	5 yıllık%	
<5	-	%95,2	%83,2	<0.001
≥5	65,06 (49,91-80,32)	%90,5	%53,9	
Adjuvan KT				
Yok	- (-)			0.020
Var	91,76 (-)			
Nüks karaciğer	Median (%95 CI)	2 yıllık%	5 yıllık%	
Yok	-	%93,4	%74,7	<0.001
Var	55,86 (46,99-64,74)	%89,8	%44,8	
Nüks Akciğer	Median (%95 CI)	2 yıllık%	5 yıllık%	
Yok	-	%92,7	%76,6	<0.001
Var	58,66 (55,13-62,20)	%93.5	%45.2	
Nüks periton	Median (%95 CI)	2 yıllık%	5 yıllık%	
Yok	-	%93,4	%69,4	<0.001
Var	36,93 (12,54-61,32)	%75	%25,7	

Lenf nodu	Median (%95 CI)	2 yıllık%	5 yıllık%	
Yok		%91,5	%81,3	<0.001
Var	58,13 (53,15-63,11)	%96,6	%43,2	
Kemik	Median (%95 CI)	2 yıllık%	5 yıllık%	
Yok	-	%92,6	%69,2	0.001
Var	51,86 (8,23-95,49)	%100	%22,2	
Albümin gr/L	Median (%95 CI)	2 yıllık%	5 yıllık%	
>34.2	-	%97,2	%77,5	<0.001
≤34.2	70,96 (56,39-85,54)	%89	%58	
Nötrofil x 103/mm3	Median (%95 CI)	2 yıllık%	5 yıllık%	
<5.98	-	%95,9	%74,1	0.001
≥5.98	78,26 (54,87-101,6)	%89,4	%57,2	
LDH U/L	Median (%95 CI)	2 yıllık%	5 yıllık%	
<216,50	-	%90,9	%83,7	0.005
≥216,50	65,43 (45,69-85,17)	%95,1	%53,7	
GRIm skoru	Median (%95 CI)	2 yıllık%	5 yıllık%	
0	-	%98,1	%90	<0.001
1	-	%96	%77,8	
2	61,26 (56,36-66,16)	%93,1	%52,6	
3	59,90 (50,31-69,48)	%87,6	%47,6	
GRIm Kod	Median (%95 CI)	2 yıllık%	5 yıllık%	
Düşük	- (-)	%93,6	%83,3	<0.001
Yüksek	59,90 (52,86-66,93)	%92,3	%48,3	
Kaplan Meier curve, Long rank test, p<0.05 istatistikçe anlamlı				

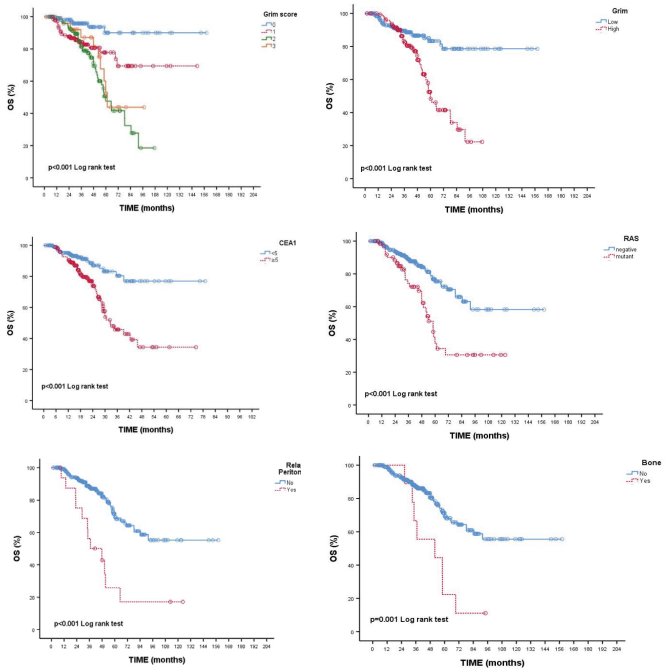
Buna göre erkek hasta olmak, RAS mutasyonun olması ve CEA düzeyinin tanıda 5ng/ml üzerinde olması daha kötü sağkalım sonuçlarıyla ilişkiliydi (sırasıyla p=0,010, p<0,001, p<0,001).

Lokal nüks varlığının, nüks yerleri ve diğer değişkenlerle olan ilişkisi incelendi. Nüks yerlerine göre; karaciğer, akciğer, periton, lenf nodu ve kemik metastazı olduğunda, genel sağkalım süresi anlamlı olarak düşüktü (sırasıyla p<0,001, p<0,001, p<0,001, p<0,001, p=0,001). Nüks durumunun çeşitli laboratuvar parametreleriyle genel sağkalım ilişkisi açısından incelendiğinde ise Albümin düzeyinin 34,2 gr/dl altında olması, Nötrofil düzeyinin 5,98 x 103/mm3 ve üstünde olması, LDH düzeyinin 216,50 U/L ve üstünde olması durumunda genel sağkalım süresi istatistiksel olarak anlamlı şekilde düşüktü (sırasıyla p<0,001, p=0,001, p=0,005). Anlamlı olan parametreleriyle ilişkili sağkalım süreleri ile 2 ve 5 yıllık sağkalım oranları Tablo 3' de gösterilmiştir.

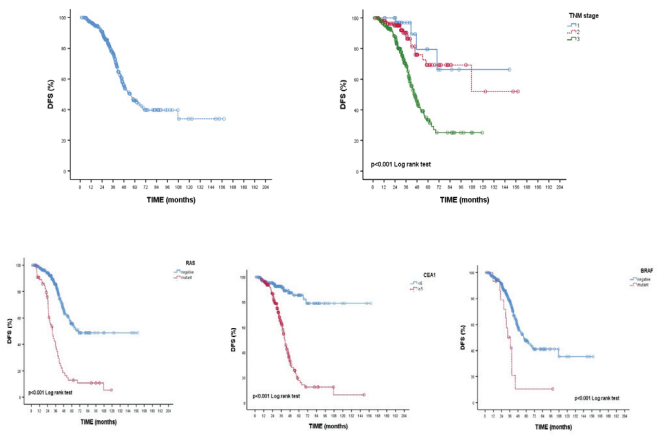
GRIm skor gruplarına göre ortanca genel sağkalım süresi ile olan ilişki istatistiksel olarak anlamlı bulundu (p<0,001). GRIm skor-0 ve 1 grubunda ortanca genel sağkalım süresine erişilemedi. GRIm skor-2 grubunda ise ortanca genel sağkalım süresi 61,26 (%95CI:56,36-66,16) ay, GRIm skor-3 grubunda ise ortanca genel sağkalım süresi 59,90 (%95CI:50,31-69,48) ay olarak belirlendi. GRIm skor-0 grubunda 2 yıllık genel sağkalım oranı %98,1'iken 5 yıllık genel sağkalım oranı %90'idi. GRIm Skor-1 grubunda 2 yıllık genel sağkalım oranı %96'iken 5 yıllık genel sağkalım oranı %77,8'idi. GRIm Skor-2 grubunda 2 yıllık genel sağkalım oranı %93,1'iken 5 yıllık genel sağkalım oranı %52,6'idi.GRIm skor-3 grubunda 2 yıllık genel sağkalım oranı %87.6'iken 5 yıllık genel sağkalım oranı %47,6'idi. Şekil 2'de GRIm skor guruplarına göre sağkalım grafiği gösterilmiştir. GRIm Kod gruplarına (0-1 düşük GRIm, 2-3 yüksek GRIm) göre ortanca genel sağkalım süresi anlamlı bulundu (p<0,001). Düşük olan grupta ortanca genel sağkalım süresine erişilemedi. Yüksek olan grupta ise ortanca genel sağkalım süresi 59,90 (%95CI:52,88-66,93) ay olarak belirlendi. Düşük olan grupta 2 yıllık genel sağkalım oranı %93,6'iken 5 yıllık genel sağkalım oranı %83,3'idi. Yüksek olan grupta 2 yıllık genel sağkalım oranı %92,3'iken 5 yıllık genel sağkalım oranı

%48,3'idi. Şekil 2'de GRIm skor guruplarına göre sağkalım grafiği gösterilmiştir. Belirtilen sağkalım süresi ile 2 ve 5 yıllık sağkalım oranları Tablo 3'de gösterilmiştir.

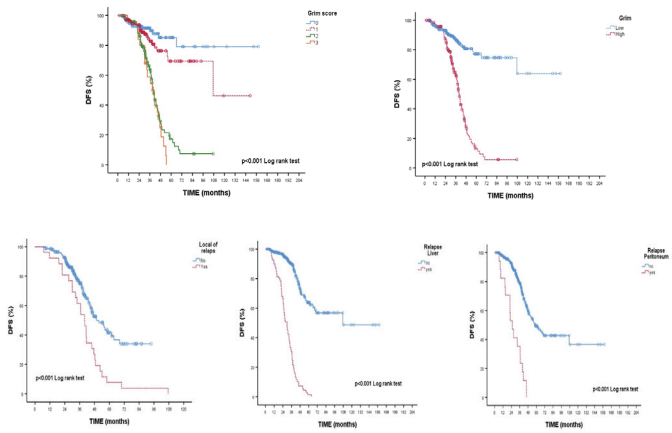
Genel ortanca hastalıksız sağkalım süresi (ay) 54,80 (%95CI:45,25-64,34) ay olarak belirlendi. 2 yıllık genel hastalıksız sağkalım oranı %90,8'iken 5 yıllık genel hastalıksız sağkalım oranı %45,9'idi. Buna göre RAS mutasyonun olması, BRAF mutasyonun olması, CEA düzeyi 5 ng/ml ve üstünde olması, Nüks veya progresyon olduğunda karaciğer, akciğer, periton, lenf nodu ve kemik metastazları ile prezente olması, albümin düzeyinin 34,2 gr/L ve altında olması, Nötrofil düzeyinin 5,98 x 103/mm3 ve üstünde olması, NLR düzeyinin 4,15 ve üstü olması, LDH düzeyinin 216,50 U/L ve üstü olması durumunda hastalıksız sağkalım süreleri anlamlı olarak daha düşük saptandı (sırasıyla p<0,001, p<0,001, p<0,001, p<0,001, p<0,001, p<0,001, p<0,001, p=0,002, p<0,001, p<0,001, p=0,004, p<0,001). Belirtilen sağkalım süresi ile 2 ve 5 yıllık sağkalım oranları Tablo 4'te gösterilmiştir. Şekil 3-4'te hastalıksız sağkalım süresi ile olan ilişkili parametreler ve anlamlılık düzeyleri ile anlamlı çıkan parametrelerin bazılarının sağkalım grafikleri gösterilmiştir.



Şekil.2 GRIm skor gurubu, GRIm durumu, CEA düzeyi - RAS mutasyon durumu ve kemik-periton metastaz durumunun sağ kalım grafikleri.



Şekil. 3 Genel DFS, TNM gruplarına göre DFS ve RAS, RAF mutasyonu ve CEA düzeyi ile DFS arasındaki ilişki.



Şekil. 4 GRIm skor gurup, GRIM düzeyi ve Lokal, Karaciğer ve Periton nüksünün DFS'ye olan etkisi

Genel Sağkalım ile ilişkili verilerin tek değişkenli analizleri sonucunda; erkek cinsiyet, TNM evresinin artması, CEA>5 olması, karaciğer, akciğer ve kemik metastazlarının olması, GRIm skorunun yüksek ve RAS mutasyonun olması, ölüm riski açısında istatistiksel olarak anlamlı bulunmuştur (p<0,05). Tek değişkenli analizler sonucunda anlamlı bulunan bu değişkenler çok değişkenli Cox regresyon modeline dahil edilmiştir. Çok değişkenli Cox regresyon modeli sonucuna göre Kadın olmak (HR:0,53;%95CI: 0,33-0,85; p=0,010) ölüm riskini azaltırken, GRIm skorunu yüksek olması (HR:1,86;%95CI: 1,06-3,26; p=0,030) ve RAS mutasyonun olması ise (HR:2,01;%95CI: 1,14-3,54; p=0.016) ölüm riskini arttırdığı bulundu (p<0,001, -2 log-likelihood= 804,571). Tablo 5'de bu çok değişkenli analizin sonuçları gösterilmiştir.

Tablo. 4 Hastalara ait Hastalıksız Sağ kalım karşılaştırmaları				
Hastalıksız Sağkalım (ay)	Median (%95 CI)/2 ve 5 yıllık %			p
Genel	Median (%95 CI)	2 yıllık%	5 yıllık%	
	54,80 (45,25-64,34)	%90,8	%45,9	
Tanıda T evresi				
T2	47,43 (15,52-79,34)			<0.001
T3	66,00 (-)			
T4	36,80 (31,66-41,93)			
Tanıda N evresi				
N0	- (-)			<0.001
N1	49,06 (43,60-54,53)			
N2	27,86 (22,76-32,97)			
TNM				
1	- (-)			<0.001
2	- (-)			
3	45,10 (39,83-50,36)			
RAS	Median (%95 CI)	2 yıllık%	5 yıllık%	
Negatif	-	%94,1	%55,8	<0.001
Mutant	31,03 (25,52-36,53)	%74,2	%12,9	
BRAF	Median (%95 CI)	2 yıllık%	5 yıllık%	
Negatif	56,36 (45,03-67,69)	%94,1	%47,8	<0.001
Mutant	37,10 (26,88-47,31)	%79	%10,5	
CEA ng/ml grup	Median (%95 CI)	2 yıllık%	5 yıllık%	
<5	-	%95,3	%85,5	<0.001
≥5	41,23 (38,29-44,17)	%86,4	%17,8	
Adjuvan KT				
Yok				<0.001
Var				
Nüks Lokal				
Yok	49,66 (41,74-57,59)			<0.001
Var	39,90 (35,43-44,36)			
Nüks karaciğer	Median (%95 CI)	2 yıllık%	5 yıllık%	
Yok	107,43 (%95CI:-)	%96,4	%63,9	<0.001
Var	29,93 (25,05-34,81)	%66,7	%1,4	
Nüks Akciğer	Median (%95 CI)	2 yıllık%	5 yıllık%	
Yok	-	%94,3	%68,6	<0.001
Var	32,03 (27,11-36,95)	%76,4	%4,2	
Nüks Periton+Primer Alan	Median (%95 CI)	2 yıllık%	5 yıllık%	
Yok	58,33 (46,87-69,79)	%92,6	%49,4	<0.001
Var	25,40 (18,45-32,34)	%52,9	%0	
Nüks Lenf nodu+Primer Alan	Median (%95 CI)	2 yıllık%	5 yıllık%	
Yok	-	%96,2	%77,2	<0.001
Var	32,63 (29,99-35,26)	%75,3	%4,3	
Nüks Kemik+Primer Alan	Median (%95 CI)	2 yıllık%	5 yıllık%	
Yok	56,36 (44,51-68,22)	%91,1	%47,9	0.002
Var	34,06 (22,28-45,85)	%77,8	%11,1	

Albümin gr/dl	Median (%95 CI)	2 yıllık%	5 yıllık%	
>34.2	-	%91,2	%67	<0.001
≤34.2	44,26 (40,26-48,27)	%90,4	%28,8	
Nötrofil x 103/mm3	Median (%95 CI)	2 yıllık%	5 yıllık%	
<5.98	-	%91,9	%62,1	0.001
≥5.98	44,56 (39,92-49,21)	%89,5	%22,1	
NLR	Median (%95 CI)	2 yıllık%	5 yıllık%	
<4,15	-	%89,5	%61,6	0.004
≥4,15	46,20 (41,05-51,34)	%92,1	%32,2	
LDH U/L	Median (%95 CI)	2 yıllık%	5 yıllık%	
<216,50	-	%94,8	%79,1	<0.001
≥216,50	41,23 (37,98-44,48)	%86	%20,1	
GRIm skoru	Median (%95 CI)	2 yıllık%	5 yıllık%	
0	-	%92,8	%85,2	<0.001
1	107,43 (-)	%93,7	%69,4	
2	39,93 (37,85-42,00)	%87,7	%17,4	
3	38,93 (27,53-50,33)	%84	%0	
GRIm Kod	Median (%95 CI)	2 yıllık%	5 yıllık%	
Düşük	-	%93,3	%77,2	<0.001
Yüksek	39,93 (38,01-41,86)	%87	%13,2	
Kaplan Meier curve, Long rank test, p<0.05 istatistikçe anlamlı				

Tablo.5 Çeşitli Klinik Değişkenlere ait Sağkalım ve Nüks riski açısından Çok değişkenli Cox Regresyon Sonuçları

Sağ Kalım	Çok değişkenli	
Değişkenler	HR (95%CI)	p
Cinsiyet (ref: Erkek)	0.53 (0.33-0,85)	0.010
TNM (ref:1)		0.502
2	2.40 (0.55-10,45)	0.241
3	2.15 (0.50-9,18)	0.299
CEA (Ref:<5 ng/ml)	1.78 (0,95-3,32)	0.068
Karaciğer (Ref:Yok)	1.03 (0.45-2,18)	0.995
Akciğer (Ref:Yok)	0.98 (0.50-1,93)	0.974
Kemik (Ref:Yok)	1.33 (0.58-3,01)	0.491
GRIm (Ref:Düşük)	1.86 (1.06-3,26)	0.030
RAS (Ref:negatif)	2.01 (1.14-3,54)	0.016
	p<0.001; -2 Log Likelihood=804,571	
Nüks	Çok değişkenli	
Değişkenler	HR (95%CI)	p
Cinsiyet (ref: Erkek)	0.90 (0.63-1,29)	0.583
TNM (ref:1)		0.833
2	0.88 (0.29-2,66)	0.821
3	0.76 (0.25-2,27)	0.633
CEA (Ref:<5 ng/ml)	1.98 (1,09-3,60)	0.025
GRIm (Ref:Düşük)	1.06 (0.65-1,72)	0.801
RAS (Ref:negatif)	2.41 (1.56-3,74)	<0.001
	p<0.001; -2 Log Likelihood=1102,47	

Hastalıksız sağkalım süresi ile ilişkili verilerin tek değişkenli analiz sonucunda ise; erkek cinsiyet, TNM evresinin artması, CEA>5 olması, GRIm skorunun yüksek ve RAS mutasyonun olması, nüks riski açısından anlamlı bulunmuştur (p<0,05). Tek değişkenli analizler sonucunda anlamlı bulunan bu değişkenler çok değişkenli Cox regresyon modeline dahil edilmiştir. Çok değişkenli Cox regresyon modeli sonucuna göre CEA'nın 5 ng/ml ve üstü olması (HR:1,98;%95CI: 1,09-3,60; p=0,025) ve RAS mutasyonun olması (HR:2,41;%95CI: 1,56-3,74; p<0,001) nüks riskini artırdığı bulundu (p<0,001, -2 loglikelihood= 1102,47). Tablo 5'de bu çok değişkenli analizin sonuçları gösterilmiştir.

Tartışma

İnflamasyon, kanser ilerlemesinde önemli bir etkendir [10]. Artan sistemik İnflamasyonun, başta kolorektal kanser olmak üzere, kansere özgü sağkalımı olumsuz yönde etkilediği bilinmektedir [11]. Kanser prognozunun tahmini için çeşitli inflamatuar ve nutrisyonel indekslere dayalı skor sistemleri geliştirilmiştir [3, 12]. Bu risk puanlama sistemleri arasında, GRIm-skor, ilkin bir immunoterapi çalışmasında [5] immün tedaviye duyarlı olan hastaların belirlenmesi amacıyla kullanılmış olup, sonrasında farklı kanserlerde bir prognoz belirteci olarak araştırılmıştır [7, 9, 13].

Kolorektal kanserli hastalarda GRIm-skor ve kompanentleriyle ilgili çeşitli çalışmalar mevcuttur. Tian ve ark. opere KRK hastalarda yaptıkları tek merkezli, 1579 hastayı dahil ettikleri çalışmalarında GRIm-skor'un opere KRK hastalarda güçlü bir prognostik indeks olduğu göstermişlerdir [2]. GRIm-skor parametrelerinden biri olan LDH ile ilgili Feng ve ark. yaptığı ve 1219 KRK hastayı içeren bir meta-analizde ise yüksek serum LDH seviyelerinin daha kötü sağkalım sonuçları ile ilişkili olduğunu göstermişlerdir [14]. Başka bir meta-analizde ise Li ve arkadaşları operasyon öncesi NLR'nin, KRK'lı hastalarda sağkalım sonuçların (Genel Sağkalım ve Hastalıksız sağ kalım) öngörmesi açısından çok etkili bir biyobelirteç olduğunu ortaya koymuşlardır [15]. Son olarak yine bir GRIm-skor komponenti olan albüminde azalmanın metastatik KRK'lı hastalarda olumsuz Genel Sağkalım için bağımsız bir risk faktörü olduğunu gösterilmiştir [16].

Çalışmamızda opere olmuş kolorektal kanserli hastaların yüksek GRIm-Skor olanlarda, düşük GRIm-Skor olanlara göre daha kısa genel sağkalım ve hastalıksız sağkalım süreleri gösterdiği saptandı. Tanı sırasında bakılan GRIm-Skor ile sağkalım sonuçları arasındaki bu ilişki, kolaylıkla hesaplanabilen GRIm-Skor' un pratik olarak kullanılması açısından önemli olduğu düşünüldü.

Çalışmamızda KRAS (%16,3, n=66) ve BRAF (%3,7, n=15) mutasyonların oranı literatürdeki erken evre kolorektal kanserli hastalar ile ilgili çalışmalara göre daha düşük oranda saptandı. Literatürde evre 2 ve 3 kolon kanserleriyle ilgili yapılan bir metanalizde; dokuz faz 3 klinik çalışmada 10.893 hastanın (minimum hasta sayısı 506 ve maksimum hasta sayısı 2226) dahil edildiği çalışmaların metanalizinde KRAS mutasyon oranı çalışma popülasyonlarında %30 ile %40 arasında saptanırken BRAF oranı %5 ile %15 oranında saptadıkları görüldü [17]. Çalışmamızda bu mutasyonların daha düşük oranda saptanmasının nedenleri olarak; RAS mutasyon analizlerinin başlangıçta daha çok sadece kodon 12 kras mutasyonu üzerinden yapılmış olması, rektum kanseri olan hasta oranın yüksekliği, RAF mutasyonu açısından sağ kolon kanserli hastalarımızın az olmasına bağlı olduğu düşünüldü.

Çalışmamızın başlangıcında hastaları GRIm yüksek ve düşük olarak genel kişisel ve onkolojik verilerini grupladığımızda kötü risk faktörleri ile GRIm yüksekliği belirgin olarak örtüşüyordu (Yüksek GRIm ile yüksek N pozitifliği ve ileri TNM evresi, yüksek CEA düzeyi, RAS ve RAF mutasyonun varlığı, yüksek yaş ortalaması ve yüksek VKİ). Tian ve arkadaşlarının 1579 opere olan kolorektal kanserli hastada yaptığı klinik bir çalışmada GRIm skorun güçlü bir güçlü bir prognostik indeks olduğunu göstermişlerdir [2].

Çalışmamızda aynı zamanda inflamatuar prognostik laboratuvar değişkenlerinden mortalite üzerine etkisi ayrıntılı olarak incelendi. Etkili olduğunu bulduğumuz; albümin, lenfosit, nötrofil, NLR ve LDH değerlerinin mortaliteyi ön görücü etkileri belirlendi. Bu yönüyle bu parametrelerin her biri için hesaplanan AUC değerleri, buna bağlı olarak cut-off değerleri ile sensivite ve spesifite değerleri belirlendiğinde, en yüksek sensivitesi olan albümin (%78) iken, en yüksek spesifisitesi olan parametre ise LDH (%61,6) olduğu bulundu. Yukarıda vurgulanan Tian ve arkadaşlarının çalışmasında da bu inflamatuar parametrelerin kolorektal kanserli hastalarda GRIm skor ile olan ilişkisi incelenmiş, bu açıdan yaptıkları korelasyon analizlerinde, yüksek GRIm-Skoruna sahip CRC hastaları, daha yüksek CEA, CA125 seviyelerine ve NLR, PLR, SII, PNI ve ALRI gibi inflamatuar indekslerle ilişkili olduğunu bulmuşlardır [2].

Genel sağkalım analizlerinde; kadın kolorektal kanserli hastalara göre erkek kolorektal kanserli hasta olmak, T1 evresi hariç ileri T, N ve TNM evresinde olmak, RAS mutasyonun olması, CEA düzeyinin >5ng/ml olması, Nüks durumunda karaciğer, akciğer, kemik, lenf nodu ve periton metastazı olması, tanı anında albümin≤ 34,2 gr/L olması, , tanı anında nötrofilin ≥ 5,98 x 103/mm3 olması, tanı anında LDH≥ 216,5

U/L olması ve GRIm skorunun yüksek (2 ve 3. gurupta) olması sağkalım açısından kötü özelliklerdi.

Hastalıksız sağkalım açısından bakıldığında ise; yine T,N ve TNM evresinin artması, RAS mutasyonun olması, CEA düzeyinin >5ng/ml olması, albümin≤ 34,2 gr/L olması, , tanı anında nötrofilin≥ 5,98 x 103/mm3 olması, tanı anında LDH ≥216,5 U/L olması ve GRIm skorunun yüksek (2 ve 3. grupta) olması da tıpkı genel sağkalım gibi hastalıksız sağkalım açısından da kötü risk faktörlerindendi. Bunların dışında BRAF mutasyonun olması ve NLR düzeyi ≥4,15 olması da hastalıksız sağkalım açısından kötü risk faktörlerindendi.

Tüm bunların sonucunda sağkalımı belirleyen faktörlerin incelemesi yapıldığında; Tek değişkenli ve ardın Çok değişkenli analizleri ile kadın olmak (HR:0,53;%95CI: 0,33-0,85; p=0,010) ölüm riskini azaltırken, GRIm skorunu yüksek olması (HR:1,86;%95CI: 1,06-3,26; p=0,030) ve RAS mutasyonun olması ise (HR:2,01;%95CI: 1,14-3,54; p=0,016) ölüm riskini arttırdığı bulundu. Hastalıksız sağkalım açısından da benzer analiz yapıldığında ise CEA'nın 5 ng/ml ve üstü olması (HR:1,98;%95CI: 1,09-3,60; p=0,025) ve RAS mutasyonun olması (HR:2,41;%95CI: 1,56-3,74; p<0,001) nüks riskini artırdığı bulundu.

Hasta sayısının azlığı çalışmamızın kısıtlılıklarındandı. Ayrıca mutasyon analizlerinin geniş panelde değerlendirilememiş olması ve özellikle mikrosatellit insitabilite açısından değerlendirme yapılmamış olmasıydı. Hasta sayımız her ne kadar belli bir sınırda olsa da inflamatuar ve prognostik laboratuvar parametrelerinden elde edilen sonuçlar ve cut-off değerleri, literatürde belirlenen cut-off değerlerine yakın sonuçlar elde edilmişti. Bu da çalışmadaki hastaların genel popülasyonu yansıtması ile çalışmamızın değerini göstermektedir.

Sonuç olarak çalışmamızda erken evre kolorektal kanserli hastalarda bir inflamatuar ve beslenme risk puanlama sistemi olan GRIm-skor 'un başta genel sağkalım olmak üzere hastalıksız sağkalımı açısından belirleyici olduğu bulundu. Çok değişkenli analizde hastalıksız sağkalım üzerinde GRIm-skoru' nun etkisi kaybolurken, sağkalım da ise diğer faktörlerden bağımız olarak etki ettiği gösterildi. Bu yönüyle GRIm-skor opere kolorektal kanserli hastalarda sağkalımı ön görmesi nedeniyle pratikte kullanışlı bir parametre olarak değerlendirilmesi önerilir.

Maddi destek ve çıkar ilişkisi

Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların herhangi bir çıkar dayalı ilişkisi yoktur.

Etik kurul onayı

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Araştırma Makalesi

Miyelodisplastik sendrom tanili hastalarin retrospektif değerlendirilmesi

Retrospective evaluation of patients diagnosed with myelodysplastic syndrome

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Öz

Amaç: Miyelodisplastik sendrom (MDS); ileri yaşta görülen, kemik iliği yetmezliği ile karakterize bir hematopoetik kök hücre hastalığıdır. Hastalığın seyri ve tedavisi hastalarda farklılık göstermekle birlikte yeni tedavilere rağmen hala allojeneik kök hücre nakli dışında küratif tedavisi olmayan bir hastalıktır. Bu çalışmanın amacı MDS serimizi geriye yönelik incelemek, hastaların demografik özelliklerini, prognostik seyirlerini, tedavilerini ve yanıtlarını incelemektir.

Gereç ve Yöntemler: Merkezimizde MDS tanısı ile takipli 56 hastanın verileri geriye yönelik incelendi. Hastaların demografik ve tanısal özellikleri, prognostik skorları, tedavileri, sağkalım bilgileri geriye yönelik olarak değerlendirildi.

Bulgular: Hastaların 25'i (%44) kadın, 31'i (%56) erkek, ortanca yaş 63 (29-85) idi. Dünya Sağlık Örgütü (DSÖ) 2022 morfolojik sınıflamasına göre hastaların 26'si (%47) düşük blastlı MDS, 12'si (%21) artmış blastlı MDS 1, 7'si (%13) artmış blastlı MDS 2, 4'ü (%7) fibrozisli MDS, 3'ü hipoplastik MDS, 1'i izole 5q delesyonlu MDS, 3'ü ise TP53 inaktivasyonu MDS olarak sınıflandırıldı. Hastaların 33'ünde (%59) en az bir eşlik eden hastalık mevcuttu. 17 (%30) hastanın ECOG performans durumu ≥2 bulundu. Hastalar risk skorlamalarına göre WPSS risk skorlamalasında çoğu yüksek riskte, R-IPSS risk skorları için çoğu orta risk grubunda, IPSS risk skorlamasında ise çoğu orta 1 risk grubunda idi. Tedavisiz izlem süresi ortalama 7,8 (0-95) aydı. Birinci basamak tedavi olarak hastaların 12 (%22) hipometile edici ajan, 13 (%23) eritropoetin tedavisi, 7 (%12) steroid ve danazol tedavisi, 4 (%7) talidomid tedavisi, 4 (%7) konvansiyonel kemoterapi, bir hasta lenalidomid, 1 hasta siklosporin ile antitimosit globulin almıştı. Üç hastaya allojeneik kök hücre nakli yapılmış, 11 (%20) hasta tedavisiz veya destek tedavi ile izlenmişti. Birinci basamak tedavi yanıt oranı 12 (%26) hastada tam yanıt, 10 (%23) hastada transfüzyon azalması ile kısmi yanıt iken 23 (%51) hastada yanıt yok idi. Diğer tedavi basamakları dahil edildiğinde toplam 7 hastaya kök hücre nakli yapılmıştı. Takipte 10 (%18) hastada akut lösemi dönüşümü izlendi. Takip süresi sonunda hayatta kalan hasta sayısı 22 (%40) iken 27 (%48) hasta hayatını kaybetmişti. 7 hasta takipten çıkmış olması nedeniyle sağkalım durumu bilinmiyordu. Ölüm nedeni bilinen 27 hastadan 5 tanesi hastalık ilerlemesi, 12'si enfeksiyon, 2 tanesi kanama nedeniyle, 6 tanesi nakil ilişkili komplikasyonlar, 2 tanesi diğer nedenlerden dolayı kaybedilmişti. Ortalama toplam sağkalım 38,6 (1-123) ay olarak tespit edildi. Yaş, ECOG performans durumu, 2016 ve 2022 DSÖ alt sınıfı, kemik iliği blast oranı, kemik iliği fibrozis durumu, IPSS-WPSS-R IPSS skoru, tedavi verilen hastalarda tedaviye yanıt durumu, şelasyon tedavisi, akut lösemi dönüşüm durumu ve allojeneik kök hücre nakli sağkalım ile ilişkili bulundu.

Sonuç: Miyelodisplastik sendrom; 2022 yılında tanı alt sınıf güncellemesi yapılması, tedavideki yeniliklerin devam etmesi nedeniyle merkezimizde izlenen hastaların verilerinin toplandığı bu çalışmada hastalığın epidemiyolojik verileri literatür ile uyumlu bulunmuştur. Güncel sınıflama ile birlikte hastaların dağılım özellikleri tespit edilmiş olup tedavi-prognoz süreçleri için ilerisi için yön gösterici olacaktır. İleri yaş hastalığı da olsa merkezimizde hastaların çoğunluğuna uygun bir tedavi seçeneği verildiği görülse de literatürde uyumlu olarak bu tedavilerin yanıtları yüksek ve kalıcı değildir. Sağkalım üzerien etkili faktörler literatürle uyumlu bulunmuştur. MDS hastalarının uygun olanları için küratif tek seçenek olan allojeneik kök hücre naklinin uygun zaman ve nakil kriterleri ile yapılması sağlansa da maalesef hala nakil ilişkili mortalite büyük bir sorun olarak görünmektedir. Çalışmamız yeni DSÖ sınıflamasının değerlendirilmesine de yer vermesi açısından literatüre katkı sağlayacaktır.

Anahtar Kelimeler: Miyelodisplastik Sendromlar; sınıflandırma; prognoz; sağkalım

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Abstract

Aim: Myelodysplastic syndrome (MDS) is a hematopoietic stem cell disease characterized by bone marrow failure that usually occurs at an advanced age. The prognosis and treatment of the disease vary in patients, despite new treatments and it is still a disease that has no curative treatment rather than allogeneic stem cell transplantation. The aim of this study is to evaluate our MDS patients retrospectively in terms of demographic characteristics, prognostic score, treatments and responses of patients.

Material and Methods: Fifty six MDS patient's data was analyzed retrospectively. Demographic and diagnostic characteristics of the patients, prognostic scores, treatments, survival information were evaluated retrospectively.

Results: 25 (44%) of the patients were female, 31 (56%) were male. The median age was 63 (29-85). According to the World Health Organization (WHO) 2022 classification, 26 (47%) of the patients were classified as MDS with low blasts, 12 (21%) MDS with increased blasts 1, 7 (13%) MDS with increased blasts 2, 4 (7%) MDS with fibrosis, 3 with hypoplastic MDS, 1 MDS with low blasts and isolated 5q deletion, and 3 MDS with biallelic TP53 inactivation. 33 of the patients (59%) had at least one concomitant disease. ECOG performance status of 17 (30%) patients was found to be ≥2. According to the risk scoring, most of the patients were at high risk in the WPSS risk scoring, most of them were in the medium risk group for R-IPSS risk scores, and most of them were in the medium 1 risk group in the IPSS risk scoring.The mean duration of follow-up without treatment was 7.8 (0-95) months. As first-line treatment, 12 (22%) patients received hypomethylating agent, 13 (23%) erythropoietin stimulating treatment, 7 (12%) steroid and danazole treatment, 4 (7%) thalidomide treatment, 4 (7%) conventional chemotherapy, one patient received lenalidomide, 1 patient received antithymocyte globulin with cyclosporine. Three patients underwent allogeneic stem cell transplantation, and 11 (20%) patients were treated with supportive care without medical treatment. The first-line treatment response rate was complete response in 12 (26%) patients, partial response with transfusion reduction in 10 (23%) patients, and no response in 23 (51%) patients. A total of 7 patients had undergone stem cell transplantation when other treatment steps were included. During the follow-up, acute leukemia transformation was observed in 10 (18%) patients. At the end of the follow-up period, the number of surviving patients was 22 (40%), while 27 (48%) patients had died. The survival status was unknown for 7 patients due to the withdrawal of the follow-up. Of the 27 patients whose cause of death was known, 5 patients died due to disease progression, 12 due to infection, 2 patients due to bleeding, 6 due to transplant-related complications, and 2 due to other causes. The median total survival was found to be 38.6 (1-123) months. Age, ECOG performance status, 2016 and 2022 WHO classification, bone marrow blast ratio, bone marrow fibrosis status, IPSS-WPSS-R IPSS score, response status to treatment in treated patients, iron chelation therapy, acute leukemia transformation and allogeneic stem cell transplantation was statistically associated with survival.

Conclusion: Epidemiological data of the disease were found to be compatible with the literature in this study, in which the data of the patients monitored at our center were collected due to the introduction of a diagnostic classification update in MDS 2022 and the continuation of improvements in treatment. Together with the current classification, the distribution characteristics of the patients have been determined and will be a guide for the treatment-prognosis processes in the future. Although it is seen that a suitable treatment option is given to the majority of patients in our center, even though MDS is an advanced age disease, the responses of these treatments are not high and not permanent in accordance with the literature. The most effective factors on survival were found to be consistent with the literature. Although allogeneic stem cell transplantation, which is the only curative option for eligible MDS patients, is provided with the appropriate time and transplantation criteria, unfortunately, transplant-related mortality still seems to be a big problem. Our study will contribute to the literature in terms of providing a place for the evaluation of the new WHO classification.

Keywords: Myelodysplastic Syndromes; classification; prognosis; survival

Giriş

Miyelodisplastik sendrom (MDS), klonal hematopoez sonucunda kemik iliğinde meydana gelen displastik değişimler, bu değişimlere bağlı sitopeniler ve bozulmuş hematopoez ile karakterize bir hematolojik hastalıktır. Yaş arttırkça artan bir insidansa sahip MDS' de izole 5q delesyonu olan alt tipler haricinde erkek dominansı söz konusudur (1). Hastalığın patogenezinin anlaşılmasındaki gelişmeler yanısıra genetik bozukların tespitindeki hassas testlerin geliştirilmesi ile birlikte tanıda ve tedavide birçok gelişme yaşanmaktadır (2-6). Halen tek küratif seçeneği allojeneik kök hücre nakli (AKHN) olsa da MDS için kişişelleştirilmesi gereken birçok tedavi mevcuttur (7-9). Teşhisiyle ilgili kriterlerde özellikle displazinin morfolojik teşhisindeki zorluklar ve genetik testlerdeki erişim problemi nedeniyle hastalığın epidemiyolojik ve tanısal süreçlerinde bilgiler hala gelişmektedir. Son 2 yılda Dünya Sağlık Örgütü (DSÖ) (5) ve Uluslarası Konsensus Sınıflamasıyla (6) birlikte yeni genetik ve morfolojik sınıflaması yapılan hastalık için bu güncellemelerin takibini yapmak, prognostik markerlar ve tedavi alanında hastaların bireysel değerlendirilmesi global bir gereklilik haline gelmektedir. Çalışmamızda,

yeni güncellemeler doğrultusunda hastalığın alttiplerinin dağılımının tespiti, ülkemizden hastalık hakkındaki yayınlara katkı sağlamak amacıyla hastanemizde MDS tanısıyla takip ettiğimiz hastalarımızın verilerini sunmayı amaçladık.

Gereç ve Yöntemler

Çalışmada merkezimizde MDS tanısı konulmuş 56 hastanın dosyası geriye yönelik incelendi. Sosyodemografik ve hastalık ilişkili veriler kayıt edildi. İstatistiksel analizler "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, ABD)" kullanılarak yapıldı. Tanımlayıcı istatistikler, kategorik değişkenler için n ve %, sürekli değişkenler için mean, median olarak sunulmuştur. Çeşitli tedavi, laboratuar, prognostik skorlama gibi parametreler ile mortalite karşılaştırılmasında Ki-kare testi kullanılmıştır.

Çalışma için merkezimiz etik kurulundan E1-22-2715 sayısıyla onay alınmıştır.

Bulgular

Değerlendirmesi yapılan 56 hastanın ortanca yaşı 63 (29-85) idi. 25 (%44) kadın ve 31 (%56) erkek hasta incelendi. Hastaların 33' ünde (%59) eşlik eden hastalık vardı. En sık eşlik eden hastalıklar hipertansiyon, diyabet, koroner arter ve kalp kapak hastalıklarıydı. DSÖ 2016 sınıflamasına göre 18 (%32) hastanın MDS alt tipi çoklu seride displazili MDS, 6 (%10,5) hastanın tek seride displazili MDS, 2 hastanın ise halka sideroblastlı MDS, 17 (%31) hastanın artmış blast 1 MDS, 7 (%12,5) hastanın artmış blast 2 MDS, 5 hastanın sınıflamayan MDS, 1 hastanın izole delesyon 5q' lu MDS tanısı mevcut idi. DSÖ 2022 yeni sınıflamasına göre morfolojik sınıflamasına göre hastaların 26' si (%47) düşük blastlı MDS, 12' si (%21) artmış blastlı MDS 1, 7' si (%13) artmış blastlı MDS 2, 4' ü (%7) fibrozisli MDS, 3' ü hipoplastik MDS olarak sınıflandırıldı. Genetik anormallikle tanımlanan alt tiplerden izole 5q delesyonlu MDS olan bir hasta, TP53 inaktivasyonu MDS olan üç hasta mevcuttu.

Hastaların tanı zamanı laboratuar değerleri ortalama ve minimum maksimum değerler Tablo 1' de sunulmuştur.

Tablo 1. Hastaların tanıdaki laboratuar test sonuçları

Değer	Ortalama	Minimum-Maksimum
Hemoglobin düzeyi (g/dl)	9,1	3,9-14
Eritrosit hacmi (MCV)	95	69-114
Lökosit sayısı (109/L)	5,41	1-28,96
Nötrofil sayısı (109/L)	2,72	0,1-9,61
Eritropoetin düzeyi (U/L)	206	10-780
Ferritin düzeyi (µg/L)	425	7-2457
Vitamin B12 düzeyi (pg/ml)	626	134-2000
Folat düzeyi (ng/ml)	9	1,9-23,5
LDH (U/L)	246	108-607

LDH: Laktat dehidrogenaz

Hastalar risk skorlamalarına göre WPSS risk skorlamalasında çoğu yüksek riskte, R-IPSS risk skorları için çoğu orta risk grubunda, IPSS risk skorlamasında ise çoğu orta 1 risk grubunda idi. Hastaların prognostik skorlarına göre dağılımı Tablo 2' de sunulmuştur.

Tablo 2. Hastaların prognostik risk skorlama dağılımları

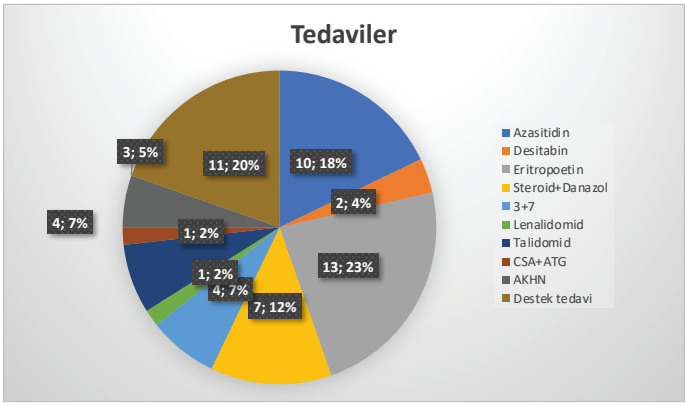
Risk skorlaması	Hasta sayısı	Hasta yüzdesi
WPSS		
0-Çok düşük risk	8	% 22
1-Düşük risk	1	% 2
2-Orta risk	8	% 22
3-Yüksek risk	18	% 49
4-Çok yüksek risk	2	% 5
IPSS		
0-Düşük	8	% 21
1-Orta 1	18	% 47
2-Orta 2	11	% 29
3-Yüksek	1	%3
R-IPSS		
0-Çok düşük risk	9	% 18
1-Düşük risk	4	% 8
2-Orta risk	23	% 47
3-Yüksek risk	10	% 21
4-Çok yüksek risk	3	% 6

Hastaların kemik iliği hücresellik değerlendirmeleri sonucunda 30 (%53) hastanın kemik iliği hiperselüler, 20 (%36) hastada normoselüler, 6 (%11) hastada hiposelülerdi. Kemik iliği blast yüzdesi ortalama % 3,7 (0-15) arası idi. 20 (%36) hastanın patolojisinde fibrozis yok iken, 25 (%45) hastada grade 1, 9 (%16) hastada grade 2, 2 (%3) hastada grade 3 retikülin lif artışı vardı. 27 (%48) hastanın iki kemik iliği hücre serisinde displazisi varken, 15 (%27) hastanın her üç seride, 14 (%25) hastanın tek seride displazisi vardı.

Hastaların tanıda konvansiyonel sitogenetik incelemesi 42 hastada yapılabilmişti. Bu hastaların 23 (%55) tanesi cinsiyetine uygun kromozom analizi sonucuna sahip iken 19 (%45) hastada 19 farklı kromozomal bozukluk vardı. Yirmi dokuz hastanın floresan in situ hibridizasyon (FİSH) testi ile MDS genetik incelemesi yapılmıştı. Bu hastalardan 5 tanesinde MDS ile FİSH bozukluğu mevcuttu.

Tedavisiz izlem süresi ortalama 7,8 (0-95) aydı.

Hastaların birinci basamakta aldığı tedaviler Grafik 1'de verilmiştir. Diğer tedavi basamakları dahil edildiğinde toplam 7 hastaya kök hücre nakli yapılmıştı. Birinci basamak tedavi yanıt oranı 12 (%26) hastada tam yanıt, 10 (%23) hastada transfüzyon azalması ile kısmi yanıt iken 23 (%51) hastada yanıt yok idi.



3+7: Konvasiyonel kemoterapi olarak antrasiklin+ ARA-C; CSA+ATG: Siklosporin+ antitimosit globulin; AKHN: Allojeneik kök hücre nakli.

Grafik 1. Hastaların birinci basamakta aldığı tedavilerin dağılımı.

Ortalama toplam sağkalım 38,6 (1-123) ay olarak tespit edildi. Takipte 10 (%18) hastada akut lösemi dönüşümü izlendi. Takip süresi sonunda hayatta kalan hasta sayısı 22 (%40) iken 27 (%48) hasta hayatını kaybetmişti. 7 hasta takipten çıkmış olması nedeniyle sağkalım durumu bilinmiyordu. Ölüm nedeni bilinen 27 hastadan 5 tanesi hastalık ilerlemesi, 12' si enfeksiyon, 2 tanesi kanama nedeniyle, 6 tanesi nakil ilişkili komplikasyonlar, 2 tanesi diğer nedenlerden dolayı kaybedilmişti.

Yaş, ECOG performans durumu, 2016 ve 2022 DSÖ alt sınıfı, kemik iliği blast oranı, kemik iliği fibrozis durumu, IPSS-WPSS-R IPSS skoru, tedavi verilen hastalarda tedaviye yanıt durumu, şelasyon tedavisi, akut lösemi dönüşüm durumu ve allojeneik kök hücre nakli sağkalım ile ilişkili bulundu. Cinsiyet, tanı anında bakılan laboratuar parametrelerinin ölüm üzerine istatistiksel anlamlı etkisi olmadığı görüldü. Tablo 3' te ölüm üzerine etkili olan ve olmayan parametrelerin bilgisi sunulmuştur.

Tartışma

MDS, displazi zeminin sonucu olarak çeşitli derecelerde sitopeniler ile bulgu gösteren ve akut miyeloid lösemiye (AML) transformasyon riski olan bir klonal hematopoetik kök hücre hastalığıdır. MDS yavaş bir klinik seyir ile tedavisiz izlem imkanı ve normale yakın yaşam süresi ile görülebileceği gibi hızlı, agresif bir seyir ile aylar içinde akut miyeloid lösemiye transforme olarak yaşam süresini kısaltabilecek, tedavinin bireysel olarak düzenlenmesi gerek ve küratif tek tedavi seçeneğinin AKHN olduğu hematolojik bir hastalıktır (10). Bu bireyselleştirilmiş tedavide hem tanı hem prognoz aşamasında son yıllarda genetik testlerin uygulanmasıyla yeni sınıflamalar ve prognostik modeller geliştirilmiştir (5, 11, 12). Çalışmamızda merkezimizde takip ettiğimiz MDS hastalarımızın yeni güncellemeler ışığında epidemiyolojik verilerini, tedavi bilgilerini ve yaşam süreleri, mortalite üzerine etkili faktörlerini incelemeyi amaçladık.

Tablo 3. Parametrelerin ölüm üzerine etkisi

Parametre	Ölüm üzerine etkisi (Var/yok)	P değeri
Yaş	Var	0,003
Cinsiyet	Yok	0,42
ECOG	Var	0,001
DSÖ sınıflaması	Var	0,001
Tanıda bakılan	Yok	
Hemoglobin		0,89
Lökosit		0,92
Trombosit		0,65
Retikülosit sayısı		
Sedimentasyon		0,73
CRP		0,91
Ferritin		0,08
B12		0,97
Folat		0,34
LDH		0,45
Eritropoetin		0,67
		0,26
Kemik iliği blast oranı	Var	0,001
Kemik iliği fibrozis derecesi	Var	0,02
Risk skorlama	Var	
WPSS		0,001
IPSS		0,001
R-IPSS		0,001
Tedavi yanıtı	Var	0,05
Şelasyon tedavisi	Var	0,01
Akut lösemi dönüşümü	Var	0,002
Allojeneik kök hücre nakli	Var	0,02

Çalışmamızda literatürle uyumlu olarak ortalama 63 ile ortanca 65 yaş olan erkek baskın bir populasyon ve mevcuttu (1, 13).

DSÖ hastalık sınıflaması dağılımı 2016 sınıflamasına göre literatürle uyumlu olarak en sık çoklu seride displazili MDS hastaları mevcuttu (14, 15). 2022 DSÖ güncellemesiyle tek seri ve çoklu seri displazi deyimi kaldırılarak temel olarak morfolojik sınıflamada blast oranı temel alındı. Yeni sınıflamada önceden olan izole 5q delesyonlu hastaların sınıflaması değişmezken TP53 biallelik inaktivasyonu yeni bir genetik grup eklendi (5). Eski sınıflamada tek seri displazi, çoklu seri displazi, refrakter anemi ve ring sideroblastlı alt tipler yeni sınıflanmadırmada yer almadığından toplamda serimizde durumu hastaların tanı kategorilerinden 31 hastanın hastalık alt tipi değişmiş oldu. Son bir yılda karşılaştırmalı yapılan çalışmalarda bu değişim oranının da benzer olduğu gözlendi (4, 16). Değişen sınıflamalarla birlikte hastaların tedavi kararlarının da değişimi ön görüldüğünden ilerleyen süreçte bu değişimler hastalık sağkalımı etkileceğinden önemli görünmektedir.

Tanı laboratuar değerleri çok değişkenlik göstermekle birlikte sitopenilerin sayısı ve derinliği prognostik skorlamalarda yer aldığından hasta populasyonlarının bazal testlerin bilinmesi önem taşımaktadır. Toplam sağkalım, ölüm üzerine yapılan değerlendirmelerde hastaların bazı laboratuar testlerinin bunlarla ilişkili olduğu bulunduğundan çalışmamızda ölüm üzerine etki açısından bu parametrelerin değerlendirmesi yapılmıştır. Bu parametrelerin ölüm ile ilişkisi tespit edilmemiştir. Literatürde birçok çalışmada farklı sonuçlar olsa da büyük sayılı hasta değerlendirmelerinde laboratuar testleriyle sağkalım arasında net vurgu yapılan hemoglobin düzeyi dışında anlamlı bir parametre mevcut değildir. MDS hastalarında geliştirilen WPSS skorlama siteminde aneminin derinliğinin önemi, R-IPSS skorlama sisteminde nötrofil ve trombosit saysının derinliği puanlamada yer alsa da günümüzde bu sistemlerden ziyade genetik temelli prognostik skorlama sistemlerinin ön planda olduğu aşikardır (17-19).

Hastalarımızın genetik değerlendirme sonuçları sitogenetik incelemede literatürde geçen % 50 bozuklukla benzer olarak % 45 olarak izlendi (20). Merkezimizde bakılan FİSH değerlendirme sonuçlarına göre genetik bozukluk tespit oranı literatürünün altında ve 29 hastada 5 hasta şeklinde idi. Bu düşüklük testin çalışılma koşullarına bağlanabilse de hem merkezimizde hem ülkemizde genetik açıdan bu konuların geliştirilmesi gerekliliği mutlaktır. Artık bu testlerin ötesinde NGS temelli genetik incelemeler birçok ülkede yerini almış ve literatüre genetik temelli çalışmalar kapsamında ileri genetik tetkiklerle gösterilebilen birçok MDS ilişkili değişiklik tanımlanmaktadır.

MDS tanıdan itibaren tedavi süreci hastadan hastaya değişen bir hastalık olmakta ve verilen tedaviler dünyanın birçok yerinde farklılık gösterebilmektedir. Ülkemizde mevcut diğer tedavi seçenekleri hipometile edici ajanlar, eritropoez uyarıcı ajanlar, anjiogenez inhibitörleri, steroid, danazol, trombopoetin reseptör agonistleri, granülosit koloni uyarıcı faktör tedavileri de hastalarda değişik sıra tedavide kullanılmıtır. Tedavi seçenekleri MDS'te var olsa da yanıtları bizim serimizde de birinci basamak için tam ve kısmi yanıtta yaklaşık yüzde 50 hastada izlenmiştir ve beklendiği üzere kalıcı olmamıştır. Populasyonumuzda destek tedavi ile izlenen hastalar yanısıra farklı basamaklarda olmak üzere tek küratif tedavi seçeneği olan AKHN 7 hastaya uygulanabilmiş ve takipte 6 hasta nakil ilişkili komplikasyon ile kaybedilmiştir. Nakle giden hasta sayısının azlığı hastalığın ileri yaşta görülmesi, hasta durumunun AKHN için uygun olmaması veya uygun donör bulunaması şeklinde yorumlanabilir. Her ne kadar kür sağlayıcı tedavi de olsa AKHN' nin hala nakil ilişkili mortaliteleri nedeniyle en uygun hastaya en uygun zamanda yapılması uygun görünmektedir.

Ortalama üç yıllık sağkalım ile takip süresi sonunda %50' ye yakın hasta kaybedilmiştir. Literatüre bakıldığında prognoz skorların geliştirildiği büyük çalışmalarda risk kategorisine göre değişmekle birlikte ortanca sağkalımlar 0,4 yıl ile 11,6 yıl arasında değişmektedir (21, 22).

Ölüm üzerine etkisi olduğu tespit edilen faktörler yaş, ECOG performans durumu, DSÖ alt sınıfı, kemik iliği blast oranı, kemik iliği fibrozis durumu, IPSS-WPSS-R IPSS skoru, tedavi verilen hastalarda tedaviye yanıt durumu, şelasyon tedavisi, akut lösemi dönüşüm durumu ve allojeneik kök hücre nakli idi. Bu bulgularda literatürle çelişen parametre mevcut değildir (3, 20).

Sonuç olarak klonal bir hematopoetik, ileri yaş hastalığı olan MDS hastaları için tanı, prognostik testler güncel bilgiler ışığında yapılarak mümkün olduğu kadar genetik temelli ve bireyselleştirilmiş kararlar ile hastaların morbidite ve hastalığın mortal seyrine karşı koymak mümkün olabilecektir.

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Research Article

Validation of the Turkish version of the pediatric early warning score

Pediatrik erken uyarı skorunun Türkçe versiyonunun geçerlilik ve güvenirlik çalışması

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Abstract

Aim: The pediatric early warning score (PEWS) identifies pediatric patients at risk for clinical deterioration and can helpless-experienced providers get a sense of which patients may need escalation of care. The purpose of the study was to adapt the PEWS into Turkish and evaluate its validity in pediatric patients admitted to the emergency.

Material and Methods: This study was conducted between May and October 2022 on 228 patients aged 17 and under in the pediatric emergency department of a tertiary care hospital. In the pilot phase of the study, scoring of the first 30 patients was performed by three nurses in the emergency department. In the second phase, the validity of the PEWS scale was evaluated. Validity of the scoring system in predicting admission was assessed using area under the receiver operating characteristics (ROC) curve (AUC), sensitivity, and specificity, positive predictive value (PPV) and negative predictive value (NPV).

Results: The mean age of the children was 6.37 ± 4.72 years. Phase I demonstrated good inter-rater reliability (kappa = 0.75). In phase II, 22 patients (9.6%) were admitted to the intensive care unit (ICU) during the study period. AUC for predicting was 0.948 (95% CI: 0.915–0.981). According to ROC curve analysis, a cut-off value for PEWS score was found to be 4 (PEWS >4) for admitted to the ICU. Sensitivity and specificity in predicting ICU admission with the cut-off PEWS ≥4 was 86.36% and 90.78%, respectively (PPV, 50%; NPV, 90.48%). The sensitivity and specificity in predicting admission with a cut-off of PEWS ≥1 was 100% and 59.22%, respectively (PPV, 20.75%; NPV, 100%).

Conclusion: The Turkish version of PEWS can be helpful in assessing patient status in pediatric emergency department with acceptable validity and can serve as a potentially screening tool for prediction of ICU admission.

Keywords: Children, emergency room, PEWS, reliability, validity

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Öz

Amaç: Pediatrik erken uyarı skoru (PEUS), acil serviste veya klinikte çocukların erken dönemde klinik kötüleşme riskini belirleyerek, kliniği kötüleşecek hastaları erken dönemde fark edip, tedavi planını düzenlemek için geliştirilmiş bir ölçektir. Çalışmanın amacı, PEUS'un Türkçe'ye uyarlanması ve acil hastalarda geçerlilik ve güvenilirliğinin değerlendirilmesidir.

Gereç ve Yöntemler: Bu çalışma Mayıs-Ekim 2022 tarihleri arasında, üçüncü basamak bir hastanenin pediatrik acil servisinde 17 yaş ve altı 228 hastada gerçekleştirilmiştir. Çalışmanın pilot aşamasında acil serviste üç hemşire tarafından ilk 30 hastanın skorlaması yapılmıştır. İkinci aşamada, PEUS ölçeğinin geçerliliği değerlendirilmiştir. Skorlamanın kabul edilebilirlik düzeyi, işlem karakteristik (ROC) eğrisi ve ROC eğrisi altında kalan alan (AUC), duyarlılık, özgüllük, pozitif tahmin değeri (PPV) ve negatif tahmin değeri (NPV) kullanılarak değerlendirilmiştir.

Bulgular: Çalışmaya yaş ortalaması 6,37 ± 4,72 yıl olan 129'u (%56,57) erkek, toplam 228 hasta alınmıştır. Faz I, iyi bir gözlemci arası güvenirlik göstermiştir (kappa = 0,75). Faz II'de, çalışma dönemi boyunca 22 (%9,6) hasta yoğun bakım ünitesine (YBÜ) kabul edilmiştir. Tahminleme için AUC değeri 0,948 (95% CI: 0,915-0,981) olarak bulunmuştur. ROC eğrisi analizine göre, YBÜ'ye kabul edilenler için PEUS skoru kesim değeri 4 olarak bulunmuştur (PEUS ≥4). PEUS ≥4 kesim değeriyle YBÜ kabulünü tahmin etmede hassasiyet ve özgüllük değerleri sırasıyla %86,36 ve %90,78 idi (PPV: %50, NPV: %90,48). PEUS ≥1 kesim değeriyle kabulü tahmin etmede hassasiyet ve özgüllük sırasıyla %100 ve %59,22 idi (PPV: %2,75, NPV: %100).

Tartışma: PEUS Türkçe versiyonu kabul edilebilir geçerlilikle, pediatrik acil serviste hastanın durumunu değerlendirmeye yardımcı olabilir ve erken klinik veya YBÜ kabulünü tahmin etmek için tarama aracı olarak kullanılabilir.

Anahtar kelimeler: Çocuklar, acil servis, PEWS, güvenilirlik, geçerlilik

Introduction

The numbers of patients presenting to pediatric emergency units are rising continually. The early identification of critical patients in emergency units with limited time and resources and the planning of treatment as quickly as possible are highly important. Hospital-acquired complications and those resulting from inappropriate or delayed diagnosis and treatment can both increase morbidity and mortality rates [1].

Warning signs of clinical deterioration in children may occur during initial presentation to hospital, or suddenly during clinical follow-up. Patients requiring treatment through admission to the ward or intensive care need to be detected early during observation in the emergency unit. However, the detection of patients requiring admission to the ward or intensive care may not be as simple and quick as desired [2]. Several scales using various physiological findings have therefore been developed for use in the decision to admit patients to the ward or intensive care [3]. One such is the Pediatric Early Warning Score (PEWS) scale. PEWS, a scoring system using physiological parameters, was developed for the early detection by healthcare professional of clinical worsening in pediatric patients under observation in the emergency department or on the ward [4]. PEWS has been validated by translation into several languages in order to permit the use of a common tool for assessing the clinical state of emergency pediatric patients in different populations and cultures [5-8]. However, a systematic review of the current literature elicited no Turkish-language version of the PEWS in clinical use. The purpose of this study was therefore to translate PEWS into Turkish and subsequently validate it.

Material and Methods

Study design

After being approved by the local ethics committee of Ondokuz Mayıs University, Faculty of Medicine with the registration number OMUKAEK-2022/188 (dated: 30 April 2022), this observational, prospective study was conducted among pediatric patients under the age of 17. All the children and their parents can understand and read the Turkish language and the parents of the children who were included in the study were fully informed about the study details and written consent was obtained from them before data collection.

Patients

Data were collected for all children who presented to the Samsun University, Samsun Maternity and Children's Training and Research Hospital emergency department between 1 May and 30 October 2022. This is a tertiary care university hospital with a 24-h emergency department. Patients who received home mechanical ventilator support or intubation, traumatic and psychiatric patients, and patients in the neonatal period (<30 day) were excluded from the study. The patients were divided into two groups. Group 1 consisted of patients who were not admitted to intensive care and Group 2 those who were admitted.

PEWS Description

PEWS consists of three dimensions involving behavioral awareness, the cardiovascular system, and the respiratory system. It yields reliable information that allows clinical nurses to evaluate the states of pediatric patients in a rapid, objective, and accurate manner. Each dimension is scored from 0 to 3, and the PEWS score representing the sum of the three dimension scores. Higher scores indicates more severe disease. In addition to these three main parameters, it also involves two further parameters of continuous nebulization for every 15 minutes and persistent vomiting following surgery. A score of 1, for each, is added to the total if these complaints are present. Total PEWS scores thus range from 0-11. A PEWS total score of 0–1 indicates that no treatment is required and that observation should be maintained. A score of 2 indicates that the responsible nurse should be notified to employ PEWS for continuous monitoring, to assess the presence of symptoms such as pain and fever, and to determine fluid balance and urine output. A score of 3 indicates that the patient should be assessed a minimum of every 24 h, observed and evaluated dynamically, and that the specialist nurse should be notified. A score of 4 indicates that evaluation should be performed at least once every 8 h, that the duty physician or resident physician should be notified, and that the patient should be prepared for transfer. Scores higher than 4, an increase >2 points, or a single score of 3 points indicate that the patient should be evaluated every 4 h, that the general inpatient and pediatric intensive care physicians should be notified to arrive within 15 minutes, to cooperate with the rescue procedures, and that the patient should be prepared for transfer [4,9,10].

The first stage of this study involved the translation and cultural adaptation of PEWS. A multi-step approach based on the guideline recommended by Guillemin and Beaton was adopted during this process [11,12]. The original version of the PEWS was first translated from English to Turkish by three individuals, including a native English speaker (a university graduate resident in Turkey for the previous three years) and two academics from the university's English Language Department. The resulting Turkish-language version was then back-translated into English by two different English linguistic academics from the university English Language Department. Following those procedures, the most comprehensible form of each question was produced by a three-member committee, including a health professional fluent in English, a Turkish linguist, and an English linguist.

Pilot testing

The pediatric emergency department nurse was first given bedside training sessions, in which the content of PEWS and how the results are evaluated were explained. This study was conducted in two phases. During the pilot phase, two triage nurses were asked to perform blind scoring in each patient for the first 30 patients, and inter-rater reliability was measured using kappa statistics. The Turkish version of the PEWS was thus finalized.

Procedure

In the second phase, the scores were then recorded on the PEWS chart–triage nurse section (Figure 1). Pediatric emergency physicians blinded to the scores were then asked to complete the PEWS chart pediatric doctor section, consisting of diagnosis, underlying diseases, and disposition. Once good inter-rater reliability (>0.70) had been ensured, the scoring was performed by one triage nurse during each shift. Based on a probability of expected sensitivity of 0.70 in the previous study, a sample size of 228 patients was calculated to be sufficient to validate the score [8]. The PEWS was used by a nurse in the pediatric emergency unit for the purpose of evaluating patients' health status.

Patient characteristics, including age, gender, and body mass index (BMI) were recorded.

Statistical analysis

Normality and variance were evaluated using the One-Sample Kolmogorov-Smirnov test for each variable. Quantitative data were presented as means and standard deviation, and qualitative data as frequency and percentage. Comparisons were completed using the Mann-Whitney U test. Categorical variables were analyzed using the Chi-square test. A cut-off value for unexpected intensive care unit admission with acceptable sensitivity and specificity, along with an appropriate confidence interval, was also calculated. The validity of the PEWS score was evaluated using the area under the ROC curves, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). A p values lower than 0.050 were considered statistically significant. Analyses were performed on Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) version 20.0 software.

Results

Two hundred twenty-eight patients, with a mean age of 6.37±4.72, 43% of whom were female, were included in the study. While a significant age difference was observed between the groups, there was no significant difference in terms of gender, BMI, spent in the emergency department, or hour

of admission. The demographic characteristics of the groups are presented in Table 1. The frequency of comorbidities was asthma in two (0.9%), congenital syndromes in three (1.3%), neurological diseases in seven (3.1%), diabetes in four (1.8%), cardiac disease in one (0.4%), and metabolic syndrome in one (0.4%). In terms of complaints during admission, dermatological problems were present in eight patient (3.2%), fever in 45 (19.8%), nausea in six (2.4%), vomiting in 84 (33.6%), abdominal pain in 32 (12.8%), sore throat in 10 (4%), respiratory problems in 29 (11.6%), and seizure in 21 (8.4%). ROC analysis among several cut-off values for PEWS scores is shown in Table 2. ROC curve analysis of the PEWS score revealed an AUC of 0.948 (Figure 2). The cut-off value for the PEWS score at ROC curve analysis was 4 (PEWS >4).

PEDIATRIC EARLY WARNING SCORE (PEWS)

Behavior	Playing /appropriate	0		
	Sleeping	+1		
	Irritable	+2		
	Lethargic/confused or reduced responsed to pain	+3		
Cardiovascular	Pink OR capillary refill 1-2 seconds	0		
	Pale OR capillary refill 3 seconds	+1		
	Gray OR capillary refill 4 seconds OR tachycardia of 20 bpm above normal	+2		
	Gray and mottled OR capillary refill ≥5 seconds OR tachycardia of 30 bpm above normal OR bradycardia	+3		
Respiratory	Within normal parameters, no retractions	0		
	>10 above normal parameters using accessory muscles OR 30+%FiO2 or 3+L/min	+1		
	>20 above normal parameters and retractions OR 40+ %FiO2 or 6+ L/min	+2		
	Five below normal parameters with retractions and grunting OR 50% FiO2 or 8+ L/min	+3		
Quarter hourly nebulizers (every 15 minutes)	No	0	Yes	+1
Persistent vomiting following surgery	No	0	Yes	+1

Figure 1. The pediatric early warning score developed by Monaghan (4).

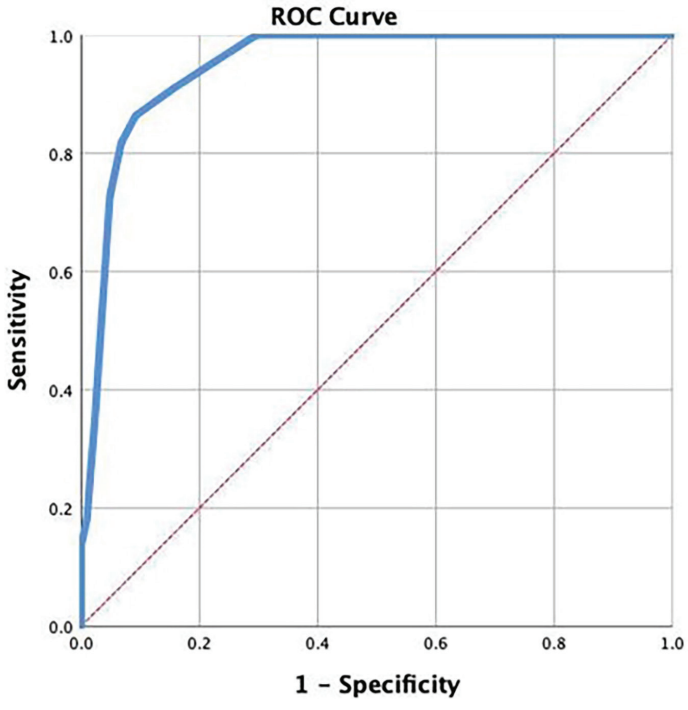

Figure 2. Receiver operating characteristic (ROC) curve of the Turkish version of PEWS(AUC = 0.948, p <0.05; CI = 0.915 – 0.981)

Discussion

The present study investigated the validation of the Turkish-language version of PEWS, one of the most widely and effectively used questionnaires for evaluating pediatric patients in the emergency department [13]. Our search of the literature showed that the scale had previously been adapted in numerous other countries, but not in Turkey. According to the results of the present study, PEWS exhibits acceptable levels of validity, reliability, and clinical feasibility in Turkish children.

Analysis for intensive care unit admission in this study showed that an AUC of 0.948 for all patients indicated excellent predictive ability. The equivalent value in Chaiyakulsil and Pandee's study was 0.97, and both values are high [5]. Using a cut-off value of ≥3, the sensitivity and specificity of PEWS were 90.91% and 84.47%, respectively. These values were superior to those of the original pilot study by Egdell et al. (AUC: 0.86, sensitivity 70%, specificity 90%), than in extensive studies in Rwanda by Rosman et al. (AUC: 0.77, sensitivity 96%, specificity 87.3%), and Chaiyakulsil and Pandee's study from Thailand (AUC: 0.97, sensitivity 100%, specificity 95%) [5,7,14].

Early warning scores for deterioration in adult patients were described as far back as the late 1990s, but PEWS was not published by Monaghan until 2005 [4]. Monaghan derived that scale from an adult tool and employed a 3 x 3 scoring matrix measuring the child's behavior, and cardiovascular and respiratory status. Further weighting was added for continuous nebulizers or persistent post-operative vomiting. By 2013, the majority of hospitals in the UK were reported to be using PEWS [15]. According to Agulnik et al., PEWS is used in almost all Spanish-speaking countries [8]. Despite being used for many years in several countries, PEWS has not been validated for Turkey. This renders the present study particularly valuable.

There are a number of limitations to this study. In particular, the research was performed at a single center, and it is therefore unclear whether the PEWS score's predictive ability is capable of direct generalization to other hospitals with their own distinct patient populations and health personnel. PEWS scores in this study were calculated by triage nurses. Another limitation of this study is the relatively small sample size.

Conclusion

The Turkish-language version of the PEWS questionnaire is a reliable, comprehensible, and valid instrument for assessing clinical deterioration in children presenting to the emergency department or hospitalized [Appendix]. The answerability and reliability of the questionnaire can be enhanced with further studies.

Table 1. Demographic characteristics of patients				
Variables	Total (n = 228)	Group 1 (n = 206)	Group 2 (n = 22)	p*
Age (years, mean±SD)	6.37±4.72	6.55±4.72	4.63±4.5	0.043
Gender (female, [n, %])	99, 43.4%	87, 42.2%	12, 54.5%	0.029
BMI (kg/m2, mean±SD)	19.75±9.37	19.8±9.71	19.23±5.34	0.793
Spent in the ED (min, mean±SD)	122.25±104.11	125.77±107.09	89.36±62.96	0.059
Admission hour (n, %)				
08:00-16:00	90 (39.5%)	82 (39.8%)	8 (36.4%)	
16:00-24:00	74 (32.5%)	66 (32%)	8 (36.4%)	
00:00-08:00	64 (28.1%)	58 (28.2%)	6 (27.3%)	0.914
* Chi-square or Mann-Whitney U test.				
BMI, Body mass index; Min, minute; ED, Emergency department; SD, Standart deviation.				

Table 2. Pediatric early warning score prediction ability by score				
Score	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]
≥1	100 [84.56 – 100]	59.22 [52.18 – 66]	20.75 [18.18 – 23.59]	100
≥2	100 [84.56 – 100]	70.39 [63.65 – 76.53]	26.51 [22.61 – 30.8]	73.25 [67 – 78.87]
≥	90.91 [70.84 – 98.88]	84.47 [78.78 ¬– 89.13]	38.46 [30.69 – 46.87]	98.86 [79.79 – 89.45]
≥4	86.36 [65.09 – 97.09]	90.78 [85.97 – 94.36]	50 [38.71 – 61.29]	98.42 [95.61 – 99.44]
≥5	81.82 [59.72 – 94.81]	93.2 [88.86 – 96.23]	56.25 [42.77 – 68.87]	97.96 [95.18 – 95.25]
≥6	72.73 [49.78 – 89.27]	95.15 [91.25 – 97.65]	61.54 [45.35 – 75.52]	97.03 [94.29 – 98.48]
PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; PEWS, pediatric early warning score.				

Conflict of interest

All authors declare that they do not have any conflicts of interest.

Disclosure Statement

The authors have no relevant financial or non-financial interests to disclose.

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Research Article

Relationship between the severity of acute pancreatitis and vitamin D level in geriatric patient population

Geriatrik hasta popülasyonunda akut pankreatit şiddeti ile D vitamini düzeyi arasındaki ilişki

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Abstract

Aim: It is important to determine the severity of acute pancreatitis (AP) and its prognosis.The aim of this study is to research the efficiency of vitamin D level on the severity of acute pancreatitis in geriatric population.

Material and Methods: Files of 4108 patients were analyzed retrospectively. Serum vitamin D levels of total 404 patients (geriatric 160 (n:160); non-geriatric 244 (n:244)) were compared between mild, moderate and severe groups according to revised Atlanta classification for acute pancreatitis. Relationship between the severity of acute pancreatitis and vitamin D levels were analyzed.

Results: No significant difference was observed in non-geriatric patients in terms of vitamin D levels according to the Atlanta classification for acute pancreatitis. However, there were significant differences both between mild and moderate groups and between moderate and severe groups in geriatric patients ($p<0.005$). AP was more severe in patients with a low vitamin D level ($p<0.005$).

Conclusion: We have concluded that vitamin D levels may be insufficient to predict the severity of acute pancreatitis considering age factor, which is a substantial indicator of its prognosis. Vitamin D levels have been found out to be efficient in the severity of disease in geriatric acute pancreatitis patients compared to non-geriatric ones.

Keywords: Acute pancreatitis, Atlanta classification, geriatric population, vitamin D

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Öz

Amaç: Akut pankreatitin (AP) şiddetini ve prognozunu belirlemek önemlidir. Bu çalışmanın amacı geriatrik popülasyonda D vitamini düzeyinin akut pankreatitin şiddeti üzerindeki etkinliğini araştırmaktır.

Gereç ve Yöntemler: 4108 hastanın dosyaları retrospektif olarak analiz edildi. Toplam 404 hastanın (geriatrik 160 (n:160); geriatrik olmayan 244 (n:244)) serum D vitamini düzeyleri akut pankreatit için revize Atlanta sınıflamasına göre hafif, orta ve şiddetli gruplar arasında karşılaştırıldı. Akut pankreatitin şiddeti ile D vitamini düzeyleri arasındaki ilişki analiz edildi.

Bulgular: Akut pankreatit için Atlanta sınıflamasına göre D vitamini düzeyleri açısından yaşlı olmayan hastalarda anlamlı bir fark gözlenmedi. Ancak, geriatrik hastalarda hem hafif ve orta gruplar arasında hem de orta ve şiddetli gruplar arasında anlamlı farklılıklar vardı (p<0,005). D vitamini düzeyi düşük olan hastalarda AP daha şiddetli idi (p<0,005).

Sonuç: Prognozun önemli bir göstergesi olan yaş faktörü göz önüne alındığında, D vitamini düzeylerinin akut pankreatitin şiddetini öngörmede yetersiz olabileceği sonucuna vardık. D vitamini düzeylerinin geriatrik akut pankreatit hastalarında geriatrik olmayanlara kıyasla hastalığın ciddiyetinde etkili olduğu bulunmuştur.

Anahtar Kelimeler: Akut pankreatit, Atlanta sınıflandırması, geriatrik popülasyon, D vitamini

Introduction

Acute pancreatitis (AP) is an inflammatory process progressing with clinical, morphological, and functional changes. The cell injury due to early activation of pancreatic proteases, constitutes the basic pathophysiology of acute pancreatitis (1).

The prevalence of AP, which is associated with high mortality and morbidity, is increasing all over the world. The annual AP incidence reported in the USA varies from 4.9 to 35 per 100,000 population (2,3). Gallstones and alcohol are the most common reasons of AP (4).

Most of AP attacks are mild and self-limited and are managable with symptomatic treatment. A serious clinical condition with a higher mortality rate up to 30% may occur in around 20% of the patients (5).

Various scoring methods including clinical, laboratory and radiological criteria have been devoleped in order to determine the severity of the disease in patients at risk and to determine the treatment correctly. Various scoring methods including clinical, laboratory, and radiological criteria have been developed in order to determine the severity of the disease in patients at high risk and to decide on the treatment approach. Ranson criteria, Imrie scoring system (Modified Glaskow 2), Acute Physiology and Chronic Health Evaluation II (APACHE II), Tomography Severity Index (CTSI), Bedside Index of Severity in Acute Pancreatitis (BISAP), Balthazar Score (BT Severity Index), and Atlanta Classification are the most common ones (6). Although each method is separately guiding, they have complicated processes and several challenges (7).

Atlanta classification based on clinical and radiological features have been defined in 1992 and revised in 2012. The severity of AP is classified as mild, moderate, and severe based on the presence of local complications in CT and that of organ failure (8).

The mechanism contributing to an increase in pancreas injury and pancreatic necrosis is mainly based on hyperinflammation (1). As the information obtained increases, the relationship between ap and metabolic diseases gains importance day by day.

Several recent studies have revealed that serum vitamin D level is closely related to the severity of AP and its prognosis (9-11).

Vitamin D is a biomarker having receptors in many organs of human body, which plays an important role on most diseases including diabetes mellitus (DM), cardiovascular diseases, cancer, infectious diseases, and otoimmune diseases. Vitamin D deficiency is commonly accepted as serum 25-hydroxyvitamin D level (25OHD) <10 ng/ml (<25 mmol/lt) because lower values are associated with rickets and/or osteomalacia. However, values <20 ng/dl and <10 ng/dl are defined as insufficiency and deficiency, respectively, by the World Health Organization (WHO) (12). On the other hand according to the Turkish Endocrine and Metabolism Society; levels above 20 ng / ml (50 nmol / L) is sufficient for bone health, levels between 30 and 50 ng / ml (75-125 nmol / L) are sufficient for extra-bone effects. And while the levels between 10 and 20 ng / ml (25-50 nmol / L) are considered as vitamin D insufficiency, levels <10 ng / ml (25 nmol) / L) are considered as vitamin D deficiency (13).

It is estimated that almost 1 billion people around the world have vitamin D deficiency. That there are different outcomes related to vitamin D in different countries, even in different parts of the same country, has been revealed by studies conducted before. It has also been revealed that vitamin D deficiency has been experienced by 40% to 100% of the elderly males and females in Europe and America. This rate is quite high in those people staying at nursing homes. Similarly, that vitamin D deficiency is common in our country has been revealed in some studies.

It is indicated that vitamin D has a great role on innate and acquired immunity. There are several published reports

indicating how it plays a role on the protection of human body against pathogens and also supporting the idea that it may be used for medical purposes in acute and chronic infections. Vitamin D deficiency is also associated with the severity of various diseases. On the other hand, it has been revealed that it has a basic role on defence against antibiotic-resistant pathogens, increases resistance to sepsis in animal models, and speeds up the healing process of epithelial injury.

Based on the effects of macrophages and of T cells on acute pancretitis prognosis and the process of necrosis, the association between the severity of AP and vitamin D levels have been demonstrated in limited studies (11), and as far as we know, there is no study conducted in geriatric population concerning to this matter in literature.

In this study; We aimed to investigate the potential effect of serum vitamin D level as a predictor for determining the severity of AP in geriatric patients and nongeriatric patients under 65 years of age at the time of admission.

Material and Methods

Files of 4108 patients who were hospitalized in Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Department of Internal Medicine, between the dates of January 2015 and March 2019 were analyzed retrospectively. 404 patients diagnosed with AP who have had a CT scan were included in the study. AP is diagnosed by the presence of the following 2 factors:

1. Abdominal pain,

2. Serum amylase and/or lipase levels more than 3 times the upper limit of normal,

3. Radiological signs

The severity of AP was classified as mild, moderate, and severe based on Atlanta classification for Acute Pancreatitis (14). Vitamin D levels were considered as follows: A level below 10 ng/ml as severe deficiency, between 10 ng/ml and 20 ng/ml as deficiency, and above 20 ng/ml normal (15). Patients were divided into two groups: the geriatric group over 65 years of age and the non-geriatric group under 65 years of age.

Patients under the age of 18, those with a history of pancreatic and patients with chronic or recurrent pancreatitis were excluded from the study. Age, gender, etiologic causes, comorbid diseases, duration of hospitalization, antibiotic use in postpancreatic period and laboratory data of patients were determined (Table 1 and 2). Acute pancreatitis severity and serum vitamin D levels were compared according to Atlanta classification between geriatric and non-geriatric group.

Our study has been approved by Clinical Research Ethics Committee of University of Health Sciences, xxxxxx Training and Research Hospital (Date: September 7, 2020; Decree no: 95/04) and conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

SPSS Statistics Version 21.0 (IBM®, Chicago, The USA) was used for statistical analysis of our data. Normality of distribution was checked by a combination of visual inspection (histogram and probability charts) of data points and the analytical method Shapiro-Wilk normality test. Descriptive statistics were expressed as mean and standard deviation in normally distributed numerical data whereas median and minimum-maximum range in those not showing normal distribution. However, descriptive statistics were expressed as numbers and percentages in nominal data. Normally distributed numerical variables were analyzed by "Independent T-test" between two groups, "One-Way ANOVA test" between three groups, and "Paired Sample T-test" within the group. Numerical variables that did not show normal distribution were compared using the "Mann-Whitney U test" between the two groups and the "Kruskal-Wallis test" between the three groups. On the other hand, nominal values between two groups were evaluated using "Chi-Squared" test or "Fisher's Exact test". P-values below 0.05 were accepted as statistically significant in this study.

Results

Mean age of all patients included in this study was 62 years. The mean age for patients under and over the age of 65 was 50 and 77, respectively. Compared with both groups in terms of comorbid diseases; hypertension, DM, and chronic obstructive pulmonary disease (COPD) were seen more in the group above 65 years, although steatosis was more common in the group below 65 years ($p<0.05$). Cholelithiasis, an etiologic factor of AP, and antibiotic use in post-pancreatic period were found out to be higher in geriatric group ($p<0.05$). Moreover, the duration of hospitalization in the group above 65 years was 7 days longer than the other one ($p<0.05$).

A statistically significant difference was found between the geriatric and non-nongeriatric groups in terms of the ratio of the mild group and the moderate-severe group defined according to the atlanta classification for AP ($p<0.05$). 72.5% of patients had mild AP and 27.5% had moderate-severe AP in the non-geriatric group whereas the ratios were 57.5% and 42.5% in the geriatric group, respectively ($p<0.001$). It was observed that the severity of AP had increased in elderly patients. The distribution of the sociodemographic characteristics of the patients according to the age factor is shown in Table 1.

There were also statistically significant differences between the geriatric and non-geriatric groups in terms of the level of change in laboratory values ($p<0.05$). Calcium, magnesium, and albumin levels were found to be lower whereas Erythrocyte sedimentation rate (ESR), C-Reactive

Protein (CRP), Haemoglobin A1C (HbA1C) and bilirubin levels were found to be higher in the geriatric group compared to nongeriatric group. In the geriatric group; Vitamin D levels were below 10 ng / ml in 86 patients, between 10 and 20 ng / ml in 50 patients and below 10 ng / ml in 24 patients. In the non-geriatric group vitamin D levels were less than 10 ng / ml in 136 patients, between 10-20 ng / ml in 85 patients and were less than 10 ng / ml 23 patients. No statistical significant difference was detected between two groups (p=0.221). The distribution of laboratory parameters of the patients by age factor is demonstrated in Table 2.

Considering the severity of AP, mean age was significantly higher in the moderate-severe group than in the mild group (65 (21-97) and 57.5 (20-98), respectively, p<0.001). Antibiotic usage rate in post-pancreatic period were 28.6% and 60.7%, respectively, in mild and moderate-severe AP (p<0.001). Hospitalization durations were 5.5 (2-19) and 9 (2-29) days in the mild and the moderate-severe groups, respectively (p<0.001). The distribution of the sociodemographic characteristics of the patients according to the severity of AP is shown in Table 3.

ESR, CRP, and parathormone (PTH) were detected to be higher whereas albumin and phosphore levels were detected to be lower in the moderate-severe group compared to the mild group in the analysis carried out between laboratory parameters and the severity of AP. The difference was statistically significant (p<0.05). No significant relationship between the other parameters and the severity of AP was detected. The distribution of laboratory parameters of the patients according to the severity of AP is demonstrated in Table 4.

66.5% of AP patients constitute the mild group, 30.6% the moderate group and 2.9% the severe group. In non-geriatric group, %72.5 (n:177) of patients constitute the mild group, %26.2 (n:64) the moderate group and %1.3 (n:3) the severe group. No statistically significant data was found regarding the difference in vitamin D levels between mild, moderate and severe groups. However, there was a significant difference between the mild group (%57.5 (n:92)), the moderate group (%37.5 (n:60)) and the severe group (%5 (n:8)) in the geriatric patient group in terms of vitamin D levels (p=0.017). When vitamin D levels of all patients were compared between groups determined according to Atlanta Classification; there were statistically significant differences both between moderate and severe groups and between mild and severe groups. (p<0.005). Relationship between vitamin D levels and the severity of AP is demonstrated in Table 5.

Table 1. Distribution of Sociodemographic Characteristics by Age

Sociodemographic characteristics			All patients (N=404)	< 65 years (N=244)	≥ 65 years (N=160)	P value
Age		Median (min-max)	60 (20-98)	50 (20-64)	77 (65-98)	
Gender		N (%)				
	Female		247 (61.1)	141 (57.8)	106 (66.3)	0.088†
	Male		157 (38.9)	103 (42.2)	54 (33.8)	
Comorbidity		N (%)				
	Hypertension		114 (28.2)	36 (14.8)	78 (48.8)	<0.001†
	Diabetes Mellitus		68 (16.8)	28 (11.5)	40 (25)	<0.001†
	COPD		27 (6.7)	9 (3.7)	18 (11.3)	0.003†
	Steatosis		156 (38.6)	105 (43)	51 (31.9)	0.024†
Etyology		N (%)				
	Cholelithiasis		269 (66.6)	151 (61.9)	118 (73.8)	0.013†
	Drug		19 (4.7)	13 (68.4)	6 (31.6)	0.464 †
	Ethanol		7 (1.7)	5 (75)	2 (25)	0.547††††
CT signs		N (%)				
	Pankreatitis (-)		107 (46.1)	63 (43.8)	44 (50)	0.354†
	Pankreatitis (+)		125 (53.9)	81 (56.3)	44 (50)	
Antibiotic use in post pancreatitis stage			166 (38.9)	76 (31.1)	83 (51.9)	<0.001†
Duration of Hospitalization		Median (min-max)	6 (2-29)	6 (2-28)	7 (2-29)	0.001††
Atlanta Classification		N (%)				
	Mild		269 (66.6)	177 (72.5)	92 (57.5)	0.002†
	Moderate-severe		135 (33.4)	67 (27.5)	68 (42.5)	

CT:Computerized Tomography; COPD: Cronic Obstructive Pulmoner Disease † Pearson Chi-Squared" test; †† Man Whitney U Test ; ††† İndependent Groups T Test; †††† Fisher Exact Testi

Table 2. Distribution of Laboratory Parameters by Age

Laboratory Parameters			All Patients (N=404)	< 65 years (N=244)	≥ 65 years (N=160)	P value
		N (%)				
Vitamin D (ng/dl)	<10		222 (55)	136 (55.7)	86 (53.8)	0.221†
	10-20		135 (33.4)	85 (63)	50 (31.3)	
	>20		47 (11.6)	23 (48.9)	24 (15)	
		Mean±sd				
Phosforus (mg/dL)			3.0±0.7	3.0±0.7	2.9±0.7	0.348†††
		Median (min-max)				
Calcium (mg(dL)			9.3 (6.5-12)	9.3 (6.9-11.1)	9.2 (6.5-12)	0.004††
Triglyceride (mg(dL)			109 (27-3705)	109 (38-3705)	109 (27-312)	0.374††
CRP (g/L)			56 (2-427)	38 (2.9-427)	74 (2-325)	<0.001††
ESR (mm/h)			23.5 (1.4-114)	19.5 (1.4-114)	29 (2-95)	<0.001††
Albumin (g/dL)			3.5 (2.2-5.6)	3.6 (2.6-5.6)	3.4 (2.2-4)	<0.001††
Magnesium (mg(dL)			1.8 (1.1-3.6)	1.9 (1.5-3.6)	1.8 (1.1-2.3)	0.001††
HbA1c (%)			5.8 (4.4-19)	5.7 (4.4-19)	6.0 (4.8-14.1)	0.001††
Amylaz (U/L)			1190 (94-10778)	1230 (94-10778)	1092 (118-5518)	0.145††
Lypaz (U/L)			3327 (102-26064)	3497 (243-26064)	3135 (102-19025)	0.146††
Parathormone (ng/L)			50 (1.4-284)	43 (1.4-284)	58.5 (3-276)	<0.001††

CRP:C-Reaktive Protein; HbA1C: Haemoglobin A1C; ESR: Erythrocyte sedimentation ratio. † Pearson Chi-Squared" test , †† Man Whitney U Testi ; ††† İndependent Groups T Testi;

Table 3. Distribution of Sociodemographic Characteristics by Severity of Acute Pancreatitis

			Atlanta Classification		
			Mild	Moderate-severe	P value
Sociodemographic Characteristics					
Age		Median (min-max)	57.5 (20-98)	65 (21-97)	<0.001††
Gender		N (%)			
	Female		165 (61.3)	82 (60.7)	0.907†
	Male		104 (38.7)	53 (39.3)	
Komorbidite		N (%)			
	Hypertension		72 (26.8)	42 (31.1)	0.360†
	Diabetes Mellitus		46 (17.1)	22 (16.3)	0.839†
	COPD		17 (6.3)	10 (7.4)	0.680†
	Steatosis		98 (36.4)	58 (43)	0.203†
Etyology		N (%)			
	Cholelithiasis		179 (66.5)	90 (66.7)	0.980†
	Drug		15 (5.6)	4 (3)	0.242†
	Ethanol		5 (1.9)	2 (1.5)	1.000††††
		N (%)			
CT findings	Pankreatit (-)		95 (70.9)	12 (12.2)	<0.001†
	Pankreatit (+)		39 (29.1)	86 (87.8)	
Antibiotic use in post pancreatitis stage			77 (28.6)	82 (60.7)	<0.001†
Duration of Hospitalization		Median (min-max)	6 (2-19)	9 (2-29)	<0.001††

CT:Computerized Tomography; COPD: Cronic Obstructive Pulmoner Disease † Pearson Chi-Squared" test; †† Man Whitney U Test ; ††† İndependent Groups T Testi; †††† Fisher Exact Testi

Table 4: Distribution of Laboratory Parameters by Severity of Acute Pancreatitis					
			Atlanta Classification		
Laboratory Parameters			Mild	Moderate-severe	P value
		N (%)			
Vitamin D (ng/dl)	<10		155 (57.6)	67 (49.6)	0.146†
	10-20		88 (32.7)	47 (34.8)	
	>20		26 (9.7)	21 (15.6)	
		Mean ± sd			
Phosphorus (mg/dL)			3.1±0.6	2.8±0.8	0.007†††
		Median (min-max)			
Calcium (mg(dL)			9.3 (6.5-12)	9.2 (6.9-10.9)	0.219††
Trygliseride (mg(dL)			112 (38-3193)	102 (27-3705)	0.201††
CRP (g/L)			38 (2.9-427)	95 (2-416)	<0.001††
ESR (mm/h)			22 (1.4-114)	27 (2-95)	0.040††
Albumin (g/dL)			3.5 (2.4-5.1)	3.4 (2.2-5.6)	0.011††
Magnesium (mg(dL)			1.9 (1.2-3.6)	1.8 (1.1-2.6)	0.320††
Amylaz (U/L)			1055 (105-10778)	1272 (94-8168)	0.082††
Lipaz (U/L)			3258 (102-26064)	3579 (162-22923)	0.652††

CRP: C-Reaktif Protein; ESR: Erythrocyte sedimantation ratio † Pearson Chi-Squared" test; †† Man Whitney U Test ; ††† İndependent Groups T Test

Table 5. The Relationship Between Vitamin D levels and The Severity of Acute Pancreatitis						
			Atlanta classification			
			Mild (N=269)	Moderate (N=124)	Severe (11)	p value
		N(%)				
<65 age			177 (65.8)	64 (51.6)	3 (27.3)	0.463
≥ 65 age			92 (34.2)	60 (48.4)	8 (72.7)	0.017
		Median (min-max)				
Vitamin D Level (ng/dL)	All patients		9 (0-47)	10.6 (0.6-119.6)	6.8 (2.4-9.4)	A**B*C*
	<65 age		9.4 (2.6-38)	9.8 (1.4-51)	6.3 (6-8.6)	A**B**C**
	≥ 65 age		8.2 (0-47)	12.5 (0.6-119.6)	6.9 (2.4-9.4)	A*B*C**

Pancreatitis
A: Comparison of Mild Group and Moderate Group; B: Comparison of Mild Group and Severe Group; C: Comparison of Mild Group and Severe Group.
*-p<0,05; **-p≥0,05. Kruskal Wallıs Test was used in comparison of 3 grroups and Mann Whitney U Test was used in comparison of 2 groups.

Discussion

Due to the rapid increase in the elderly population all over the world, there is an increase in the incidence, severity and mortality of all diseases in this population. One of these diseases is AP.

The high mortality and morbidity of AP have caused to be conducted more studies to determine its prognosis and to take required precautions. Although there are few publications in the literature showing the relationship between vitamin D and the severity of AP, there is no study conducted in the geriatric population so far (11).

In a prospective study conducted by Bang et al. In patients with acute pancreatitis, vitamin D levels were measured at 0 and 48 hours, and vitamin D levels were shown to decrease in the first 48 hours. This has been attributed to the increased use of vitamin D due to the inflammatory process in AP (9,10). Increased macrophages during inflammation reduce the formation of 1.25 OH vitamin D by decreasing the 25 OH-vitamin D level (16). As a result, hypercalcemia, which exacerbates inflammaton is prevented. In this study, a negative correlation of vitamin D level with CRP in AP was shown, and it was suggested that vitamin D could be considered as a negative acute phase reactant.

Hummel et al have revealed that 25 OH-vitamin D and CYP24A1 expressions increase in the inflamed pancreatic tissue (17). On the other hand, El-Mahdy et al demonstrated that etiologic factors may be associated with the severity of AP, and vitamin D receptor (VDR) cannot predict the severity of the disease (5).

In the first and only study conducted by Huh et al. with 242 patients with AP, which investigated the relationship between vitamin D level and the severity of pancreatitis, 28.5% of the patients were found to have vitamin D deficiency and it was found that vitamin D deficiency could be used as an independent factor in predicting severe AP (OR 5.37, 95% CI

1.13-25.57) (11). Although there were mostly elderly people, no distinction was made especially regarding age in the study.

Although it differs from other studies in the literature because it takes the age factor as a criterion, when the results of the study are evaluated regardless of age we obtained similar results in our study. On the other hand, we could not detect any relationship with vitamin D levels and the severity of AP in the non-geriatric group considering age factor which has kept in mind that the increase in AP severity may be derived from age factor rather than vitamin D levels. The severity of AP has been detected to be higher in the geriatric population, which has been an expected outcome.

Kara et al have revealed that the severity of AP and duration of hospitalization in geriatric population is higher than in non-geriatric population (18). Similar results have been indicated in the other studies (19-21).

Age factor, various laboratory parameters, and long-term duration of hospitalization is are the most prominent indicators of severe AP (5). Some laboratory parameters such as CRP, procalcitonin, albumin, and lactate dehydrogenase (LDH) have been evaluated in several studies. In compliance with the literature, we have found CRP levels to be higher, and albumin levels to be lower in severe AP (22-24). We have also found a relationship between vitamin D levels and the severity of AP in the geriatric group in particular. The study conducted by Huh et al had been consisting of the elderly patients. The reason of why the relationship between vitamin D levels and the severity of AP has not been detected in the non-geriatric group may be derived from this difference.

Our study has some limitations. First, only one method has been preferred to evaluate the severity of AP, although there are some other methods like RANSON, BISAP, and CTSI. Second, the cause-effect relationship between vitamin D levels and the severity of AP cannot be evaluated due to the retrospective study design of our study.

In conclusion, vitamin D deficiency is more common in the elderly and the levels are affected by many factors such as age, gender, geographical location and race (12,25,26). This may prevent vitamin D from being a prognostic factor for AP. We think that multicenter and prospective studies are needed on the relationship between vitamin D and AP, especially in the geriatric population.

Conclusion

Vitamin D level is a guiding factor for most studies thanks to its being an easily accessible test and its well-known role on inflammation. It is also found out to be associated with the severity of AP. However, issues such as the fact that vitamin D levels are affected by many factors and the lack of consensus in the world in terms of insufficiency / deficiency, limit making a general inference. Additional studies are needed, especially on elderly patients.

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Declarations

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Competing interests

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Author contributions

MT and CG contributed to the conception and design of the work, acquisition, analysis, interpretation of data, drafting, revision, and final approval of the work. All authors had the data access and contributed to the article.

Ethical conduct of research

Research ethics approval dated September 7, 2020 and numbered 95/04 has been received from Clinical Research Ethics Committee of University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital and informed consents have also been taken from all patients in accordance with the Declaration of Helsinki.

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Araştırma Makalesi

Dikkat eksikliği ve hiperaktivite bozukluğu tanısı olan çocuklarda sosyal beceri eğitiminin yaşam kalitesi üzerine etkisi

The effect of social skills training on quality of life in children with attention deficit and hyperactivity disorder

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Öz

Amaç: Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) ailelerin ve çocukların yaşamını etkileyen kronik bir bozukluk olmasından dolayı birçok çalışmada bu bozukluğun yaşam kalitesi üzerindeki etkileri araştırılmıştır. DEHB'de bozulan diğer bir alan da sosyal işlevselliktir. Sosyal işlevsellikte bozulma DEHB'nin hem uzun hem de kısa dönem olumsuz gidişatı açısından önemlidir. Ancak sosyal işlevselliğin yaşam kalitesini nasıl etkilediği daha az bilinmektedir. Çalışmamızda DEHB tanılı çocuklarda sosyal becerilerin geliştirilmesinin yaşam kalitesi üzerine etkisini araştırmak amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya çocuk ve ergen ruh sağlığı polikliniğinde DEHB tanısı ile takipli, en az 6 aydır ilaç tedavisi alan, kronik hastalığı olmayan, 8-12 yaş aralığında olan, 15 çocuk ve ebeveyn dahil edilmiştir. Çalışmaya dahil edilen çocuklardan Çocuklar İçin Yaşam Kalitesi Ölçeği (ÇİYKÖ)- Çocuk Formu'nu, ebeveynlerinden ise Çocuklar İçin Yaşam Kalitesi Ölçeği (ÇİYKÖ)- Ebeveyn Formu'nu eğitim öncesi ve sonrası doldurmaları istenmiştir. Çocuklar ile haftada bir gün bireysel olarak uygulanan sosyal beceri eğitim seansları uzman tarafından on iki hafta boyunca yapılmıştır. Sosyal beceri eğitimine başlamadan önce ve eğitim sonunda ebeveynin ve klinisyenin Sobece Çocukta Sosyal Becerileri Değerlendirme Ölçeği'ni doldurmaları istenmiştir.

Bulgular: Çalışmamıza 8'i erkek ve 7'si kız olmak üzere 15 çocuk dahil edilmiştir. Çocukların yaş ortalaması 10,26+1,33 olarak hesaplanmıştır. Olguların ve ebeveynlerinin sosyal beceri eğitimi öncesi ve sonrası doldurduğu Çocuklar İçin Yaşam Kalitesi Ölçeği puanları karşılaştırıldığında; psikososyal işlevsellik alt boyutu ve toplam ölçek puanı eğitim sonrasında istatistiksel olarak anlamlı yüksek saptanmıştır. Ebeveynlerin ve uzmanın sosyal beceri eğitimi öncesi ve sonrası doldurmuş olduğu Sobece Çocukta Sosyal Becerileri Değerlendirme Ölçeği puanları karşılaştırıldığında; "İlişki Başlatma ve Sürdürme Becerileri" ve "Saldırgan Davranış ve Dürtülerle Başa Çıkma Becerileri" alt ölçek puanları eğitim sonrasında istatistiksel olarak anlamlı düzeyde yüksek bulunmuştur.

Sonuç: Dikkat eksikliği ve hiperaktivite bozukluğu olan çocuklarda sosyal becerilerin geliştirilmesinin yaşam kaliteleri üzerinde olumlu bir etki yaratacağı söylenebilir. İleriki dönemde daha geniş örneklem grubu ile daha fazla sosyal becerinin çalışıldığı yeni çalışmalar planlanabilir.

Anahtar Kelimeler: Çocuk, Dikkat Eksikliği ve Hiperaktivite bozukluğu, Sosyal Beceri Eğitimi, Yaşam Kalitesi

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Abstract

Aim: Since Attention Deficit Hyperactivity Disorder (ADHD) is a chronic disorder that affects the lives of families and children, many studies have investigated the effects of this disorder on quality of life. Another area that is impaired in ADHD is social functioning. Impairment in social functioning is important in terms of both long-term and short-term prognosis of ADHD. However, little is known about how social functioning affects quality of life. In our study, it was aimed to investigate the effect of improving social skills on the quality of life in children with ADHD.

Material and Methods: The study included 15 children and their parents, who were followed up in the child and adolescent mental health outpatient clinic with the diagnosis of ADHD, were on medication for at least 6 months, had no chronic disease, were between the ages of 8-12. The children were asked to fill out the the Pediatric Quality of Life Inventory (PedsQL)-Child Form and their parents were asked to fill out the the Pediatric Quality of Life Inventory (PedsQL)-Parent Form before and after the education. Social skills training sessions, which were applied individually to the children once a week, were conducted by the child psychiatrist. Before starting the social skills training and at the end of the training, the parents and the clinician were asked to fill out the Sobece Child Social Skills Assessment Scale. Makıng Questıonnaıre and Problem Solving Inventory were applied to the patient and control groups.

Results: Our study included 15 children, 8 boys and 7 girls. The average age of the children was calculated as 10.26+1.33. When the scores of the Pediatric Quality of Life Inventory (PedsQL) filled by the children and parents before and after the social skills training were compared; the psychosocial functionality subscale and total scale score were found to be statistically significantly higher after the training. When the Sobece Child Social Skills Assessment Scale scores, which were completed by the parents and the clinician before and after the social skills training, were compared; it was determined that parents had statistically significantly higher levels of "Relationship Initiation and Maintenance Skills" and "Aggressive Behavior and Coping with Impulses" subscale scores after the training.

Conclusion: It can be said that the development of social skills in children with attention deficit and hyperactivity disorder will have a positive effect on their quality of life. In the future, new studies in which more social skills are studied with a larger sample group can be planned.

Keywords: Children, Attention Deficit and Hyperactivity Disorder, Social Skills Training, Quality of Life

Giriş

Dikkat, hiperaktivite ve dürtü kontrol bozuklukları ile karakterize olan Dikkat Eksikliği ve Hiperaktivite Bozukluğu (DEHB) çocukluk çağının en sık karşılaşılan sorunlarından biridir. Genellikle çocukluk çağı bozukluğu olarak bilinen DEHB, gelişimsel bir bozukluktur. Gelişim dönemine uygun olmayan dikkat ve aktivite sorunları çocukluk döneminde açıkça ortaya çıkmaktadır ve dürtüsel davranışlar ergenlikte artmaktadır [1]. Tüm okul yaşı göz önüne alındığında, DEHB'li öğrenciler ile tipik öğrencileri karşılaştıran çalışmalar, DEHB'li öğrencilerin daha fazla psikolojik problemleri olduğunu ve akademik başarılarının daha düşük olduğunu göstermektedir. Ayrıca bu öğrenciler diğer bireylerle daha fazla sorun yaşamakta ve sosyal ipuçlarını cevaplamakta zorlanmak gibi nedenlerle sosyal dışlanmaya uğramaktadırlar [2].

DEHB ile gelişimsel, bilişsel, sosyal ve akademik yetersizlikler arasında bir ilişki olduğu bilinmektedir. Bu sebepten dolayı da hem çocukların hem de ailelerinin yaşamları önemli ölçüde etkilenmektedir [3]. DEHB'si olan çocuk ve ergenler DEHB'si olmayan akranlarına göre sosyal ilişkilerde özellikle bir ilişki kurma açısından daha çok güçlük yaşarlar [4]. Daha başka birçok alanda güçlüklere sebep olan ve kronik seyreden bu bozukluğun yaşam kalitesine etkisinin değerlendirilmesi son dönemdeki çalışmalarda ön plana çıkmıştır ve DEHB'si olan bireyler sağlıklı kontrollerle karşılaştırıldığında psikososyal alan üzerine olan etkinin yanı sıra yaşam kalitesinin bütün alanlarında önemli azalmalar gösterilmiştir [5,6]. Ülkemizde yapılan iki çalışmada da benzer sonuçlara ulaşılmıştır [7,8].

DEHB'de yaşam kalitesininin bozulmasında rolü olan bir alan da bu bireylerdeki sosyal yetersizliklerdir. DEHB'si olan çocuklar diğer çocuklardan daha düşük sosyal becerilere sahip olma eğilimindedirler. Ayrıca çocukların depresyona girmesine neden olması muhtemeldir ve sosyal becerilerin özellikle kızlarda DEHB ile depresyon arasındaki ilişkinin önemli bir parçası

olması olasıdır [9]. DEHB'si olan çocukların sosyal becerileri ile ilgili sorunlar arasında başkalarını dinlememek, uygun olmayan zamanlarda konuşmaya başlamak ve sosyal ipuçlarını okuyamamak sayılabilir. Sosyal durumu ve başkalarına verdikleri tepkileri anlamama veya farkında olmama eğilimindedirler. Buna ek olarak, DEHB'si olan çocuklar gürültülüdür ve kuralları çiğneme gibi davranışlar sergilerler, bu da onları sosyal reddedilme riskine sokar, böylece kabul edilmemiş, izole edilmiş, farklı, sevilmemiş ve yalnız hissederler.

Normand et al. (2018) tarafından yapılan araştırmalar, DEHB'si olan çocukların ve arkadaşlarının arkadaşlıklarının kalitesinden önemli ölçüde daha az memnun olduklarını ortaya koymuştur. DEHB'si olan çocuklardaki hiperaktivite ve dürtüsellik rekabetçi oyunlarda kuralları çiğneme eğiliminde olmalarını sağlar, bu da akranları tarafından reddedilme faktörü olabilir [10].

DEHB'li bazı çocukların, kurallara ve eşitliğe uymaya kıyasla eğlenmek gibi sosyal hedeflere sahip olma olasılıkları daha yüksektir. DEHB'si olan çocuklar, taklit etmek için iyi prososyal davranış modellerine sahip olmayabilir, çünkü akranları tarafından sevilmeme eğilimindedirler. Diğer akranların ebeveynleri de sıklıkla çocuklarının yıkıcı davranışlar sergileyen çocuklarla oynamasını engeller [11].

Birkaç makalenin gözden geçirilmesinin sonuçlarına dayanarak, DEHB'li çocuklarda sosyal becerileri geliştirmek için kullanılan yedi tür müdahale halinde gruplandırılmış çeşitli müdahale türleri saptamışlardır. Bu tür müdahaleler arasında oyun temelli terapi, bilişsel-davranışçı terapi, sosyal beceri eğitimi, ebeveyn eğitimi, yaşlar arası akran eğitimi, duygusal yönetim eğitimi ve öz kontrol eğitimi bulunmaktadır [12].

Coelho ve ark. (2017) araştırmalarında kullanılan bilişsel-davranışçı terapi, sadece ilaç kullanan ve ilaçları müdahalelerle birleştiren tedavilerin sonuçlarını karşılaştırmıştır. Terapötik hedefler olarak altı alan vardır: (1) psikoeğitim: ebeveynlerle oturumlar ve çocuklarla oturumlar, (2) ebeveyn eğitimi, (3) ebeveynler için planlama ve düzenleme, (4) problem çözme, (5) duygusal düzenleme ve (6) sosyal beceriler. Bu çalışmanın sonuçları, bilişsel-davranışçı terapi ile çocukların sosyal becerilerinin empati, girişkenlik ve özdenetim alt ölçeklerinde sıklığının arttığını, öz kontrol alt ölçeğinde ise girişkenlik ve güçlüklerdeki zorlukların algılanmasının azaldığını göstermektedir [13].

Ebeveyn eğitimi ile birleştirilen sosyal beceri eğitimlerinde DEHB'li çocuklarının sosyal becerilerini geliştirmek için sosyal beceri eğitiminin daha etkin kullanıldığı tespit edilmiştir. Bununla birlikte, Storebø, ve ark. tarafından yapılan araştırmalar, ebeveyn eğitimi ile birlikte sosyal beceri eğitiminin DEHB çocukları için standart tedaviye kıyasla önemli faydalar göstermediğini söylemektedir [14].

Yapılan çalışmalarda sosyal beceri eğitimlerinin DEHB'si olan çocuklarda daha etkili olabilmesi için iki önemli noktanın üzerinde durulması gerektiği söylenmiştir. DEHB'si olan çocuklara uygulanacak sosyal beceri eğitiminin gerçek hayattaki sosyal ilişkilerinde uygun davranış sergileme için pekiştirme yapma fırsatı sunması ve hatırlatıcılar geliştirmesi gerekmektedir. DEHB'si olan çocukların bu tür hatırlatmalara açık olmasının sağlaması da sosyal beceri eğitiminin hedeflerinden olmalıdır. Diğer önemli nokta da DEHB'si olan çocukların arkadaşlarının sosyal olarak onları daha kabul etmeye ve kapsayıcı olmaya teşvik edilmesidir.

Yapılan çalışmalardaki bulgular göz önüne alındığında DEHB'si olan çocuklara uygulanacak sosyal beceri eğitiminin onların bu alandaki yetersizliklerini azaltacağı ve yaşam kaliteleri üzerinde olumlu etki yapacağı düşünülmüştür. Çalışmamızda DEHB tanılı çocuklarda sosyal becerilerin geliştirilmesinin yaşam kalitesi üzerine etkisini araştırmak amaçlanmıştır.

Gereç ve Yöntemler

Çalışmaya çocuk ve ergen ruh sağlığı polikliniğinde DEHB tanısı ile takipli, en az 6 aydır ilaç tedavisi alan, kronik hastalığı olmayan, 8-12 yaş aralığında olan, 15 çocuk ve ebeveyni dahil edilmiştir. Çalışmaya dahil edilen çocuklardan Çocuklar İçin Yaşam Kalitesi Ölçeği (ÇİYKÖ)- Çocuk Formu'nu, ebeveynlerinden ise Çocuklar İçin Yaşam Kalitesi Ölçeği (ÇİYKÖ)- Ebeveyn Formu'nu eğitim öncesi ve sonrası doldurmaları istenmiştir. Çocuklar İçin Yaşam Kalitesi Ölçeği (ÇİYKÖ)- Ebeveyn Formu, ebeveynlerin çocuklarının yaşam kalitelerini değerlendirdiği bir formdur. Çocuklar ile haftada bir gün bireysel olarak uygulanan sosyal beceri eğitim seansları on iki hafta boyunca uzman tarafından yapılmıştır. Bu seanslarda her çocuğa sosyal beceri eğitiminin İlişki Başlatma ve Sürdürme Becerileri, "Duygulara Yönelik Beceriler", "Saldırgan Davranış ve Dürtülerle Başa Çıkma Becerileri", "Plan Yapma" olmak üzere toplam dört alt alanı çalışılmıştır. Sosyal beceri eğitimine başlamadan önce ve eğitim sonunda ebeveynin ve klinisyenin Sobece Çocukta Sosyal Becerileri Değerlendirme Ölçeği'ni doldurmaları istenmiştir. Çalışmaya katılmayı kabul eden ve çalışma kriterlerine uyan çocuk ve ebeveynlerinden yazılı onam alınmıştır. Çalışmaya başlanmadan önce Sağlık Bilimleri Üniversitesi İzmir Dr. Behçet Uz Çocuk Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulundan 22.12.2022 tarih ve 2022/22-09 numaralı etik onam alınmıştır.

Her ergen ve ailesi ile görüşülerek yarı yapılandırılmış bir görüşme olan Okul Çağı Çocukları İçin Duygulanım Bozuklukları ve Şizofreni Görüşme Çizelgesi-Şimdi ve Yaşam boyu Şekli Türkçe uyarlaması (Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version, K-SADS-PL) uygulanmıştır. Bu uygulama ile diğer psikiyatrik hastalıklar dışlanmıştır. Başka bir fiziksel kronik hastalığı olan çocuklar çalışmaya dahil edilmemiştir. Klinik olarak mental kapasitesi normal olan çocuklar çalışmaya alınmıştır. Araştırmacı tarafından sosyodemografik veri formu doldurulmuştur.

Uygulanan sosyal beceri eğitimi Türkiye'de çocuklar için yapılandırılmış SOBECE (Sosyal Beceri Çocuk Eğitim Programı) adındaki bir sosyal beceri programıdır. Toplam 7 modül ve 76 beceri alanından oluşan bu programın çalışmaya katılan çocuklara sadece 4 modülü uygulanmıştır. Bu programdaki beceri alanları SOBECE'ye özel yüzlerce egzersiz, oyun, görsel-yazılı olay kartları ile çocukla çalışılır. SOBECE kognitif davranış terapisi, psikodrama, sosyal öğrenme kuramı, rol canlandırma, akran destekli öğrenme yaklaşımları temel alınarak hazırlanmış bir programdır.

Veri Toplama Araçları

Sosyodemografik Veri Formu;

Çocuğun yaşı, cinsiyeti, DEHB tanısının konulduğu tarih, ne kadar süredir ilaç tedavisi aldığı, daha önce sosyal beceri eğitimi alıp almadığı bilgileri yer almaktadır.

Çocuklar İçin Yaşam Kalitesi Ölçeği (ÇİYKÖ);

ÇİYKÖ, 2-18 yaşları arasındaki çocukların fiziksel ve psikososyal yaşantılarını hastalıktan bağımsız olarak değerlendiren genel bir yaşam kalitesi ölçeğidir. Varni ve arkadaşları tarafından 1999'da geliştirilmiş, ülkemizde Üneri ve Memik ve arkadaşları tarafından Türkçe geçerlik ve güvenirlik çalışması yapmıştır [16]. Çalışmamızda bu ölçeğin hem çocuk hem de ebeveyn formu kullanılmıştır.

Sobece Çocukta Sosyal Becerileri Değerlendirme Ölçeği;

Çocukların sosyal becerilerinin değerlendirilmesi için Türkiye koşullarına uygun olarak Akçamete ve ark. Tarafından 2021 yılında düzenlenmiş ve geçerlilik güvenilirlilik çalışması yapılmıştır [17]. Ölçek, 5'li Likert tipi cevaplama seçeneği içeren 76 madde ve "İlişki Başlatma ve Sürdürme Becerileri", "Atılganlık Becerileri", "Duygulara Yönelik Beceriler", "Saldırgan Davranış ve Dürtülerle Başa Çıkma Becerileri", "Sorun Çözme Becerileri", "Plan Yapma, Grupla Etkileşim" ve "Bir İş Yürütme Becerileri" olmak üzere yedi alt boyuttan oluşmaktadır.

İstatiksel Analiz

SPSS 20.0 programı kullanılmıştır. Kategorik değişkenler sıklık (s) ve yüzde (%) cinsinden ifade edilmiştir. Verilerin değerlendirilmesinde tanımlayıcı istatistikler kullanılmıştır (ortalama, standart sapma, minimum, maksimum, yüzde). Sosyal beceri eğitimi öncesi ve sonrası aynı gruptan elde edilen yaşam kalitesi ölçeği ve çocukta sosyal becerileri değerlendirme ölçeği skorları (öntest-sontest) SPSS programında split plot ANOVA (SPANOVA) ve paired T Testi ile değerlendirilmiştir. $p<0,05$ değeri istatistiksel anlamlılık düzeyi olarak kabul edilmiştir.

Bulgular

Çalışma başlangıcında 19 çocuk ile sosyal beceri eğitimlerine başlanmıştır ancak 4 çocuk on iki haftalık sosyal beceri eğitimini tamamlayamadığından bu çocukların verileri çalışmaya alınmamıştır. Sonuç olarak çalışmamıza 8'i erkek ve 7'si kız olmak üzere 15 çocuk dahil edilmiştir. Çocukların yaş ortalaması 10,26+1,33 olarak hesaplanmıştır. Olguların sosyal beceri eğitimi öncesi ve sonrası doldurduğu Çocuklar İçin Yaşam Kalitesi Ölçeği- Çocuk Formu puanları karşılaştırıldığında; psikososyal işlevsellik alt boyutu ve toplam ölçek puanı eğitim sonrasında istatistiksel olarak anlamlı yüksek saptanmıştır ($p<0,001$). Bununla birlikte ebeveynlerin doldurduğu Çocuklar İçin Yaşam Kalitesi Ölçeği- Ebeveyn Formu sonuçlarında da benzer şekilde psikososyal işlevsellik alt boyutu ve toplam ölçek puanı eğitim sonrasında istatistiksel olarak anlamlı yüksek saptanmıştır ($p<0,001$). Hem çocukların hem de ebeveynlerin doldurmuş olduğu Çocuklar İçin Yaşam Kalitesi Ölçeği'nin sonuçları sosyal beceri eğitimi öncesi ve sonrası karşılaştırıldığında ölçeğin fiziksel sağlık toplam puanında anlamlı bir farklılık saptanmamıştır. Ebeveynlerin sosyal beceri eğitimi öncesi ve sonrası doldurmuş olduğu Sobece Çocukta Sosyal Becerileri Değerlendirme Ölçeği puanları karşılaştırıldığında; "İlişki Başlatma ve Sürdürme Becerileri" ve "Saldırgan Davranış ve Dürtülerle Başa Çıkma Becerileri" alt ölçek puanları eğitim sonrasında istatistiksel olarak anlamlı düzeyde yüksek bulunmuştur ($p<0,001$). Benzer şekilde uzmanın doldurmuş olduğu Sobece Çocukta Sosyal Becerileri Değerlendirme Ölçeği'nin "İlişki Başlatma ve Sürdürme Becerileri" ve "Saldırgan Davranış ve Dürtülerle Başa Çıkma Becerileri" alt ölçek puanları eğitim sonrasında istatistiksel olarak anlamlı düzeyde yüksek saptanmıştır ($p<0,001$). Ancak aynı ölçeğin "Atılganlık Becerileri", "Duygulara Yönelik Beceriler", "Sorun Çözme Becerileri", "Plan Yapma, Grupla Etkileşim" ve "Bir İş Yürütme Becerileri" alt ölçek puanları sosyal beceri eğitimi öncesi ve sonrası ne ebeveynlerin doldurduğu ne de uzmanın doldurduğu ölçeklerde istatistiksel anlamlı olarak değişmediği görülmüştür.

Tartışma

Dikkat eksikliği hiperaktivite bozukluğu olan çocuklara uygulanan sosyal beceri eğitimin yaşam kaliteleri üzerindeki etkisinin değerlendirildiği bu çalışmada; sosyal beceri eğitiminin çocukların yaşam kalitelerini hem kendi hem de ebeveynlerinin görüşüne göre olumlu yönde etkilediği gösterilmiştir. Uygulanan sosyal beceri eğitimi sonrasında hem ebeveyn görüşüne hem de uzman görüşüne göre çocuklarda ilişkiyi başlatma ve sürdürme becerileri, saldırgan davranış ve dürtülerle başa çıkma becerilerinde anlamlı ölçüde düzelme olması da ulaşılan diğer bulgular arasındadır.

Çalışmamızda dikkat eksikliği ve hiperaktivite bozukluğu olan çocuklara uygulanan sosyal beceri eğitimi sonrası hem çocukların hem de ebeveynlerinin sağlıkla ilgili yaşam kalitesini daha iyi olarak algıladığı bulunmuştur. Aynı zamanda hem çocuğun hem de ebeveynin sosyal beceri eğitimi sonrası duygusal, sosyal ve okul işlevselliklerini daha iyi olarak algıladıkları saptanmıştır. Yaşam kalitesi açısından önemli göstergelerden birisinin kişinin sosyal çevresi ve bu çevre ile kurduğu ilişki olduğu bilinmektedir. Çocuğun kurduğu sosyal ilişkiler ile kendini ait hissedebileceği destekleyici bir aile çevresi yaşam kalitesinin gelişmesi için olmazsa olmazlardandır [18]. Böylelikle yaşam kalitesi sosyal kalite ile genişler [19]. Yapılan çalışmalarda öncelikle aile içi iletişimin kuvvetlendirilmesi gerektiği gösterilmiştir. Aile içinde herkesin duygularını ve düşüncelerini rahatça ifade edebilmesi ile ilk önce aile yaşam kalitesi artar [18]. Daha sonra da arkadaşlar, komşular ve akrabalar ile ilişkiler önem kazanır. Çocuğun kurduğu bu sosyal ilişkiler yaşam kalitesi açısından önemli destek sağlayıcılarıdır [19]. Yapılan bir çalışmada arkadaş sahibi olmanın ve aktivitelerde bulunmanın yaşam doyumunu dolayısıyla yaşam kalitesini artırdığı gösterilmiştir [20]. Yine benzer başka bir çalışmada da üniversite öğrencileri arasında herhangi bir öğrenci topluluğuna üye olanların yaşam kalitesinin herhangi bir topluluğa üye olmayanlardan yüksek olduğu bulunmuştur [21]. Çalışmamızda da dikkat eksikliği ve hiperaktivite bozukluğu olan çocukların sosyal beceri eğitimi sonrası sosyal becerilerinin belli alanlarda artması ile kendileri ve ebeveynleri tarafından algılanan yaşam kalitelerinin olumlu yönde etkilenmesi yazındaki diğer sonuçlarla uyumludur.

Sosyal becerilerin boyutlarının belirlenmesinde yazında birçok çalışma yapıldığı görülmektedir. Ataş ve ark. yaptığı bir çalışmada da sosyal beceriler yedi boyutta ele alınmıştır. Bu boyutlar ilişki başlatma ve devam ettirme becerileri, girişimcilik becerileri, duygularla ilgili beceriler, davranış ve dürtüleri düzenleyebilme becerileri, problem çözme becerileri, planlama ve grupla etkileşim becerileri ile iş yürütme becerileridir [22]. Dikkat eksikliği ve hiperaktivite bozukluğu olan çocuklarda bu yedi boyuttan özellikle ilişkiyi başlatma ve devam ettirme, duygularla ilgili beceriler, davranış ve dürtü düzenleyebilme becerileri ve planlama becerilerinin eksik olduğu düşünülerek yapılan sosyal beceri eğitiminde bu boyutlar üzerinde durulmuştur. Eğitimin sonunda hem ebeveyn hem de uzman görüşüne göre bu çocuklarda ilişkiyi başlatma ve devam ettirme, davranış ve dürtü düzenleyebilme becerileri anlamlı olarak olumlu yönde gelişmiştir. Ancak duygularla ilgili becerilerde ve planlama becerilerinde anlamlı bir değişim saptanmamıştır.

Günümüzde sosyal hayatta birilerine yardım etmek, onlara dikkatimizi vermek ve etkinliklerdeki kuralları izlemek çok önemlidir. Bunlar biri ile ilişkiyi sürdürmenin en önemli bileşenlerindendir ve çocuklarda farklı yaşlarda gelişim gösterirler ama DEHB tanılı çocuklar için bu alanlar özellikle zorlandıkları alanlardandır [23]. İlişkiyi başlatma ve sürdürme ile başlayabilen arkadaşlık ilişkileri de çocuğun sosyalleşme sürecinde çok önemlidir. İyi arkadaşlık ilişkileri kuramayan çocukların hayatları boyunca sorunlarla karşılaştığı bilinmektedir [24]. DHEB tanılı çocukların da arkadaşlık ilişkilerinde süreğen bir şekilde sorunlar yaşadığı ve bu yüzden arkadaşlardan sağlanan sosyal desteğin az olduğu çalışmalarda gösterilmiştir [25]. Çalışmamızda da bu becerilerde zorluk yaşadığı bilinen DEHB tanılı çocukların eğitim sonrasında becerilerinde olumlu yönde artış olması ile çocukların bu ilişkileri başlatma ve sürdürmekle bilgi ve becerilerini geliştirildikleri ve liderlik için önemli bir beceri olan meydan okuma yeterliliği kazandıkları söylenebilir [26].

Saldırgan davranışla başa çıkma becerileri çocuğun sosyal ilişkileri sırasında hem kendisinden gelen hem de karşı taraftan gelen saldırgan davranışlarla başa çıkmasını içerir. Bu beceriler içerisinde kendisinden istenilen bir şeye hayır diyebilme, kendisinin istemediği bir davranışa maruz kaldığında bunu karşısındakine söyleyebilme, suçlamalara uğradığında kendisini savunabilme ve kedisiyle alay edildiğinde veya küçümsendiğinde görmezden gelebilme bulunmaktadır [17]. Bu becerileri edinen çocuklar daha fazla kendilerini kontrol edebilmekte, hakkını doğru şekilde savunabilmekte, şakalara uygun şekilde karşılık verebilmekte, çatışmadan kaçınabilmekte ve kavga dan uzak durabilmektedirler [27]. DEHB tanılı çocukların sosyal ilişkilerinde yaşadıkları en büyük sorunlardan biri de fiziksel ve sözel agresyonu kullanmaları ve davranışlarını kontrol etmekte zorlanmalarıdır [28]. Genelde kişiler arası

sorunları çözmek için agresif atılımlar yaparlar ve öfkelerini kontrol etmekte zorlanırlar [29]. Bu sebepten de arkadaşları ile yaptıkları etkinliklere uygun şekillerde katılmakta güçlük yaşarlar [29]. Çalışmamızda yapılan sosyal beceri eğitiminde bu alanların çalışılmış olması sonucunda bu becerilerin anlamlı düzeyde olumlu yönde gelişmesi DEHB tanılı çocukların ön planda bu alanlarda sorun yaşamalarından dolayı olabilir.

Çalışmamızda sosyal beceri eğitimi sırasında çocuklarla çalışılan diğer alan da duygulara yönelik becerilerdir. Bu beceriler; başkalarıyla ilgili olumlu ve olumsuz duygularını ifade etme, başkalarının kendisine karşı neler hissettiğini ifade etme, gerektiğinde kendisi ile ilgili olumlu ifadeler kullanma, arkadaşlarının başarıları karşısında olumlu duygularını açığa vurma (övgü gibi) becerileri gibi becerilerden oluşmaktadır [17]. Duygularla ilgili beceriler, aslında birçok alt bileşeni içerebilmektedir. Saldırgan tutumlar dahil olmak üzere kendini kontrol etme becerilerinin hemen hemen hepsi duygusal yapıya göre şekillenen becerilerdir. Çalışmamızda uygulanan sosyal beceri eğitimi sonrası DEHB tanılı çocukların duygulara yönelik becerilerinde anlamlı bir değişim olmamasının sebebi, öncelikle ilk değişimin davranışsal olarak kendini kontrol etme ile saldırgan davranış ve dürtülerle baş etmenin artması ile kendini göstermesi olabilir. Sosyal beceri eğitiminin devam etmesi ile sonraki aşamada duygulara yönelik becerilerin gelişiminin daha gözlenilebilir hale geleceği düşünülebilir.

Barkley, DEHB tanılı çocukların sosyal sorunlarının merkezinde zaman duygularının gelişmemiş olması ve anda yaşamaya eğilimli olmaları olduğuna değinmiştir [30]. Planlama ve zaman yönetimi ile ilgili ciddi sorunlar yaşayan DEHB tanılı çocuklarda sosyal beceri eğitimi ile bu beceriler de çalışılmıştır. Ancak eğitim sonrası bu becerilerde anlamlı miktarda değişim gözlenmemiştir. Bu becerinin daha düşünsel bir beceri olması ve matematiksel hesaplar yapmak, düşünerek seçenekler arasında seçim yapmak ve belirli bir strateji doğrultusunda hareket etmeye başlamak gibi becerileri içermesi, soyut düşüncenin tam olarak gelişmediği daha küçük yaşta olan bir örneklem ile çalışılması nedeniyle eğitim sonrası değişim göstermemiş olabilir [31].

Çalışmamızın bazı kısıtlılıkları da bulunmaktadır. Seçilen örneklem sadece kliniğe başvuran çocuklardan oluştuğundan kliniğe başvurmayan çocuklar temsil edilememiştir. Bununla birlikte uygulanan sosyal beceri eğitimi kısa süreli eğitim şeklinde planlanmıştır. Uygulanan bu eğitim de sadece sosyal becerinin dört alt boyutu çalışılmıştır. Sosyal becerinin her boyutunun birbirini etkilediği düşünüldüğünde bu bir kısıtlılık olarak sayılabilir. Çalışmamızın diğer bir kısıtlılığı da örneklem sayısının azlığıdır. İleriki dönemde daha geniş örneklem grubu ile daha fazla sosyal beceri alt boyutunun çalışıldığı yeni çalışmalar planlanabilir.

Sonuç

DEHB'de bozulan bilişsel ve akademik alanlar kadar sosyal işlevselliğin etkilendiği bilinmektedir. DEHB'li çocuklar diğer kişilerle iletişim kurma isteği içindedirler ama çevrelerindeki insanlara ayak uydurmakta zorlanmaktadırlar. Ayrıca bu çocuklar bazı sosyal becerileri bilseler de bunları gerçek hayata uygulama konusunda güçlükler yaşamaktadırlar Tüm bu sebeplerden dolayı DHEB tanılı çocuklarda sosyal becerilerinin geliştirilmesi ve bu gelişimin yaşam kalitesi üzerine olan etkisinin ölçülmesi; bu bozukluktaki farklılıkların değerlendirilmesini, yaklaşımlar sonrasındaki hastalığın gidişatının tanımlanmasını, yaşadığı çevre, toplum ve ulusal sağlık politikalarının yeniden gözden geçirilmesini kolaylaştırabilir.

Çıkar Çatışması

Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların herhangi bir çıkar dayalı ilişkisi yoktur

Etik Kurul Kararı

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Research Article

Microsurgical anatomy of the craniovertebral junction: An anatomical study with far lateral approach

Kraniovertebral bileşkenin mikrocerrahi anatomisi: posterolateral yaklaşımla anatomik çalışma

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Abstract

Aim: The far lateral approach is indicated for lesions located anterior to the dentate ligament between the lower third of the clivus and the upper part of the C2 body. Modified subgroups have also been described for increasing the exposure of level of this highly crowded anatomical region. We present an anatomical and clinical study demonstrating the feasibility of a far lateral approach that provides access to multiple lesions at the craniovertebral junction.

Material and Methods: Four formalin-fixed and mummified adult cadaver specimens were used in this study. Skin incision, followed by careful dissection of various muscle groups, exposed the suboccipital triangle. C1 and C2 posterior arches were removed to reveal the course of the vertebral artery. Finally, suboccipital craniectomy was performed to reach craniovertebral junction and associated regional anatomy was openly exposed.

Results: Numerous anatomical structures that have vast clinical significance provides the delicacy and complexity of this region. Vertebral artery, hypoglossal nerve, spinal accessory nerve, dentate ligaments, first and second cervical neural roots and brainstem were carefully exposed and identified during the dissection process.

Conclusion: Far lateral approach increases the surgical dominance and maneuverability of the pathologies located in craniovertebral junction and upper cervical spine. With this approach, surgical difficulties of the region can be overcome with the development of anatomical knowledge and technical infrastructure. Knowledge of the microtopographic surgical anatomy of this region is the fundamental element to achieve an effective surgery.

Keywords: craniovertebral junction, microsurgery, anatomy, cadaver, far lateral approach

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Öz

Amaç: Kranioservikal posterolateral yaklaşım, klivusun alt üçte biri ile C2 gövdesinin üst kısmı arasındaki dentat ligamanın önünde yer alan lezyonlar için endikedir. Bu oldukça kalabalık anatomik bölgenin açığa çıkarılma seviyesini artırmak için bu yaklaşım modifiye edilmiş alt grupları da tanımlanmıştır. Bu makalede, kraniovertebral bileşkedeki lezyonlara erişim sağlayan posterolateral yaklaşımın uygulanabilirliğini gösteren anatomik ve klinik bir çalışma sunuyoruz.

Gereç ve Yöntemler: Bu çalışmada formalinle sabitlenmiş ve mumyalanmış dört yetişkin kadavra örneği kullanıldı. Cilt insizyonunu takiben çeşitli kas gruplarının dikkatli diseksiyonu suboksipital üçgeni açığa çıkardı. Vertebral arterin seyrini göstermek için C1 ve C2 arka arkusları çıkarıldı. Son olarak kraniovertebral bileşkeye ulaşmak için suboksipital kraniyektomi yapıldı ve ilişkili bölgesel anatomi açık bir şekilde ortaya kondu.

Bulgular: Geniş klinik öneme sahip çok sayıda anatomik yapı, bu bölgenin hassaslığını ve karmaşıklığını sağlamaktadır. Diseksiyon işlemi sırasında vertebral arter, hipoglossal sinir, spinal aksesuar sinir, dentat ligamanlar, birinci ve ikinci servikal nöral kökler ve beyin sapı dikkatlice açığa çıkarılıp tanımlandı.

Sonuç: Kranioservikal posterolateral yaklaşım, kraniovertebral bileşke ve üst servikal omurgada yer alan patolojilerin cerrahi hakimiyetini ve manevra kabiliyetini arttırır. Bu yaklaşımla anatomik bilgi ve teknik altyapının geliştirilmesi ile bölgenin cerrahi zorlukları aşılabilir.

Anahtar Kelimeler: kraniyovertebral bileşke, mikrocerrahi, anatomi, kadavra, posterolateral yaklaşım

Introduction

With the description of the unilateral suboccipital approach in 1972, the foundations of the far lateral approach were laid [1]. In 1986, Roberto Heros first described the far lateral approach for vertebral artery (VA) aneurysm and in 1988, George et al. first described this approach for the surgery of lesions located anterior-anterolateral to the foramen magnum (FM) [2, 3]. Today, this approach continues to be used in many modified forms [3-5]. This approach is typically a more lateral approach to the lateral suboccipital approach in which the posterolateral aspect of FM is removed and a C1 (cervical) hemilaminectomy is added, greatly increasing the working space anterior to the brainstem and thus eliminating the need for retraction. Modified subgroups have also been described, including bone resection in the transcondylar, supracondylar or paracondylar region [6, 7].

The far lateral approach is indicated for lesions located anterior to the dentate ligament between the lower third of the clivus and the upper part of the C2 body. Lesions located in the premedullary and lateral cerebellomedullary cistern, including FM meningiomas, neurenteric cysts, aneurysms of the V4 segment of VA, vertebrobasilar junction aneurysms, anterior and lateral medullary segment aneurysms of the posterior inferior cerebellar artery (PICA), schwannomas of the lower cranial nerves, lower brainstem arteriovenous malformations with nidus anterior to the dentate ligament, gliomas and cavernous hemangiomas affecting the anterolateral aspect of the medulla oblongata and upper cervical cord can be accessed through a far lateral approach [8, 9].

Many different skin incisions have been described in which the myocutaneous flap is elevated in the far lateral approaches. The most commonly used are long curved and hockey stick shaped incisions [2, 3, 5]. One of the most important steps of this procedure is muscle dissection and recognition of triangulation points while maintaining anatomical orientation. The most important structures to be considered from muscle dissection to the end of the procedure, including bone excision, are the suboccipital triangle and VA located there [10]. Many anatomical studies have been conducted to clarify this issue as much as possible [7, 11].

We present an anatomical and clinical study demonstrating the feasibility of a far lateral approach that provides access to multiple lesions at the craniovertebral junction (CVJ) and involves many complex anatomical structures from start to finish.

Material and Methods

Four formalin-fixed and mummified adult cadaver specimens were used in this study. The mean age of these specimens was 73.5 years, ranging from 61 to 83 years. Dissections were performed with the cadavers in prone position. The head was fixed with a Mayfield head holder with the cervical spine in the neutral position.

First transverse skin incision was performed, allowing for the visualization of the bilateral asterion and the highest nuchal line, starting approximately 2 cm superior to the external occipital protuberance. Secondly, a posterior midline skin incision was made starting from the midpoint of this incision and extending to the spinous process of C7. Carefully dissecting the trapezius, sternocleidomastoid, splenius capitis, and semispinalis capitis muscles bilaterally, they were gently displaced laterally to expose the suboccipital triangle, formed by the boundaries of the three muscle groups (Rectus capitis posterior major, superior and inferior oblique capitis muscles). In addition, the rectus capitis posterior minor was identified (Figure 1 A, B). Within the boundaries of the suboccipital triangle, the posterior arch of C1 and VA were visualized (Figure 1 B, C). For ease of the procedure, the rectus capitis posterior major and minor on the working side, along with the inferior oblique capitis muscles, were removed, revealing the posterior atlantooccipital membrane (Figure 1 D, 1E). The close relationship between the bone structures where hemilaminectomy will be performed on C1 and C2, and where suboccipital craniectomy will be applied, was more easily visualized.

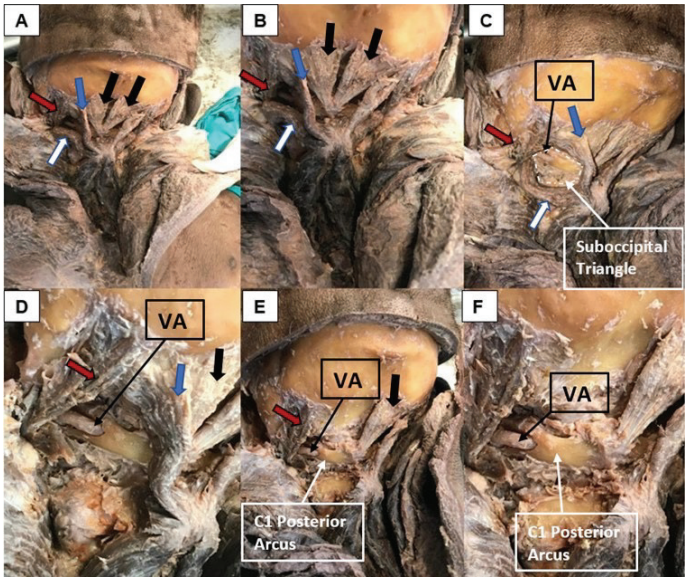

Figure 1: A, B: After the skin incision and dissection of the superficial muscle layer, posterior view, thick black arrow: rectus capitis posterior minor muscle, thick blue arrow: rectus capitis posterior major muscle, thick red arrow: obliquus superior capitis muscle, thick white arrow: obliquus inferior capitis muscle; **C, D:** Posterior oblique view, area delimited by the white dashed line: Suboccipital Triangle formed by the three muscle groups, thin black arrow: vertebral artery visible in the suboccipital triangle; **E, F:** After unilateral removal of rectus capitis major/minor and obliquus capitis inferior muscles, posterior oblique view, thin black arrow: vertebral artery, thin white arrow: C1 posterior arch.VA: Vertebral Artery

After thinning the lamina of C2 unilaterally using a high-speed drill, hemilaminectomy of C2 was performed using a Kerrison rongeur-2 mm (Figure 2 A, B, C). Once again, utilizing a drill and Kerrison rongeur, the posterior arch of C1 was removed, taking into consideration the course of VA. The removal of the posterior arch of C1 revealed the course of VA clearly, thereby facilitating the preservation of this structure in the subsequent steps of the procedure (Figure 2 D, E, F, G). After the relevant bone structures of C1 and C2 were removed, a suboccipital craniectomy was performed. The size of this craniectomy could vary based on the characteristics of the present pathology; therefore, an average-sized craniectomy not exceeding 3x3 cm and not crossing the midline was performed. By removing the posterolateral border of the FM, the dural surface of the CVJ was exposed in an open manner (Figure 2 H, I). Subsequently, the dura was opened linearly up to the border of C2 (Figure 2 J, K).

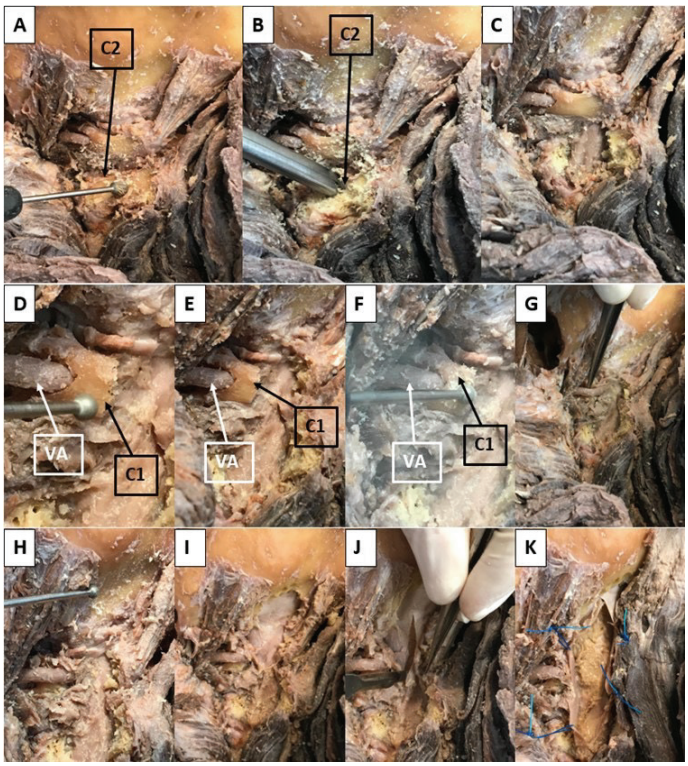

Figure 2: A, B, C: Execution of C2 hemilaminectomy using a drill and Kerrison rongeur; **D, E, F, G:** Accomplishment of C1 posterior arch removal while preserving the vertebral artery using drill and Kerrison rongeur, and visualization of the vertebral artery; **H, I:** Performance of suboccipital craniectomy and removal of the posterior-lateral bony border of the foramen magnum; **J, K:** After the dura is opened linearly up to the border of C2, achieving a broad surgical window. VA: Vertebral Artery

Results

VA is an important anatomical structure to be carefully preserved during this approach. It supplies blood to the brainstem, cerebellum, and parts of the spinal cord. It arises from the subclavian artery, which is a major artery that branches off from the aorta. The course of VA involves several segments. With this study, we had the chance to clearly observe the course of the V2 and V3 segments of VA.

VA originates from the subclavian artery. It runs between the Longus colli and the Scalenus anterior muscles. It passes through the transverse foramina of the C6 in the neck. The artery continues its course and runs vertically upward through the foramina in the transverse processes of the C6 to C2 vertebrae. Within these foramina, the artery is protected by the bony vertebral column. As it ascends through these transverse foramina, it gives off small branches to the muscles and structures in the neck. After passing through the transverse foramen of C1, VA becomes horizontal curving medially and posteriorly behind the superior articular process of C1, Here, it travels within a groove on the posterior aspect of the atlas (C1). This part of VA is more vulnerable to compression or damage due to its close proximity to the cervical vertebrae. Then, it enters the vertebral canal by passing beneath the posterior atlantooccipital membrane. The intracranial part of VA begins with piercing of dura when the artery enters the skull through FM. Inside the skull, after giving rise to ipsilateral PICA's, the two vertebral arteries come together to form the basilar artery, which provides blood supply to the brainstem, cerebellum, and other brain structures.

The suboccipital triangle is composed by the rectus capitis posterior major muscle, above and medially, by the superior oblique muscle above and laterally, and by the inferior oblique muscle below and laterally. It is covered by the semispinalis capitis muscle medially and the splenius capitis muscle laterally. Its floor is formed by the posterior atlantooccipital membrane. Inside the triangle we can find the terminal extradural VA and first and second cervical neural root. In our study, we traced VA and explored the suboccipital triangle step by step and found similar courses as described in the literature.

Eleventh cranial nerve is another critical structure to be exposed during far lateral approach. The accessory nerve, (XI) primarily operates as a motor nerve, controlling specific muscles involved in movements of the head and neck. Its trajectory encompasses two main segments: the cranial and spinal portions.

Cranial Portion (Origin in Brainstem): The accessory nerve's cranial portion originates from a cluster of motor neurons called the nucleus ambiguus. Situated within the from the lateral aspect of the medulla oblongata, this nucleus gives rise to fibers forming the cranial root of the accessory nerve. This root merges with the vagus nerve (cranial nerve X), contributing to motor functions in the pharynx and larynx.

Spinal Portion (Emergence from Spinal Cord): Emerging from upper cervical segments of the spinal cord, specifically from the anterior horn cells of spinal segments C1 to C5/C6, is the spinal portion of the accessory nerve. The spinal root of the accessory nerve takes form from these fibers and exits the skull through the jugular foramen, in partnership with the cranial root.

Once outside the skull, the accessory nerve journeys into the posterior triangle of the neck. Here, it branches to innervate two major muscles: Sternocleidomastoid and Trapezius Muscle. Extracranial course of the accessory nerve is relatively superficial. Hence it is difficult to trace this part. Spinal portion of its origin can be seen within the opened dura.

Condylar approaches give access to hypoglossal canal serving as the exit route of hypoglossal nerve (cranial nerve XII). Condylectomy during transcondylar approach reveals the hypoglossal canal. After exiting the base of the skull through the hypoglossal canal, course of the hypoglossal nerve turns anteriorly alongside carotid sheath descending throgh the neck.

Opening of spinal dura while reaching ventral FM lesions, exposes thin delicate extensions of the pia mater originating from the nerve roots, attaching to dura mater. These extensions are called dentate, denticulate ligaments. They play significant role in suspension and stabilization the spinal cord in the vertebral canal. In our mummified cadaver specimens, dentate ligaments were not easily observed.

Discussion

CVJ and upper cervical spine pathologies can be challenging for neurosurgeons. Especially anterior dural wall pathologies such as FM meningiomas or schwannomas may be difficult to handle because of the regions anatomical neighboring structures. Vascular and neuronal structures of the area such as VA, accessory nerve, hypoglossal nerve, dentate ligaments, first and second cervical neural roots, and brainstem has to be preserved. On the other hand, any failure on the approach is going to be fatal. This study is focused on the the far lateral suboccipital approach anatomical neighboring structures to be safe, also with a wider approach to ensure precise control on the surgical experience of CVJ pathologies.

Advancements in neurosurgical infrastructure like operative visualization and improved surgical instruments gives the surgeon the chance to look from wider and more dominant angles by providing comfort [12-14]. Wider exposure with hemilaminectomy of C2 and the removal of the posterior arch of C1 (clear visualization and preserving the VA more easily ensured with this step) will provide range of motion to the surgeon on surgical treatment of the region.

It should be kept in mind that 2-3% of anatomical variations of VA in normal population can be found in the far lateral approach to the CVJ [15, 16]. Detection of anomalies and observing the course of VA with preoperative 3-dimensional computerized tomography angiography will be useful to prevent complications.

When this approach is considered in conjunction with the bone tissues removed from the relevant vertebrae and the craniectomy, along with the expanded surgical bone window, and with the appropriate dural incision, it offers a comfortable surgical window opportunity for posterior-posterolateral-anterolateral lesions extending from the lower 1/3 of the clivus to C2, while ensuring the ease of preserving neurovascular structures specific to this region, depending on their size and characteristics.

Conclusion

CVJ and upper cervical spine pathologies can be managed with far lateral approach. This approach increases the surgical dominance and maneuverability of the pathology, which is already in a difficult location. With this approach, surgical difficulties of the region can be overcome with the development of anatomical knowledge and technical infrastructure. Thus, defining the microtopographic surgical anatomy of this region will allow an effective surgery by spreading the range of motion over a wider area in the surgical intervention to be performed.

Conflicts of interest: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Ethical Approval

Conducting scientific studies on cadavers or cadaveric body parts, contribution to education and science is not "human subjects" research and do not require ethical approval. The

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Araştırma Makalesi

Sol Vetrikül destek cihazı olan hastalarda sağ kalp yetmezliği ile sol vetrikül destek cihazı trombozu arasında ilişki var mıdır?

Is there a relationship between right heart failure and left ventricular assist device thrombosis in patient with left ventricular assist device ?

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Öz

Amaç: Sol ventrikül destek cihazı (LVAD) ileri dönem kalp yetmezliği tedavisinde kullanılan metodlardan biridir. Erken dönemde kalp nakline köprülemek amacı ile kullanılan sol ventrikül destek cihazları kalp nakli verici sayısının kısıtlı olması sebebi ile artık destinasyon tedavisi olarak kullanımı her geçen gün artmaktadır. LVAD ile geçirilen süre uzadıkça komplikasyonlarda artmaktadır. Bu komplikasyonlardan en mortal olanı LVAD trombozudur. Bu mortal komplikasyonun önlenebilmesi amacı ile risk faktörlerinin aydınlatılması çok önemlidir.

Gereç ve Yöntemler: Nisan 2012 ile ocak 2020 tarihleri arasında, toplam 80 LVAD hastası retrospektif olarak değerlendirilmiştir. Hastaların veri tabanından demografik özellikleri, yandaş hastalıkları, preoperatif tetkikleri, LVAD data kayıtları kayıt altına alınılmıştır. Sağ ventrikülün kasılma fonksiyonlarını değerlendirmek amacı ile ameliyat öncesi dönemde yapılmış olan ekokardiyogram tetkiklerinde triküspid kapak anüluler hareketinin ölçümü (TAPSE) değeri kullanılmıştır.

Bulgular: Çalışmaya toplam 60 hasta dahil edilmiştir. Bu hastalardan sağ ventrikül fonksiyonları, normal veya hafif etkilenmiş olan (TAPSE≥17) ve orta veya ileri etkilenmiş (TAPSE<17) olarak ikiye ayrılmıştır. TAPSE değeri normal veya hafif etkilenmiş grupta (TAPSEN) 28 (%46.7) hasta varken; orta veya ileri etkilenmiş (TAPSE<17) olan grupta (TAPSED) 32 (%53.3) hasta mevcuttur. Gruplar arasında yaş, cinsiyet, BMI,DM, AF,REDO,LVAD trombozu ve trombozun geliştiği gün açısından istatistiksel olarak fark saptanmadı.

Sonuç: Sonuç olarak, LVAD ile takip edilen hastaların yaşam sürelerini uzatmak için gelişebilecek komplikasyonların önlenmesi hayatı öneme sahiptir. Bu çalışmada preoperatif sağ ventrikül fonksiyonlarının bozulmuş olması ile LVAD trombozu arasında herhangi bir ilişki olmadığını ortaya koymuş bulunmaktayız. LVAD trombozu açısından risk faktörü olma ihtimali olan tüm parametrelerin yapılacak çalışmalarla aydınlatılması bu hasta grubu açısından hayatı öneme sahiptir.

Anahtar Kelimeler: LVAD, lvad tromboz, sağ ventrikül yetmezliği

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Abstract

Aim: Left ventricular assist device (LVAD)is one of the treatment method of advanced heart failure. LVAD, which are used to bridge heart transplantation in the early period, are now increasingly used as destination therapy due to the limited number of heart transplant donors. As the time spent with LVAD increases, complications increase. The most mortal of these complications is LVAD thrombosis. It is very important to clarify the risk factors in order to prevent this mprtal complication.

Material and Methods: Between April 2012 and January 2020, a total of 80 LVAD patients were evaluated retrospectively. Demographic characteristics, co-morbidities, preoperative examinations, LVAD data records of the patients were recorded from the database. Tricuspid valvw annular motion measurement (TAPSE) value was used in echogradiogram examinations performed in the preoperative period to evaluate the contractile functions of the right ventricle.

Results: A total of 60 patients included in the study. Patients divided into two according to right ventricular functions. Normal or mildly affected right ventricular functions (TAPSE≥17) and modarete or severely affected right ventricular functions (TAPSE<17). While there were 28 (%46.7) patients in normal or mildly affected group (TAPSEN); There were 32 (%53.3) patients in moderately or severely affected group (TAPSED). There was no statistical difference between the groups in terms of age, gender, BMI, DM, AF, REDO, LVAD thrombosis and the day the thrombosis developed.

Conclusion: In conclusion, it is vital to prevent complications that may develop in order to prolong the life expectancy of patients followed up with LVAD. In this study, we have shown that there is no relationship between preoperative right ventricular dysfunction and LVAD thrombosis. It is vital fort his patients group to clarify all the parametres that are likely to be risk factors for LVAD thrombosis with fytyre studies.

Keywords: LVAD, LVAD thrombosis, right ventricular failure

Giriş

Kalp yetmezliği önemli bir sağlık sorunudur progresif bir hastalıktır (1). İleri evre kalp yetmezliğinde en iyi tedavi metodu kalp naklidir (2). Türkiye'de yıllık yapılan kalp nakli sayısı 100 civarındadır fakat her yıl binlere hasta bu listeye eklenmektedir. Erken dönemde kalp nakline köprülemek amacı ile piyasaya sürülmüş olan kalp destek sistemleri, günümüzde uzun süreli tedavi (DT) olarakta kullanımaktadır. Kullanım süreleri uzadıkça kalp destek sistemlerine (VAD) bağlı komplikasyonlarda artmaktadır. En sık karşılaşılan komplikasyonlar arasında enfeksiyon, emboliler, GIS intoleransı, böbrek fonksiyon bozuklukları ve VAD trombozları sayılabilir. Aralarında mortalitesi en yüksek olan komplikasyon VAD trombozlarıdır (3).

VAD trombozunun tedavisi yüksek doz antikoagülan (heparin veya düşük molekül ağırlıklı heparin), trombolitik tedavi ve bu ikili tedaviye dirençli olgularda VAD değişim ameliyatıdır.

VADD trombozu için risk faktörleri olarak literatürde araştırıldığında mean arteriyel basıncın 90 mmHg'nın üzerinde olması, antikoagulan kullanımının inefektif olması (INR<3) ve hastanın asetil salisilik asit kullanımının günde 81 mg'dan düşük olması yaygın olarak kabul edilmektedir().

Şuana kadar yapılmış çalışmalarda sol ventriküler destek cihazı (LVAD) implantasyonu yapılmış olan hastalarda sağ ventrikül fonksiyonlarının VAD trombozu için risk faktörü olup olmadığı araştırılmamıştır.

Gereç ve Yöntemler

Başkent Üniversitesi etik komitesinden gerekli onaylar alınıldıktan sonra. Nisan 2012 ile ocak 2020 tarihleri arasında,toplam 80 LVAD hastası retrospektif olarak değerlendirilmiştir. Hastaların veri tabanından demografik özellikleri (yaş, cinsiyet ve vücut kitle indexi (BMI)), yandaş hastalıkları (diabetes mellitus (DM), atrial fibrilasyon (AF)), daha önceden açık kalp ameliyatı geçirip geçirmediği (REDO), ameliyat öncesi ekokardiyogram parametreleri, kalp kateterizasyon parametreleri, LVAD data kayıtları (watt, akım hızı) kayıt altına alınılmıştır. Tüm hastaları ameliyat sonrasında bilgilendirme yapılarak watt değeri veya akım hızı değerlerinde değişiklik olması durumunda hastanemize başvurması önerilmiştir. Bu şikayet ile hastaneye başvuran hastaların daha önceki watt değerinden 1 watt veya üzerinde artış olması ve/veya akım hızında değişkenlikler olması durumunda LVAD trombozu ön tanısı ile hastaneye yatırılmıştır. Yatışı yapılan tüm hastalardan kesin tanıyı belirlemek amacı ile tam idrar analizi, Kan testleri (LDH, Haptoglobulin, direkt ve indirekt bilirubin, tam kan sayımı, üre, kreatinin, sodyum, potasyum, alanin aminotransferaz, aspartat aminotransferaz ve koagülasyon parametreleri (aPTT ve PTZ)), ekokardiyogram ve ön arka akciğer grafisi istenilmiştir. Bu test ve tetkikler sonucunda LVAD trombozu tanısı konulan hastalarda tedaviye başlanılmıştır.

Çalışmadaki tüm hastalar LVAD implantasyonu ameliyatı sonrasında 100 mg/gün asetil salisilik asit, warfarin sodyum (INR 3-3,5) tedavisini almışlardır.

Sağ ventrikülün kasılma fonksiyonlarını değerlendirmek amacı ile ameliyat öncesi dönemde yapılmış olan ekokardiyogram tetkiklerinde triküspid kapak anüluler hareketinin ölçümü (TAPSE) değeri kullanılmıştır. TAPSE değeri 17 ve üstünde olan hastalar normal kabul edilirken 16 ve altındaki değerler düşük kabul edilmiştir. Çalışmaya Erken dönemdeki mortalite (ilk 1 ay) ve doğumsal kalp hastalığı olan hastalar dahil edilmemiştir.

İstatistiksel analiz

İstatistiksel analiz SPSS 22 (SPSS: An IBM Company, version 22.0, IBM Corporation, Armonk, NY, USA) versiyonu kullanılarak yapıldı. Chi-square test and the Mann-Whitney U testleri kullanılarak gruplar karşılaştırıldı. P değeri 0.05 ve altı anlamlı kabul edildi. Veriler, sürekli değişkenler için ortalama değerler standart sapma olarak ve kategorik değerler için ise yüzde olarak ifade edildi.

Sonuçlar

Çalışmaya toplam 60 hasta dahil edilmiştir. Bu hastalardan sağ ventrikül fonksiyonları, normal veya hafif etkilenmiş olan (TAPSE≥17) ve orta veya ileri etkilenmiş (TAPSE<17) olarak ikiye ayrılmıştır. TAPSE değeri normal veya hafif etkilenmiş grupta (TAPSEN) 28 (%46.7) hasta varken; orta veya ileri etkilenmiş (TAPSE<17) olan grupta (TAPSED) 32 (%53.3) hasta mevcuttur.

Tablo 1. Gruplar arasında yaş, cinsiyet, BMI, DM, AF, REDO, LVAD trombozu ve trombozun geliştiği gün açısından istatistiksel olarak fark saptanmadı.

	TAPSEN	TAPSED	P değeri
Yaş (yıl)	44,38±13,72	46,24±12,36	p>0,05
Erkek cinsiyet	25 (%89,3)	28 (%87,5)	p>0,05
BMI	23.9± 6.4	24.7± 6.7	p>0,05
DM	5 (%17,85)	7 (%21,87)	p>0,05
AF	6 (%21,42)	7 (%21,87)	p>0,05
REDO	13 (%46,43)	15 (%46,87)	p>0,05
LVAD trombozu	7 (%25)	9 (%28,15)	p>0,05
Tromboz günü	587,33±127,67	617,78±157,37	p>0,05

Tablo 2. yıllarda göre LVAD trombozu sayıları: Birinci yılda 2; ikinci yılda 3, üçüncü yılda 2 ve dördüncü yılda 1 hasta kalp nakline köprülenmiştir ve birinci yılda bir hastada da iyileşme sebebi ile LVAD çıkarılmıştır.

	LVAD ile yaşayan hasta sayısı	Tromboz gelişen LVAD sayısı
İlk yıl	60	5 (%8,3)
İkinci yıl	46	4 (%8,9)
Üçüncü yıl	37	3(%8,1)
Dördüncü yıl	31	2 (%6,5)
Beşinci yıl	26	2 (%7,7)

Tartışma

DT amacı ile LVAD kullanımının artması sonucunda komplikasyonlar ile karşılaşılma oranları artmıştır. LVAD implantasyonu sonrasında sağ ventrikül disfonksiyonu gelişme oranı literatürde %20-50 oranında saptanılmıştır (9-11). Sağ ventrikül yetmezliği gelişmesi LVAD implantasyonu sonrasında mortalite ve morbidite için major risk faktörü olarak saptanılmıştır (12-14). Benzer şekilde LVAD tromboz gelişmeside ciddi mortalite ile seyretmektedir (7).

Najjar ve arkadaşlarının yapmış olduğu çalışmada 12 aylık süreç içinde LVAD trombozu yaklaşık olarak %8 olarak saptanılmıştır. Benzer şekilde Bizim çalışmamızdada ilk yıl meydana gelen LVAD tromboz oranı %8,3 iken yıllık ortalama %6,5-8,3 oranında LVAD trombozu saptanıldı.

Sağ ventrikül yetersizliğine bağlı olarak santral venöz konjesyon meydana gelmektedir. Santral venöz konjesyona bağlı olarak karaciğer konjesyonu oluşmaktadır. Buna bağlı olarak karaciğer dokusu fonksiyonları bozulmaya başlar. Karaciğer fonksiyonlarında önemli bir tanesi koagülasyon faktörlerinin sentezidir. Bu faktörlerin sentezindeki bozukluğa bağlı olarak PTZ ve aPTT düzeylerinde sürekli olarak değişkenlikler olabilir. Buna bağlı warfarin sodyum düzeyini ayarlamadaki zorluklar sonucunda LVAD trombozlarının artabileceğini düşenmemize rağmen yapmış olduğumuz istatistiksel analizde anlamlı bir fark sağlanamamıştır.

Sonuç olarak, LVAD ile takip edilen hastaların yaşam sürelerini uzatmak için gelişebilecek komplikasyonların önlenmesi hayatı öneme sahiptir. Bu çalışmada preoperatif sağ ventrikül fonksiyonlarının bozulmuş olması ile LVAD trombozu arasında herhangi bir ilişki olmadığını ortaya koymuş bulunmaktayız. LVAD trombozu açısından risk faktörü olma ihtimali olan tüm parametrelerin yapılacak çalışmalarla aydınlatılması bu hasta grubu açısından hayatı öneme sahiptir.

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Araştırma Makalesi

Covid 19 hastalığı sırasında yoğun bakıma yatış ile postoperatif yoğun bakım ünitesi yatışı arasında bir ilişki var mı: Retrospektif çalışma

Is there a relationship between ıntensive care unit admission and postoperative ıntensive care unit admission during covid 19 disease: a retrospective study

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Öz

Amaç: Çalışmamızda Covid-19 enfeksiyonu tedavisi olduktan sonra elektif ameliyat edilen hastaların postoperatif mortalite, morbidite ve yoğun bakım ünitesi (YBÜ) gereksinimlerini inceledik.

Gereç ve Yöntemler: Çalışmaya hastanemizde Temmuz 2020–Temmuz 2021 döneminde yatarak Covid-19 enfeksiyonu tedavisi olan ve sonrasında herhangi bir nedenle elektif ameliyat edilen 18 yaş üstü hastalar dahil edildi. Bu hastaların hastanemiz arşiv kayıtlarından dosyaları incelendi. Covid-19 tanısı için PCR test pozitifliği baz alındı. Hastalık sonrası PCR testi negatif olan elektif olarak ameliyat edilen hastalar incelendi.

Bulgular: Hastanemizde bu dönemde 38,136 hasta yatırılarak tedavi edilmiş ve bu hastaların 2,463'ü Covid-19 enfeksiyonu tanısı ile takip edilmişti. Hastanemizde ameliyat edilen hasta sayısı 24,375 iken; bu hastalardan 423'ü Covid-19 tanısıyla hastanemizde yatırılarak takip edilmiş hasta idi. 423 hastadan 102'si elektif, 321'i acil ameliyata alınmıştı. Elektif olarak ameliyat edilen ve PCR testi negatifleşen 30 hasta çalışmaya dahil edilerek kayıtları incelendi. Bu 30 hastadan 5'i (%16.6) postoperatif YBÜ'de takip edilmişti. Önceden Covid-19 nedeniyle YBÜ'de yatmış olan 2 hasta postoperatif dönemde de YBÜ'de takip edildi. Covid-19 YBÜ yatışı ile postoperatif YBÜ ihtiyacı arasında anlamlı bir ilişki bulundu ($p<0.05$).

Sonuç: Covid-19 enfeksiyonu sonrasında elektif olarak ameliyat edilen hastalarda, Covid 19 enfeksiyonu sırasında yoğun bakıma yatış ile postoperatif YBÜ yatışı arasında pozitif bir ilişki vardır.

Anahtar Kelimeler: Post Covid-19, yoğun bakım ünitesi, elektif cerrahi, postoperatif, pandemi, perioperatif

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Abstract

Aim: In our study, we examined the postoperative mortality, morbidity and intensive care unit (ICU) requirements of patients who underwent elective surgery after treatment for Covid-19 infection.

Material and Methods: Patients over the age of 18 who were admission in our hospital during the period of July 2020-July 2021, treated for Covid-19 infection and subsequently underwent elective surgery for any reason were included in the study. The files of these patients from the archive records of our hospital were examined. The PCR test positivity was taken as the basis for the diagnosis of Covid-19. Electively operated patients with negative PCR test were examined.

Results: During this period, 2,463 of 38,136 patients who were hospitalized in our hospital were followed up with the diagnosis of Covid-19 infection. In the same period, 423 of 24,375 patients who underwent surgery had been hospitalized with the diagnosis of Covid-19 and followed up. Of 423 patients, 102 underwent elective surgery and 321 underwent emergency surgery. Thirty patients who underwent elective surgery and whose PCR test became negative were included in the study and their records were reviewed. It was determined that there were 5 patients (16.6%) who were taken to the intensive care unit after the operation, and 2 of these patients were hospitalized in the ICU due to Covid-19 in the preoperative period. A significant correlation was found between Covid-19 ICU admission and postoperative ICU requirement ($p<0.05$).

Conclusion: In patients who underwent elective surgery after Covid-19 infection, there is a positive relationship between hospitalization in ICU during Covid-19 infection and postoperative ICU admission.

Key words: Covid-19; elective surger; intensive care unit; peritoperative; postoperative.

Giriş

Mart 2020'de Covid-19'un dünya çapında yaygınlığının artması nedeni ile Dünya Sağlık Örgütü tarafından pandemi ilan edilmiştir (1). Covid-19 enfeksiyonu küresel bir sağlık krizine yol açmasının yanı sıra, Covid-19 enfeksiyonundan iyileşen hasta sayısı arttıkça onları ilgilendiren sağlık sorunları ile ilgili bir alan oluşmuştur. Covid-19 enfeksiyonundan sonra kalıcı ve uzun süreli etkilere ilişkin raporlar artmaktadır. Bu hastaların bakımı için kanıta dayalı bir multidisipliner ekip yaklaşımı geliştirmek ve Covid-19 enfeksiyonu sonrası sekelleri sistematik olarak incelemek gerekir (2).

Covid-19 enfeksiyonu sonrası solunum kaslarında zayıflık, pulmoner fibrozis sebebi ile hasarlanmış difüzyon bozukluğuna bağlı restriktif pulmoner yetmezlik görülür. Akut respiratuar yetmezlik (ARDS) ve uzamış hastanede kalış süreleri fiziksel ve psikolojik disfonksiyona yol açar (3). En büyük risk ise; ağır hastalık durumlarında uzamış hastanede kalış sonucu Post İntensive Care Syndrome (PICS) gelişimidir. PICS; kritik hastalık ve akut bakım sonrasında devam eden, taburculuk sonrası yeni ortaya çıkan veya kötüleşen fiziksel, kognitif, mental sağlık durumlarında bozulma olarak tanımlanmıştır. PICS' in farklı tanımları olabilir, ama ortak semptomlar; kas güçsüzlüğü, yorgunluk, hareket kabiliyetinde azalma, ilerleyen düşkünlük, kondüsyon bozukluğu gibi fiziksel rahatsızlıklar; anksiyete, depresyon, seksüel disfonksiyon, uyku bozuklukları gibi psikolojik rahatsızlıklar; hafıza zayıflığı, yavaşlamış mental işlev, zayıflamış konsantrasyon yeteneği ve deliryum gibi kognitif bozuklukları içerir (3).

Şiddetli Akut Solunum Sendromu (SARS, 2003) ve Orta Doğu Şiddetli Akut Solunum Sendromu (MERS, 2012) salgını gibi daha önceki koronavirüs enfeksiyonundan kurtulanlar, bize Covid-19 enfeksiyonunun endişelenmemiz gereken kalıcı semptomlarının olabileceğini göstermiştir. Covid-19 enfeksiyonu semptomların devam etmesine göre 2 grupta kategorize edilmiştir. Akut Covid-19 enfeksiyonu sonrasında, 4-12 hafta süre ile devam etmekte olan semptom ve anormallikleri içeren dönem subakut veya devam eden semptomatik Covid-19 dönemi olarak adlandırılırken; başlangıçtan itibaren 12 hafta ve sonrasında mevcut olan ve alternatif tanılarla ilişkilendirilemeyen semptom ve anormallikleri içeren klinik tablo ise kronik veya Covid-19 sonrası sendrom olarak kategorize edilir (2). Devam etmekte olan çalışmalar göstermiştir ki; enfeksiyonun akciğer hasarı dışında uzun dönem etkileri pek çok patofizyolojik mekanizma ile çoklu organ disfonksiyonuna bağlı uzun dönem sağlık sorunlarını oluşturmuştur (4). Covid-19 enfeksiyonu sonrası kalpte yapısal fonksiyonel değişiklikler olabilir. Özellikle erken evrede subklinik myokard hasarı ve daha sonra diyastolik disfonksiyon görülür (5). MERS ve SARS'tan farklı olarak Covid-19 enfeksiyonunda venöz tromboemboli ve tromboz riski de yüksektir (6).

Elektif cerrahiler için beklenmesi gereken süre hastalığın şiddetine

göre değişmekle beraber bu konu ile ilgili veriler halen net değildir. Hastaların fonksiyonel durumlarının optimize edilerek en iyi biyolojik ve klinik durumun sağlanması önemlidir (4).

Biz bu çalışmada hastanemizde yatarak Covid-19 enfeksiyonu tedavisi olmuş ve sonrasında elektif olarak ameliyat edilen hastaların perioperatif mortalite, morbidite durumlarını ve postoperatif YBÜ serüvenlerini incelemeyi amaçladık.

Gereç ve Yöntemler

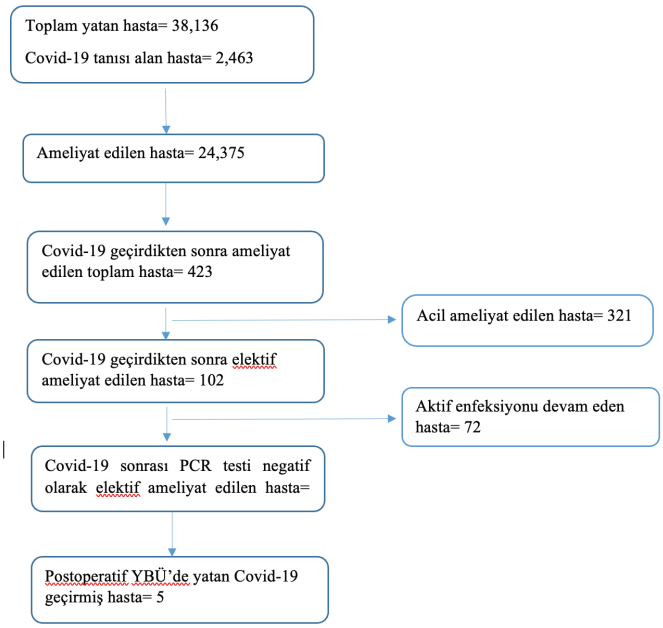
Bu çalışma Samsun Üniversitesi Samsun Eğitim ve Araştırma Hastanesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'nun GOKA/2021/14/7 sayılı onayı alındıktan sonra 'Helsinki Deklarasyonu' prensiplerine uygun olarak yapıldı (Clinical Trials Number: NCT05372341). Çalışmaya Temmuz 2020–Temmuz 2021 döneminde hastanemizde elektif ameliyat edilen 18 yaş üstü hastalar (hastanemizde yatarak tedavi edilen Covid-19 enfeksiyonu geçirmiş olanlar) arşiv kayıtlarından bulunarak dahil edildi. Covid-19 hastalığı sonrası PCR testi negatif olan (PCR testi negatifliği için; PCR pozitifliğinden itibarenen az 7 gün beklendikten sonra test tekrarlanarak negatiflik gözlenmesi baz alındı) elektif olarak ameliyat edilen hastaların dosya bilgilerine ulaşılarak perioperatif kayıtları incelendi. Postoperatif YBÜ'ye yatanlar araştırıldı.

İstatistiksel Analiz

SPSS 18.0 programı kullanılarak veriler kaydedildi ve analizler yapıldı. Tanımlayıcı istatistikler frekans, yüzde, ortalama, standart sapma, minimum, maksimum değerleri ile sunuldu. Karşılaştırmalar Ki-Kare Testi kullanılarak yapıldı, $p<0.05$ değeri anlamlı kabul edildi. Hastaların yaş, cinsiyet, hastalığı hastanede nasıl geçirdikleri (serviste veya, YBÜ'de oksijen ihtiyacı, ventilatör ihtiyacı, yüksek akımlı oksijen (HFO) ihtiyacı, servis ya da YBÜ yatış gün sayıları kaydedildi), ASA klasifikasyonu, ek hastalıkları, pulmoner tutulum, Covid-19 hastalığının üzerinden geçen süre, ameliyat türü, ameliyat süresi, anestezi tekniği, ameliyat sırasında hemodinamik ve solunumsal komplikasyon varlığı kaydedildi. Veriler istatiksel olarak analiz edildikten sonra Covid-19 dışı postoperatif YBÜ'ye yatış oranları değerlendirildi.

Bulgular

Hastanemizde Temmuz 2020–Temmuz 2021 döneminde 38,136 hasta yatırılarak tedavi edilmiş, Covid-19 enfeksiyonu tanısı ile 2,463 hasta takip edilmişti. Bu bir yıl boyunca hastanemizde toplam ameliyat edilen hasta sayısı 24,375 iken; bu hastalardan 423'ü Covid-19 tanısı ile hastanemizde yatırılarak takip edilmiş, bu hastaların 102'si elektif olarak ameliyata alınmıştı. PCR test pozitif olanlar aktif enfeksiyon olduğu için (n= 72) çalışma dışı bırakıldı. Elektif olarak ameliyat edilen ve PCR testi negatifleşen 30 hasta çalışmaya dahil edilerek kayıtları ayrıntılı olarak incelendi (Şekil 1).



Şekil 1. Çalışmaya alınan hasta diyagramı.

Hastalar 27-75 yaş aralığındaydı (ortalama yaş: 53.6 ±16.7) ve hastaların 19'u erkek, 11'i kadın hasta idi, ameliyat süresi 10-400 dakika (dk) (ortalama süre: 76.7±78.57 dk) olarak hesaplandı (Tablo 1).

Tablo 1. Demografik veriler	
Yaş (yıl)	53.6±16.7
Cinsiyet (K/E) (n)	19/11
ASA (I/II/III) (n)	3/16/11
Ameliyat süresi (dk)	76.7±78.57
Değerler Ortalama±standart sapma, n=hasta sayısı	

Ameliyat türleri Tablo 2'de belirtildiği gibiydi. Hastaların 17 tanesi spinal anestezi, 7 tanesi genel anestezi, 1 hasta popliteal sinir bloğu, 4 hasta sedoanaljezi ve 1 hasta lokal anestezi ile ameliyata alındı, ameliyata kadar geçen bekleme süresi (76.6±67.8 gün) idi.

Postoperatif YBÜ' de takip edilen hastaların % 80'i ASA III, %20 'si ASA II idi. Hastaların ASA sınıflandırması ile postoperatif YBÜ ihtiyaçları arasında anlamlı ilişki bulundu (p=0.041). ASA sınıfı arttıkça YBÜ yatış oranının arttığı gözlendi. Covid-19 enfeksiyonu sırasında pulmoner tutulum mevcudiyeti ile postoperatif YBÜ ihtiyacı arasında anlamlı bir ilişki yoktu (p>0.05). Covid-19 YBÜ yatışı ile postoperatif YBÜ gereksinimi arasında yapılan karşılaştırmada Covid-19 YBÜ yatışı ile postoperatif YBÜ gereksinimi arasında anlamlı ilişki saptandı

(p= 0.023). Çalışmaya dahil edilen 30 hastadan 25'inin en az bir kronik hastalığı mevcut idi, ameliyat sonrası YBÜ'de takip edilen hastaların ise hepsinde en az bir kronik hastalık vardı, fakat kronik hastalık varlığı ile postoperatif YBÜ ihtiyacı arasındaki ilişki anlamlı değildi (p=0.556) (Tablo 3).

Tablo 2. Ameliyat Türleri

Ameliyat Türü	Sayı	Yüzde
Diz Altı Amputasyon	2	6.7
Yumuşak Doku Apse Drenajı	3	10.0
Bronkoskopi	1	3.3
Büyük Kemik Kırığı	3	10.0
Sezaryen	3	10.0
Koroner Arter Bypass Greftleme	2	6.7
Dekübit Ülseri	1	3.3
Endobronşiyal Ultrasonografi	2	6.7
Femur Kırığı	2	6.7
Göğüs Tüpü Takılması	1	3.3
Yumuşak Doku Grefti	4	13.3
Güdük Revizyonu (Alt Ekstremite)	1	3.3
Kolesistektomi	1	3.3
Sistoskopi	1	3.3
Tonsil Biyopsisi	1	3.3
Üretral Stent Takılması	1	3.3
Whipple Ameliyatı	1	3.3
Toplam	30	100.0

Tablo 3. Postoperatif YBÜ Yatış Durumları

		n	Postoperatif YBÜ yatışı var (n)	Postoperatif YBÜ yatışı yok (n)	p
ASA klasifikasyonu	I	13	0	13	[a]0.041
	II	6	1	5	
	III	11	4	7	
Anestezi tekniği	Genel	7	2	5	[a]0.232
	Spinal	17	1	16	
	Sinir Bloğu	1	0	1	
	Lokal	4	1	3	
	Sedoanaljezi	1	1	0	
Kronik hastalık	Var	25	5	20	[b]0.556
	Yok	5	0	5	
Pulmoner tutulum	Var	5	2	3	[b]0.565
	Yok	20	3	17	
Covid YBÜ'de yatış	Var	2	2	0	[b]0.023
	Yok	28	3	25	

n: Sayı, aKi-Kare Linear-By-Linear Association , bKi-Kare Fisher's Exact Test

Postoperatif YBÜ'de takip edilen hastaların endikasyonları Tablo 4'te verilmiştir. Cerrahi endikasyon ile postoperatif YBÜ'ye alınan hastaların 2'si koroner bypass greftleme, 1'i Whipple ameliyatı geçirmiş hasta idi.

Tablo 4. Ameliyat Sonu Yoğun Bakım Yatışı Endikasyonu

Ameliyat Sonu Yoğun Bakım Endikasyonu	Yok	25
	Sistemik Hastalık	2
	Cerrahi Endikasyon	3
	Toplam	30

Hastanemizde 1 yılda ameliyat edilen hastalarımızda postoperatif YBÜ'ye yatış oranı %3.97 iken; Covid 19 enfeksiyonu geçirdikten sonra elektif olarak ameliyat edilen 30 hastadan 5'inin (%16.66) postoperatif YBÜ'ye yatırıldığı görüldü. Mortalite oranımız ise %3.3 olarak saptandı.

Tartışma

Covid-19 enfeksiyonu geçirdikten sonra elektif ameliyat edilen hastaları incelediğimiz bu çalışmada Covid-19 enfeksiyonu sebebi ile YBÜ'de takip edilen hastaların Covid-19 enfeksiyonu düzeldikten sonraki elektif ameliyatlarında da YBÜ yatışlarının anlamlı olarak yüksek olduğu gördük. Pandemi döneminde Covid-19 enfeksiyonu geçirdikten sonra erken dönemde cerrahi tedavi yapılan hastalarda, özellikle majör cerrahi uygulananlarda komplikasyon oranlarının yüksek olduğu gözlenmiştir (1). Covid-19 geçiren hastaların elektif cerrahisinde preoperatif değerlendirmede birkaç konu önemlidir. Bunlar; Covid-19 enfeksiyonu tanısı üzerinden geçen süre, enfeksiyonun sebep olduğu rezidüel semptomlar veya organ disfonksiyonunun varlığı ve hastaların fonksiyonel durumlarının optimize edilerek en iyi biyolojik ve klinik durumun sağlanmasıdır (4). Elektif cerrahiler için beklenmesi gereken süre hastalığın şiddetine göre değişmekle beraber bu konu ile ilgili veriler halen net değildir. Bunun yanı sıra daha fazla ertelenemeyen ve ameliyata alınması gereken durumlarda komplikasyon oranları ile ilgili bilgi yetersizdir (1). Covid-19 enfeksiyonu sonrası ilk 4 haftada tromboembolik komplikasyonlar daha çok izlenirken, 4-8 hafta sonra yapılan cerrahilerde postoperatif pnömoni riski daha fazladır. Aktif Covid-19 enfeksiyonu olan hastaların cerrahi gerekliliklerini değerlendirirken özellikle risk/yarar oranı dikkatlice değerlendirilip ileri bir tarihe ertelemek önemli olabilir. Elektif cerrahi için karar vermek daha komplike bir durumdur. Klinisyen hastalığa bağlı organ hasarını, ciddi hastalık ve enfeksiyonun üzerinden geçen süreyi de düşünerek karar vermelidir. Çünkü, Covid-19 enfeksiyonu ve cerrahi prosedür, her ikisi birden sitokin fırtınası ve oksidatif hasar gibi fatal olabilen durumları indükler (4).

Covid-19 enfeksiyonu olan hastalarda yapılan ameliyatlarda perioperatif mortalite oranının daha yüksek olduğunu gösteren çalışmalar artmaktadır (7,8). Haffner ve arkadaşları

10,940 cerrahi hastayı kapsayan retrospektif kohort çalışmasında Covid-19 aktif enfeksiyonu esnasında hastalarda mortalitenin %14.8 olduğunu göstermişlerdir. Covid-19 aktif enfeksiyonunun postoperatif mortaliteyi arttıran bağımsız bir risk faktörü olduğu sonucuna ulaşmışlardır. Daha da önemlisi; preoperatif PCR test pozitifliği olan hastalarda hayat kurtarma ya da uzuv kurtarma önlemleri gibi acil durumların dışında ameliyatın ertelenmesi önerilir. Covid-19 enfeksiyonu geçirmekte olan cerrahi planlanan hastalara hastane içi ölüm riskinin yüksek olduğu konusunda bilgi verilmelidir (9). Kanada merkezli bir başka çalışmada Covid-19 enfeksiyonu sırasında ameliyat olan hastalarda 30 günlük postoperatif mortalite %15.9 gibi önemli bir oranda yüksek gözlenmiştir (7). Bu sebeplerden ötürü elektif ameliyatlar diğer ülkelerde olduğu gibi hastanemizde de pandemi süresince ertelendi. Pandeminin erken dönemlerinde Avrupa'da ve diğer bazı ülkelerde olduğu gibi ertelenemeyecek kadar acil olan ameliyatlar, travma hastaları ve onkolojik cerrahiler dışında elektif ameliyatlar yapılmadı (10). Sezaryen, kemik kırıkları, akut batın, onkolojik ameliyatlar, amputasyon, açık kalp cerrahisi, üriner retansiyona sebep olan acil durumlar ve diğer bekletilemeyecek acil ameliyatlar dışında elektif ameliyatlar ASA önerileri doğrultusunda ertelendi. Bu ertelenmenin sebebi mevcut sağlık gücünün ve ekipmanının pandemi için kullanılması, aynı zamanda enfeksiyon ile ilgili sonuçların öngörülememesiydi.

Uluslararası yapılan bir kohort çalışmasında Covid-19 enfeksiyonunu takiben en az 7 hafta beklenmesi önerilmiştir (11). Başka bir çalışmada ise Covid-19 enfeksiyonu sonrası asemptomatik hastalarda en az 4 hafta, semptomatik hastalarda ise 6-8 hafta beklenmesi önerilmiştir (12). Kliniğimizde ASA'nın önerilerine uygun olarak elektif cerrahiler için asemptomatik olan PCR testi pozitif vakalarda 4 hafta, semptomatik olup evde takip edilen hastalarda 6 hafta, serviste takip edilen komorbiditesi olan hastalarda 8-10 hafta, YBÜ'de takip edilenlerde ise 12 hafta beklenmiştir (13). Covid-19 enfeksiyonu geçirmiş hastaları dahil ettiğimiz bu çalışmada, aktif enfeksiyon dönemi bitmiş hastaları belirlemek için ateş, halsizlik, öksürük gibi klinik bulguları düzelmiş olan ve PCR testi negatifleşmiş olan hastaları inceledik. Esendağlı ve arkadaşlarının çalışmasında Covid-19 enfeksiyonunun zaman çizelgesinde 7-10 gün içinde iyileşme olacağı, eğer kötü yönde ilerleyiş olacak ise 9-10. günde bozulma olduğu belirtilmiştir (14). Tosun ve arkadaşlarının çalışmasında ise hastalığın üzerinden en az 2 hafta, en fazla 31 hafta süre geçmiş olan hastalar çalışmaya dahil edilmiştir (8). Çalışmamızda hastanemizde Covid-19 enfeksiyonu sonrası elektif olarak ameliyat edilen 30 hastanın %16.6'sının YBÜ'de takip edildiği görüldü ve mortalite oranı %3.3 bulundu. Lei ve arkadaşları Covid-19 enfeksiyonu varlığında ameliyat edilen hastalarda %20.6 perioperatif ölüm bildirmişler (6). Kuyubaşı ve arkadaşlarının çalışmasında Covid-19 enfeksiyonlu kalça kırıklarında postoperatif morbidite ve mortalitenin Covid-19 olmayan kalça kırıklarına göre daha fazla olduğu görülmüştür. Bunun sebepleri arasında preoperatif bekleme süresi, ameliyat süresi ve hastanede yatış süresinin uzun olması da düşünülmüştür. Bu hastaların mobilizasyon oranlarının da daha düşük olduğunu ve dolayısıyla yara iyileşme problemlerinin daha fazla olduğunu belirtmişlerdir (15). Haffner ve arkadaşları cerrahi hastalarda Covid-19 varlığında mortalitenin %14.8, covid-19 olmayan hastalarda mortalitenin ise %7.1 olduğunu bulmuşlar; ancak bu çalışmada acil ve elektif cerrahi ayrımı yapılmamıştır (9). Biz çalışmamızda PCR testi negatifleşen tüm cerrahi branşlardaki elektif hastaları değerlendirdiğimiz için mortalite oranımız daha düşüktü. Maldonado ve arkadaşları özefageal ve pankreatik cerrahilerde elektif ameliyat edilen hastaları inceledikleri çalışmalarında Covid-19 enfeksiyonu olan hastalarda mortalite oranını %10 bulmuşlar. Aynı dönemde enfeksiyonu olmayan hastalardan elektif ameliyat olanlarda mortalite görülmezken acil ameliyat edilen hastalarda ise %6.5 olarak bulmuşlar. Onlar çalışmalarında sadece özefageal ve pankreatik cerrahileri dahil etmişlerdir (11). Literatürde Covid-19 enfeksiyonu geçirdikten sonra elektif ameliyat olan hastaların postoperatif YBÜ yatışı insidansı ile ilgili veriye rastlayamadık. Biz çalışmamızda Covid-19 enfeksiyonu sonrası PCR negatif olup elektif olarak ameliyat edilen hastalarımızda postoperatif YBÜ yatış oranını %16.6 olarak hesapladık. Bu değer hastanemizde postoperatif YBÜ yatış oranımız olan %3.97 değerine göre oldukça yüksektir.

Çalışmamıza Covid-19 için aktif enfeksiyon dönemindeki hastaları dahil etmediğimiz ve PCR testi negatifleşmiş olan hastaları incelediğimiz için hasta sayımız az idi. Hasta sayımızın az olması çalışmamızın kısıtlılığı olarak düşünülebilir. Literatürde bizim çalışmamız gibi Covid-19 enfeksiyonu tedavisi sonrası elektif olarak opere edilen bütün cerrahi türlerini içeren hastaların incelendiği başka bir araştırmaya rastlamadığımız için çalışmamızın bu açıdan özellikli olduğunu düşünüyoruz.

Sonuç

Covid-19 enfeksiyonu esnasında YBÜ ihtiyacı olan hastaların sonraki dönemlerindeki elektif ameliyatlarda postoperatif YBÜ

ihtiyacı artmaktadır. Covid-19 enfeksiyonunun multisistemik etkilerinin sonuçları henüz tam olarak bilinememektedir. Daha fazla sayıda hastanın olduğu çalışmalar yapıldıkça Covid-19 enfeksiyonu geçiren hastaların postoperatif sonuçları ile ilgili bilgiler artacaktır. İlerleyen dönemde bu konu ile ilgili literatür bilgisi arttıkça, henüz bizim için karanlık olan noktaların da aydınlığa kavuşacağını ve preoperatif dönemde daha yüksek öngörü ile hazırlıklarımızı yapabileceğimizi düşünmekteyiz.

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Research Article

A new marker in post-pancreatectomy fistulas; hypophosphatemia

Post-pankreatektomi fistüllerinde yeni bir belirteç; hipofosfatemi

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Abstract

Aim: Postoperative hypophosphatemia is associated with morbidity after many gastrointestinal surgeries. In this study, we aimed to investigate the relationship between hypophosphatemia and POPF, which is one of the morbidities after pancreatectomy.

Material and Methods: All adult patients who underwent pancreatectomy in our surgical oncology clinic from 2010 to 2020 were included in the patient data recording system to the Faculty of Medicine of Ankara University, Surgical Oncology clinic. Exclusions were made for those under 18, without postoperative Jackson-Pratt (jp) amylase levels, and with previous pancreatic surgery.

Results: Examination of a total of 185 patients showed that fistula occurred in 20% of cases. Statistical analysis revealed that postoperative 2nd and 3rd-day phosphorus levels are markers for pancreatic leak.

Conclusion: Decreased phosphate values after pancreatic surgery may be an indicator for pancreatic fistula, especially significant on the 2nd and 3rd postoperative days

Keywords: Pancreatectomy, Postoperative Fistula, Hypophosphatemia, Surgical Oncology, Pancreatic Leak, Phosphorus Levels

Öz

Amaç: Postoperatif hipofosfatemi, birçok gastrointestinal cerrahi sonrası morbidite ile ilişkilidir. Bu çalışmada, hipofosfatemi ile pankreatektomi sonrası morbiditelerden biri olan POPF arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntemler: 2010 ile 2020 yılları arasında cerrahi onkoloji kliniğimizde pankreatektomi uygulanan tüm yetişkin hastalar, Ankara Üniversitesi Tıp Fakültesi, Cerrahi Onkoloji Kliniği hastaların veri kayıt sistemine dahil edildi. 18 yaşından küçük hastalar, postoperatif Jackson-Pratt (jp) amilaz seviyesi olmayan hastalar ve önceki pankreas cerrahisi olan hastalar bu çalışma dışı bırakıldı.

Bulgular: Toplam 185 hastanın takibinde fistül gelişip gelişmediği kaydedildi ve vakaların %20'sinde fistül meydana geldi. Fistül ile BMI, yaş, cinsiyet, ca-19.9 seviyeleri ve ameliyat öncesi fosfor seviyeleri, pankreas cerrahisi türü ve ameliyat sonrası günlerdeki 0-1-2-3 fosfor seviyeleri arasındaki ilişki incelendi. POPF olmayan ve olan grup arasında POPL 0 değerleri arasında istatistiksel olarak anlamlı bir fark bulunmadı (p=0.422). POPF olmayan ve olan gruplardaki POPL 1 değerlerindeki fark önemli değil (p=0.296). POPF olmayan ve olan gruplardaki POPL 2 değerlerindeki fark anlamlı (p=0.002). POPF olmayan ve olan grup arasında POPL 3 değerlerindeki fark anlamlıydı (p=0.001). İstatistiksel analiz, ameliyat sonrası 0. gün fosfor seviyeleri ve ameliyat sonrası 1. gün fosfor seviyelerinin pankreas kaçağının bir göstergesi olmadığını, ameliyat sonrası 2. ve 3. gün fosfor seviyelerinin ise çalışma grubumuzda pankreas kaçağının belirleyicisi olduğunu gösterdi.

Sonuç: Pankreas cerrahisi sonrası azalan fosfat değerleri, pankreatik fistül için bir gösterge olabilir. Fosfor seviyeleri, özellikle ameliyat sonrası 2. ve 3. günlerde kaçak açısından anlamlı bulundu.

Anahtar Kelimeler: Pankreatektomi, Postoperatif Fistül, Hipofosfatemi, Cerrahi Onkoloji, Pankreatik Sızıntı, Fosfor Seviyeleri

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Introduction

Pancreaticoduodenectomy (pd)distal pancreatectomy and total pancreatectomy is one of the most complex procedures in gastroenterological surgery and is often indicated for a variety of diseases; therefore, surgical techniques are constantly being improved(1).

The first Pancreaticoduodenectomy (PD) was operated in the 1800s. William Halsted performed the first transduodenal local excision of the ampulla Vater tumor in 1898 (2), while in the same year Alessandro Codivilla became the first person to perform PD in Imola, Italy. In 1909, Walter Kausch performed the first successful 2-stage PD in Berlin (3) Allen Whipple et al reported the first series of PDs in 1935, and the operation has since been known as the "Whipple" operation.(4) Mortality in Whipple operations until the 1970s was over 25%.(5,6)

Mortality due to pancreatectomy in developed centers is below 5%, and morbidity due to pancreatectomy is still common and is estimated as high as 40-50%.(7,8)

The most common causes of morbidity following pancreatic resection include delayed gastric emptying, postoperative bleeding, and postoperative pancreatic fistula (POPF) (9). Pancreatic fistula is typically associated with significant perioperative morbidity such as bleeding, sepsis, longer hospital stay, and increased cost and higher perioperative mortality risk10).

POPF is a common complication of pancreatic surgery associated with increased hospital costs and prolonged hospital stay(11). The sequelae of POPF include sepsis, intra-abdominal abscess formation and intra-abdominal bleeding associated with high mortality rates(12). POPF prevalence estimates are highly variable, frequently ranging from 10% to 20% (8,13) and up to 30% following distal pancreatectomy(14,15.)As POPFs pose a significant risk and cost for both patients and hospitals, studies have focused on estimating the risk of developing POPF. Soft pancreatic parenchyma(16-18), small pancreatic duct(16,17), low surgeon/hospital volüme(19,20),and increased BMI(21,22) Pancreaticojejunostomy vs. pancreaticogastrostomy (23,24), stump closure method(25,26), internal and external drainage(27,28), and administration of somatostatin/pasireotide (29) are accepted risk factors for the development of POPF.

Hypophosphatemia is a common manifestation after various surgical procedures, as well as in patients with infections, burns, and trauma (30-32). The presence of hypophosphatemia is associated with poor outcomes, including arrhythmia, heart failure, longer hospital stays, and increased postoperative complications (33). There is new evidence that following hypophosphatemia may be associated with increased morbidity, including the development of POPF(34).

In this retrospective study, we aimed to investigate whether there is a relationship between early postoperative phosphorus low and pancreatic fistula

Materıal and Methods

All adult patients who underwent pancreatectomy in our surgical oncology clinic for any reason from 2010 to 2020 were included from the patient data recording system of Ankara University Faculty of Medicine, Surgical Oncology Clinic. Patients younger than 18 years of age, patients with no postoperative Jackson-Pratt (jp) amylase levels, and patients with previous pancreatic surgery were excluded from the study.

Age at surgery, gender, year of surgery, type of surgery, duration of surgery, body mass index (bmi), albumin levels, presence or absence of pancreatic ductaladenocarcinoma, and phosphorus levels on postoperative day 0-1-2-3 (POPL 0-1-2-3) were included as covariates.

Those with POPF more than 3 times the upper serum limit of drain amylase on the postoperative day were considered as leaks. Postoperative serum phosphorus levels, demographic characteristics and comorbidities were evaluated and phosphorus levels of the group with fistula and the group without fistula were compared in the preoperative and postoperative days using univariate analysis methods. The importance of phosphorus level as an independent variable in the development of fistula was examined by multivariance analysis. In this study, the variables of age, gender, bmi, type of surgery and preoperative albumin levels were taken. Mann-whitney-u test was used to compare continuous variables that did not show normal distribution. The repeatanova test was performed to test whether there was a difference between the phosphorus levels on the day of surgery, day 1, day 2 and day 3 without considering the pancreatic fistula status, and it was examined with bonferroni, one of the multiple comparisons tests, to find the different one or ones. Unadjusted analyzes were performed with Pearson's chi-square tests, Fisher's exact test, and anova for categorical dependent variables.

Results

A total of 185 adult patients were included in the study. Of these patients, 93 (50.2%) were male and 92 (48.8%) were female. Of the patients who underwent pancreatectomy, 130 (70.3%) underwent proximal pancreaticoduodenectomy (Whipple pancreaticoduodenectomy), 52 (28.1%) underwent distal pancreatectomy, and 3 (1.6%) underwent total pancreatectomy. All operations were performed as open surgery. The mean BMI of the patients was 25.9 (SD 0.24).), the

mean age was 57.1 (SD 1.02). 68.6% of the patients were under 65 years of age, 31.4% were 65 years or older.

The pathological diagnosis of the majority of the patients was adenocarcinoma (78.4%). Whipple procedure was performed in 70% of the patients, distalpancreatectomy in 28.1% and total pancreatectomy in 1.6% (table 1).

Table 1 Baseline variables	
N=185	
Male (n,%)	93(%50.3)
Type of pancreatectomy(n,%)	
Distal	52(%28.1)
Proksimal	130(%70.3)
Total	3(%1.6)
Age (mean,SD)	57.1(1.02)
Age <65 (n,%)	127(68.6)
Age ≥65 (n,%)	58(31.4)
Pancreaticcancer(n,%)	145(78.4)
BMI(mean,SD)	25.9 (0.24)
Lenght of procedure (min; mean, SD)	300(111.3)
EBL (mean, SD)	710.5(940)
Charlson Comorbidity Index Score (n, %)	
0	
1	
2 or more	
Fistula patient (n,%)	37(%20)
POPL 0 phosphate (mean, SD)	3.75(0.84)
POPL 1 phosphate (mean, SD)	3.63(1.21)
POPL 2 phosphate (mean, SD)	2.92(1.28)
POPL 3 phosphate (mean, SD)	2.57(1.27)

It was noted whether fistula developed or not in the follow-up of a total of 185 patients who underwent pancreatic surgery. Accordingly, fistula occurred in 20% of the cases.The relation between fistula development and BMI, age, gender, CA-19.9 levels, preoperative phosphor levels, type of pancreatic surgery, pancreatic specimen pathology, phosphorus levels on postoperative days 0-1-2-3 was looked at.

The difference in POPL 0 values in the group with and without POPF was not significant (p=0.422). The difference in POPL 1 values in the groups with and without POPF was not significant (p=0.296).

The difference in POPL 2 values in the groups with and without POPF was significant (p= 0.002). The difference in POPL 3 values in the group with and without POPF was significant (p=0.001). Statistical analysis showed that postoperative Day 0 phosphorus levels and postoperative Day 1 phosphorus levels were not a marker for pancratic leak, whereas phosphorus levels on post operative Days 2 and 3 are markers in our study group for pancreatic leak (figüre 1).

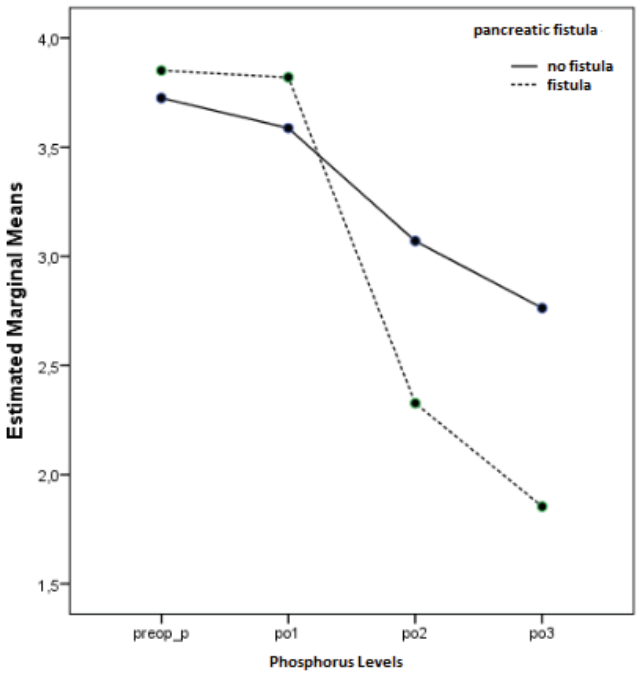

Figure 1.

After determining that the level of POPL values is an independent and important variable, the cut-off value was determined in the ROC analysis and its sensitivity and specificity were determined in the prediction of whether there would be fistula or not.

The area under the curve (AUC) relative to the ROC curve was 0.789, p<0.001. When the cutoff value was taken as 1.6 for POPL values, the sensitivity was determined as 88.4% and the specificity as 62.2%. If the p value is above 1.6 on the postoperative Day 3, there will be no leakage with a prediction of 88%. in the opposite case (p value < 1.6), the estimated leakage is 62.2% (figüre 2).

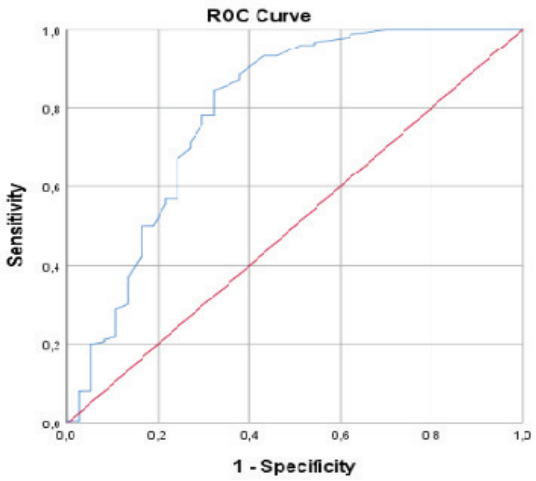

Figure 2.

It showed that 1 unit decrease in phosphorus level on the postoperative day 3 also increased the probability of pancreatic leak by 3.1. Considering gender, 2.6 times more pancreatic leak was observed in male gender in our study. (P=0.029)

The relationship between pancreatic fistula and age (categorical) was not significant (p=0.154)

No relationship was found between pancreatic fistula and age. (P = 0.615) BMI was associated with pancratic fistula and increased BMI was found to be associated with pancreatic leak.(.p=0.001). As the BMI rate increases, the risk of fistula development also increases. There was no relationship between pancreatic fistula development and preoperative ca-19.9 levels (.p=0.564)

The relationship between pancreatic fistula and operation was not significant (p=0.078). The relationship between pancreatic fistula and pathology result was not significant.(p=1.00)

After pancreatic surgery, 15 of 185 patients died in the first week due to surgery and complications.

POPF was present in 6 of these 15 patients, and there was no significant relationship between POPF and these deaths (p=0.083).

The median life expectancy was 33 months in those without POPF, and 29 months in those with POPF. There was no significant difference in survival probability between those with and without POPF (p=0.286) (log-rank test)(figure -3) Table 2.

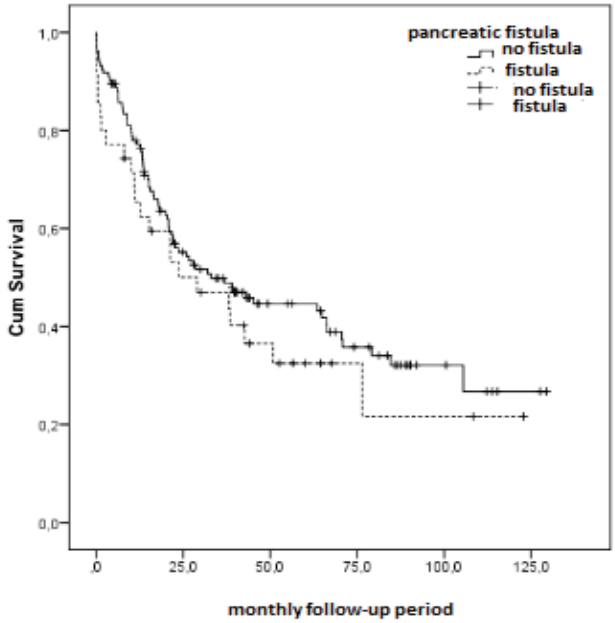

Figure 3.

Table -2			
	fistula	No fistula	P value
Male (n, %)	24(25.8)	69(74.2)	0.047
Age (mean,SD)	56.11 (11.9)	57.43(14.4)	0.615
BMI(mean,SD)	30.1(2.21)	24.8(2.72)	0.001
CA-19,9(mean,SD)	226.6(450.2)	316.8(630.8)	0.433
Adenokarsinom	29	116	1.00
Pankreatikoduodenktomi	30	100	0.78
POPL 0 (mean,SD)	3.85 (0.6)	3.72 (0.9)	0.422
POPL 1 (mean,SD)	3.82 (1.14)	3.58 (1.53)	0.296
POPL2 (mean,SD)	2.32 (1.31)	3.07 (1.24)	0.002
POPL3 (mean,SD)	1.85 (1.16)	2.76 (1.24)	0.001

Dicussion

This retrospective study showed that early postoperative low phosphorus levels are a risk factor and marker reliably associated with POPF. POPL 2 and POPL 3 serum phosphate levels were significantly lower in patients who developed POPF. The reason why we did not include POPL 4 and POPL5 in the study was that low phosphorus levels were usually replaced on the 4th and 5th days. In addition, while male gender and increased BMI were found to be associated with pancreatic fistula in our study, it was

found that age, CA-19.9 levels, type of pancreatic surgery performed and pancreatic specimen pathology were not associated with pancreatic fistula.

By calculating the POPF formation rate, sensitivities, and specificities at different serum phosphate thresholds in POPL 3, we were able to determine a serum phosphate threshold lower than 1.6 as predictive for the 62% fistula risk.

In previous studies, many causes of pancreatic fistula such as age, gender, BMI, pancreatic parenchymal stiffness, type of surgery performed, pancreatic duct width, pancreatic pathology were investigated(12,25,26). In fact, the aim of this study was to investigate whether phosphorus levels could be a marker rather than causing pancreatic leak.

There are few studies suggesting that hypophosphatemia following pancreatectomy can predict leakage-related complications, and our findings are consistent with existing studies(34).

It has been known for years that hypophosphatemia is common in hospital populations and seen in burn and trauma patients, but recently, there are rare studies showing that it may be associated with organ-related complications after gastric, colorectal and pancreatic surgery(35). Eransadot et al. described a consistent hypophosphatemia pattern in a large number of patients following three different

gastrointestinal operations. In addition, low phosphate levels were associated with an increased risk of organ-specific complications, independent of other established risk factors. They stated that early postoperative hypophosphatemia may predict early identification of patients at risk of organ-specific complications(35). Although there are very few studies on hypophosphatemia and pancreatic surgery, there are many studies on the relationship between liver surgery and hyposphataemia. This is because hypophosphatemia is a common phenomenon following hepatic resection(36. While hypophosphatemia is associated with poor outcomes after pancreatic surgery, hypophosphatemia after hepatectomy is associated with good results. Initially it was only predicted to be a result of reduction along the growth of the liver. Although it has been proven that the active incorporation of phosphate into the liver reaches its maximum level in the immediate first 72 hours after hepatectomy (37), this cannot clarify the mechanism of hypophosphatemia.

In a study mentioned in the literature, there was a significant increase in phosphate excretion in the urinary system after hepatectomy. They hypothesized that it was caused by an unidentified phosphaturic protein resulting in postoperative renal phosphate loss (38). This opinion is confirmed by urinary phosphate increases emerging within the first few hours postoeratively. In addition, an experimental animal study in the literature revealed a phosphaturic protein associated with urinary phosphate loss after hepatectomy(39).In fact, in the light of the above literature; Any factor causing hypophosphatemia; The lack of decrease in serum phosphate levels in the early postoperative period suggests that it is associated with a much more significant risk of mortality or non-fatal postoperative liver dysfunction after hepatectomy. In a study by Zheng et al., which was also recently declared in the literature, "serum nicotinamidephosphoribosyl-transferase (NAMPT)" as the main cornerstone; It is understood that they defined it as a phosphaturic touchstone that plays a leading role in phosphatauria and related hypophosphatemia in the period after hepatectomy or pancreatectomy(40). Thus it appears that the mechanism of hypophosphatemia following both procedures may actually be similar, despite opposing prognostic implications. In addition, low serum phosphate levels plays an important role in onset sepsis and infection, as different proinflammatory cytokines are correlated with hypophosphatemia(41). On the other hand; Even if the hypophosphatemia pathway that occurs after partial liver or pancreas resection has gained more and more attention and studies have increased (40), unfortunately, the relationship between POPF and hypophosphatemia is still not clear. Because the relationship between POPF and hypophosphatemia is not clearly known, the therapeutic results of phosphorus replacement remain unclear. Large sample and prospective studies are needed to reveal this relationship.

The limitations of our study were the retrospective nature of our study, insufficient records related to pancreatic parenchyma and ductal structure in our data, and the number of our patients and therefore the number of POPF patients was not high.

In summary, in our study, by calculating the POPF formation rate, sensitivities and specificities at different serum phosphate threshold values in POPL 3, we were able to determine a serum phosphate threshold value less than 1.6 as an estimator for the 62% fistula risk. Hypophosphatemia can be interpreted as a marker with good sensitivity but poor specificity. Evaluating the severity and timing of hypophosphatemia after pancreatectomy provides an opportunity for early detection of possible fistula-related complications.

Conclusion

Decreased phosphate values after pancreatic surgery may be a warning for pancreatic fistula. Phosphorus levels were found to be significant in our study in terms of leakage, especially on the 2nd and 3rd postoperative days. In larger patient groups and with meta-analyses, it is possible that phosphorus level will enter the literature widely as a leak indicator, with possible positive results.

Evaluating the severity and timing of hypophosphatemia after pancreatectomy provides an opportunity for early detection of possible fistula-related complications. Future studies should prospectively examine the relationship between phosphorus levels and pancreatic fistula and investigate the effect on leakage rates and decrease in morbidity and mortality due to leakage after early or prophylactic phosphorus replacement, and the physiopathological relationship between phosphorus level and POPF should be examined.

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Araştırma Makalesi

Jinekolojik onkoloji cerrahisi hastalarında öngörülen ve öngörülemeyen zor havayolu olgularının karşılaştırılması

Comparison of predictable and unpredictable difficult airway cases in gynecologic-oncology surgery patients

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Öz

Amaç: Anesteziye bağlı morbidite ve mortalite nedenlerinden bir tanesi zor ve/veya başarısız entübasyondur. Havayolu muayenesinin zor havayolu (ZH) varlığını öngörmedeki rolü bilinmekle birlikte, ameliyat öncesi dönemde bu amaçla kullanılan testlerin özgüllüğü yüksek, ancak özgünlüğü düşüktür. Bu çalışmada, genel anestezi altında cerrahi tedavi uygulanacak komorbiditesi yüksek bir hasta popülasyonunda, preoperatif havayolu değerlendirmesi ile öngörülen ve öngörülemeyen zor havayolu olgularını belirlemek, karşılaştırmak ve zor entübasyon için olası risk faktörlerini ortaya koymak amaçlanmıştır.

Gereç ve Yöntemler: Jinekolojik onkoloji cerrahisi için genel anestezi uygulanan, 18 yaş ve üzeri, toplam 162 hasta prospektif olarak çalışmaya dahil edildi. Preoperatif havayolu incelemeleri sonrasında; Basitleştirilmiş Havayolu Risk İndeksi (Simplified Airway Risk Index: SARI)'ne göre, ZH öngörülen ve öngörülemeyen olgular belirlendi. Endotrakeal entübasyon sonrasında Entübasyon Zorluk Skalası (Intubation Difficulty Scale: IDS)'na göre entübasyonu zor olan ve olmayan olgular gruplandırıldı, ZH'na neden olan etmenler ortaya konuldu.

Bulgular: SARI'ya göre toplam 162 hastanın 32'si (%19,75) ZH öngörülen, 130'u (%80,25) ise ZH öngörülemeyen olarak değerlendirildi. Entübasyon sonrasında IDS'ye göre 59 (%36,4) olguda zor entübasyon varlığı kayıt edildi. Boyun uzunluk ölçümü ($p<0,003$), vücut kitle indeksi ($p=0,01$), uzun üst ön kesici dişler ($p=0,046$), Modifiye Mallampati Skoru ($p=0,002$), tiromental mesafe ($p=0,003$), yüksek damak varlığı ($p=0,016$) ZH varlığını etkileyen faktörler olarak bulundu. Ayrıca bu hasta grubunda, ileri yaş (>60 yaş; $p=0,006$) ve kronik hastalık varlığında ($p=0,032$) ZH ile karşılaşılma ihtimalinin arttığı da izlendi.

Sonuç: Bu çalışma ile preoperatif hasta değerlendirmesinde kullanılan Modifiye Mallampati skoru, boyun uzunluk ölçümü, tiromental mesafe ve ön kesici dişlerin uzun olmasının ZH varlığını etkileyen en önemli etmenler olduğu gösterilmiştir. Ameliyat öncesi dönemde yapılacak özenli havayolu muayenesinin ZH yönetimi için planlama yapılmasına olanak sağladığı düşünülmektedir.

Anahtar kelimeler: Genel anestezi; entübasyon; prediktif testler; zor havayolu

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Abstract

Aim: One of the factors contributing to anesthesia-related morbidity and mortality is difficult intubation. Although it is well established that airway examination plays a crucial role in predicting the presence of a difficult airway (DA) during preoperative assessment, the predictive tests currently being utilized have a high specificity but a poor sensitivity. In this study, we sought to identify and compare the predictable and unpredictable DA cases with preoperative airway examination in a patient population with high comorbidity who underwent surgical intervention under general anesthesia. We also determine the possible risk factors for difficult intubation.

Material and Methods: Between January and April 2022, a total of 162 patients who underwent general anesthesia for gynecological-oncology surgery and were at least 18 years old were evaluated prospectively. Following preoperative airway assessments, predictable and unpredictable DA were identified using the Simplified Airway Risk Index (SARI). In order to determine the factors that contributed to DA, patients were divided into groups with and without difficult intubation after endotracheal intubation using the "Intubation Difficulty Scale" (IDS).

Results: In the study, 32 patients (19.75%) were found to have predicted DA, and 130 individuals (80.25%) were found to have unpredicted DA. According to the IDS, DA was detected in 59 (36.4%) patients after intubation. A high palate (p = 0.016), long anterior incisors (LAI) (p = 0.046), Modified Mallampati Score (MMS) (p = 0.002), Thyromental distance (TD) (p = 0.003), and neck length measurement (NLM) were shown to be the factors determining the existence of DA. Furthermore, advanced age (>60 years, p=0.006) and the presence of chronic diseases (p=0.032) increased the probability of encountering DA.

Conclusion: The findings of the study demonstrated that preoperative MMS, NLM, TD, LAI are found to be the most significant factors affecting the occurrence of DA. Attentive preoperative airway evaluation is critical while planning the DA and its management.

Keywords: General Anesthesia; intubation; predictive tests; difficult airway

Giriş

Genel anestezi uygulanacak hastaların anestezi öncesi fizik muayenesinde, havayolunun ayrıntılı değerlendirilmesi önemlidir. Anesteziye bağlı morbidite ve mortalitenin yaygın nedenlerinden bir tanesi zor ve başarısız endotrakeal entübasyondur. Zor hava yolu, eğitimli bir anestezistin, ilgili olgunun üst solunum yolunda yüz maske ventilasyonunda zorluk, endotrakeal entübasyonunda zorluk veya her ikisinin birden yaşadığı klinik durum olarak tanımlanmıştır [1]. Hava yolu fizik incelemesi ile elde edilen bilgilerin zor havayolu varlığını öngörmedeki rolü bilinmekle birlikte, bu amaçla kullanılan testlerin özgüllüğü yüksek, duyarlılığı düşüktür [1]. Hastada zor havayolu kriterlerinden birden fazlasının saptanması durumunda, sadece bir tane kriter varlığına kıyasla, zor havayolu olasılığında artışa neden olduğu gösterilmiştir [1].

Planlı ve sistematik havayolu yönetimi ile ameliyattan önce olası sorunların tanımlanması sağlanarak süreç güvenli hale getirilebilmekte ve böylelikle komplikasyonların da mümkün olduğunca önüne geçilebilmektedir. Havayolu yönetiminde zorluğun öngörülmesi tamamen güvenilir olmasa da cerrahi girişim uygulanacak hastalarda preoperatif hava yolu değerlendirmesi; yüz maske ventilasyonu, supraglottik havayolu araçları yerleştirme, trakeal entübasyon veya boyun önü erişim ile ilgili zorluklara yol açabilecek faktörleri belirlemek için rutin olarak yapılmalıdır [2].

Jinekolojik onkoloji cerrahisi hastaları, genellikle birçok yandaş hastalığı olan, daha önce radyoterapi ve/veya kemoterapi uygulanmış, görece yüksek riskli bir popülasyon olarak tanımlanmaktadır [3]. Bu kohortta, hastalıkların seyri nedeniyle vücut kitle indeksi düşük veya morbid obez hastalar ile de karşılaşılabilmektedir. Özellikle obezitenin eşlik ettiği olgularda havayolunun bütünlüğünün sağlanması ile ilgili problemler yaşanabilmektedir [4]. Bu bağlamda, havayolu açıklığının sağlanması sürecinde var olan herhangi bir güçlüğün işlem öncesinde bilinerek gerekli önlemlerin alınması ile hasta güvenliği sağlanabilmekte ve oluşabilecek komplikasyonların önüne geçilebilmektedir.

Bu çalışmada, komorbiditesi yüksek olduğu bilinen jinekolojik onkoloji cerrahisi olgularında ameliyat öncesi havayolu değerlendirilmesi ile zor havayolu öngörülen ve öngörülemeyen olguları ortaya koymak, bunları karşılaştırmak ve zor entübasyon için olası risk faktörlerini belirlemek amaçlanmıştır.

Gereç ve Yöntemler

Bu çalışma Tıp ve Sağlık Bilimleri Araştırma Kurulu ve Etik Kurulu tarafından onaylanmış (Proje No: KA21/541) ve Araştırma Fonunca desteklenmiştir.

Prospektif olarak tasarlanan bu çalışmaya, Ocak 2022 ile Nisan 2022 tarihleri arasında elektif koşullarda jinekolojik onkoloji cerrahisi için genel anestezi uygulanan, 18 yaş ve üzeri, toplam 162 hasta dahil edildi. Tüm hastalara çalışma ile ilgili bilgi verildi ve çalışmaya katılmayı kabul eden hastalardan aydınlatılmış onamları alındı.

Ameliyat öncesi dönemde, anestezi polikliniğinde hastaların demografik özellikleri ile eşlik eden hastalık(lar) varlığı, kemoterapi (KT) ve radyoterapi (RT) öyküleri not edildi. Hastanın zor havayolu değerlendirmesinde kullanılan belirteçler; daha önce bilinen zor entübasyon varlığı, romatoid artrit veya ankilozan spondilit hikayesi ile birlikte kısıtlı boyun hareket varlığı, obstrüktif uyku apne sendromu, yüzde deformite varlığı, vücut kitle indeksi (VKİ), Modifiye Mallampati skoru (MMS) (Derece III-IV), ön kesici dişler arası mesafe (interinsizal mesafe < 3cm), tiromental mesafe (TMM) (< 6,5 cm), sternomental mesafe (SMM) (<12,5 cm), mandibula protrüzyonu, boyun çevresi (> 40 cm), boyun uzunluğu (processus mastoideus ile sternum'un en üst yukarı ucu ve medial noktası arası) (< 16,5 cm), hiyomental mesafe (HMM)(< 4 cm), üst dudak ısırma testi, protez diş varlığı, eksik maksiller ön tek diş, uzun üst ön kesici diş, dişlerin yokluğu, submandibuler boşluk muayenesi ve dilin dışarı hareketi değerlendirildi (belirteçler ile birlikte parantez içerisinde verilen değerler zor entübasyon için eşik değerleri ifade etmektedir) [5-10].

"Basitleştirilmiş Havayolu Risk İndeksi (Simplified airway risk index: SARI)" preoperatif dönemde zor entübasyon varlığını değerlendirmek üzere kullanıldı ve SARI ≥ 4 olan hastalar zor entübasyon öngörülen olgular olarak gruplandırıldı [11].

Anestezi indüksiyonu sonrası tüm hastaların endotrakeal entübasyonu aynı anestezi uzmanı (sorumlu yazar) tarafından gerçekleştirildi. Laringoskopi sonrası hastaların zor entübasyon varlığı not edilerek, zor entübasyon varlığına sebep olabilecek etmenler kayıt edildi. Cormack-Lehane vokal kord görünümü (Evre III-IV), entübasyon sırasında kullanılan yardımcı araçlar, kullanılan laringoskop bıçak (blade) tipi, trakeal bası uygulanması, kılavuz tel, gum elastik buji, videolaringoskop kullanımı, laringeal maskeye geçiş, anestezi plan değişikliği gözden geçirilerek trakeal entübasyon zorluk derecesi "Entübasyon zorluk skalası (Intubation Difficulty Scale: IDS)" ile değerlendirildi ve IDS > 5 olan olgular zor entübasyon olarak gruplandırıldı [12]. Ek olarak, zor havayolu varlığını gösteren belirteç sayısı ve niteliği ile zor entübasyon ile karşılaşılma olasılığı arasındaki ilişki de değerlendirildi.

İstatistiksel Analiz

Sayısal değişkenlerin normal dağılıma uygunluğu için Shapiro-Wilk testi kullanılarak, normal dağılıma uygun değişkenler için ortalama ± standart sapma, normal dağılıma uymayanlar için tanımlayıcı istatistik olarak medyan (minimum-maksimum) değerleri verildi. Çalışmada tanımlayıcı istatistik olarak; kategorik değişkenlerin değerlendirilmesinde frekans (n) ve yüzde (%) değerleri kullanıldı. Çalışmada hipotez testi yöntemleri, parametrik test varsayımlarının sağlandığı durumda Nicel değişkenler açısından "Independent sample t testi", sağlanmadığı durumda "Mann Whitney U testi", kategorik değişkenler arasındaki ilişkinin incelenmesinde, test varsayımları sağlandığında "Pearson Ki-Kare Testi", sağlanmadığı durumda ise "Fisher Exact Testi" kullanıldı. Tüm hipotez testlerinde I. Tip hata olasılığı α=0,05 olarak alınarak, istatistiksel değerlendirmeler için SPSS v25.0 paket programı kullanıldı. Araştırma hipotezinin test edilebilmesi için gerekli örnek genişliği hesaplanırken Cohen'in tanımladığı orta etki genişliği kullanılmış olup hesaplamalar G*Power 3.1.9 programı ile yapılmıştır. Çalışma için gerekli minimum örnek genişliği, çalışmanın ana amacını oluşturan zor hava kanalı öngörülen grupla öngörülemeyen grupta yer alan hastaların, anestezi indüksiyonu sonrası, zor havayolu ile karşılaşılma oranları karşılaştırmak amacına göre hesaplanmış olup, "Ki-kare testi" için orta etki genişliği w=0,3* olmak üzere %80 test gücünü %95 güven düzeyinde sağlayacak, df=6 olmak üzere çalışmada minimum örneklem genişliği 152 hasta olarak hesaplanmıştır.

Bulgular

Çalışmaya dahil edilen toplam 162 kadın hastanın ortalama yaşı 50 ± 13,6 yıl, ortalama VKİ 28,03 ± 6,4 kg/m2 olarak bulundu. Preoperatif değerlendirme sonrasında SARI kriterlerine göre, hastaların 32'si (%19,75) zor havayolu öngörülen, 130'u (%80,25) ise zor havayolu öngörülemeyen olarak değerlendirildi. Endotrakeal entübasyonun ardından, IDS'ye göre yapılan değerlendirmede ise 59 (%36,4) hastada zor entübasyon ile karşılaşıldı. Dolayısı ile SARI ile öngörülemeyen 27 hastada zor havayolu ile karşılaşıldığı tespit edildi.

Hastaların demografik ve klinik özellikleri Tablo 1'de özetlenmiştir.

Tablo 1. Hastaların gruplara göre demografik ve klinik özellikleri.

Parametre	Zor Entübasyon9)	Kolay Entübasyon	p
Yaş (yıl)			0,006
<60	35 (59,3)	82 (79,6)	
≥60 yaş	24 (40,7)	21 (20,4)	
VKİ (kg/m2)			0,01
Düşük kilolu	3	3	
Normal kilolu	12	48	
Kilolu	19	25	
Obez	25	27	
Morbid Obez	0	0	
ASA			0,561
I-II	48 (%81,36)	90 (% 87,37)	
III-IV	11 (%18,64)	13 (% 12,63)	
Sigara kullanımı	10 (%16,95)	18 (%17,47)	0,543
Radyoterapi/ Kemoterapi	19 (%32,2)	24 (%23,3)	0,371
Yandaş Hastalıklar	50 (% 84,7)	71(%68,9)	0,032
Hipertansiyon (HT)	31 (%52,5)	37 (%35,9)	0,039
Koroner Arter Hastalığı (KAH)	16 (%27,1)	15 (%14,6)	0,051
Kalp yetmezliği	2 (%3,4)	0 (%0,0)	0,631‡
Hiperlipidemi	4 (%6,8)	7 (%6,8)	0,997
Diabetes Mellitus	16 (%27,11)	13 (%12,6)	0,021
Guatr	13 (%22,0)	15 (%14,6)	0,226
Romatoid Artrit	5 (%8,5)	4 (% 3,9)	0,220
Ankilozan spondilit	1 (%1,7)	3 (%2,9)	0,631
Obstrüktif Uyku Apne Sendromu	2 (%3,58)	1 (%0,97)	0,272
Yüzde deformite varlığı	4 (%6,8)	5 (%4,85)	0,448
Zor entübasyon öyküsü	2 (%3,58)	1 (%0,97)	0,272
Protez diş varlığı	8 (%13,5)	10 (%9,8)	0,077
Üst kesici diş yokluğu	7 (%11,86)	8 (%7,8)	0,153

İleri yaş (60 yaş ve üzeri) ve VKİ artışı ile zor entübasyon ile karşılaşılma arasında istatistiksel açıdan anlamlı ilişki tespit edildi (sırası ile p=0,006 ve p=0,01). Ek olarak, kronik hastalıkların varlığında zor havayolu ile karşılaşılma ihtimalinin arttığı (p=0,032), özellikle diabetes mellitus ve hipertansiyon ile zor havayolu varlığı arasındaki ilişkinin istatistiksel açıdan anlamlı olduğu izlendi (sırası ile p=0,021, p=0,039).

Kısıtlı boyun hareketi (KBH)(p<0,001), interinsizal mesafe (İM) (p=0,001), TMM (p=0,003), SMM (p=0,005), HMM (p=0,001), boyun çevresi (BÇ)(p=0,009), boyun uzunluğu (BU) (p=0,003), uzun ön kesici dişler (UÖKD) (p=0.046), MMS (p=0,002), üst dudak ısırma testi (ÜDIT)(p=0,002), yüksek damak varlığı (p=0,016) zor entübasyonu istatistiksel bakımdan anlamlı olarak etkileyen belirteçler olarak bulundu. Zor entübasyon olan ve olmayan hastaların prediktif testler açısından karşılaştırılması Tablo 2'de verilmiştir.

Zor havayolu prediktif testleri incelendiğinde; IDS>5'ten büyük olan olgularda istatistiksel olarak anlamlı fark izlendi (p<0,05). Bu prediktif testlerden biri olan boyun uzunluk ölçümü zor entübasyon grubunda daha kısa idi (p=0,003). Aynı zamanda bu test, en yüksek duyarlılığa sahip olup (%97,42), pozitif öngörü değeri %67,54 olarak hesaplandı (OR=0,657). Benzer olarak, TMM ölçümü de %95,29 ile yüksek duyarlılığa ve %68,64 pozitif öngörü değerine sahip idi. Uzun üst ön kesici diş varlığı zor entübasyon için istatistiksel açıdan anlamlı öneme sahipken (p=0,046), testin duyarlılığı %94,17 oranında, yüksek olarak bulundu ve pozitif öngörü değeri ise %65,99 olarak ölçüldü (OR=2,910). Zor entübasyon olgularının %28,8'inde MMS 3 veya 4 iken; MMS 1'den 4'e doğru zor entübasyon görülme ihtimali de artmakta idi (p=0,002, OR= 5,111). MMS'nin duyarlılığı %91,26 pozitif öngörü değeri ise %69,12 idi.

Zor entübasyon görülen hastaların, prediktif testlerinin duyarlılık ve özgüllük oranları ile pozitif ve negatif öngörü değerleri Tablo 3'de özetlenmiştir.

Tablo 2. Ameliyat öncesi havayolu parametreleri ve dağılımlarına göre zor entübasyon olan ve olmayan hastaların havayolu prediktif testleri açısından karşılaştırılması.

Parametre	Zor entübasyon (n=59)	Kolay entübasyon (n=103)	pp
Mallampati Skoru (3-4)	17 (%28,8)	9 (%8,7)	0,002‡
Kesici dişler arası mesafe	3,83 ± 0,72	4,33 ± 0,76	0,001†
Tiromental mesafe	7,40 ± 1,25	8,08 ± 1,14	0,003†
Sternomental mesafe	13,06 ± 1,41	13,85 ± 1,53	0,005†
Hiyomental mesafe	4,66 ± 0,75	5,37 ± 1,07	0,001†
Boyun çevresi	37,31 ± 4,12	35,55 ± 3,75	0,009†
Boyun uzunluğu	11,76 ± 1,65	12,68 ± 1,48	0,003†
Yumuşak damak	4 (%6,9)	0 (%00,0)	0,016‡
Mandibula protrüzyonu	5 (%8,5)	3 (%2,9)	0,140‡
Kısıtlı boyun hareketi	31 (%52,5)	17 (%16,5)	<0,001‡
Dilin dışarı çıkarılabilmesi	1 (%1,7)	3 (%2,9)	0,631‡
Submandibular alan muayenesi	6 (%10,2)	3 (%2,9)	0,052‡
Üst dudak ısırma testi 2/3	24/1 (%40,7/1,7)	19/0 (%18,4/0)	0,002‡
Uzun üst ön kesici dişler	9 (%15,3)	6 (%5,8)	0,046‡

† ortalama ± SD, ‡ düzeltilmiş χ2 test, p <0,05.

Tablo 3. Zor entübasyon görülen hastaların, preoperatif parametreleri için duyarlılık (sensitivite), özgüllük (spesifite), pozitif öngörü ve negatif öngörü değerleri.

Parametre	Sn (%)	Sp (%)	PPD (%)	NPD (%)	p-değeri	OR	A (%)
MMS	91,26	28,81	69,12	65,38	0,002‡	5,111	68,5
İM	72,07	60,71	87,91	35,42	0,001†	0,425	69,8
TMM	95,29	21,28	68,64	71,43	0,003†	0,580	68,9
SMM	88,89	37,74	68,57	68,97	0,005†	0,675	68,7
HMM	94	26,79	69,63	71,43	0,001†	0,380	69,9
BÇ	91,09	15,52	65,25	50,00	0,009†	1,118	63,5
BU	97,42	19,57	67,54	81,82	0,003†	0,657	68,8
KBH	83,50	52,54	75,44	64,58	<0,001	5,601	72,2
ÜDIT	81,55	42,37	71,19	56,82	0,002‡	3,121	67,3
UÖKD	94,17	15,25	65,99	60,00	0,046‡	2,910	65,4

Sn: sensitivite; Sp: spesifite; PPD: pozitif prediktif değer; NPD: negatif prediktif değer; A: Doğruluk (Accuracy); p < 0,05.
MMS: Modifiye Mallampati skoru, İM: kesici dişler arası mesafe, TMM: tiromental mesafe, SMM: sternomental mesafe, HMM: hiyomental mesafe, BÇ: boyun çevresi, BU: boyun uzunluğu, KBH: kısıtlı boyun hareketi, ÜDIT: üst dudak ısırma testi, UÖKD: uzun üst ön kesici dişler.

Tartışma

Komorbiditesi yüksek olduğu bilinen jinekolojik onkoloji cerrahisi olgularında preoperatif havayolu değerlendirilmesi ile zor havayolu öngörülen ve öngörülemeyen olguları karşılaştırmak ve zor entübasyon için olası risk faktörlerini belirlemek amacı ile yapılan bu çalışmada preoperatif değerlendirmede kullanılan boyun uzunluk ölçümü, tiromental mesafe, ön kesici dişlerin uzun olması, hiyomental mesafe ile yüksek mallampati skorunun zor entübasyonu istatistiksel açıdan anlamlı olarak etkilediği ve duyarlılıklarının da yüksek olduğu bulunmuştur.

Genel anestezi uygulanan hastalarda bildirilen zor laringoskopi ve trakeal entübasyon olguları %1,5 ile %13 arasında değişkenlik göstermektedir [13]. Bu çalışmada, preoperatif süreçte SARI ile yapılan değerlendirmede %19,75 zor havayolu beklenirken, laringoskopi sonrasında %36,4 oranında zor entübasyon ile karşılaşılmıştır. Dolayısı ile, literatür ile karşılaştırıldığında, çalışmamızda daha fazla sayıda zor entübasyon olgusu ile karşılaşılmıştır. Belirli bir hasta kohortunda yapılan bu çalışmada ileri olgu yaşı ile [60 yaş ve üzeri hasta grubu ile zor entübasyon arasında istatistiksel açıdan anlamlı ilişki bulunmuştur (p=0,006)] eşlik eden hastalık sayısının çokluğu, zor entübasyon oranlarının literatür ile karşılaştırıldığında daha yüksek olarak ifade edilmesinin sebepleri arasında sayılabilmektedir. Benzer şekilde, diş kaybı ve dejeneratif değişikliklere bağlı olarak baş boyun eklem hareketlerinde kısıtlılık gibi problemlerden ötürü de yaşlı hastalarda zor entübasyon beklenebilmektedir. Ezri ve ark.'nın

yapmış olduğu çalışmada artan yaşla birlikte zor laringoskopi ve zor havayolu ile karşılaşıldığı bildirilmiştir [14].

Obezite ile normal kilolu olguları zor entübasyon açısından değerlendiren çeşitli araştırmalarda belirgin bir farklılık saptanmamıştır [4,5,7,15]. Ancak çalışmamızda VKİ'inde olan artışla birlikte zor entübasyon oranlarında da artış olduğu izlenmiştir (p=0,01). Alıç ve ark.'nın obez gebelerde yapmış oldukları çalışmada da benzer sonuçlar bulunmuştur [16]. Çalışmamızdaki bu sonuçların, hasta popülasyonu ile ilişkilendirilebileceği düşünülmektedir.

Preoperatif değerlendirme rutininde kullanımı az da olsa, Wilson ve ark. tarafından yapılan bir çalışmada, boyun uzunluk ölçümünün referans değere göre 16,5 cm ve altında olması zor havayolu kriteri olarak tanımlanmıştır [17]. Çalışmamızda prediktif testlerden BU ölçümü %97,42 ile en yüksek duyarlılığa sahip iken pozitif öngörü değeri de %67,54 bulunmuştur. Bu bağlamda, klinik uygulamalarda BU ölçümünün ZE tayininde destekler nitelikte olduğu tayin edilmiş olup, yazarlar tarafından kullanımı tavsiye edilmektedir.

Zor havayolu muayenesinde sıklıkla kullanımı olan TMM, bu çalışmada da ZE tayini açısından istatistiksel bakımdan anlamlı ve testin duyarlılığı da yüksek olarak bulunmuştur (%95,29). Diğer taraftan bu belirtecin zor entübasyon tayininde tanısal değerinin düşük olduğunu bildiren araştırmalar da mevcuttur [18]. Obstetrik olguları değerlendiren bir çalışmada zor havayolu SMM, TMM ve HMM başlıkları altında değerlendirilmiş ancak zor havayolu için istatistiksel açıdan anlamlı fark yaratmadığı izlenmiştir [18,19]. Daha önce de ifade edildiği üzere belirli bir hasta popülasyonunu değerlendiren çalışmamızda, zor havayolu grubunda, obez hasta sayısının fazla olması bulguların literatürden farklı çıkmış olabileceğini düşündürmektedir.

Amerikan Anesteziyoloji Derneği güncel zor hava yolu kılavuzunda üst ön kesici dişlerin uzun olması zor havayolu öngörüsünde tanımlanmış olan anatomik özelliklerden bir tanesidir [20]. Çalışmamızda zor entübasyon grubunda %15,3 oranında uzun üst ön kesici diş varlığı tespit edilmiştir (p=0,046). Yine uzun üst ön kesici diş varlığı %94,17 ile yüksek duyarlılık ve %65,99 ile pozitif öngörü değerine sahip olarak bulunmuştur. Bu bağlamda, kılavuzlarda da yer alan bu belirteç, çalışmamızda da öngörüsü yüksek testlerden biri olarak saptanmış ve bu bulgu literatürü destekler nitelikte yorumlanmıştır.

Artan MMS ile zor entübasyonun istatistiksel açıdan anlamlı olarak değişiklik gösterdiği tespit edilirken, literatürde söz konusu prediktif test ile ilgili %10-%90 gibi değişken oranlarda duyarlılık değerleri bildirilmektedir [18]. Testin yanlış uygulanması veya uygulayan kişilerdeki tecrübe farklılıklarına bağlı olarak değişken sonuçlar ile karşılaşılabileceği akılda bulundurulmalıdır.

Çalışmamızda boyun çevresi ölçümü %91 duyarlılık ve %65,25 pozitif öngörü değeri ile önemli prediktif testlerden biri olarak bulundu. Riad ve ark.'nın morbid obez hastalarda yapmış olduğu çalışmada da boyun çevresinin 42 cm'den kalın olması zor entübasyon için prediktif olarak bulunmuştur [21]. Acer ve ark.'nın yapmış olduğu çalışmada da Cormack-Lehane sınıflaması ile boyun çevresi ölçümünün birlikte kullanılmasının duyarlılık değerini artırdığı gösterilmiştir (%94,74) [22].

Literatürdeki çalışmalara benzer olarak çalışmamızda kısıtlı boyun hareketi (%83,5) duyarlılık ölçümü yüksek testlerden biri olarak bulunmuştur [14,15,23].

Üst dudak ısırma testi %81,55 ile yüksek duyarlılığa sahip testlerden biri olarak bulundu (p=0,002). ÜDIT yapılan birçok çalışmada yüksek duyarlılık (%80-%99) ve değişken pozitif öngörü değerleri (%28-%83) ile zor entübasyonu gösteren önemli prediktif testlerden biri olarak görünmektedir [9,18]. Daha öncede belirtildiği üzere 60 yaş üstü ve dişleri eksik hasta sayısının yüksek olması bu testin ölçümünde yüksek duyarlılık sonuçları ile karşılaşılmasına neden olmuş olabilir.

Bu çalışma akademik bir 3. basamak sağlık merkezinde, kadın cinsiyetteki jinekolojik kanser cerrahisi uygulanacak olguları değerlendirmektedir. Bu bağlamda, tek merkez ve her ne kadar farklı hastalıkları içeriyor da olsa spesifik bir hasta grubunun değerlendirilmesi çalışmanın en önemli kısıtlılığı gibi gözükmektedir. Diğer taraftan, sözü geçen hasta kohortunun verilerini ortaya koyan önemli bir çalışma niteliğini de taşımaktadır.

Sonuç

Havayolu muayenesi, anestezi öncesi hasta değerlendirmesinde önemli yer tutar. Ameliyat öncesi özenli havayolu muayenesi, zor havayolunun tespitine ve zor havayolu varlığında uygun yönetim ve planlama yapılmasına olanak sağlar. Bu çalışma ile preoperatif değerlendirmede kullanılan boyun uzunluk ölçümü, tiromental mesafe, ön kesici dişlerin uzun olması, hiyomental mesafe, Modifiye Mallampati skorunun zor entübasyonu etkileyen, duyarlılıkları yüksek testler olduğu ortaya konulmuştur.

Araştırmacıların Katkı Oranı

Tüm yazarlar çalışmanın tasarımında, verilerin toplanmasında ve analizinde katkıda bulunmuşlardır. Tüm yazarlar verileri ve sonuçları onaylamaktadır.

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Research Article

ENG: comparative evaluation of side effects and the factors affecting vaccine preferences of healthcare workers within the booster COVID-19 vaccination in Turkey

TR: Türkiye'de güçlendirici COVID-19 aşılaması kapsamında sağlık çalışanlarının aşı yan etkilerinin ve aşı tercihini etkileyen faktörlerin karşılaştırmalı değerlendirilmesi

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ABSTRACT

Aim: The study's primary aim is to evaluate the frequency and distribution of 3rd dose vaccines' side effects, especially for the rare heterologous vaccine scheme. The secondary objective is to determine the factors affecting the booster COVID-19 vaccination preferences of HCWs.

Material and Methods: This single-center, retrospective descriptive study was conducted on 1058 HCWs, through an online survey. In this study, 3rd dose COVID-19 vaccine preferences, the affecting factors, and the side effects were questioned and analyzed.

Results: 87% of the participants (n=921) had the 3rd booster COVID-19 vaccine. Of those vaccinated, 82.4% (n=759) had Pfizer/BioNTech, and 17.6% (n=162) had CoronaVac/Sinovac. The most common factors that affect the 3rd dose vaccine choice are physicians'/HCWs' recommendations (53.4%; n=492), scientific publications (42.7%; n=393), and recommendations of the Ministry of Health (41.6 %, n=383). 83% (n=630) of 759 who were vaccinated with Pfizer/BioNTech developed post-vaccine side effects, while 59% (n=96) of 162 HCWs who were vaccinated with CoronaVac/Sinovac developed ($p<0.001$). The most common side effect observed was muscle-joint pain (49.2%), and it occurred most frequently in the first 48 hours after vaccination (36%). The most commonly reported side effects in the 2-7 days and 7-28 days post-vaccination were muscle-joint pain (11.6%) and fatigue (1.6%), respectively. It was observed that fatigue, headache, muscle-joint pain, local reaction at the injection site, fever, and lymphadenopathy side effects were more common in those who administered the Pfizer/BioNTech vaccine.

Conclusion: Although it is associated with developing more frequent side effects, mRNA vaccines are preferred by HCWs. Physician/HCWs recommendations and scientific publications were found to be the most valuable sources on the decision of vaccine preference.

Keywords: Coronavac/Sinovac, healthcare worker, Pfizer/BioNTech, side effects, vaccine preferences

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ÖZ

Amaç: Çalışmanın birincil amacı, özellikle nadir görülen heterolog aşı şeması için 3. doz aşıların yan etkilerinin sıklığını ve dağılımını değerlendirmektir. İkincil amaç ise sağlık çalışanlarının rapel COVID-19 aşılama tercihlerini etkileyen faktörlerin belirlenmesidir.

Gereç ve Yöntemler: Bu tek merkezli, retrospektif tanımlayıcı çalışma, çevrimiçi anket aracılığıyla, 1058 sağlık çalışanı ile yürütülmüştür. Bu çalışmada 3. doz COVID-19 aşısı tercihleri, tercihi etkileyen faktörler ve 3. COVID-19 aşısı ile gelişen yan etkiler sorgulanmış analiz edilmiştir.

Bulgular: Katılımcıların %87'si (n=921) 3. rapel COVID-19 aşısı oldu. Bunların %82,4'ü (n=759) Pfizer/BioNTech ve %17,6'sı (n=162) CoronaVac/Sinovac ile aşılandı. 3. doz aşı seçimini etkileyen en yaygın faktörler hekim/sağlık çalışanlarının önerileri (%53,4; n=492), bilimsel yayınlar (%42,7; n=393) ve Sağlık Bakanlığı tavsiyeleridir (%41,6; n=383). Pfizer/BioNTech ile aşılanan 759 kişiden %83'ünde (n=630), CoronaVac/Sinovac ile aşılanan 162 sağlık çalışanının %59'unda (n=96) aşı sonrası yan etki gelişti (p<0.001). En sık görülen yan etki kas-eklem ağrısı (%49,2) olup, en sık aşılamadan sonraki ilk 48 saatte (%36) ortaya çıktı. Aşılamadan sonraki 2-7. gün ve 7-28. gün en sık bildirilen yan etkiler sırasıyla kas-eklem ağrısı (%11,6) ve yorgunluktu (%1,6). Pfizer/BioNTech aşısı yaptıranlarda CoronaVac/Sinovac aşısı yaptıranlara göre yorgunluk, baş ağrısı, kas-eklem ağrısı, enjeksiyon yerinde lokal reaksiyon, ateş ve lenfadenopati yan etkileri daha sık görüldü.

Sonuç: Sonuçta, daha sık yan etki gelişimi ile ilişkili olmakla birlikte, mRNA aşıları sağlık çalışanları tarafından daha fazla tercih edilmektedir. Aşı olma kararı ve aşı tercihleri konusunda en değerli kaynakların doktor/sağlık çalışanı tavsiyeleri ve bilimsel yayınlar olduğu görülmüştür.

Anahtar kelimeler: aşı tercihleri, Coronavac/Sinovac, Pfizer/BioNTech, sağlık çalışanı, yan etkiler

Introduction

The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed an extraordinary threat and burden of disease to global public health. Although the COVID-19 public health emergency ended on May 11, 2023, the pandemic is still ongoing, and most tools, like vaccines, treatments, and testing, remain available [1]. Vaccination against SARS-CoV-2 is still a key measure to prevent infection, serious illness, hospitalization, and death.

As of July 2023, WHO has validated 15 vaccines for COVID-19 emergency use listing (EUL). Seven vaccines are recombinant, three are inactivated, and five are mRNA vaccines [2]. Inactivated virus vaccines use a weakened form of the virus so it does not cause disease but generates an immune response. RNA and DNA vaccines are cutting-edge approaches that use genetically engineered RNA or DNA to create a protein that safely prompts an immune response [3]. The CDC recommends primary series vaccination for three monovalent COVID-19 vaccines (Moderna, Novavax, and Pfizer-BioNTech). People ages six months and older who previously received only monovalent doses are recommended to receive 1 or 2 bivalent mRNA doses, depending on age and vaccine product [4].

COVID-19 vaccination in Turkey started with the CoronaVac/Sinovac vaccine on January 14, 2021, after the "Emergency Use Approval" of the Turkish Medicines and Medical Devices Agency [5], the Pfizer-BioNTech vaccine became available in April 2021 [6]. When the studies showed that the antibody response 90 days after two doses of vaccination with inactivated vero cell vaccine decreased significantly, the third vaccine dose became necessary [7]. The third vaccine dose was implemented for people over 50 and healthcare workers (HCWs) in July 2021, and people were freed to choose their vaccine[8].

In this study, we aimed to investigate the factors affecting the 3rd dose of COVID-19 vaccine preferences of HCWs, and the comparative side effects of the COVID-19 vaccines available in our country.

Material and Methods

Study Design and ethical statement

This single-center, retrospective descriptive study was conducted on HCWs who had previously received two doses of the CoronaVac/Sinovac vaccine and agreed to participate. The study was approved by the Gazi University Clinical Studies Ethical Committee (Decision number: 116 and date:17.02.2021). The study was conducted in accordance with the Declaration of Helsinki Principles (www.wma.net/e/policy/b3.htm) All participants provided informed consent.

Study population and definitions

In this study, 3rd dose COVID-19 vaccine preferences, the factors affecting these preferences, and the side effects that

developed up to the 28th day after the third dose of COVID-19 vaccination were questioned and analyzed. The questionnaire forms were distributed online to 1058 HCWs

In the study, HCWs were defined and grouped according to the definitions determined by the WHO in 2006 [9]. The vaccine-related adverse events evaluated in the study were selected from the US Vaccine Adverse Event Reporting System (VAERS) Table of Reportable Events and a recent report from a European consortium on vaccine surveillance (ADVANCE project) [10]. In addition, side effects frequently reported during phase studies of the Coronovac and Pfizer/BioNTech vaccines were evaluated [11, 12]. In the study, 'Known vaccine side effect after vaccination or anything thought to be due to the vaccine' is described as a vaccine-related adverse event.

Serious adverse event report - These reports meet the definition of "serious" specified by the Code of Federal Regulations because one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, congenital anomaly, or congenital disability [10].

Non-serious adverse event report - These reports do not meet the regulatory definition of a serious adverse event report [10].

Possible side effects after getting a COVID-19 vaccine to be defined as local reactions (pain, redness, swelling), systemic reactions (tiredness, headache, muscle pain, chills, fever, nausea, and others), by CDC (Centers for Disease Control and Prevention) [13].

Statistical analysis

All data were analyzed by IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, N.Y., USA) and summarized with tables and graphs. Shapiro-Wilk test, histogram, and Q-Q plot were used to determine the normality distribution of the data. Categorical variables were expressed with numbers and percentiles. Continuous variables are defined as mean, standard deviation, median, and interquartile range. $p < 0.005$ was accepted as statistically significant.

Results

1058 HCWs participated in the online survey. 87% of the participants (n=921) had the third dose of the COVID-19 vaccine. The descriptive characteristics of HCWs who received the 3rd dose of the COVID-19 vaccine are shown in Table 1.

Of those vaccinated, 82.4% (n=759) had Pfizer/BioNTech, and 17.6% (n=162) had CoronaVac/Sinovac vaccine. Of those who received the Pfizer/BioNTech vaccine as the third dose, 77.3% (n=587) have had any vaccine in the last ten years. Of those who had the CoronaVac/Sinovac vaccine, 79.6% (n=129) have had any vaccine in the previous ten years. 3.6% (n=27) of those who received the Pfizer/BioNTech vaccine as the 3rd dose of the COVID-19 vaccine, 2.5% (n=4) of those who received the CoronaVac/Sinovac vaccine had a previous allergic reaction to any vaccine. 17.4% (n=132) of those who received the Pfizer/BioNTech vaccine as the 3rd dose COVID-19 vaccine and 18.5% (n=30) of those who received the CoronaVac/Sinovac vaccine had a history of food/drug/cosmetics allergy. 44.1% (n=335) of those who received the Pfizer/BioNTech vaccine as the 3rd dose of the COVID-19 vaccine and 40.1% (n=65) of those who received the CoronaVac/Sinovac vaccine had a COVID-19 infection history.

The most common sources HCWs use to decide on the choice of the 3rd dose vaccine are summarized in Figure-1.

Table 1. The descriptive characteristics of HCWs who received the 3rd dose of the COVID-19 vaccine (n=921)

Age, median(IQR 25-75)	40 (33-46)
Gender, n (%)	
Male	363 (39,4)
Female	558 (60,6)
Occupational distribution of HCWs, n(%)	
Physician	126 (13,7)
Nurse	234 (25,4)
Technical personnel	89 (9,7)
Secretary	53 (5,8)
Cleaning staff member	83 (9)
Patient transport staff	94 (10,2)
Security	89 (9,7)
Others	153 (16,6)
Comorbid diseases, n(%)	
Hypertension	74(8)
Diabetes mellitus	60 (6,5)
Cardiovascular disease	36 (3,9)
Chronic lung disease	34 (3,7)
Chronic kidney disease	1 (0,1)
Malignancy	10 (1,1)
Hypothyroidism	63 (6,8)
Others	77 (8,4)
Smoking,n(%)	300 (32,6)
Previously known food, drug cosmetic allergy, n(%)	162 (17,6)
Vaccine allergy other than the COVID-19 vaccine, n(%)	31 (3,4)
Being vaccinated except COVID-19 vaccine in the last 10 years, n(%)	716 (77,7)
Have a relative who has been vaccinated except COVID-19 vaccine in the last ten years, n(%)	533(57,9)
Have COVID-19 history, n(%)	400 (43,4)
Have a relative who have COVID-19 history, n(%)	711 (77,2)
Any relative who has died due to COVID-19, n(%)	173 (18,8)
Any child going to kindergarten/school in the house you live in, n(%)	465 (50,5)
Any people over the age of 65 in your home, n(%)	145 (15,7)
Using public transport,n(%)	550 (59,7)

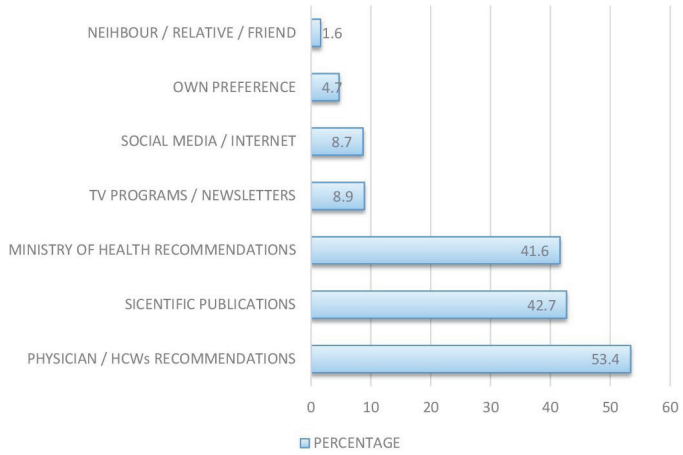

Figure 1. The most common sources HCWs use to decide on the choice of the 3rd dose vaccine

A comparative evaluation of sources affecting the preferences for 3rd dose of the COVID-19 vaccine in HCWs was summarized in Table 2.

Table 2. Comparative evaluation of sources that are affecting the preferences of 3rd dose COVID-19 vaccine in HCWs

	Pfizer/ BioNTech (n=759)	CoronoVac/ Sinovac (n=162)
Physician / HCWs recommendation, n(%)	433(57)	60(37)
Scientific publications, n(%)	336(44)	57(35)
Ministry of Health recommendation, n(%)	307(40)	76(46)
TV programs/newsletters, n (%)	77(10)	5(3)
Social media/internet, n(%)	75(9,8)	5(3)
Own preference, n(%)	22(2,8)	21(12)
Neighbor / relative / friend, n(%)	11(1,4)	4(2,4)

Local and systemic side effects that developed after the third dose of COVID-19 vaccines are summarized in Figure 2 in terms of the development time.

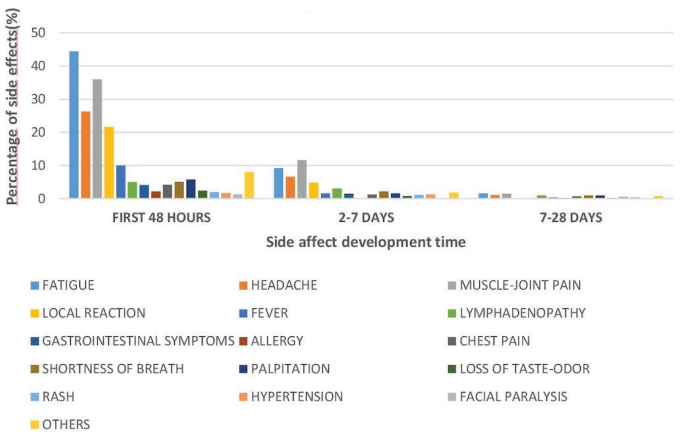

Figure 2. Distribution of side effects after 3rd dose of COVID-19 vaccine according to duration of side effect development, n=921

In the first 48 hours after vaccination, the most common side effect was fatigue (n=410, 44.5%); in the 2-7 day period, the most common side effect was muscle-joint pain (n=107, 11.6%); in the 7-28 day period the most common side effect was also reported as fatigue (n=15, 1.6%). The most common side effect observed after the 3rd dose of the COVID-19 vaccine was muscle-joint pain (n=453, 49.2%), and it occurred most frequently in the first 48 hours after vaccination. (suppl table 1)

Side effects were observed at any time after vaccination in 83% (n=630) of 759 HCWs who received the 3rd dose vaccine from Pfizer/BioNTech and 59% (n=96) of 162 HCWs who received CoronaVac/Sinovac (p< 0.001). (suppl table 2 and 3)

Comparative evaluation of post-vaccine side effects according to the preferred 3rd dose COVID-19 vaccine being Pfizer/ BioNTech or CoronaVac/Sinovac is summarized in Table 3.

Table 3. Comparative evaluation of post-vaccine side effects according to the preferred 3rd dose COVID-19 vaccine being Pfizer/BioNTech or CoronaVac/Sinovac (n=759, n= 162)

	Pfizer/BioN-Tech, n (%)	CoronaVac/ Sinovac, n (%)	p value
Fatigue	449 (59,2)	61 (37,7)	< 0,001
Headache	272 (35,8)	41 (25,3)	0,010
Muscle-joint pain	411 (54,1)	42 (25,9)	<0,001
Local reaction	219 (28,9)	25 (15,4)	<0,001
Fever	100 (13,2)	8 (4,9)	0,002
Lymphadenopathy	78 (10,3)	6 (3,7)	0,006
Vomiting, diarrhea	46 (6,1)	9 (5,6)	1
Allergy	17 (2,2)	6 (3,7)	0,27
Loss of taste-odor	25 (3,3)	6 (3,7)	0,81
Facial paralysis	10 (1,3)	4 (2,5)	0,28
Rash	25 (3,3)	8 (4,9)	0,34
Hypertension	23 (3)	9 (5,6)	0,15
Chest pain	47 (6,2)	9 (5,6)	0,85
Shortness of breath	68 (9)	8 (4,9)	0,11
Palpitation	63 (8,3)	14 (8,6)	0,87
Others	78 (10,3)	20 (12,3)	0,48

Discussion

In our study, most HCWs received the 3rd dose of the COVID-19 vaccine, and the preferred one is mostly the Pfizer/BioNTech vaccine. The factors affecting vaccine choice were mostly physicians' recommendations and scientific publications. It was determined that the advice of the Ministry of Health was the situation that most influenced the preference of those who chose the Coronavac vaccine for the 3rd dose of the COVID-19 vaccine. It was observed that fatigue, headache, muscle-joint pain, local reaction at the injection site, fever, and

lymphadenopathy side effects were more common in those who received the Pfizer/BioNTech vaccine compared to those who received the CoronaVac/Sinovac vaccine.

When the studies conducted worldwide are evaluated, COVID-19 booster dose vaccination is preferred by 55-92% of healthcare professionals [14-16]. Similarly, in our study, 87% of the participants (n=921) had the third dose of the COVID-19 vaccine. Of those vaccinated, 82.4% (n=759) had Pfizer/BioNTech, and 17.6% (n=162) had CoronaVac/Sinovac.

The recommendations of physicians/healthcare professionals and scientific publications are the most valuable resources for getting vaccinated [17]. In a study conducted by Alhasan K. et al., it was observed that participants preferred social media (50.5%), hospital announcements (36.0%), and scientific journals (30.5%) as sources of information in their booster vaccine decision [18]. Our study found that the factors affecting booster vaccine decisions were mostly physicians' recommendations, scientific publications, and Ministry of Health recommendations. Physicians' recommendations mainly affected the Pfizer/BioNTech choice, and Ministry of Health advice mostly acted the Coronavac/Sinovac choice as a 3rd booster dose.

Vaccine resources may be unevenly distributed worldwide, so there may be delays in vaccine supply. Using heterogeneous booster doses for COVID-19 has been an alternative strategy [19]. When the 3rd dose vaccination was started for HCWs, there was no vaccine in our country except CoronaVac/Sinovac and Pfizer/BioNTech. Vaccine preferences are not interfered with; everyone chooses different vaccines according to the source they received information from. Thus, various side-effect profiles emerged in heterologously vaccinated populations.

Various local and systemic side effects have been reported in many studies on COVID-19 vaccines. In a meta-analysis of 23 studies compared with the homologous booster group, there was a higher risk of fever, myalgia, and fatigue within seven days after boosting and a higher risk of malaise or fatigue within 28 days after boosting in the heterologous vaccination group [19]. In our study, those who received the Pfizer/BioNTech vaccine after two doses of the CoronaVac/Sinovac vaccine were an example of a heterologous booster vaccination. And fatigue, headache, muscle-joint pain, local reaction at the injection site, fever, and lymphadenopathy were observed more frequently after heterologous vaccination than homologous vaccination.

A systematic review and meta-analysis of randomized controlled trials examining the safety of SARS-CoV-2 vaccines found that inactivated COVID-19 vaccine candidates had the lowest reported adverse effects [20]. A meta-analysis evaluating 49 placebo-controlled clinical trials found that inactivated vaccines had the most safety profile when COVID-19 vaccine types were compared regarding systemic side effects. mRNA vaccines had the worst safety profile [21]. The low risks of adverse events from inactivated vaccines are because inactivated vaccines do not replicate in the recipient [22]. In our study, the post-vaccine side effects of those who received the Pfizer/BioNTech vaccine, which is an mRNA vaccine, developed at a higher rate than those who received the CoronaVac/Sinovac vaccine, which is an inactivated vaccine (83% and 59% respectively, $p<0.001$).

According to a meta-analysis, injection site pain was the most common local symptom, and fatigue was the most common side effect in people receiving the mRNA vaccine (29-85% of participants [23]. In a single-blind randomized study conducted in Brazil, 1,205 people who received booster vaccination after two doses of the CoronaVac/Sinovac vaccine were evaluated. Pfizer/BioNTech vaccine was given to 333 people, CoronaVac/Sinovac to 281 people, and recombinant adenoviral vector vaccines to the rest. The most common side effects were pain at the injection site, headache, and myalgia [24].

In a study involving 428 HCWs who received the Pfizer/BioNTech as a 3rd dose vaccine after two doses of CoronaVac/Sinovac vaccine in Turkey, the most common side effects were fatigue (58,6%), muscle-joint pain (51,1%) and headache (40,7%), respectively [25]. Our study found the most common side effects in the same order. In patients who received the Pfizer/BioNTech as a 3rd dose vaccine (n=759), side effects were found to be fatigue (59,1%), muscle joint pain (54,1%), and headache (35,8%), respectively.

If we handle another side effect in our survey results, post-vaccine lymphadenopathy was found in 84 people (9,1%). Of these, 78 had received the Pfizer/BioNTech vaccine. A review of 10 studies pooled the incidence of clinically detectable axillary lymphadenopathy after COVID-19 vaccination was 91/22,532 (0,4%) [26]. In another review that included 15 studies, the incidence of lymphadenopathy was found to vary between 14.5% and 53% [27].

In our study, post-vaccine side effects were observed most frequently in the first 48 hours. The most commonly reported side effects in the 2-7 days and 7-28 days post-vaccination were muscle-joint pain (11.6%) and fatigue (1.6%), respectively. Although rare, serious adverse events may occur in the late

post-vaccine period. Between 10 and 23 December 2020, 1,893,360 people received the first dose of the Pfizer-BioNTech Covid-19 vaccine, and 21 people developed severe allergic reactions, including anaphylaxis, accounting for 11.1 cases per million. However, no deaths from anaphylaxis have been reported [28]. Based on an analysis of 40 case reports [29], the epidemiology and clinical picture of myocarditis related to the COVID-19 vaccine were presented in another study. Most cases were seen in males with 90% predominance, which were seen in the age group of 29.13 years old (mean, SD of 14.39 years). In 65% of cases, patients took the BNT162b2 vaccine; 30% of cases were reported with the mRNA-1273 vaccine, and 5% of cases with JNJ-78436735. Of all the cases, 80% are reported after the second dose of the vaccine with either Moderna or Pfizer. In our study, anaphylaxis or myocarditis did not occur in any of the HCWs who received the Pfizer/BioNtech vaccine for the first time. Post-vaccine adverse event monitoring should not be limited to the first 48 hours.

Conclusion

According to our study, although the safety profile of inactivated COVID-19 vaccines is better, mRNA vaccines are preferred when considering efficacy. It has been determined that the recommendations of physicians/healthcare professionals and scientific publications are the most valuable resources for getting vaccinated. Post-vaccine adverse event monitoring should continue for a long time.

Author contributions

1. Creating the concept and design of the study: Yeşim Yıldız, H. Selçuk Özger, and Esin Şenol. 2. Data collection: Yeşim Yıldız, H. Miraç Mavi, Fidan Sultanova, Merve Büyükkörük. 3. Analysis of data and expression of findings: Merve Büyükkörük, Yeşim Yıldız, H. Selçuk Özger, H. Miraç Mavi. 4. Drafting of the article: Yeşim Yıldız and H. Miraç Mavi, review of the scientific content by H. Selçuk Özger and Esin Şenol. 4. Approval of the final ready-to-print manuscript: all authors.

Conflict of interest

No person/organization financially supports the work, and the authors have no conflict of interest.

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Research Article

The assessment of Tp-e interval and Tp-e/QT ratio in patients with morbid obesity before and after laparoscopic sleeve gastrectomy

Morbid obezite hastalarında laparoskopik sleeve gastrektomi öncesi ve sonrası Tp-e aralığı ve Tp-e/QT oranının değerlendirilmesi

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Abstract

Aim: Tp-e/QT ratio is a novel marker of ventricular repolarisation. Obesity has been associated with various cardiovascular changes and an increased risk of cardiovascular disease. Obesity may be associated with prolongation of the QT interval, which could potentially increase the risk of ventricular arrhythmias. We aimed to research the assessment of Tp-e interval and Tp-e/QT ratio before and after laparoscopic sleeve gastrectomy (LSG) in patients with morbid obesity.

Material and Methods: In this study, we enrolled 93 consecutive patients with a BMI >40 kg/m2 or BMI >35kg/m2 with comorbidities who had previously failed to lose weight with conservative methods underwent LSG between January 2012 and December 2016.

Results: Heart rate (75.7 ± 4.7 vs. 72.8 ± 11.4; p=0.486), QT interval (358.1 ± 32.0 vs. 362.6 ± 30.4; p=0.399) and QTc interval (399.0 ± 34.3 vs. 396.2 ± 30.9; p=0.621) were similar before and after LSG. Tp-e interval (81.3 ± 11.4 vs. 76.3 ± 10.9; p=0.004), Tp-e/QT ratio (0.23 ± 0.04 vs. 0.21 ± 0.04; p=0.002), Tp-e/QTc ratio (0.20 ± 0.03 vs. 0.19 ± 0.03; p=0.001) were significantly different before and after LSG.

Conclusion: Our study showed that morbid obesity may have a negative effect on ventricular repolarization. Substantial weight loss following laparoscopic sleeve gastrectomy in obese patients is accompanied by a significant improvement in ventricular repolarization.

Keywords: Laparoscopic sleeve gastrectomy, morbid obesity, QT interval, Tp-e interval, Tp-e/QT ratio, ventricular repolarization.

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Öz

Amaç: Tp-e/QT oranı, ventriküler repolarizasyonun yeni bir belirtecidir. Obezite, çeşitli kardiyovasküler değişiklikler ve artan kardiyovasküler hastalık riski ile ilişkilendirilmiştir. Obezite, ventriküler aritmi riskini potansiyel olarak artırabilen QT aralığının uzaması ile ilişkili olabilir. Morbid obezitesi olan hastalarda laparoskopik tüp mide operasyonu (LSG) öncesi ve sonrası Tp-e aralığı ve Tp-e/QT oranının değerlendirilmesini araştırmayı amaçladık.

Gereç ve yöntemler: Bu çalışmada, Ocak 2012 ile Aralık 2016 tarihleri arasında BMI >40 kg/m2 veya komorbiditeleri ve BMI >35kg/m2 olan ve daha önce konservatif yöntemlerle kilo vermeyi başaramayan 93 hastaya ardışık olarak LSG uygulandı.

Bulgular: Kalp hızı (75,7 ± 4,7 vs 72,8 ± 11,4; p=0,486), QT aralığı (358,1 ± 32,0 vs 362,6 ± 30,4; p=0,399) ve QTc aralığı (399,0 ± 34,3 vs 396,2 ± 30,9; p=0,621) LSG öncesi ve sonrası benzerdi. Tp-e aralığı (81,3 ± 11,4 vs 76,3 ± 10,9; p=0,004), Tp-e/QT oranı (0,23 ± 0,04 vs 0,21 ± 0,04; p=0,002), Tp-e/QTc oranı (0,20 ± 0,03) vs. 0,19 ± 0,03; p=0,001) LSG öncesi ve sonrasında anlamlı olarak farklıydı.

Sonuç: Çalışmamız morbid obezitenin ventriküler repolarizasyon üzerinde olumsuz etkisi olabileceğini göstermiştir. Obez hastalarda laparoskopik sleeve gastrektomiyi takiben önemli kilo kaybına, ventriküler repolarizasyonda önemli bir iyileşme eşlik eder.

Anahtar Kelimeler: Laparoskopik sleeve gastrektomi; morbid obezite, QT aralığı, Tp-e aralığı, Tp-e/QT oranı, ventriküler repolarizasyon.

Introduction

The Tp-e interval represents the time interval from the peak of the T wave to the end of the T wave on an electrocardiogram (ECG), while the QT interval represents the total duration of ventricular depolarization and repolarization.(1)

Obesity has been associated with various cardiovascular changes and an increased risk of cardiovascular disease. It can lead to alterations in cardiac structure and function, such as left ventricular hypertrophy and changes in electrical conduction. Some studies have suggested that obesity may be associated with prolongation of the QT interval, which could potentially increase the risk of ventricular arrhythmias.(2, 3)

However, the specific relationship between the Tp-e/QT ratio and obesity has not been extensively studied.(4) The Tp-e/QT ratio is a relatively new parameter that has been proposed as a marker of ventricular repolarization in certain cardiac conditions.(5) It has been associated with an increased risk of arrhythmias in some clinical populations, but its significance in obesity remains unclear.

While sleeve gastrectomy has been shown to improve various cardiovascular risk factors and cardiac structure and function, there is limited research specifically examining its impact on the Tp-e/QT ratio.(6) Bariatric surgery, including sleeve gastrectomy, can lead to weight loss, improvements in metabolic parameters, and reduction in cardiac strain, all of which may potentially influence ventricular repolarization.

In this study, we aimed to research the assessment of Tp-e interval and Tp-e/QT ratio before and after laparoscopic sleeve gastrectomy (LSG) in patients with morbid obesity.

Material and Methods

Study population

In this study, we enrolled 93 consecutive patients with a BMI >40 kg/m2 or BMI >35kg/m2 with comorbidities who had previously failed to lose weight with conservative methods underwent LSG between January 2012 and December 2016. Patients with any of the followings were excluded: significant mitral or tricuspid valvular heart disease, previous myocardial infarction, significant coronary artery disease, wall motion abnormalities with left ventricular ejection fraction below 50%, severe pulmonary disease, malignancy and complete or incomplete bundle branch block, atrial fibrillation, paced rhythm. Baseline demographic and clinical characteristics were reviewed. The study was in compliance with the principles outlined in the Declaration of Helsinki and approved by local ethics committee.

Laparoscopic Sleeve Gastrectomy

Patients eligibility for bariatric surgery was based on the criteria for surgical intervention proposed by the NIH consensus panel in 1991 (7) and established by the international medical and surgical societies: the International Federation for the Surgery of Obesity (IFSO), the International Federation for the Surgery of Obesity-European Chapter (IFSO-EC), and the European Association for the Study of Obesity (EASO)) (8, 9) The study patients

underwent LSG based on their preference after discussing with the surgeon and presenting the surgical choices. The patients underwent routine preoperative work-up, including dedicated history taking, multidisciplinary clinical assessment, laboratory investigations, and upper gastrointestinal (GIT) endoscopy. Patients with severe gastroesophageal reflux disease (GERD), based on clinical presentation and/or endoscopic assessment, and those with large hiatus hernias were not candidates for LSG. Written informed consent was obtained from the included patients before surgery.

Echocardiography

Echocardiographic assessment was performed by using a VIVID 7 Dimension Cardiovascular Ultrasound System (Vingmed-General Electric, Horten, Norway) with a 3.5 MHz transducer. Echocardiographic examination was performed in the left lateral decubitus position. Parasternal long- and short-axis views and apical views were used as standard imaging windows. Ejection fraction (EF) was calculated by using modified Simpson method. All echocardiographic examinations were performed by an experienced cardiologist.

Electrocardiography

The 12-lead electrocardiogram (ECG) was recorded at a paper speed of 50 mm/s (Hewlett Packard, Page-writer, USA) in the supine position. All of the ECGs were scanned and transferred to a personal computer to decrease the error measurements, and then used for x400% magnification by Adobe Photoshop software. ECG measurements of QT and Tp-e intervals were performed by two cardiologists who were blinded to the patient data. Subjects with U waves on their ECGs were excluded from the study. An average value of three readings was calculated for each lead. The QT interval was measured from the beginning of the QRS complex to the end of the T wave and corrected for heart rate using the Bazett formula: cQT = QT$\sqrt{}$ (R-R interval). The Tp-e interval was defined as the interval from the peak of T wave to the end of T wave. Measurements of the Tp-e interval were performed from precordial leads.(10) The Tp-e/QT ratio was calculated from these measurements. ECG was performed one hour before procedure and repeated again three months after the LSG. Interobserver and intraobserver coefficients of variation were 2.5% and 2.1% respectively.

Statistical Analysis

For statistical analysis, SPSS 20.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) was used. In order to test normality of distribution Kolmogorov-Smirnov test was used. Quantitative variables with a normal distribution were specified as the mean ± standard deviation and variables with non-normal distribution were shown as median (interquartile range), categorical variables were shown as number and percentage values. To determine the mean of the differences between two paired samples Paired T-Test and Wilcoxon signed-rank test was used. Categorical variables were compared with Chi-square test. A p value of <0.05 was accepted as statistically significant.

Results

A total of 93 patients with morbid obesity before and after LSG were enrolled in our study. Baseline characteristics of study population are shown in Table 1. The mean age of the study population was 38.1 ± 9.1 years and 84.9 % of patients were female and 17.2% of patients had hypertension and 23.7% of patients had diabetes mellitus. Weight and body mass index levels before and after surgery are shown in Table 2. The electrocardiographic findings of the study groups are demonstrated in Table 3. Heart rate (75.7 ± 4.7 vs. 72.8 ± 11.4; p=0.486), QT interval (358.1 ± 32.0 vs. 362.6 ± 30.4; p=0.399) and QTc interval (399.0 ± 34.3 vs. 396.2 ± 30.9; p=0.621) were similar before and after LSG. Tp-e interval (81.3 ± 11.4 vs. 76.3 ± 10.9; p=0.004), Tp-e/QT ratio (0.23 ± 0.04 vs. 0.21 ± 0.04; p=0.002), Tp-e/QTc ratio (0.20 ± 0.03 vs. 0.19 ± 0.03; p=0.001) were significantly different before and after LSG.

Table 1. Baseline characteristics of the study patients (n=93)

Variables	
Age,years	38.1 ± 9.1
Female, n(%)	79 (84.9)
Hypertension, n(%)	16 (17.2)
Diabetes Mellitus, n(%)	22 (23.7)
Smoking, n(%)	32 (34.4)
EF, %	61.3 ± 2.8
Height, cm	1.63 ± 0.8
Glucose, mg/dL	108.3 ± 36.8
Creatinine, mg/dL	0.70 ± 0.07
Total cholesterol, mg/dL	201.6 ± 31.7
LDL-C, mg/dL	101.8 ± 26.3
HDL-C, mg/dL	41.7 ± 8.2
Triglyceride, mg/dL	141 (104 – 195)
Postoperative time interval, month	6 (4 – 12)

Data are given as mean ± SD, n (%) or median (interquartile range). EF, ejection fraction; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2. Weight and Body mass index levels of the study patients before and after procedure (n=93)

Variables	Preoperative	Postoperative	p value
Weight, kg	119.8 ± 16.2	84.5 ± 14.0	<0.001
BMI	44.9 ± 4.6	31.7 ± 5.1	<0.001

Data are given as mean ± SD, n (%). BMI, body mass index.

Table 3. Electrocardiographic parameters of the patients

Parameters	Before LSG	After LSG	p value
Heart rate, bpm	75.7 ± 4.7	72.8 ± 11.4	0.486
Tp-e interval, ms	81.3 ± 11.4	76.3 ± 10.9	0.004
QT interval, ms	358.1 ± 32.0	362.6 ± 30.4	0.399
QTc interval, ms	399.0 ± 34.3	396.2 ± 30.9	0.621
Tp-e/QT ratio	0.23 ± 0.04	0.21 ± 0.04	0.002
Tp-e/QTc ratio	0.20 ± 0.03	0.19 ± 0.03	0.001

Data are given as mean ± SD. LSG, laparoscopic sleeve gastrectomy; QTc, corrected QT interval.

Discussion

We found that Tp-e interval, Tp-e/QT and Tp-e/QTc ratios were significantly shortened in patients with morbid obesity after LSG than before LSG. This is the largest study about this topic as we known. We showed that surgical weight loss significantly improves the variables associated with fatal arrhythmia in morbidly obese patients. Furthermore, following LSG in morbidly obese patients may prevent the risk of the fatal arrhythmias and sudden cardiac death (SCD).

As reported by the Framingham Heart Study, obesity alone is a strong predictor of SCD. Factors such as ventricular remodeling, hypertrophy, fibrosis, cardiomyopathy, increased inflammatory response, and neurohormonal activation may contribute to the development of malignant arrhythmias in obesity patients.(11, 12) It has been found to be associated with a prolonged QT interval in obesity.(13) However, it is still unclear whether obesity-related QT interval prolongation is associated with an increased risk of cardiac arrhythmias that can lead to SCD. (14) There is an established association between obesity and SCD. Every 5-unit increment in BMI confers a 16% higher risk of SCD, and obesity has been identified as the most common nonischemic cause of SCD.(15, 16) Data suggest that there may be an important role for body fat distribution, implicating abdominal adiposity as a marker of SCD.(16) The potential mechanisms for this association are varied and may include LVH, QT prolongation, premature ventricular complexes, and autonomic imbalance. (12) Both mild obesity and severe obesity are reported to be associated with greater risk of ventricular tachycardia (VT)/ventricular fibrillation (VF))(17) and late potentials, highlighting a role in the formation of arrhythmic substrate.

The JT interval determines the repolarization time. Morbidly obese patients had higher JTc and JTc-d values than normal weight controls.(18)

Increasing of ventricular repolarization dispersion is associated with malign arrhythmias and has prognostic importance in terms of mortality and sudden cardiac death(19). QT dispersion was clarified as a sign of increased dispersion of repolarization but finally lost its importance as a defective concept(4, 20). Nowadays, the Tp-e interval and Tp-e/QT ratio have been evaluated as actual markers of increased dispersion of ventricular repolarization(5, 21). Prolongation of Tp-e interval was related with increased mortality in Brugada syndrome , long QT syndrome, and in patients with acute ST-segment elevation myocardial infarction(21). Nevertheless, Tp-e interval is affected by alterations in body weight and heart rate(22). In recent studies, the Tp-e/QT ratio was proposed to be a more accurate measure of the dispersion of ventricular repolarization, than QT dispersion, QTc dispersion and Tp-e intervals, and to be independent of variations in heart rate(5, 22). Based on evidence obviously proposes the applicability of Tp-e/QT ratio as a potency significant index of arrhythmogenesis, both under the conditions of short, normal and long QT interval(21). Similar to the results in the literature, (6) we demonstrated that that surgical weight loss significantly improves the variables associated with fatal arrhythmia in morbidly obese patients.

Study Limitations

There are some limitations of this study. First, our study has relatively small sample size. Second, the study is single-center study. Also, the follow-up period time of the study was short to investigate long-term effects of the LSG procedure on the electrocaridographic parameters. Also, left ventricular diastolic functions have not been evaluated. Advanced echocardiographic techniques such as strain, strain rate and speckle tracking could have been more helpful to detect early and subclinical structural abnormalities in patients with morbid obesity. The relationship between ventricular arrhythmias and Tp-e interval and Tp-e/QT ratio was not assessed in patients with morbid obesity. Therefore, long-term follow-up and large-scale prospective studies are needed to investigate the predictive value of the Tp-e interval and Tp-e/QT ratio in patients with morbid obesity.

Conclusion

Finally, Tp-e interval,Tp-e/QT and Tp-e/QTc ratios were decreased in patients with morbid obesity after LSG procedure.

Our study is important to show that morbid obesity may have a negative effect on ventricular repolarization, which potentially may lead to increased risk of ventricular arrhythmias. Tp-e interval, Tp-e/QT and Tp-e/QTc ratios are simple, easily accessible, inexpensive and non-invasive methods that may be useful index of left ventricular dysfunction that caused by ventricular arrhythmias in patients with with morbid obesity.

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Disclosure

No conflicts of interest.

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Research Article

Comparıson of cumulus cells and follıcular fluıd obtaıned from ınfertile ındıvıduals dıagnosed wıth polycystıc ovary syndrome (PCOS) and endomethrıosıs wıth samples obtaıned from healthy ındıvıduals

Polikistik over sendromu (PCOS) ve endometriozis tanili infertil bireylerden elde edilen kumulus hücreleri ve foliküler sivinin sağlikli bireylerden elde edilen örneklerle karşilaştirilmasi

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Abstract

Aim: Investigating the relationship between Growth differentiation factor-9 (GDF-9), Bone morphogenetic protein-15 (BMP-15) markers, apoptosis levels in cumulus cells and total oxidant (TOS)/ anti-oxidant (TAS) stress levels, inflammation parameters (interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-alpha)) in follicular fluid belonging to patients with polycystic ovary syndrome (PCOS), endometriosis (END) and male factor (MF) (control) groups.

Material and Methods: GDF-9 and BMP-15 markers are determined by immunohistochemical methods, apoptosis levels are studied with TUNEL. TOS and TAS statuses are investigated with spectrophotometry, IL-6 and TNF – alpha levels are examined by Enzyme-Linked Immuno Sorbent Assay (ELISA).

Results: According to the data obtained in the study; GDF-9 and BMP-15 levels are found to be lower in PCOS and END groups and apoptosis levels of cumulus cells were significantly higher at these groups . TOS levels were significantly higher in PCOS and END groups whereas follicular fluid TAS levels were not statistically significant for these groups. IL-6 and TNF – alpha levels of follicular fluid was significantly higher in PCOS. These parameters were also higher for END group, however the difference was not found to be significant.

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Conclusion: Our results imply that correlation between GDF-9, BMP-15 markers, apotosis levels, oxidative status, inflammation levels may be interpreted with improper environment for oocyte maturation for patients diagnosed with PCOS or END.

The need for further studies on subject proceeds. However, if similar datas are obtained in further studies, it is thought that evaluation of cumulus cell properties together with especially follicular fluid oxidative stress levels will contribute to the selection of the best oocyte.

Keywords: cumulus cell, follicular fluid, polycystic ovary syndrome, endometriosis, oxidative stress

Öz

Amaç: Polikistik over sendromu (PKOS), endometriozis (END) ve erkek faktör (MF) (kontrol) gruplarında bulunan hastalara ait kumulus hücrelerinde Büyüme farklılaşma faktörü-9 (GDF-9), Kemik morfogenetik protein-15 (BMP-15) belirteçleri, apoptoz seviyeleri ile foliküler sıvı inflamasyon parametreleri (interlökin-6 (IL-6), tümör nekroz faktör alfa (TNF-alfa), total oksidan (TOS)/anti-oksidan (TAS) stres seviyeleri arasındaki ilişkinin araştırılması.

Gereç ve Yöntemler: Kumulus hücrelerinde büyüme farklılaşma faktörü-9 (GDF-9) ve kemik morfogenetik protein-15 (BMP-15) belirteçleri immünohistokimyasal yolla değerlendirilmiş olup; hücre ölümü TUNEL yöntemi kullanılarak araştırılmıştır. Folikül sıvısı örneklerinde toplam oksidatif stres (TOS) ve toplam anti-oksidan düzey (TAS) spektrofotometrik olarak araştırılmış, interlökin-6 (IL-6) ve tümör nekrozis faktör alfa (TNF-alfa) düzeyleri ELISA (Enzyme-Linked ImmunoSorbent Assay) yöntemi ile incelenmiştir

Bulgular: GDF-9 ve BMP-15 düzeyleri sağlıklı gruba kıyasla PCOS ve END gruplarında düşük seviyede saptanırken, hücre ölümüne ilişkin veriler bu gruplarda daha yüksek gözlenmiştir. Endometriozis grubunda GDF-9, BMP-15 değerleri en düşük, hücre ölümü düzeyleri ise en yüksek olarak bulunmuştur. Sağlıklı gruba kıyasla PCOS ve endometriozis gruplarında folikül sıvısı TOS düzeyleri istatistiksel olarak anlamlı yüksek bulunmuştur. Folikül sıvısı TAS düzeyleri ise sağlıklı gruba kıyasla PCOS ve endometriozis gruplarında daha yüksek bulunmuş ancak gruplar arasındaki fark istatistiksel olarak anlamlı bulunmamıştır.

Sonuç: Sonuçlarımız, GDF-9, BMP-15 belirteçleri, apotoz seviyeleri, oksidatif durum, inflamasyon seviyeleri arasındaki korelasyonun PCOS veya END tanılı hastalarda oosit olgunlaşması için uygun olmayan mikroçevre ile yorumlanabileceğini düşündürmektedir.

Konu ile ilgili ileri çalışmalara ihtiyaç devam etmektedir. İleri çalışmalarda benzer verilerin elde edilmesi halinde kumulus hücre özelliklerinin, özellikle foliküler sıvı oksidatif stres düzeyleri ile birlikte değerlendirilmesinin, oosit seçimine katkı sağlayacağı düşünülmektedir.

Anahtar Kelimeler: kumulus hücresi, folikül sıvısı, polikistik over sendromu, endometriozis, oksidatif stres

Introduction

It is declared that approximately %17 of couples encounter with a failure to achieve a clinical pregnancy, after 12 months or more of regular unprotected sexual intercourse. Many factors are blamed to cause infertility but almost %50 of these are based on factors concerning female reproductive tract (1). Besides being an economic burden infertility has a big role as psychological effect. It is declared that desire to have a child can convert a depression inducement after being diagnosed as infertile is common in woman than man (2).

Under favour of all developments in intracytoplasmic sperm injection (ICSI) technique, a significant success has been gained. This improvement is accelerated by follicular monitoring, identification of top-quality embryos, embryo transfer and controlled ovarian hyperstimulation (COHS), procedures. Despite of all these progressions, still inefficiency at successful pregnancy outcome is seen at some of patients which had consulted assisted reproductive techniques (ART) (3). Undoubtfully, picking up the best quality oocyte has a significant importance in this area (3, 4).

Polycystic ovary syndrome (PCOS) effects almost %5-10 of women at reproductive age. It can be said that it is a common and complex disorder which provides a poor oocyte quality (5). Many authors defines PCOS as the most common endocrinological disorder in women at reproductive ages (6). Infertility is also seen at %40 of patients who are diognosed with PCOS (5, 7). As it is declared in literature parameters like oxidative stress, chronic inflammation, oocyte quality takes a significant importance in the success of ART techniques for PCOS patients (8, 9)

Endometriosis can be defined as the existance of endometrial tissue outside the uterine cavity. It is known that this chronic inflammatory condition affects approximately 6-10% of women of reproductive age worldwide. Although there are many different opinions about the etiology of the disease, it has been shared in the literature that the increase in inflammation and oxidative stress levels can have a big role in the pathogenesis (10-13).

Oocytes which are released with ovulation are surrounded closely with cumulus cells. It is known that bi-directional relationship between cumulus cells and oocyte has a significant importance on oocyte maturation. These cells provide the network which supplies the proper microenvironment for oocyte. The connection between oocyte and cumulus cells is bidirectional and this connection ensures capable oocyte maturation (14). Oocyte development is known to be essential for fertilization and embryo development processes. This maturation duration includes important steps such as nucleer maturation or changes of ooplasm (15). It has been demonstrated that the network between cumulus cells and oocyte is essential for competant oocyte maturation. Many studies have shown that molecules secreted from oocyte can be effective in many processes from ovulation to embryo development as a result of paracrine and autocrine interactions (16-18). Among these factors, especially GDF-9 and BMP-15, members of the TGF-β family, are of great importance (19). TGF-β is the largest family of extracellular protein groups found in mammals (20). These signal molecules which are secreted by the oocyte, provides a bidirectional connection with somatic cells which also plays a role in many critical earlier stages of follicle development, such as migration of germ cells (21-23).

In many studies number of apopitotic cumulus cells were interpreted with poor oocyte maturation. Pocar et al showed that cumulus oocyte complex (COC) cultured with enviromental toxin (polychlorinated biphenyls) caused an increase at number of apopitotic cumulus cells in company with poor maturated oocytes (24). It was demonstrated that attendance of cumulus cells can even modulate transcription and genomic remodelling of oocytes in mouse (25). Traditionally, apopitotic biomarkers of cumulus cells effect oocyte quality and clinic outcomes. In conclusion, apopitotic status of cumulus cell level is commonly interpreted with oocyte maturation, fertilization, healthy pregnancy outcomes in previos studies.(15, 18, 26).

Follicular fluid which is secreted by granulosa cells supplies the appropriate metabolites which are neccesary for oocyte maturation process. Oocyte quality is known to be essential for ART and this environment which houses this maturation directs the fate of follicular development process. Because of that the properties of this fluid has a profound effect at reproductive functions. It is also declared that the data gained from follicular fluid is important to determine the staus of follicle (5, 27). Oocyte cumulus complex maturates in the environment provided by follicular fluid, and oxidative stres levels in this area has an impulse on oocyte quality and clinic values like pregnancy outcomes, healthy placentation, implantation, embryological development (27). Oxidative stress which reflects an overbalance of reactive oxygen species (ROS) in contrast with antioxidant defense systems is a key factor that effects reproductive system. In many articles it is declared that this imbalance between oxidant and ant-oxidant parameters has a non-negligible effect on fertility (28). Compatibly anti –oxidant nutrient supplementation caused a decrease at oxidative status of follicular fluid besides an increase of number of good quality oocytes (29). These data is competibe with previous studies which have blamed oxidative stress as a significant agent for infertility (1, 27, 30).

In addition to oxidative stress levels of follicular fluid, inflammatory markers of this environment are also known to be effective in folliculogenesis and oocyte maturation. The impact of increased inflammation in many diseases of the female reproductive system has been shared. In accordance with this information, inflammatory marker levels with increased follicular fluid have been investigated in important diseases affecting female reproductive health such as PCOS(8) and END(10).

This research is a prospective study which aimed to investigate the relationship of GDF-9, BMP-15 markers and apopitotic status of cumulus cells with TAS/TOS levels and enflammatory status in folicular fluid in patients at PCOS, END or MF groups.

Material and Methods

Patient population

This prospective study was approved by the ethical committee of Gazi University Faculty of Medicine and included 30 patients (10 patients at each group) between March 2018 and December 2018. Two independent and blinded researchers had run experiments and analyzed the data. PCOS, END and MF patients with consent were recruited.

Immunohistochemical assay

Cumulus cells belonging to the groups taken by spreading method on slide were first kept in xylol and then rehydrated by passing through decreasing alcohol series. The cells were washed with PBS (Phosphate Buffer Saline, pH: 7.4). Samples applied for 10 minutes serum blocking solution (Cat: 54-003, Lot: 40522067, Acusine mause + rabbit HRP kit, Genemed Biotechnologies, USA) to prevent non-specific binding. Samples with primary antibodies GDF-9 (Cat: ab15640, Lot: 962605, Santa Cruz Biotechnology Inc., Europe) and anti-BMP-15 (Cat: ab198226, Lot: GR211311-2, Abcam) at 4 °C overnight incubated. Samples washed with PBS afterwards were applied with 3% hydrogen peroxide solution. After washing with PBS, biotin secondary antibody (Cat: 54-003, Lot: 40522067, Acusine mause + rabbit HRP kit, Genemed Biotechnologies, USA) were applied to the samples. Again, samples were washed with PBS, and chromogen (Cat: DABS-125, Lot: HD25395, Thermo Fisher Sci., CA) containing diaminobenzedin substrate was applied until a visible immune reaction occurred. Mayer's Hematoxylin was used as the Ground stain. Samples were dehydrated by passing through the alcohol series were kept in xylol and then covered with entellan. All samples were evaluated by taking pictures in Leica QVin3 program with the help of Leica DM4000 (Germany) computer aided imaging system. The presence of GDF-9 and BMP-15 were evaluated in the cell counts provided in 5 independent areas at 400X magnification selected for each slide.

TUNEL assay

Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) method was used to assess DNA fragmentation in cumulus cells with ApopTag Aoptosis kit (Millipore). Cumulus cells belonging to the groups taken by spreading method on the slide were incubated with 20 µg/ml proteinase K (Roche Diagnostics, GmbH) for 15 minutes at room temperature. Then, cells were incubated with 3% hydrogen peroxide (LabVision, Fremont, USA) for the inhibition of endogenous peroxidase activity, in a humid environment for 5 min at room temperature. Equilibration buffer was applied for 5 min at room temperature. After the excess liquid was aspirated, the slides were incubated in TdT enzyme solution for 1 hour at 37 ° C in a humidity chamber. The slides were incubated at room temperature in the stop/wash buffer for 10 min, then slides were incubated in anti-digoxigenin peroxidase solution at room temperature for 30 min in a humidity chamber. Subsequent staining with diaminobenzidine (DAB) was used to determine TUNEL-positive cells. Methyl green was used for background. Slides were evaluated under a light microscope using a computer-supported imaging system, and the pictures were taken by using the Leica QVin3 programme.

Spechtrophotometry procedure

TAS (REL Assay Diagnostics, LOT: ST18083A) and TOS (REL Assay Diagnostics, LOT: AK17092O) levels were measured colorimetrically using a commercial kit. Throughout the experiment, the application was carried out as stated in the kit contents. Absorbance was determined using SHIMADZU UV-1601 spectrophotometer.

ELISA procedure

IL-6 (Cat. No. E0090Hu, Lot: E201904017) and TNF-alpha (Cat. No. E0082Hu, Lot: E201903008) levels were determined by ELISA method by following kit protocols.

Biotech ELISA reader was used for analysis of IL-6 (ng / L) and TNF-a (ng / L).

Statistical analysis

The consistency of continuous variables to normal distribution was examined graphically and by Shapiro-Wilk test. Mean ± standard deviation to define the number of viable cells that provide normal distribution condition, brightness and sample volume; For other variables that do not meet the normal distribution condition, the median (width between quarters) value was used.

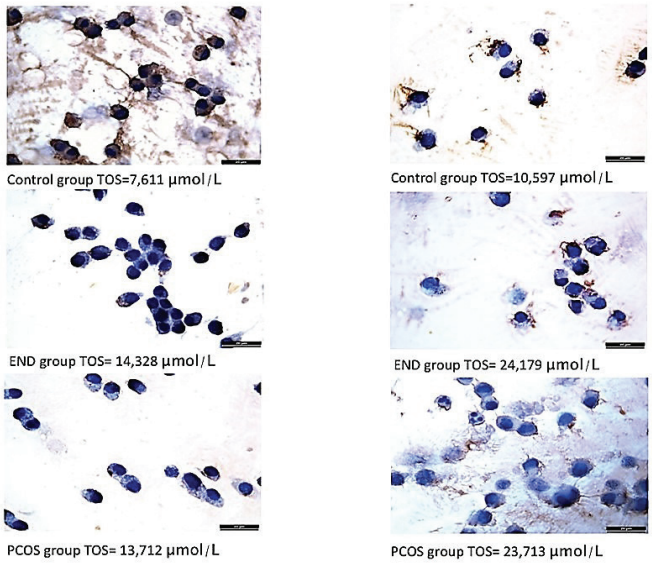
Student's t test was used to compare the variables that provide parametric test assumptions, and one-way analysis of variance (ANOVA) was used to compare sample volume by treatment groups. When a difference was found as a result of ANOVA, the source of the difference was investigated with Bonferroni post-hoc test.

Mann-Whitney test was used to compare distorted data (nonparametric) (variables). Kruskal-Wallis nonparametric for binary comparison of distorted data variance analysis was used. Post-hoc binary comparisons were made with the Bonferroni-corrected Mann-Whitney test to identify the different group when a difference was found.

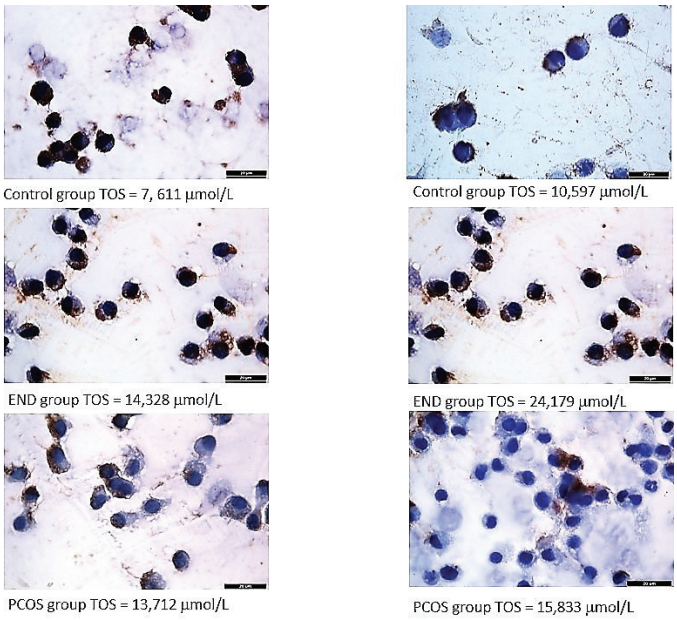
Results

GDF-9, BMP-15 markers

Both GDF-9 and BMP-15 markers were detected at lowest level for END group and at highest levels for MF group (Picture 1,2). The difference between PCOS-MF groups and END-MF groups was found to be statistically significant for both GDF-9 and BMP-15 ($p < 0,05$ (ANOVA)). Besides that difference of GDF-9 between the PCOS and END groups was also found to be significantly different ($p= 0,004$ (t test)). None the less BMP-15 levels were not evaluated with a significant difference between PCOS-END groups (Figure 1).



Picture 1. GDF-9 detection for Control, PCOS, END groups with TOS values



Picture 2. BMP-15 detection for Control, PCOS, END groups with TOS values

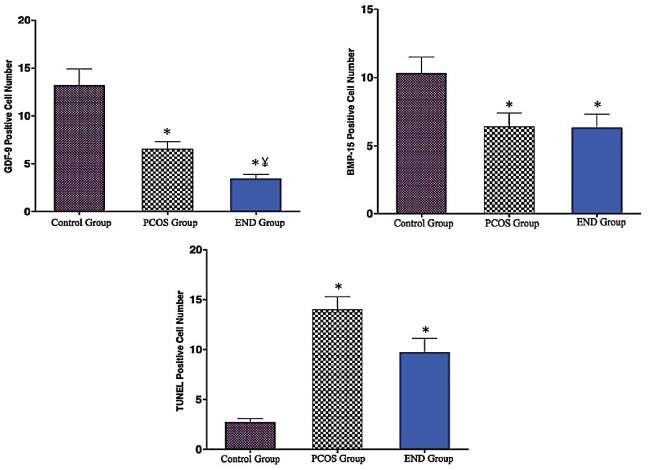


Figure 1. Comparing, PCOS and END groups in terms of GDF-9, BMP-15 markers and TUNEL positivity (* = different from Control group (Control - PCOS / Control - END: $p < 0.05$))

In all groups, both GDF-9 and BMP-15 markers levels were determined in relation to the TOS grades. The individuals at all gruops were sort ascended according to the TOS values in each group. Due to TOS values alignment each group had a subgroup with lower (5 patients) and higher TOS values (5 patients) in itself. Lower levels of GDF-9 and BMP-15 positivity were detected in cumulus cells from patients with higher TOS levels at follicle fluids. This relationship was found to be statisticallly significant (Figure 2).

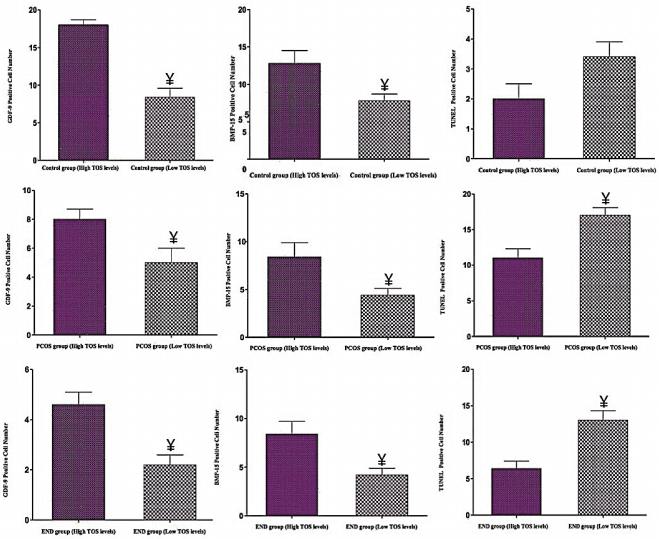
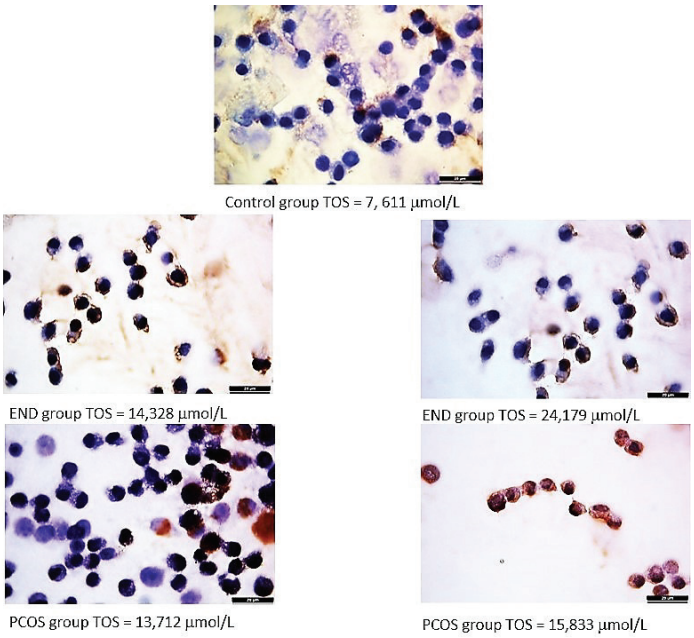


Figure 2. The relationship between GDF-9, BMP-15 markers and TUNEL positivity rates of cumulus cells and follicular fluid TOS values (¥: statistically different from control group, p<o.o5)

TUNEL results

TUNEL positive cumulus cells were found to be highest for

PCOS gruop and lowest for MF group (Picture 3). There was no statistically significant difference for TUNEL positivity between PCOS and END groups. However, a statistically significant difference was detected between both PCOS-MF and END-MF groups in terms of TUNEL positivity. (Figure 1) . Cumulus cells at PCOS and END groups showed, higher and statistically significant TUNEL positivity for patients with higher TOS levels (Figure 2).



Picture 3. TUNEL positivity for Control, PCOS, END groups with TOS values

TAS/TOS values

TAS results were obtained as 1.221 ± 0.427 for MF group, 1.446 ± 0.408 for PCOS group, and 1.282 ± 0.230 for endometriosis group. When the obtained results were evaluated statistically, no significant difference was found between MF – PCOS groups (p = 0.2277), MF – END groups (p= 0.655), and PCOS - END groups (p = 0.225). TOS results were obtained as 10,632 ± 2,150 for MF group, 19,942 ± 3,060 for PCOS group, and 22,527 ± 3,410 for END group (Table 1). TOS results showed a significant differance between MF - PCOS (p = 0.002), and MF – END (p = 0.002). However, there was no statistically significant difference between PCOS – END groups (p = 0.225) (Table 1).

Table 1. TAS and TOS values for groups (* = different from the control group, p = 0.002)

Group name	TAS (mmol/L)	TOS (µmol/L)
MF	1.078±0.295	10.625±1.351
PCOS	1.686±0.322	11.111±1.547*
END	1.236±0.399	14.120±0.439*

IL-6/TNF-alpha values

The IL-6 findings were determined as 18.09 ± 7.19 for the MF group, 51.40 ± 43.32 for the PCOS group and 34.64 ± 38.11 for the END group. When the obtained results were evaluated statistically, a significant difference was found between the MF -PCOS groups (p = 0.012). In contrast with this finding, no significant difference was found between the MF – END (p = 0.074), as well as the PCOS - END (p = 0.246) groups for IL-6 results.

TNF-α results were obtained as 19.34 ± 23.65 for the MF group, 61.46 ± 52.13 for the PCOS group, and 28.34 ± 39.15 for the END group. When the TNF-α results of the PCOS group were compared with the MF group, a statistically significant difference was observed (p = 0.046). However, there was no significant difference between the MF – END (p = 0.753) and PCOS – END (p = 0.059) groups (Table 2).

Table 2. IL-6 and TNF-α values belonging for groups (* = different from control group p = 0.012, ¥ = different from control group p = 0.046)

Group name	IL-6 (ng/L)	TNF-α (ng/L)
MF	18,09 ± 7,19	19,34 ± 23,65
PCOS	51,40 ± 43,32*	61,46 ± 52,13 ¥
END	34,64± 38,11	28,34 ± 39,15

Discussion

PCOS Group

The amount of GDF-9 in cumulus cells obtained from individuals diagnosed with PCOS were decreased compared to the cumulus cells belonging to MF group. This result was consistent with the research data discussed when compared with similar studies in the current literature, which were tend to conclude that GDF-9 affects oocyte maturation processes (31-36).

A reduction was observed for the amount of BMP-15 in cumulus cells obtained from PCOS group compared to the cumulus cells belonging to MF group. This data on BMP-15 levels is consistent with the literatüre (31, 32, 35-37). The synergistic relationship between GDF-9 and BMP-15 has been presented in the literature. As a result of the decrease detected in both marker levels, it can be concluded these components may have an effect on oocyte quality. (16, 31, 38).

ZHAO et al shared that cumulus cells from individuals diagnosed with PCOS showed a decrease in the amount of GDF-9, while a significant difference was not observed in BMP-15 levels compared to the control group. This decrease in GDF-9 levels has been associated with premature lutinization and increased risk of luteal dysfunction, which can be seen in patients diagnosed

with PCOS. It was also emphasized in the study that GDF-9 and BMP-15 can be supplemented in order to support ovulation if the deficiency of paracrine factors is detected (33)

Karagül et al. found a decrease in GDF-9 and BMP-15 levels in patients diagnosed with PCOS and reported that this decline was associated with follicle development, zona pelusida maturation, as well as subfertility and infertility that can be observed in these individuals (32). Vireque et al. declared that the increase in GDF-9 and BMP-15 transcription levels in mature oocyte samples obtained from volunteers diagnosed with PCOS was associated with follicle fluid androgen levels. With same study it was shared that GDF-9 and BMP-15 levels affected progesterone release from follicular cells, preventing early luteinization in cumulus cells (39).

In our research results, increased apoptosis levels were obtained in cumulus cells belonging to PCOS patients are compatible with many data presented(40-42). Song et al declared that insulin levels in patients with PCOS were compatible with the apopitosis levels of the cumulus cells (41). Likewise, Ding et al detected high levels of apoptosis in patients belonging to the PCOS group compared to the control group. Obesity and insulin resistance parameters of these patients were also evaluated in relation to granulose cell death(42). Due to obtained resulst of our study it was hypothesied that increase in the insulin levels, obesity or insülin resistance of the patients diagnosed with PCOS may have an affect on the female fertility by showing a synergistic effect with the follicular fluid TOS level and the apoptosis levels of the cumulus cells.

With the results of the study, follicular fluid TOS values were significantly higher in the PCOS group compared to the control group. This result is congruous with previos datas in the literatüre (5, 8, 9, 27) The obtained result was interpreted to show the effect of total oxidative capacity on oocyte maturation.

It is known that the quality of the follicle fluid exerts an influence on even the relationship of oocyte with sperm and implantation. Therefore, follicle fluid is considered to affect even embryonic development levels closely (5, 27). Our results concluded that, lower levels of GDF-9 and BMP-15 and higher numbers of TUNEL (+) cumulus cells were observed belonging to patients with high TOS levels in follicular fluid for both PCOS and END groups. These data pointed out that it GDF-9 and BMP-15 molecules synthesized by the oocyte, and the TUNEL positivity of cumulus cells may have an impact in subfertility or infertility cases for patients with PCOS or END with the reciprocal cooperation of oxidative stress levels at folicular fluid. This impact may be efficient at a wide range from fertilization to many processes of embryonic development. These results brought to mind the need to elaborate the relationship between follicular fluid oxidative stress levels and oocyte markers. However, TAS values did not differ significantly in the PCOS group compared to the control group. This was associated with the need for further research with larger patients.

Another parameter associated with insulin resistance in individuals with PCOS is increased inflammation. We had significantly higher results of IL-6 and TNF-alpha at folicular fluid of the patients diagnosed with PCOS. It has been reported that certain levels of cytokines known to have an effect in the inflammatory process, such as IL-6, TNF-a, were found to be higher in follicular fluid samples of PCOS patients compared to healthy individuals (8). It was stated by Artimani et al's study that increased inflammation may have an effect on insulin resistance as well as impaired oxidative stress balance (8). In the light of these data, it could be suggested that increased inflammation should also be considered in the clinical approach if insulin resistance is detected unbalenced in patients diagnosed with PCOS. Besides this vision, the need for studies with larger number of patients, including different inflammatory markers continues.

End Group

With the study results, lower rates of GDF-9 and BMP-15 data were obtained in the cumulus cell samples belonging to individuals in the END group compared to the MF group and this result is compatible with several previous datas. The mentioned parameters have been associated with many steps that affect fertility, such as oocyte quality, implantation, pregnancy rates, or even embryo development (17, 18). Considering the synergistic relationship between both factors, these results seem to be consistent with the dynamics of the relationship between the cumulus cell and oocyte (16, 31, 38). With the study conducted by Kawabe et al., it has been reported that progesterone and estrogen levels, which have a large place in the endometriosis clinic, changed in accordance with the amount of GDF-9 (17). In the light of the cumulus cell data obtained from our research results, it can be thought that the decrease in the GDF-9 synthesis plays a more effective role in the pathogenesis of END compared to the pathogenesis of PCOS and ultimately leads to endocrinological disorders in the clinic of END.

High apoptosis levels observed in the cumulus cells belonging to individuals in the END group are compatible with the

literature (27, 43, 44, 45). With the results of the study, it was thought that cell death due to increased oxidative stress may be effective in endometriosis pathology by observing higher apoptosis in the cumulus cell samples of individuals with high TOS levels at folliculer fluid. With certain data presented to the literature, it supports the effect of increased oxidative stress on cumulus cell death and suggests the relationship of this effect with female infertility (11, 45,46, 47).

In our research results, both the individuals diagnosed with PCOS and END, GDF-9 and BMP-15 values were obtained lower comparing with MF group, while the number of apoptotic cells was higher. Another task of oocyte secreted molecules is to increase the synthesis of apoptosis-inhibiting B-cell lymphoma 2 (Bcl-2) proteins in somatic cells surrounding the oocyte and to create a protective effect by inhibiting the synthesis of Bcl-2-associated X (Bax) proteins known for their pro-apoptotic activity (16, 48). This result suggested that anti-apopitotic system formed by the synergistic effect of GDF-9 and BMP15 molecules could be insufficient for patients diagnosed with PCOS or END.

TOS values, which were significantly higher than the MF group in the END group, are also compatible with the literature. In contrast with this finding, TAS levels were significantly higher in the END group comparing with MF group but the difference was not significant. This result differs with some studies reporting decreased TAS values for patients diagnosed with END (27, 43, 44). The limited number of patient groups in our research data is thought to be a cause of this situation. In addition, in our research, total level of oxidant and antioxidant levels were obtained. Specific markers on these parameters could also evaluate oxidant and anti-oxidant differences at detailed ranges. Prieto et al. investigated specific parameters such as Vitamin C, Vitamin E, malonildialdehyde (MDA), superoxide dismutase (SOD) in patients diagnosed with END comparing with control group. They shared decreased antioxidant data alongside higher oxidative stress level at END group.

Increased cytokine levels in follicular fluid samples have been shared in individuals diagnosed with END with many data presented to the literatüre (10, 11, 44). In contrast with this finding, within the results of the study no significant difference was obtained for IL-6, TNF-alpha levels in END group.

This the situation is related to the limited number of volunteers in the research group. It is believed further studies in larger groups will provide a wider perspective for the effect of inflammatory cytokines at follicular fluid.

Limitations

It was made out for all authors that, a further research with a larger number of patient groups and long-term patient follow-up would provide wiser results. Also the necessity of adding clinical data such as embryo development and neonatal findings was also absorved at the end of the study. This enterprise would supply a larger contribution to the affect of examined paramaters on clinical processes.

Conclusion

The relationship of cumulus cells with female infertility continues to be researched with increasing interest. Common sight on the relationship between oocyte and cumulus cells is that communication is effective on many parameters of female fertility from fertilization, implantation to to the newborn health. In this communication, which attracts a great deal of attention, which molecule / or which molecules has a wider effect through its own pathway is still not fully known. To find out more of which molecules are involved in this interaction and which pathophysiological mechanisms contribute will provide reflection of new parameters in the selection of healthy oocytes to the clinic.

It is known that oocyte quality is of great importance in obtaining pregnancy. The healthiest oocyte can be effective as one of the biggest goals for the success of obtaining pregnancy. Levels of GDF-9 and BMP-15 which are of great interest in molecules synthesized by oocyte, or the cell death rates of cumulus cells can cause a decrease in certain clinical pathologies and this situation is associated with fertility.

In our study, cumulus cells were examined at both PCOS, END and MF groups. Besides GDF-9 and BMP-15, apoptosis levels were examined. Compared to healthy individuals in MF group cumulus cells belonging to individuals diagnosed with PCOS and END, GDF-9 and BMP-15 levels were evaluated low and apoptosis levels were high.

Compared to each other, GDF-9 and BMP-15 decline was more prominent in the END group, whereas the increase in apoptosis level was obtained more evident for the PCOS group. Based on these results it can be thought that, GDF-9 and BMP-15 has a clear effect on infertility for patients with END. Similarly, the higher rate of apoptosis levels of cumulus cells at PCOS group were more significant and this result was associated with the relationship of cumulus cell death rate and infertility for patients diagnosed with END. In the selection of the best oocyte within the ART techniques, it can be thought

that a different perspective can be brought in by evaluating the properties of cumulus cells. In the light of our research data, it can be thought that GDF-9 and BMP-15 molecules will be of greater importance especially in individuals diagnosed with END, while TUNEL positivity rates of endometrial cells can be evaluated in individuals diagnosed with PCOS.

Although within the data obtained from the results of our study, it can be said that cumulus cell evaluation could be supportive, the need for molecular studies to be conducted with larger patient groups continues in order to consider cumulus cells as a criterion in the selection of oocytes belonging to individuals diagnosed with PCOS and / or END.

It can be thought that, the evaluation of follicular fluid oxidative stress level could promote the determination of GDF-9 and BMP-15 markers and/or TUNEL positivity rates. These criterias could provide a more comprehensive selection for best oocyte treatment with ART for patients diagnosed with PCOS or END.

The results of the study were determined in relation to increased TOS value, decreased GDF-9, BMP-15 levels as well as increased TUNNEL positivity rate. Data highlighting the relationship between increased oxidative stress levels, cumulus cell and embryo quality are available in literatüre (13). In the light of the data obtained, when the follicular fluid properties of the cumulus cell properties are evaluated together with the oxidative stress levels, it can be thought that it can also provide data on embryo quality in individuals with PCOS and END. TNF-alpha and IL-6 levels at follicular fluid did not exhibit significantly evaluated rates between groups. Therefore it cannat not be said that the levels of TNF-alpha and IL-6 levels of follicular fluid could be an evaluation criteria of selecting best oocyte. Further studies are still needed for this perspective.

Many studies in the literature investigate the effect of oxidative stress in PCOS pathology. However, as provided in our study, it is the first data which evaluates both mentioned criterias in cumulus cells while examining the oxidative stress and inflammation levels together at follicle fluid. Considering the results of our study, it can be thought that more satisfactory results can be expected in embryo development by providing the necessary supplements (GDF-9 and BMP-15 molecules) to the media of embryos for patients diagnosed with PCOS or END. Folicular fluid oxidative stress level can have a big effect fort his clinical judgement.

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Research Article

In the management of febrile neutropenia; evaluation of the factors affecting the lenght of hospital stay

Febril nötropeni yönetiminde yatış süresine etki eden faktörlerin değerlendirilmesi

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Abstract

Aim: Febrile neutropenia (FEN) is one of the most serious and commonly seen complications of patients receiving chemotherapy for a diagnosis of hematological malignancy. FEN is an emergency condition with mortality rates reaching 40% because of an increase in antimicrobial-resistant pathogens in particular. In a situation with such high mortality rates, parameters that can predict prognosis play an important role in the approach to the patient. The aim of this study was to investigate the parameters that could affect prognosis in the follow-up of FEN.

Material and Methods: The study included 58 patients hospitalised in the Hematology Clinic with a diagnosis of FEN. The patients were evaluated in respect of the recorded demographic characteristics, blood group, MASCC score, hemogram, procalcitonin, C-reactive protein (CRP), Interleukin-6 (IL-6), D-dimer, fibrinogen, pre-albumin, albumin, HbA1c, anthropometric measurements and length of stay in hospital.

Results: According to the statistical analysis results, patients with a length of hospital stay of ≥14 days were determined to have a significant decrease in the MASCC score and thrombocyte count and the procalcitonin, Il-6, D-dimer values and the number of antibiotics used were higher. No significant difference was determined between the groups in respect of the other parameters.

Conclusion: In the management of febrile neutropenia, the most important points are the establishment of indications for hospitalisation, rapid and early recognition of a worsening status and intervention made in the right place at the right time. Parameters with prognostic benefit will help the clinician in decision-making.

Keywords: febrile neutropenia, hematological malignancy, length of hospital stay, IL-6, procalcitonin

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Öz

Amaç: Febril nötropeni (FEN); kemoterapi alan hematolojik malignite tanılı hastalarda en yaygın karşılaşılan ve en ciddi komplikasyonlardandır. .FEN ; özellikle antimikrobiyal dirençli patojenlerin artışı nedeniyle mortalitesi %40 lara varan acil bir durumdur. Mortalitesi bu kadar yüksek olan bir durumda prognozu öngören parametrelerin olması ; hastaya yaklaşımda önemli rol oynayabilir. Çalışmamızda FEN takibinde prognozu etkileyebilecek parametreler araştırılmıştır.

Gereç ve Yöntemler: FEN tanısı ile hematoloji kliniğine yatmış olan 58 hasta çalışmaya dahil edilmiştir. Hastaların demografik özellikleri, kan grubu, MASCC skoru, hemogram, procalsitonin, CRP(C-reaktif protein), IL-6(interlökin-6), D-Dimer, Fibrinojen, prealbumin , albümin, HbA1c, antropometrik ölçümler ve yatış süresi kayıt edilmiştir.

Bulgular: Yapılan istatistiksel analiz sonucuna göre yatış süresi 14 gün ve üstünde olan grupta MASCC skoru , trombosit sayısı , anlamlı düşük saptanmış iken prokalsitonin, IL-6, D-dimer , kullanılan antibiyotik sayısı yüksek saptanmıştır. Diğer parameterlerde iki grup arasında anlamlı farklılık saptanmamıştır.

Sonuçlar: Febril nötropeni yönetiminde; hastaya yatış endikasyonu konulması, kötüye gidişin hızlı ve erken farkedilmesi, müdahalelerin yerinde ve zamanında yapılması en önemli noktalardandır. Bunlara karar verilmesinde prognostik yararı olan parameterelerin olması klinisyene yarar sağlayacaktır.

Anahtar Kelimeler: febril nötropeni; hematolojik malignite; yatış süresi; IL-6; prokalsitonin

Introduction

Febrile neutropenia (FEN) is one of the most serious and commonly seen complications of patients receiving chemotherapy for a diagnosis of hematological malignancy. Neutropenic fever is defined as a single measurement of >38.3°C or fever ≥38°C lasting for 1 hour with absolute neutrophil count <500µl, or expected to fall to <500 within 48 hours. Neutrophil values of <100µl are defined as deep neutropenia and this creates a higher risk of bacteremia (1). FEN is an emergency condition with mortality rates reaching 40% because of an increase in antimicrobial-resistant pathogens in particular, and there are documented microbial infections in only 30%.

Therefore, a rapid first evaluation with full blood count for the degree of neutropenia, then performing the necessary tests for infection focus screening (blood culture, urine culture, the necessary tests for the potential infection region) will allow a rapid transition to empirical treatment (2, 3). In a condition with such high mortality rates, parameters that can predict prognosis and response to treatment can play an important role in the approach to the patient, the early initiation of empirical treatment, and a change in treatment. The aim of this study was to investigate the parameters that could affect prognosis in patients with hematological malignancy who were receiving chemotherapy and were hospitalised because of FEN.

Material and Methods

The study included 58 patients hospitalised in the Hematology Clinic of Dışkapı Yıldırım Beyazıt Training and Research Hospital between July 2021 and August 2022. The patients were receiving chemotherapy for a diagnosis of hematological malignancy and were then hospitalised with a diagnosis of FEN. The patients were evaluated in respect of the recorded demographic characteristics, blood group, MASCC score, hemogram, procalcitonin, C-reactive protein (CRP), Interleukin-6 (IL-6), D-dimer, fibrinogen, pre-albumin, albumin, HbA1c, anthropometric measurements, and length of stay in hospital.

Statistical Analysis

The data obtained were analyzed using SPSS vn 28.0 software. Descriptive statistics were stated as mean ±standard deviation, median, minimum and maximum values, number (n) and percentage (%). Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test. In the analysis of independent quantitative data, the Mann Whitney U-test was used. Qualitative data were analyzed using the Chi-square test, or the Fischer test if Chi-square conditions were not met.

Ethical approval and informed consent

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 approved by the Ethics Committee of Etlik City Hospital, Ankara, Turkey (03.05.2023-AESH-EK1-2023-143).

Results

Evaluation was made of 58 patients, comprising 40 (69%) males and 18 (31%) females with a mean age of 55.8 ± 16.5 years. The demographic characteristics and descriptive statistics of the patients are shown in Table 1.

Table 1. Descriptive statistics of the data and distribution of demographic parameters of the patients

		Mean±SD/n-%		
Age (years)		55.8	±	16.5
Gender	Female	18		31.0%
	Male	40		69.0%
Fever		40		69.0%
Cough		21		36.2%
Abdominal pain		5		8.6%
Anal pain		7		12.1%
Difficulty swallowing		5		8.6%
Toothache		3		5.2%
Cellulite		4		6.9%
Duration of fever		3.1	±	2.1
MASCC		18.1	±	4.3
WBC		732.2	±	579.2
HGB		8.0	±	2.0
PLT		55190	±	79287
PDW		11.5	±	2.9
PCT		0.1	±	0.1
MPV		10.5	±	1.2
Glucose		120.3	±	36.6
Procalcitonin		10.6	±	25.6
CRP		171.6	±	102.2
IL-6		170.9	±	283.0
D-Dimer		6.5	±	24.2
Fibrinogen		438.1	±	184.6
Pre-albumin		0.1	±	0.1
Albumin		3.5	±	3.6
HbA1C		6.2	±	1.0
Malnutrition Risk	(-)	31		53.4%
	(+)	27		46.6%
Number of antibiotics		2.6	±	1.5

MASCC: Multinational Association for Supportive Care in Cancer, WBC:White Blood Count, HBG:Hemoglobin , PLT:Platelet
PDW: Platelet Distribution Width, PCT:Plateletcrit, MPV: Mean Platelet Volume, CRP: C-Reactive Protien, IL-6:Interleukin-6

The factors affecting length of hospital stay were examined. According to the statistical analysis results, patients with a length of hospital stay of ≥14 days were determined to have a significant decrease in the MASCC score and thrombocyte count and the procalcitonin, IL-6, D-dimer values, and the number of antibiotics used were higher. No significant difference was determined between the groups in respect of the other parameters (Table 2).

Discussion

Febrile neutropenia (FEN), which has a high mortality rate, is one of the most frequently encountered complications in patients receiving chemotherapy. In a 1966 study by Bodey et al., increased mortality was determined in patients diagnosed with acute myeloid leukemia who had neutrophil values <500 (4). Approximately 40%-50% of the hospital costs of cancer patients have been reported to be due to FEN (5).

The Multinational Association for Supportive Care in Cancer (MASCC) score was developed in 2000 and is recommended to be used for the risk classification of patients. The MASCC score is used mostly for outpatients, with a value of ≥21 evaluated as low risk and a value <21as high risk. With this evaluation, it is predicted that low-risk patients can be treated with oral antibiotics as outpatients (6). Although there is no routine use of this score for hospitalised patients, some studies have recommended that it can be used for hospitalised patients (7, 8). In the current study, a relationship was determined between the MASCC score and the length of stay in hospital, and the score was determined to be statistically significantly low in patients with a hospital stay of ≥14 days.

The thrombocyte count, which is affected by the production and destruction of platelets, may decrease with an imbalance between these two states. One of these factors is infection and fever. Thrombocytopenia has been found to be associated with increased mortality in intensive care patients (9). The results of the current study also showed that thrombocytopenia was associated with a longer length of stay in hospital. As a longer length of hospital stay indirectly shows the severity of the patient, these data obtained were consistent with the literature.

Procalcitonin (PCT), which is a precursor of calcitonin hormone, was first described as a sepsis marker in 1993 (10). It has been shown in many studies that PCT is a marker with high sensitivity for the diagnosis of infection and the follow-up of progression (11, 12). In the current study, PCT was found to be statistically significantly associated with a long stay in hospital.

D-Dimer is a cross-linked fibrin degradation product, which has been shown to be a marker of fibrinylosis and indirectly of thrombotic activity (13). Other than in thrombotic events, D-dimer can also be elevated in conditions of inflammation and severe infection (14). In the current study, D-dimer was found to be elevated proportional to a longer hosptial stay. FEN of varying degrees can be confused with infection. The examination of D-dimer at the time of diagnosis can be of guidance in respect of severe infection, a severe course, and the decision for hospitalisation and rapid intervention.

Table 2. Comparisons of the parameters of the groups with length of hospital stay of more or less than 14 days

		Hospital stay <14 days			Hospital stay ≥14 days			P	
		Mean±SD/n-%			Mean±SD/n-%				
Age (years)		54.7	±	10.6	56.3	±	18.5	0.472	m
Gender	Female	8		47.1%	10		24.4%	0,089	X^2
	Male	9		52.9%	31		75.6%		
Fever		2.5	±	1.7	3.3	±	2.2	0.231	m
Cough		4		23.5%	17		41.5%	0.156	X^2
Abdominal pain		3		17.6%	2		4.9%	0.144	X^2
Anal pain		1		5.9%	6		14.6%	0.182	X^2
Difficulty swallowing		1		5.9%	4		9.8%	0.548	X^2
Toothache		1		5.9%	2		4.9%	0.504	X^2
Cellulite		2		11.8%	2		4.9%	0.504	X^2
MASCC		20.2	±	3.3	17.1	±	4.4	0.007	m
WBC		648	±	466	767	±	622	0.871	m
HGB		8.4	±	1.7	7.9	±	2.1	0.171	m
PLT		94706	±	112159	38805	±	54658	0.038	m
PDW		11.3	±	1.9	11.6	±	3.2	0.765	m
PCT		0.08	±	0.09	0.05	±	0.05	0.203	m
MPV		10.3	±	0.95	10.5	±	1.2	0.510	m
Glucose		118	±	30.4	121	±	39.2	0.952	m
Procalcitonin		7.4	±	24.3	11.9	±	26.3	0.010	m
CRP		160	±	86.2	177	±	109	0.758	m
IL-6		49.0	±	27.9	221	±	324	0.029	m
D-Dimer		2.6	±	3.8	8.1	±	28.6	0.030	m
Fibrinogen		432	±	158	441	±	196	0.905	m
Pre-albumin		0.15	±	0.08	0.12	±	0.08	0.111	m
Albumin		3.2	±	0.65	3.7	±	4.3	0.183	m
HbA1C		5.8	±	0.93	6.4	±	1.02	0.065	m
Malnutrition Risk	(-)	12		70.6%	19		46.3%	0,092	X^2
	(+)	5		29.4%	22		53.7%		
Number of antibiotics		1.8	±	1.3	2.9	±	1.5	0.001	m
Length of hospital stay (days)		11.2	±	2.4	28.4	±	12.7	0.000	m

X^2 Chi-square test / m Mann Whitney U-test
MASCC: Multinational Association for Supportive Care in Cancer, WBC:White Blood Count, HBG:Hemoglobin , PLT:Platelet
PDW: Platelet Distribution Width, PCT:Plateletcrit, MPV: Mean Platelet Volume, CRP: C-Reactive Protien, IL-6:Interleukin-6

IL-6 is a cytokine that has an effect on hematopoietic cell differentiation with T and B lymphocytes. In literature, IL-6 has been shown to be a sensitive biomarker for disease severity and infection, it can be more effective than CRP and some other markers in severe infectious conditions, and it has been emphasized that specificity can be further increased when it is evaluated combined with some other markers (15-17). In the current study, the IL-6 level was found to be statistically significant in patients with a length of hospital stay of ≥14 days.

Conclusion

In patients diagnosed with cancer and especially those with a diagnosis of a hematological malignancy, neutropenia is frequently seen and is an inevitable condition following chemotherapy. FEN must be kept in mind at all times as it is a complication that requires good management. The most important points in the management of FEN are the establishment of indications for hospitalisation, rapid and early recognition of a worsening status, and intervention made in the right place at the right time. Parameters with prognostic benefit used singly or combined will help the clinician in decision-making.

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Conflict of Interests

The authors have no conflict of interests to declare

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Araştırma Makalesi

Üniversite öğrencileri arasında COVID-19 hastalığı ile ilgili bilgi düzeyi, tutum ve davranışların değerlendirilmesi

Evaluation of knowledge, attitudes and behaviors related to COVID-19 disease among university students

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Öz

Amaç: Dünyada 11 Mart 2020 tarihinde ilan edilen, Ağır Akut Solunum Sendromu-Koronavirüs-2 (Severe Acute Respiratory Syndrome, SARS-CoV-2) etkeninin neden olduğu COVID-19 pandemisinin etkileri varyantları ile günümüzde de devam etmektedir. Aşılama ve korunma önlemleri ile kontrol altına alınmaya çalışılan salgında dünyada konfirme edilen sayılara göre 769.774.646 insan hastalanıp ve 6.955.000 ölüm saptanmıştır. Bu çalışmada COVID-19 hastalığı ile ilgili üniversite öğrencilerinin bilgi düzeyini araştırmak, hastalığa yönelik tutumlarını belirlemek ve davranış şekilleri değerlendirerek ileride yapılacak çalışmalar ve uygulamalar için yol gösterici olmak amaçlanmıştır.

Gereç ve Yöntemler: Araştırmamız tanımlayıcı türde, kesitsel bir saha çalışmasıdır. Araştırmanın evrenini Tıp, Diş Hekimliği, Mühendislik Fakültesi öğrencileri oluşturmaktadır. Anket ulusal ve uluslararası literatür taraması sonucu oluşturularak, çevrimçi sistemle uygulanmıştır.

Bulgular: Ankete, Mühendislik fakültesinden 472, Tıp fakültesinden 113, Diş hekimliğinden 25, toplam 610 öğrenci katılmıştır. Öğrencilerin 317'si kadın, yaş ortalamaları 21.4 ± 1.9 yıl saptanmıştır. Doksanbir öğrenci COVID-19 hastalığı geçirmiştir. Sadece 50'si COVID-19 aşısı olmuştur. Aşı olanlar 37 öğrencide kol ağrısı, baş ağrısı ve kas ağrısı gibi yan etkiler görmüştür. Aşı olmayanların 447'si aşı olmayı düşünüyorken, 113 kişi yan etkisinden çekindiği için, etkinliğine inanmadığı için ve iğneden korktuğu için aşı olmayı istememektedir

Mühendislik öğrencileri; COVID-19 virüsü antibiyotikle tedavi edilebilir (p=0.001), hastalığın kesin tedavisi vardır (p=0.001), evden çıktığımda eldiven takıyorum (p=0.011), virüsün laboratuvarda üretildiğini düşünüyorum (p=0.001), bağışıklığım güçlü, virüse karşı önlem almam gerektiğini düşünmüyorum (p=0.013) cevapları ile diğer bölümlere göre bilgi eksiklikleri daha yüksek bulunmuştur.

Sonuçlar: Üniversite öğrencileri arasında COVID-19 hastalığı ile ilgili yanlış bilgi ve davranışlar olduğu görülmüştür. Temel eğitimlerin tüm bölümlere verilmesi sağlanmalıdır.

Anahtar kelimeler: COVID-19, üniversite öğrencileri, bilgi, tutum, davranış

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Abstract

Aim: The effects of the COVID-19 pandemic caused by the Severe Acute Respiratory Syndrome-Coronavirus-2 (Severe Acute Respiratory Syndrome, SARS-CoV-2), which was announced in the world on March 11, 2020, continue today with its variants. In the epidemic, which was tried to be controlled with vaccination and protection measures, 769,774,646 people became ill and 6,955,000 deaths were determined according to the confirmed numbers in the world. In this study, it is aimed to investigate the knowledge level of university students about COVID-19 disease, to determine their attitudes towards the disease and to evaluate their behavior patterns and to guide for future studies.

Material and Methods: Our research is a descriptive, cross-sectional field study. The population of the research consists of the students of the Faculty of Medicine, Dentistry and Engineering. The questionnaire was created as a result of national and international literature review and applied with an online system.

Results: A total of 610 students, 472 from the Faculty of Engineering, 113 from the Faculty of Medicine, 25 from the Dentistry Faculty, participated in the survey. 317 of the students were female, their mean age was 21.4 ± 1.9. Ninety-one students suffered from COVID-19 disease. Only 50 have been vaccinated against COVID-19. Those who received the vaccine experienced side effects such as arm pain, headache and muscle pain in 37 students. While 447 of those who are not vaccinated are considering getting vaccinated, 113 people do not want to be vaccinated because they fear side effects, do not believe in its effectiveness and are afraid of injections.

Engineering students; COVID-19 virus can be treated with antibiotics (p=0.001), there is a definite cure for the disease (p=0.001), I wear gloves when I leave the house (p=0.011), I think the virus was produced in the laboratory (p=0.001), my immunity is strong, I do not take precautions against the virus I don't think it's necessary (p=0.013) and the lack of knowledge was found to be higher than the other sections.

Conclusion: It has been observed that there is false information and behaviors about COVID-19 disease among university students. Basic training should be provided to all departments.

Keywords: COVID-19, university students, knowledge, attitude, behavior

Giriş

Koronavirüsler (CoV), hafif soğuk algınlığı bulgularından, Orta Doğu Solunum Sendromu (Middle East Respiratory Syndrome, MERS) gibi ciddi enfeksiyonlara neden olabilen virüslerdir. Misk kedilerinden 2013 yılında SARS CoV'un salgını ve 2012 yılında develerden MERS-CoV salgınlarına neden olmuştur. Çin'in Hubei eyaletinin Wuhan şehrinde 31 Aralık 2019'da, etiyolojisi bilinmeyen pnömoni vakalarını bildirilmiştir. 7 Ocak 2020'de etken daha önce insanlarda tespit edilmemiş yeni bir koronavirüs (2019-nCoV) olarak tanımlanmıştır. Daha sonra 2019-nCoV hastalığının adı COVID-19 olarak kabul edilmiş, virüs SARS CoV'e yakın benzerliğinden dolayı SARS-CoV-2 olarak isimlendirilmiştir [1].

Dünya sağlık örgütü 11 Mart 2020 tarihinde pandemi ilan etmiş, ülkemizde de aynı tarihde ilk vaka bildirimi olmuştur Alfa, beta, gama, delta, omicron varyantları ile 20 Ağustos 2023 itibariyle dünyada toplam konfirme vaka sayısı 769.774.646, ölüm 6.955.000'dir. Ülkemizde ise 17.004.677 konfirme vaka ve 101.419 ölüm gerçekleşmiştir [2].

Hastalık esas olarak damlacık yoluyla, öksürme, hapşırma ile saçılan damlacıklara diğer kişilerin elleri ile temas etmesi, ellerini ağız, burun veya göz mukozasına götürmesi ve temas etmesi ile bulaşmaktadır. Asemptomatik kişilerin solunum yolu salgılarında da virüs tespit edilebildiğinden bu kişiler bulaştırıcı olabilmektedir. Genel olarak inkubasyon süresi 2-14 gün arasında değişmektedir. COVID-19'un bulaştırıcılık süresi kesin olarak bilinmemektedir. Semptomatik dönemden 1-2 gün önce başlayıp semptomların kaybolmasıyla sona erdiği düşünülmektedir. Yetişkinlerde COVID-19 asemptomatik enfeksiyondan, hafif solunum yolu semptomlarına, akut solunum sıkıntısı sendromu ve çoklu organ fonksiyon bozukluğu ile birlikte seyreden ciddi pnömoniye kadar değişmektedir [1,3].

Pandeminin kontrol altına alınmasında toplumdaki bilinç seviyesi, alınacak kontrol önlemlerine uyum açısından çok önemlidir. Özellikle üniversite öğrencilerinin farkındalığını, bilgi düzeyini artırmak için gerekli eğitimler sağlanmalıdır. Çalışmada, gelecekte topluma sağlık hizmeti verecekleri düşünüldüğünde tıp ve diş hekimliği fakültesi öğrencilerinin ve sosyal alanlarda paylaşımları yüksek olabileceği düşünülen mühendislik fakültesi öğrencilerinin bilgi düzeylerini

belirlemek, hastalığa karşı tutum, davranış ve yaklaşımlarını araştırmak, eksikleri tespit etmek, ileride yapılacak çalışmalara, uygulamalara ve eğitimlere katkıda bulunmak amaçlanmıştır.

Gereç ve Yöntemler

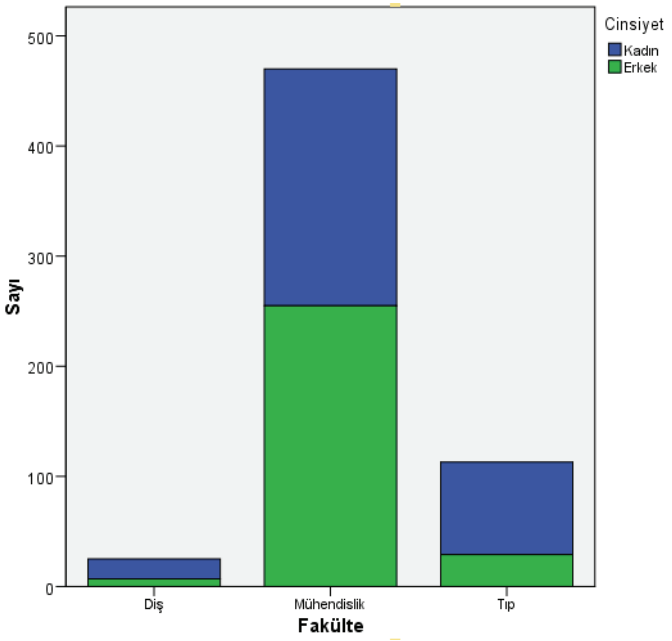
Çalışmamız tanımlayıcı türde kesitsel bir saha çalışmasıdır. Araştırma yeri Başkent Üniversitesi olup, araştırmanın evrenini Başkent Üniversitesinde sağlık alanında eğitim alan Tıp Fakültesi, Diş Hekimliği Fakültesi ile sağlık dışı eğitim alanından Mühendislik Fakültesi öğrencileri oluşturmaktadır. Örneklem hacminin belirlenmesinde $\alpha=0.05$, $d=0.05$ ve $p=0.50$ olmak üzere %95 güven düzeyi kullanılmıştır. Çalışmada kullanılan hipotez testleri kategorik değişkenlere ait yanıtların karşılaştırılmasında "Pearson Ki-Kare testi" kullanılmıştır. Tanımlayıcı istatistik olarak; kategorik değişkenlerin değerlendirilmesinde frekans (n) ve yüzde (%) değerleri kullanılmıştır. Tüm hipotez testlerinde I. Tip hata olasılığı $\alpha=0.05$ olarak alınmıştır.

COVID-19 hastalığı konusundaki bilgi düzeylerini saptamak, farklılıkları ortaya koymak, öğrencilerin bilgi düzeylerinin tutumlarını ne yönde etkilediğini araştırmak için dünyadan ve ülkemizden yapılmış benzer literatür verileri taranarak anket formu oluşturulmuştur. Anket içeriği demografik veriler, yaş, cinsiyet, fakülte, sınıf, COVID-19 hastalığı geçirme durumu, aşılanma durumu, sigara/alkol kullanımı, kronik hastalık varlığı, SARS-CoV-2 virüsü genel bilgi, bulaş yolları, semptomlar, tutum ve davranışlar ile ilgili sorulardan oluşturulmuştur. Sorular pandemi koşulları nedeni ile çevrimiçi olarak kaydedilmiştir. Anketin uygulama tarihi 27 Nisan-8 Mayıs 2021 tarihleri arasındadır. Çalışmaya katılan tüm öğrencilerin bilgilendirilmiş onamı alınarak anket başlatılmıştır.

Alınan veriler SPSS 25 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA) istatistiksel paket programı kaydedilerek, istatistiksel analizleri yapılmıştır.

Bulgular

Ankete, Mühendislik fakültesinden 472, Tıp fakültesinden 113, Diş hekimliğinden 25, toplam 610 öğrenci katılmıştır. Öğrencilerin 317'si kadın (%51.9), 293'i (%48.1) erkekdi (Şekil1). Yaş ortalamaları 21.4±1.9 yıl, medyan 21 (minimum 17- maksimum 27) saptanmıştır. Katılımcıların 172'si aktif sigara içmekte, 293 kişi alkol kullanmaktaydı. Öğrencilerin 58'inde kronik hastalık (astım, bronşit, diyabet vb.) mevcuttu. Ankete katılanların 91'i COVID-19 hastalığı geçirmişti. Bunların 55 tanesi ayakta hafif bulgularla, 23 tanesi ayakta ama daha ağır bulgularla, 3 kişi hastanede yatarak, 2 kişi yoğun bakıma yatarak tedavi aldığını belirtmiştir. Sekiz öğrenci şikayeti olmamasına rağmen tarama amaçlı yaptırdıkları testlerinin sonucu pozitif çıkmıştır (Tablo 1).



Şekil 1. Ankete katılan 610 öğrencinin cinsiyet ve fakültelerine göre dağılımı

Tablo 1. Ankete katılan 610 öğrencinin demografik verileri

	Sayı	%
Cinsiyet		
Kadın	317	51.9
Erkek	393	48.1
Yaş (yıl) Ortalama±standart sapma, Medyan (min, mak.)	21.4±1.9, 21 (minimum17, maksimum 27)	
Sınıf		
1	145	23.8
2	111	18.3
3	174	28.6
4	155	25.5
5	14	2.3
6	11	1.5
Fakülte		
Tıp Fakültesi	113	18.5
Mühendislik Fakültesi	472	77.4
Diş Hekimliği Fakültesi	25	4.1
Sigara kullanımı		
Evet	172	28.2
Hayır	438	71.8
Alkol kullanımı		
Evet	295	48.4
Hayır	315	51.6
Kronik Hastalık varlığı		
Evet	58	9.5
Hayır	552	90.5
COVID-19 geçirme durumu		
Evet	91	14.9
Hayır	519	85
Hastalığı geçirme şiddeti	n=91	
Ayakta hafif semptomlu	55	60.4
Evde yatarak	23	25.3
Hastanede yatarak	3	3.3
Yoğun bakımda yatarak	2	2.2
Asemptomatik	8	8.8

Öğrencilerin sadece 50'si (%8.2) COVID-19 aşısı olmuştur. Aşı olanlardan 37 (%6,1) öğrencide ateş, kol ağrısı, baş ağrısı ve kas ağrısı başta olmak üzere yan etkiler görmüştür. Aşı olmayanların 447'si (%73.3) aşı olmayı düşünüyorken, 113 öğrenci (%27.7) yan etkisinden çekindiği için, etkinliğine inanmadığı için ve iğneden korktuğu için aşı olmayı istememektedir (Tablo2).

Tablo 2. Ankete katılan öğrencilerin COVID-19 aşılanma durumu

	Sayı (n=610)	Yüzde(%)
COVİD-19 aşısı oldunuz mu?		
Evet	50	8.2
Hayır	560	91.8
Aşı sonrası yan etki oldu mu?		
Evet	37	74.0
Hayır	13	26.0
Aşı sonrası hangi yan etkiler oldu?		
Ateş	10	27
Baş ağrısı	17	45.9
Kas ağrısı	16	43.2
Kol ağrısı	31	83.8
Bulantı	6	16.2
Aşı olmadıysanız olmayı düşünüyor musunuz?		
Evet	447	79.8
Hayır	113	20.2
Aşı olmayı neden istemiyorsunuz ? (n=113)		
Etkinliğine inanmıyorum	45	39.8
Yan etkilerinden çekiniyorum	76	67.3
İğneden korkuyorum	6	5.3

Öğrencilerin COVID-19 hakkında bilgi edindikleri kaynaklar incelendiğinde toplamda %72.2 oranında televizyon, sırayla sosyal medya (%70.9), bilimsel yayınlar (% 70.1), aile (%53.5), arkadaşlar (%47), gazete (34.3), doktorlar (%30) ve okul (28.2) olarak sıralanmaktaydı. Mühendislik fakültesi öğrencilerinin %17.6'sı, Tıp veya Diş hekimliği bölümünde okuyan öğrencilerin %65 'inin ilk bilgi kaynağı okuldu.

Hastalığın bulaş yolları ile ilgili, enfekte bireylerin eşyalara temas yolu ile bulaş %75.9, cinsel yol ile bulaş %27.4, açık havada dolaşırken bulaş %13.7, hayvanları severken bulaş olabileceği %8.4 oranında bildirilmiştir. Hastalığın sık görülen semptomları ile ilgili ateş %94.4, öksürük 94.3, koku tat alma bozukluğu %89.2, kas ağrısı %82.1, nefes darlığı %88.9, baş ağrısı %72.6, ishal %53.4, çarpıntı %24.9 oranında doğru bilinmiştir.

Hastalığın etkeni ile ilgili, virüs %98, bakteri %1.2, kimyasal etken %0.8 olduğu cevabı verilmiştir. Bakteri ve kimyasal etken cevapları Mühendislik bölümünde yüksek bulunmuştur öğrencilerin %24.7'si hastalığın antibiyotikler ile tedavi edilebileceğini bildirmiştir. Çocuklara ve gençlere tedavi gerekmediğini bildiren öğrenci oranı %2'dir. Kronik hastalığı olanlarda hastalığın daha ağır geçebileceğini bildiren öğrenci oranı %91.4'dür ve %99.2'si semptomu olmayanlarda da pozitif sonuç çıkabileceğinin farkındadır.

Ankete katılanların %51.6'sı COVID-19 hastalığı ile ilgili yeterli, %22' si yetersiz bilgiye sahip olduğunu, %26.3' ü kararsız olduğunu bildirmiştir. Öğrencilerin %92'si pandemi boyunca toplu taşımayı kullanmaktan kaçındıklarını, %82 'si gerekmedikçe seyahat etmediklerini, %50'si pandemi bitmeden yüz yüze eğtimin başlamaması gerektiğini işaretlemiştir. Tıp ve Diş hekimliğinde okuyanların %94'ü, Mühendislik Fakültesi öğrencilerinin % 88.1 pandemi döneminde el sıkışmaktan kaçındığını belirtmiştir. Öğrencilerin %98'i evden çıkarken maske taktıklarını, Mühendislik Fakültesi öğrencilerinin %21'i eldiven de taktığını, yaklaşık %80'i toplumun pandemi önlemlerine uymadığını düşünmektedir.

COVID-19 virüsü antibiyotik ile tedavi edilebilir (p=0.001), hastalığın kesin tedavisi vardır (p=0.001), evden çıktığımda eldiven takıyorum (p=0.011), COVID-19'un laboratuvarda üretildiğini düşünüyorum (p=0.001), bağışıklığım güçlü, virüse karşı önlem almam gerektiğini düşünmüyorum maddelerinde (p=0.013) bölümler arasında arasında istatistiksel anlamlı farklılık bulunmuştur (Tablo3).

Tartışma

Pandemi dönemlerinde enfeksiyon etkeninin kontrol altına alınabilmesi için toplumsal bilgi düzeyi, önlemlere uyum önem arz etmektedir. Üniversiteler bilgi ve sosyal paylaşımın yüksek olduğu ortamlardır bu nedenle evrensel olaylar ile ilgili öğrenci eğitimlerinin düzenli yapılması gerekmektedir. Çalışmamız pandemi döneminde üniversite öğrencileri arasındaki bilgi düzeyilerini araştırmak, farkındalıklarını artırmak, bölümler arası farklılıkları tespit edip gelecekte yapılacak eğitim ve çalışmalara yol göztermek amaçlanmıştır.

Çalışmaya Mühendislik Fakültesinden 472, Tıp Fakültesinden 113, Diş Hekimliği Fakültesinden 25, olmak üzere toplam 610 öğrenci katılmıştır. Öğrencilerin 317'si kadın (%51.9), 293'i (%48.1) erkekdi. Mühendislik Fakültesinden ve kadın öğrencilerden katılımıdaha yüksek olarak saptanmıştır. Üçüncü sınıf öğrencileri (%28.6) diğer sınıfllara göre daha fazla katılım sağlamıştır. Öğrencileri yaş ortalamaları 21.4±1.9, medyan 21 (minimun 17- maksimum 27) olarak saptanmıştır. Vietnamda 5952 üniversite öğrencisi arasında yapılan çalışmada kadın öğrencilerin %69.5 oranında olduğu, erkeklerden daha yüksek oranda katılım sağladıkları, birinci ve ikinci sınıfların katılım oranının ise %79.2 olduğu bildirilmektedir [4].

Tablo 3. COVID-19 hastalığı ile ilgili bilgi, tutum ve davranışlar

	Sağlık alanı (Tıp+Diş Hekimliği)		Mühendislik		
	n	%	n	%	p
COVID-19 Hastalık etkeni Bakteri Virüs Kimyasal	 1(137) 136 (137) 0(137)	 0,7 99.3 0	 6(465) 454 (465) 5 (465)	 1.3 96.4 1.1	0.055
COVID-19 antibiyotik ile tedavi edilebilir.	2 (137)	1,4	41(468)	8.7	0.001
COVID-19 hastalığı ile ilgili yeterli bilgiye sahibim.	72 (137)	52.5	240 (469)	51.1	0.521
COVID-19 hastalığının kesin tedavisi vardır.	8(134)	5,9	196(467)	41.9	0.001
COVID-19 hastalığının laboratuvar ortamında üretildiğini düşünüyorum.	74(137)	14.5	176(467)	37.7	0.001
Pandemi bitmeden kafe ve restoranlara gitmem.	73(137)	53.3	262(468)	55.9	0.127
Evden çıkarken maske takıyorum.	135(137)	98,5	460(468)	98.3	0.891
Evden çıkarken eldiven takıyorum.	4(137)	2,9	99(468)	21.1	0,011
Toplumun kurallara uyduklarını düşünüyorum.	35(137)	25.5	92(468)	19.6	0.563
Pandemi bitmeden yüz yüze eğitimin başlamaması gerektiğini düşünüyorum.	93(136)	68,3	344(468)	73,5	0.462
Bağışıklığım güçlü olduğu için önlem almam gerektiğini düşünmüyorum.	2(137)	1,4	55(468)	11.7	0,013
Bağışıklığım güçlü tutmak için yeterli ve dengeli besleniyorum	127(137)	92.7	411(466)	88.2	0.072
Sağlıklı olmak için düzenli egzersiz yapıyorum.	89(137)	64,9	205(468)	43.8	0.071
Pandemi döneminde insanlarla el sıkışmaktan kaçındım.	135(137)	98.5	415(468)	88.7	0.045
Pandemi döneminde psikolojik yardım almayı düşündüm.	57(137)	41.6	195(467)	42.2	0.848
Çocukların ve gençlerin korunmak için önlem almasına gerek yoktur	0(137)	0	11(469)	4.05	0,019
Pandemiden korunmak için vitamin kullanmayı (C,D) faydalı buluyorum.	126(137)	91.9	384(466)	82.4	0.016

Kronik hastalığı olanlarda ve ileri yaşlarda COVID-19 daha ağır seyirli olsa da gençlerde de enfeksiyon yapmaktadır. Ankete katılanların öğrencilerinde 91 tanesi COVID-19 hastalığı geçirmişti. Bunların 55'i ayakta hafif bulgularla, 23'ü ayakta ama daha ağır bulgularla, üçü hastanede yatarak, ikisi yoğun bakıma yatarak tedavi aldığını belirtmiştir. Sekiz öğrenci şikayeti olmamasına rağmen tarama amaçlı yaptırdıkları testlerinin sonucu pozitif çıkmıştır. Hastalığı ağır geçiren, yoğun bakıma yatan öğrenciler olduğu görülmesine rağmen öğrencilerin sadece 50'si (%8.2) COVID-19 aşısı olduğunu bildirmiştir. Aşı olanlardan 37 (%6,1) öğrencide ateş, kol ağrısı, baş ağrısı ve kas ağrısı başta olmak üzere yan etkiler görmüştür. Aşı olmayanların 447'si (%73.3) aşı olmayı düşünüyorken, 113 öğrenci (%27.7) yan etkisinden çekindiği için, etkinliğine inanmadığı için ve iğneden korktuğu için aşı olmayı istememektedir. Aşı ile ilgili gelişen yan etkiler çalışmalarda da benzerdir [5]. Hastalıktan temel korunma yolu aşı ve önlemler olması, öğrencilerde aşılama sonrası ciddi bir yan etki görülmemesine rağmen yan etki, etkisizlik çekincelerinin ve korkunun eğitimlerle desteklenmesi gerekmektedir.

Öğrencilerin COVID-19 hakkında bilgi edindikleri kaynaklar incelendiğinde toplamda %72.2 oranında televizyon, sırayla sosyal medya, bilimsel yayınlar, aile, arkadaşlar, gazete, doktorlar ve okul olarak sıralanmaktaydı. Mühendislik Fakültesi öğrencilerinin %17.6'sı, Tıp veya Diş Hekimliği bölümünde okuyan öğrencilerin %65 'inin ilk bilgi kaynağı okuldu. Çalışmalarda COVID-19 hakkında bilgi edinmek için sıklıkla sosyal ağ/çevrim içi gazetelerin (%61-87) kullanıldığı bildirilmektedir [4,6,7]. Ankete katılanların %51.6'sı COVID-19 hastalığı ile ilgili yeterli, %22' si yetersiz bilgiye sahip olduğunu, %26.3' ü kararsız olduğunu bildirmiştir. Bilgi kirliliği nedeni ile sosyal platformlarda da bilimsel program ve eğitimlerin artırılması ve denetlenmesinin önemli olduğu düşünülmektedir.

Damlacak yolu ile bulaş solunum yolu virüslerinde temel bulaş yoludur [8]. Öksürük, hapşırma yolu ile bulaş olduğu öğrenciler arasında doğru bilinirken, hayvanlara temasla, cinsel yol ile bulaşabileceği gibi yanlış bilgiler mevcuttur. Yapılan çalışmalarda dışkı, idrar, meni veya hayvanlardan geçiş kanıtlanmamıştır. Geçişin yakın temas yolu ile olabileceği bildirilmektedir [9-11]. Hastalığın sık görülen semptomları ateş, öksürük, koku tat alma bozukluğu, kas ağrısı, nefes darlığı, baş ağrısı, ishal öğrenciler arasında %53-94 oranında doğru bilinmiştir. Hastalığın etkeni ile ilgili, virüs %98, bakteri %1.2, kimyasal etken %0.8 olduğu cevabı verilmiştir. Bakteri ve kimyasal etken cevapları mühendislik bölümünde yüksek bulunmuştur. Öğrencilerin %24.7'si hastalığın antibiyotikler ile tedavi edilebileceğini

bildirmiştir. Benzer şekilde farklı ülkelerden öğrenciler ve toplumda yapılan bazı anket çalışmalarında antibiyotiklerin enfeksiyona karşı koruduğuna inandıklarının bildirmişlerdir [6,12,13]. Antibiyotiklerin yanlış ve uygunsuz kullanımı direnç ve yan etkileri beraberinde getirecektir.

Bölümler arasında karşılaştırma yapıldığında, COVID-19 virüsü antibiyotik ile tedavi edilebilir (p=0.001), hastalığın kesin tedavisi vardır (p=0.001), evden çıktığımda eldiven takıyorum (p=0.011), COVID-19'un laboratuvarda üretildiğini düşünüyorum (p=0.001), bağışıklığım güçlü, virüse karşı önlem almam gerektiğini düşünmüyorum maddelerinde (p=0.013), sağlık eğitimi alan öğrencilerle ve Mühendislik Fakültesi öğrencileri arasında istatistiksel anlamlı farklılık bulunmuştur. Bu farklılıkların sağlık dışı bölümlerde de bazı toplumu ilgilendiren konularda tekrarlayan temel eğitimlere ihtiyaç olduğunu düşündürmektedir.

Çalışmamızda üniversite öğrencileri arasında pandeminin ilk aylarında olunmasına rağmen bilgi düzeylerinin yüksek olduğu görülmüştür. Öğrencilerin bulaş yolu, semptomlar, önlemler ile farkındalığı yüksektir. Bölümler arasında bazı farklılıklar olması beklenen bir sonuçtur. Ancak tüm toplumu ilgilendiren pandemi durumunda tüm öğrencilerin kendileri ve çevresini koruyabilmesi ve gerekli önlemleri alabilmeleri, doğru bilgiye ulaşılabilmeleri gerekir. Bu nedenle yeterli, temel seviyede bir eğitimin tüm bölümlere verilebilmesi önemlidir.

Çalışmanın kısıtlıklıkları arasında, pandemi nedeni ile öğrencilerle yüz yüze görüşme yapılamamıştır. Anket öğrencilere kurumsal onay alınarak çevrim içi program mesajı gönderilmiştir. Tüm üniversite öğrencilerine ulaşım zorluğu nedeni ile üniversite evreninden hesaplanan örneklem büyüklüğüne göre 610 öğrenci ile çalışmaya devam edilmiştir. Daha anlamlı sonuçlar için daha geniş kapsamlı çalışmaların faydalı olacağı düşünülmektedir.

Sonuç

Üniversite öğrencileri arasında COVID-19 hastalığı ile ilgili yanlış bilgi ve davranışlar olduğu görülmüştür. Farkındalığın artmasında üniversite öğrencilerinin önemli rol oynadığı düşünülmektedir. Gelecekte topluma sağlık hizmeti ve sağlık eğitimi verecekleri düşünüldüğünde Tıp fakültesi öğrencilerinin ve sosyal ortamda paylaşımları yüksek olan diğer fakülte öğrencilerinin COVID-19 hastalığı ile ilgili bilgi açıklarının olması yaklaşımlarını olumsuz etkileyebilecektir. Üniversite öğrencileri arasında bilgi düzeyi, tutum ve davranışlarının araştırılarak, dünyada ve ülkemizdeki çalışmalar ile karşılaştırılarak eksiklerin, yanlış uygulamaların belirlenmesi, üniversite öğrencilerine verilecek eğitimlerde yer alacak konuların saptanması, ileride yapılacak çalışmalara veri oluşturması için yol gösterici olacağı düşünülmektedir. Daha kapsamlı, geniş öğrenci gruplarının katıldığı çalışmalarla gelecekte yaşanabilecek salgınlarda önleyici tedbirler için sağlık hizmeti birimlerine ve personeline, okullara ve öğrencilere temel eğitimler sağlanabilecektir.

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Research Article

Evaluation of left atrial appendage functions by transthoracic echocardiography and comparison with left atrial strain values in renal transplant candidates

Böbrek nakli adaylarında transtorasik ekokardiyografi ile sol atriyal apendiks fonksiyonlarının değerlendirilmesi ve sol atriyal strain değerleri ile karşılaştırılması

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Abstract

Aim: The incidence of stroke in patients with chronic kidney disease (CKD) is increased independent of atrial arrhythmias. The goal of this study is to evaluate, left atrial appendage (LAA) functions by transthoracic echocardiography (TTE) and comparison with left atrial (LA) strain values in patients with in renal transplant candidates with end stage renal disease (ESRD) with sinus rhythm.

Material and Methods: Fifty two renal transplant candidates and 60 age- and sex-matched healthy participants were included in the study. LAA emptying velocity (EV) was measured with pulse wave Doppler, early diastolic (LAA Em), contraction (LAA Am) and systolic (LAA Sm) velocities were measured using tissue Doppler imaging from parasternal short axis view. Atrial peak longitudinal strain (PLS), peak contraction strain (PCS) and conduit strain (CdS) were calculated using two dimensional speckle tracking echocardiography.

Results: LAA EV, Am and Sm and LA PLS, PCS, CdS measurements were found to be significantly lower in the patient group compared to controls. LAA EV measurements showed a strong positive correlation with left atrial volume index (LAVI), LA PLS and LA PCS values, and a negative correlation with left ventricular (LV) diameters, and E/e' value. In the multivariate regression analysis LA PLS and LAVI were found to be independent factors for LAA EV.

Conclusion: Our findings suggest that the evaluation of LAA functions with TTE may help determine the increased risk of developing atrial arrhythmias and ischemic stroke in renal transplant candidates. Supporting the current findings with larger studies may change the follow-up and treatment approaches in these patients.

Keywords: Left atrial strain, left atrial appendage functions, end stage renal disease, kidney transplantation.

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Öz

Amaç: Kronik böbrek hastalığı (KBH) olan hastalarda inme insidansı, atriyal aritmilerden bağımsız olarak yüksektir. Bu çalışmanın amacı, sinüs ritmindeki son dönem böbrek hastalığı (SDBY) olan böbrek nakli adaylarında transtorasik ekokardiyografi (TTE) ile sol atriyal apendiks (SAA) fonksiyonlarını değerlendirmek ve sol atriyal (SA) strain değerleri ile karşılaştırmaktır.

Gereç ve Yöntemler: Çalışmaya 52 böbrek nakli adayı hasta ve yaş ve cinsiyet uyumlu, KBH olmayan 60 katılımcı dahil edildi. Parasternal kısa eksenden pulse wave Doppler ile SAA boşalma hızı (BH), doku Doppler görüntüleme kullanılarak erken diyastolik (SAA Em), kasılma (SAA Am) ve sistolik (SAA Sm) hızları ölçüldü. Atriyal pik longitudinal strain (PLS), pik kontraksiyon strain (PKS) ve konduit strain (KdS), iki boyutlu "speckle tracking" ekokardiyografi kullanılarak hesaplandı.

Bulgular: SAA BH, Am ve Sm ve SA PLS, PKS, KdS ölçümleri hasta grubunda kontrollere göre anlamlı olarak daha düşük bulundu. SAA BH ölçümleri, sol atriyal volüm indeksi (SAVİ), SA PLS ve SA PKS değerleri ile güçlü bir pozitif korelasyon ve sol ventrikül (SV) çapları ve E/e' değeri ile de anlamlı negatif korelasyon gösterdi. Çok değişkenli regresyon analizinde SA PLS ve SAVİ'nin SAA BH için bağımsız faktörler olduğu bulundu.

Sonuçlar: Bulgularımız, TTE ile SAA fonksiyonlarının değerlendirilmesinin böbrek nakil adaylarında artmış atriyal aritmiler ve iskemik inme gelişme riskinin belirlenmesine yardımcı olabileceğini düşündürmektedir. Mevcut bulguların daha büyük çalışmalarla desteklenmesi bu hastalarda takip ve tedavi yaklaşımlarını değiştirebilir.

Anahtar kelimeler: Sol atriyal strain, sol atriyal apendiks fonksiyonu, son dönem böbrek yetersizliği, böbrek nakli.

Introduction

Cardiovascular disorders (CVD) are common in chronic kidney disease (CKD) and the major cause of morbidity and mortality in patients with end stage renal disease (ESRD) [,]. Fluid retention, hormones, cytokines and enzymes released in response to kidney failure constitute the main causes of CV pathologies in these patients along with the common risk factors [, ,]. Arterial stiffness, myocardial fibrosis, left ventricular hypertrophy (LVH), enlargement of the heart chambers, LV diastolic and systolic dysfunction may develop over time with the contribution of all these factors [, ,].

The incidence of stroke in CKD patients is increased compared to the general population, especially in patients on dialysis [ ]. Although atrial fibrillation (AF) is one of the major causes of ischemic stroke, a significant number of patients with ischemic cerebrovascular event (CVE) are in sinus rhythm [ ]. There are studies showing that left atrial (LA) size and functions are associated with the risk of ischemic stroke independent of AF rhythm [ ]. Most of the thrombi that develop in the left atrium are located in the left atrial appendage (LAA) [,]. Therefore, the evaluation of LAA functions has gained importance in determining the risk of ischemic stroke.

Cardiac structural and functional changes affect LA functions in patients with CKD [,]. Apart from atherosclerotic vascular changes and AF, which are the most important causes of ischemic stroke in these patients, impaired LA and LAA functions may also increase the risk of stroke. Transesophageal echocardiography (TEE) is the most sensitive method to assess LAA functions [ ]. However, recent studies have revealed that the LAA evaluation with transthoracic echocardiography (TTE), which is a more feasible method, also correlates well with the TEE measurements [ ]. The aim of this study is to evaluate the functions of LA and LAA with TTE in kidney transplantation candidates.

Material and Methods

Study design and patient selection

Our study was designed prospectively, and 52 patients with ESRD and 60 healthy participants who were similar regarding age and gender were included in the study. The patient group was selected from ESRD patients who were planned for kidney transplantation and referred to the cardiology outpatient clinic for preoperative evaluation. The control group consisted of participants without heart failure and kidney disease, who applied to the cardiology outpatient clinic for routine control or check-up. Patients with left ventricular ejection fraction (LVEF) <55%, more than mild degree of valvular heart disease, congenital heart disease, rhythm or conduction disorders on electrocardiography (ECG) were excluded from the study.

Blood samples were taken in the morning fasting, mostly the day before echocardiography. In patients undergoing dialysis, blood tests were performed before dialysis. Renal functions were evaluated with the estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for adults in line with the guideline published by the Turkish Public Health Agency.

The study was performed in accordance with the Declaration of Helsinki after having approval of the research protocol from the Local Ethics Committee. Additionally, all participants provided signed detailed written informed consent.

Echocardiographic evaluation

Transthoracic echocardiographic evaluation of all patients was performed with the Epiq 7C ultrasound system (Philips, Andover, MA, USA) using a 2.3-3.5 MHz transducer probe. During the test simultaneous ECG recording was made. Left ventricular wall thicknesses, heart chamber diameters, and LV systolic function

were evaluated from standard parasternal and apical windows, B-mode and M-mode images, according to the current recommendation guidelines of the American Society of Echocardiography [ ]. Diastolic function of LV was assessed with pulse wave (PW) Doppler from the trans-mitral velocities and with tissue Doppler imaging (TDI) measurements from the mitral annular region.

Left atrial appendage evaluation was performed from parasternal short axis view using PW Doppler and TDI. The cursor was placed on the apex of the LAA after visualizing LAA and making required adjustments (Figure 1). Then LAA emptying velocity (LAA EV) was measured with PW Doppler (Figure 2), early diastolic (LAA Em), contraction (LAA Am) and systolic (LAA Sm) velocities were measured using TDI (Figure 3) and averaged for five consecutive cardiac cycles.

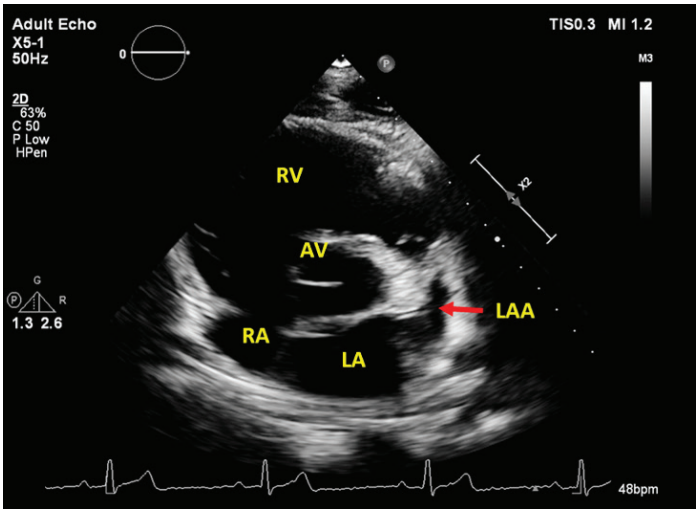

Figure 1. Parasternal short axis view image showing left atrial appendix (LAA) in transthoracic echocardiographic assessment. LA, left atrium; RA, right atrium; RV, right ventricle; AV, aortic valve.

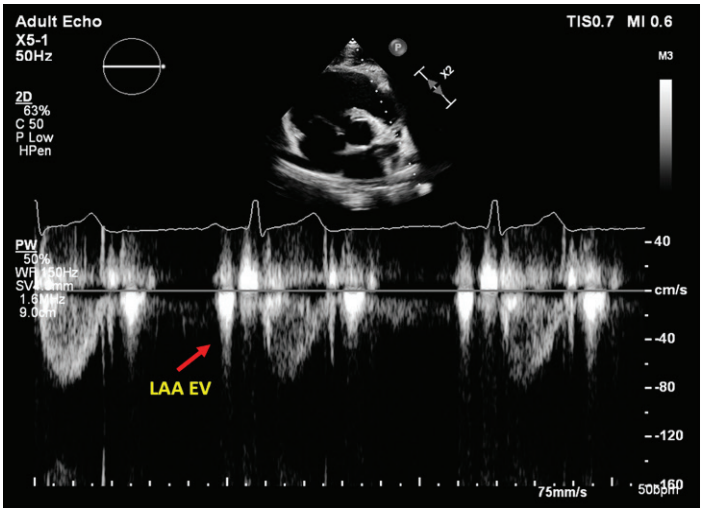

Figure 2. Parasternal short axis view image showing the left atrial appendix emptying velocity (LAA EV) obtained using pulse wave Doppler.

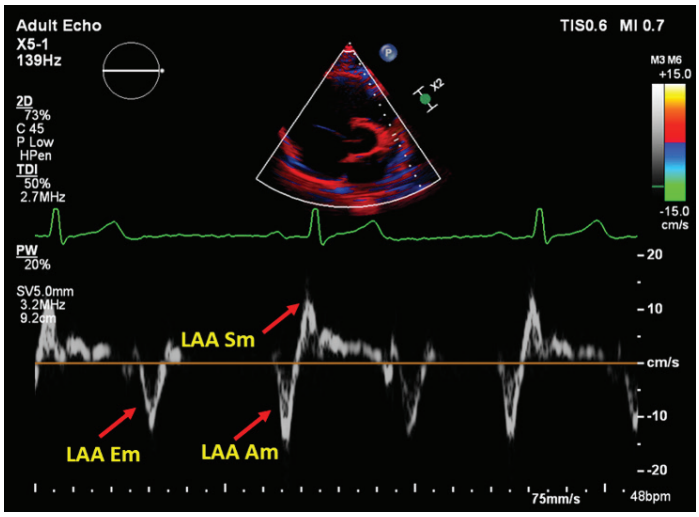

Figure 3. Parasternal short axis view image showing the left atrial appendix early diastolic (LAA Em), contraction (LAA Am) and systolic (LAA Sm) velocities were measured using tissue Doppler imaging.

For LA strain analysis, standard apical two- and four-chamber images were recorded at a speed of 60-100 frames/sec on gray scale for 3 cycles. Offline LA strain analysis was performed using dedicated software (Qlab advanced quantification software version 10.1, Philips Medical Systems, Bothell, WA, USA). After LA endocardial borders were determined manually, the region of interests (ROI) were designated. Atrial peak longitudinal strain (PLS), and peak contraction strain (PCS) reflecting the reservoir function, and the atrial pump function, respectively, were calculated from the strain curves obtained by two-dimensional speckle tracking analysis (2DSTE). Atrial conduit function was calculated by subtracting the PCS value from the PLS value. The QRS onset was taken as a reference point (Figure 4).

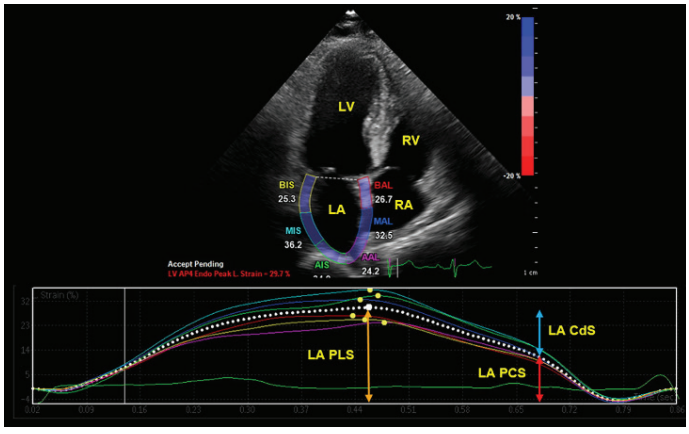

Figure 4. Left atrial strain imaging with two dimensional speckle tracking echocardiography from apical four chamber view of a study patient. Yellow arrow shows peak longitudinal strain (PLS), red arrow shows peak contraction strain (PCS), blue arrow shows conduit strain (CdS).

Statistical Analysis

SPSS 26 program was used to evaluate the data obtained in

the study. The normality of the distribution was determined by the Kolmogorov-Smirnov test. Results were expressed as mean ± standard deviation. Normally distributed variables were compared with Student's T test, and non-normally distributed variables were compared with Mann Whitney-U test. Chi-square test was used to compare categorical variables. P value less than 0.05 was considered statistically significant. Pearson analysis was used for continuous variables and Spearman test was used for non-continuous variables in the correlation analysis. The correlation coefficient (r) was calculated. Independent determinants of LA PLS and LAA EV parameters were ascertained by multivariate linear regression analysis.

Results

The patient group constituted of 52 subjects with ESRD (mean age, 46.01±11.08 years; 40.4% female) while there were 60 individuals (mean age, 48.26±10.63; 53.3% female) in the control group. Age, gender, BSA, history of diabetes mellitus (DM), smoking, hyperlipidemia (HL) and CAD were similar in both groups. Presence of hypertension (HT), use of beta blockers and calcium channel blockers (CCBs), and systolic blood pressure (SBP) were found to be significantly higher in the patient group (Table 1).

Table 1. Evaluation of demographic and clinical characteristics of the study groups

Parameter	Patients group (n=52)	Control group (n=60)	p value
Age	46.01±11.98	48.08±10.73	0.338
Female, % (n)	40.4 (21)	53.3 (32)	0.171
SBP (mmHg)	125.76± 14.15	118.51±15.38	0.011
DBP (mmHg)	76.25±7.40	74.08±9.18	0.176
Heart rate (beat/m)	73.23±10.65	72.45±10.07	0.691
BSA (m2)	1.85±0.24	1.86±0.19	0.770
Hypertension, % (n)	78.8 (41)	23.3 (14)	<0.001
Hyperlipidemia, % (n)	26.9 (14)	20 (12)	0.387
Diabetes mellitus, % (n)	21.2 (11)	11.7 (7)	0.173
Smoking, % (n)	23.1 (11)	10 (6)	0.06
CAD, % (n)	11.5 (6)	5 (3)	0.204
ACEI /ARB, % (n)	19.2 (10)	12.2 (6)	0.315
Beta blockers, % (n)	38.5 (20)	10 (6)	<0.001
CCB, % (n)	69.2 (36)	6.7 (4)	<0.001
Diuretics, % (n)	3.8 (2)	3.3 (2)	0.884
Statin % (n)	23.1 (12)	11.7 (7)	0.109
Dialysis % (n)	50 (26)	-	

SBP, systolic blood pressure; bpm, beat per minute DBP, diastolic blood pressure; BSA, body surface area; CAD, coronary artery disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blockers.

Half of ESRD patients (n=26) were on dialysis. The mean dialysis time was 15.19±23.82 months (min 1 month, maximum 108 months). Patients undergoing dialysis did not differ significantly from non-dialysis patients in terms of demographic and echocardiographic characteristics.

In the echocardiographic evaluation, left ventricular wall thickness and diameters of all heart chambers were significantly higher in the patient group. Although EF was normal in both groups, it was found to be significantly lower in the patient group. In addition, E/e' ratio, which is a sensitive indicator of diastolic function, and systolic pulmonary artery pressure were significantly higher in the patient group compared to the control group. When the left atrium size and functions are examined, ESRD patients had significantly increased LAV and LAVI values compared to controls. Demonstrating left atrial appendage functions and left atrial strain assessment, LAA EV, Am and Sm values and LA PLS, PCS, CdS measurements were found to be significantly lower in the patient group (Table 2).

Table 2. Laboratory findings of the study groups

Parameter	Patients group (n=52)	Control group (n=60)	p value
Glucose (mg/dl)	103.67±31.48	100.11±18.96	0.467
Creatinine (mg/dl)	6.61±1.79	0.92±0.81	<0.001
eGFR (ml/min/1.73m2)	8.82± 3.25	101.50±17.56	<0.001
Sodium (mmol/L)	138.63±4.51	141±2.29	0.001
Potassium (mmol/L)	5.25±0.66	4.40±0.30	<0.001
Uric aside (mg/dl)	7.99±1.78	4.86±1.27	<0.001
Total cholesterol (mg/dl)	202.52±43.82	207.15±34.84	0.543
LDL (mg/dl)	130.19±34.67	136.10±31.59	0.356
HDL (mg/dl)	43.01±12.48	52.40±15.02	0.01
Triglycerides (mg/dl)	170.29±82.53	131.54±75.55	0.012

eGFR, estimated glomerular filtration rate; LDL, low density lipoprotein; HDL, high density lipoprotein.

In correlation analyzes performed in ESRD patients LAA EV did not showed significant correlation with demographic characteristics, risk factors, and laboratory findings except for uric acid (r= -0.387, p=0.006). LAA EV measurements showed a strong positive correlation with LAVI, LA PLS (Figure 5), and LA PCS values, and a negative correlation with LV diameters, and E/e' value. While LA PLS was negatively correlated with the presence of HT, and DM, and uric acid levels (r= -0.315, p= 0.023; r= -0.282, p= 0.043; r= -0.429, p= 0.02, respectively) there was no significant correlation with other baseline clinical features and laboratory findings. Besides a significant negative correlation was observed between LA PLS and LV wall thickness and diameters, LA diameter, volume, volume index, and E/e' measurements. Table 4 demonstrates the echocardiographic parameters that were significantly associated with the parameters showing LAA and LA functions.

Table 3. Comparison of echocardiographic measurements of the groups

Parameter	Patients group (n=52)	Control group (n=60)	p value
IVS (cm)	1.07± 0.16	0.93±0.10	<0.001
PW (cm)	1.05±0.14	0.92±0.10	<0.001
LVEDD (cm)	4.91±0.46	4.64±0.37	0.001
LVESD (cm)	3.26±0.41	2.99±0.26	<0.001
LV EF (%)	59.30±2	60.81±1.50	<0.001
LA (cm)	3.91±0.35	3.64±0.22	<0.001
RA (cm)	3.69±0.34	3.50±0.21	0.001
RV (cm)	3.44±0.28	3.31±0.23	0.012
sPAP (mmHg)	26.73±4.71	23.58±3.61	<0.001
E wave velocity (cm/s)	83.84 ±19.73	78.85 ±15.52	0.139
A wave velocity (cm/s)	81.86±15.04	69.86±14.10	<0.001
E/A ratio	1.06±0.27	1.14±0.23	0.094
DT (msn)	195.29±35.99	182.33±23.73	0.025
IVRT (msn)	96.11±14.85	92.33±11.17	0.123
E' wave velocity (cm/s)	12.80±3.38	13.92±3.45	0.092
E/E' ratio	6.94±2.19	5.81±1.10	0.001
LAV (ml)	59.57±20.12	41.72±10.49	<0.001
LAVI (ml/m2)	31.81±8.82	22.28±4.89	<0.001
LAA EV (cm/s)	52.36±8.87	67.80±7.35	<0.001
LAA Em (cm/s)	9.15±1.78	11.38±1.94	<0.001
LAA Am (cm/s)	15.38±2.87	19.55±3.53	<0.001
LAA Sm (cm/s)	10.10±1.64	12.78±1.56	<0.001
LA PLS (%)	31.73±7.61	38.43±5.61	<0.001
LA PCS (%)	13.15±3.90	18.28±3.23	<0.001
LA CdS (%)	18.57±5.76	20.14±4.45	0.039

IVS, interventricular septal thickness; PW, posterior wall thickness ; LVEDD, Left ventricular end diastolic diameter; LVESD, Left ventricular end systolic diameter; LV EF, Left ventricular ejection fraction; LAD, left atrial end systolic diameter; RAD, right atrial end systolic diameter; RVD, right ventricular end diastolic diameter; DT, deceleration time; IVRT, isovolumetric relaxation time; LAV, left atrial volume, LAVI, left atrial volume index; LAA EV, left atrial appendage emptying velocity; LAA Am, LA contraction velocity; LAA Sm, systolic velocity; PLS, peak longitudinal strain; PCS, peak contraction strain; CdS, conduit strain.

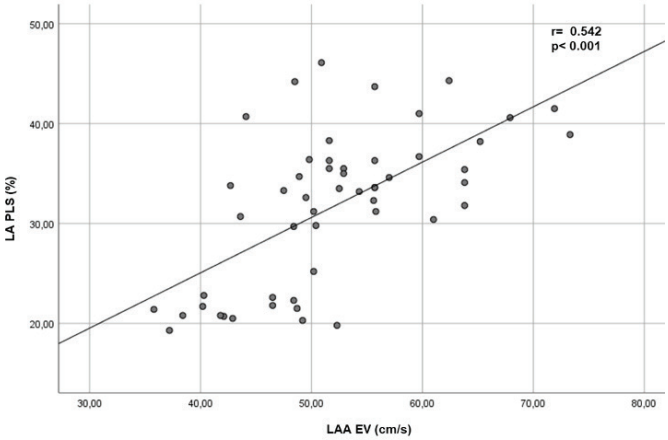

Figure 5. The correlation analysis graph showing the relationship between the left atrial appendix emptying velocity and left atrial peak longitudinal strain.

The study group was also evaluated according to the lowest expected LA PLS value (23%) determined in the multicenter studies [,]. LA PLS was <23% in 14 patients (26.9%) in the ESRD group and 4 subjects (6.7%) in the control group (p=0.004). In the patients group, 14 patients with LA PLS <23% and 38 patients with LA PLS ≥ 23% were compared in terms of demographics, clinical features and laboratory findings. Demographic and clinical characteristics of the two groups were similar except for the BSA. There was no significant difference between risk factors and biochemistry parameters. In echocardiographic evaluation, LV wall thickness and diameters, LA dimensions, E/e, and sPAP values were significantly higher in the group with PLS<23%, while LAA EV and LAA Am values were significantly lower (Table 5).

In the multivariate regression analysis LA PLS and LAVI were found to be independent factors for LAA EV. No significant independent relationship was detected between LA PLS and LAVI, E/e' and uric acid (Table 6). In different multivariate regression analysis models including IVS, PW, LVEDD, LVEDS, no different independent significant variables were found for LAA EV and LA PLS.

Table 4. Correlation analysis of left atrial and left atrial appendage functions in the patients group.

	LAA PLS	LAA PCS	IVS	PW	LVEDD	LVEDS	LAVI	E/e'
LAA EV	0.542**	0.498**	-0.266	-0.228	-0.307*	-0.329*	-0.499**	-0.314*
LAA Am	0.558**	0.554**	-0.245	-0.234	-.0407**	-0.432**	-0.289*	-0.246
LA PLS	-	-0.673**	-0.366**	-0.377**	-0.450**	-0.461**	-0.319*	-0.377*
LA PCS	0.673**	-	-0.227	0.0212	-0.303*	-0.298*	-0.282*	-0.231

LAA EV, left atrial appendage emptying velocity; LAA Am, LA contraction velocity; LAA Sm, systolic velocity; PLS, peak longitudinal strain; PCS, peak contraction strain; IVS, interventricular septal thickness; PW, posterior wall thickness; LVEDD, Left ventricular end diastolic diameter; LVESD, Left ventricular end systolic diameter; LAVI, left atrial volume index. *p<0.05; **p<0.01

Table 5. Echocardiographic features of the groups according to LA PLS value.

Parameter	LA PLS <23% (n=14)	LAP PLS ≥ 23% (n=38)	p value
IVS (cm)	1.20± 0.16	1.02±0.13	<0.001
PW (cm)	1.17±0.15	1.02±0.13	<0.001
LVEDD (cm)	5.29±0.34	4.77±0.41	0.001
LVESD (cm)	3.59 ±0.32	3.14±0.38	<0.001
LV EF (%)	58.85±2.34	59.47±1.87	0.330
LA (cm)	4.22±0.41	3.80±0.25	<0.001
sPAP (mmHg)	29.07±5.18	25.86±4.28	0.028
E/E' ratio	8.11±2.70	6.48±1.80	0.017
LAV (ml)	71.87±23.57	55.04±16.88	0.006
LAVI (ml/m2)	36.27±10.41	30.16±7.67	0.026
LAA EV (cm/s)	49.97±11.20	54.35±7.03	0.007
LAA Em (cm/s)	8.43±1.80	9.41±1.72	0.078
LAA Am (cm/s)	13.13±2.44	16.21±2.58	<0.001
LAA Sm (cm/s)	10.77±1.96	11.07±1.53	0.565

IVS, interventricular septal thickness; PW, posterior wall thickness ; LVEDD, Left ventricular end diastolic diameter; LVESD, Left ventricular end systolic diameter; LV EF, Left ventricular ejection fraction; LAD, left atrial end systolic diameter; RAD, right atrial end systolic diameter; RVD, right ventricular end diastolic diameter; DT, deceleration time; IVRT, isovolumetric relaxation time; LAV, left atrial volume, LAVI, left atrial volume index; LAA EV, left atrial appendage emptying velocity; LAA Am, LA contraction velocity; LAA Sm, systolic velocity.

Table 6. Univariate and multivariate linear regression analysis for left atrium and left atrial appendage function parameters in patients group

LAA EV	Univariate	analysis	Multivariate	analysis
Variables	Beta coefficient	p value	Beta coefficient	p value
LAVI	-0.499	<0.001	-0.352	0.005
LA PLS	0.542	<0.001	0.365	0.008
E/e'	-0.314	0.026	-0.052	0.670
Uric aside	-0.387	0.006	-0.194	0.118
LA PLS	Univariate	analysis	Multivariate	analysis
Variables	Beta coefficient	p value	Beta coefficient	p value
LAVI	-0.319	0.021	-0.030	0.833
LAA EV	0.542	<0.001	0.413	0.008
E/e'	-0.377	0.007	-0.174	0.175
Uric aside	-0.429	0.02	-0.243	0.065

LAA EV, left atrial appendage emptying velocity; LAVI, left atrial volume index; LA PLS, left atrial peak longitudinal strain.

Discussion

In the present study, LAA functions in patients with ESRD with sinus rhythm, candidates for transplantation were examined with TTE for the first time to the best of our knowledge. LAA EV value were found to be significantly lower in the patients group than in the control group. Left atrial functions were evaluated using 2D strain analysis, significantly decreased LA strain values were found in the patients group. Additionally, regression analysis revealed that LA PLS and LAVI were independent markers for LAA EV.

Evaluation of LA functions is of great importance in predicting the prognosis and development of CV events in CKD patients [ ]. Ayer et al. showed that the LA reservoir and conduit strain were independently associated with major adverse cardiovascular events at 2-year follow-up in ESRD patients [ ]. Left atrial functions are affected by various mechanisms in patients with renal failure such as CV risk factors, volume overload, chronic inflammation, neurohumoral changes and increased oxidative stress [,]. In our study, high HT rate, high SBP levels, and volume overload may explain the increased LV wall thickness, and diameters of heart chambers, diastolic dysfunction, and the resulting decrease in LA functions compared to the control group. LA strain assessment with 2DSTE is a sensitive, reliable and less load dependent method that can show the deterioration of LA functions earlier [ ]. Ohara et al. investigated the LA strain with 2DSTE in CKD patients with normal left atrial size and found a significant decrease in LA reservoir strain compared to the control group. These findings were interpreted in favor of subclinical deterioration in LA functions before the change in atrial volume in CKD patients [ ]. Our study was conducted in patients with ESRD patients, and significant structural cardiac changes were observed compared to the control group. Although LA PLS was significantly correlated with LV wall thickness, and diameters, and LAVI in the patients group, they were not found to be independent predictors of LA PLS. These findings may support that apart from overt structural changes, atrial fibrosis associated with uremic toxins, increased renin-angiotensin system activity and chronic inflammation may affect LA functions.

Cardiovascular risk factors, atherosclerosis, hypercoagulability, cardiac structural and functional changes, and atrial arrhythmias are among the causes of increased stroke risk in patients with CKD. Studies have shown that CKD is an independent factor for the structural and functional changes in the left atrium [,], and atrial mechanical changes and remodeling contribute to the development of ischemic stroke independent of CV risk factors and AF [, ,]. In general population, 15-30% of all ischemic cerebral infarcts are considered to be of cardiac origin [,] and in approximately 90% of cardio-embolic events, the thrombus originates from LAA [ ]. In a study by Handke et al. in stroke patients, it was shown that the LAA EV value measured by TEE, regardless of rhythm, is an important determinant of thromboembolism, and that it significantly predicts the development of thrombus and SEC at a value of <55 cm/s [ ]. Karabay et al. demonstrated that LA strain parameters predicted

LAA functions in patients who had cardioembolic stroke in sinus rhythm [ ]. In our study, a significant relation was observed between LAA EV and LA PLS in ESRD patients with sinus rhythm. Additionally, regression analysis revealed that LA PLS and LAVI were independent markers for LAA EV. Supporting these findings, LAA flow rates were found to be significantly lower in patients with LA PLS < 23% in the patients group.

Another important finding in our study is the significant correlation between blood uric acid level and LAA EV and LA PLS values. Çelik et al. demonstrated that increased uric acid levels were associated with decreased LAA peak flow velocity in AF patients [ ]. Proposed mechanism for this relationship is that increased uric acid levels may cause atrial fibrosis and remodeling associated with chronic inflammation and increased oxidative stress.

It has been shown that the risk of stroke and AF is higher in ESRD patients who are on hemodialysis [,]. In a study by Yıldırım et al., it was shown that left atrial deformation parameters were better in transplant patients than in hemodialysis patients [ ] In our study, the basic clinical and echocardiographic features of hemodialysis patients did not differ significantly compared to patients who did not undergo hemodialysis. Although half of the patients were dialysis patients, it was thought that this might be related to the short average dialysis times.

In conclusion, decreased LAA mechanical functions was observed in relation to LA volume and functions in patients with ESRD who were planned for transplantation in sinus rhythm. These findings may suggest that evaluation of LAA functions may be helpful in detecting CKD patients at increased risk of developing atrial arrhythmias and stroke. Although TEE is the gold standard in investigating LAA functions, it will not be routinely applied, and it is difficult to tolerate in patients with ESRD, especially in dialysis patients. TTE is a readily applicable test in clinical practice and follow-ups in these patients. Supporting the current findings with larger studies may change the follow-up and treatment approaches in these patients.

Limitations of the study

The main limitation of the study is that it was conducted on a small sample. Functions of LAA was evaluated with only TTE, TEE was not performed. We did not perform ambulatory rhythm monitoring for paroxysmal AF detection. Since it was an observational study, development of AF or cerebrovascular event (CVE) was not investigated in the follow-up of the patients and whether our findings predicted these events. Additionally, the QLAB software system developed for LV strain analysis were used for left atrial strain analysis. Several studies have shown that the QLAB software system is reliable and has good reproducibility for atrial strain analysis [,].

Declaration of conflict of interest

Each author has contributed, read, and approved the manuscript; and none of the authors has any conflict of interest, financial or otherwise.

Conflict of interest

The study did not get any type of financial support. The authors declared no conflict of interest.

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Research Article

The first 100-day outcomes of autologous hematopoietic stem cell transplantation in multiple myeloma patients: melphalan 200 mg/m² versus 140 mg/m² conditioning regimen

Multiple myelom hastalarında otolog hematopoietik kök hücre naklinin ilk 100 gün sonuçları: melfalan 200 mg/m² 'ye karşı melfalan 140 mg/m² hazırlama rejimi

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Abstract

Aim: Melphalan 200 mg/m² (Mel200) is a standard accepted conditioning regimen during the autologous hematopoietic stem cell transplantation (auto-HSCT) for multiple myeloma (MM) patients. Whereas melphalan 140 mg/m² (Mel140) is generally preferred either in patients with renal disease or elderly patients. We aimed to compare the first 100-day outcomes of the Mel140 and Mel200 conditioning after auto-HSCT in this study.

Material and Methods: We retrospectively analyzed 69 consecutive MM patients who underwent their first auto-HSCT at the Adult Hematopoietic Stem Cell Transplantation Unit at Akdeniz Universi-ty Hospital.

Results: While 41 (59.4%) of patients were male, 28 (40.6%) patients were female. The median age at auto-HSCT was 61 years old (range, 40-75). The ratio of patients with glomerular filtration rate (GFR)<60 ml/min was significantly higher in the Mel140 group than the Mel200 group (P < 0.001). Despite not to reach statistical significance, the median age tended to be higher in the Mel140 group (P = 0.064). There were not any significant difference between the Mel200 and Mel140 groups in terms of hospitalisation time at transplantation (P = 0.691), neutrophil engraftment time (P = 0.907), platelet engraftment time (P = 0.234), febrile neutropenia during the transplantation (P = 1), number of eryth-rocyte transfusion during the hospitalisation (P = 0.661), number of platelet transfusion during the hospitalisation (P = 0.569), patient status at post-transplant day 100 (P = 0.882), and disease status at post-transplant day 100 (P = 0.967), respectively.

Conclusion: Our study shows that the Mel200 and Mel140 conditioning have similar first 100-day outcomes after auto-HSCT in MM. Further comprehensive randomised trials would clarify the impact of melphalan conditioning intensity on early term post-transplant outcomes.

Keywords: multiple myeloma, autologous hematopoietic stem cell transplantation, melphalan, early term post-transplant outcomes

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ÖZ

Amaç: Melfalan 200 mg/m² (Mel200), multiple myelom (MM) hastaları için otolog hematopoietik kök hücre nakli (oto-HKHN) sırasında standart olarak kabul edilen bir hazırlama rejimidir. Melfalan 140 mg/m² (Mel140) ise genellikle böbrek hastalığı olan hastalarda veya yaşlı hastalarda tercih edilir. Bu çalışma-da oto-HKHN sonrası Mel140 ve Mel200 hazırlama rejimlerinin ilk 100 günlük sonuçlarını karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Akdeniz Üniversitesi Hastanesi Erişkin Hematopoietik Kök Hücre Nakli Ün-itesinde ilk oto-HKHN uygulanan ardışık 69 MM hastasını retrospektif olarak inceledik.

Bulgular: Hastaların 41'i (%59,4) erkek, 28'i (%40,6) kadındı. Hastaların nakil sırasındaki ortanca yaşı 61 idi (aralık, 40-75). Glomerüler filtrasyon hızı (GFR) <60 ml/dk olan hastaların oranı Mel140 grubunda Mel200 grubuna göre anlamlı olarak daha yüksekti (P < 0.001). İstatistiksel anlamlılığa ulaşmamakla birlikte, medyan yaş Mel140 grubunda daha yüksek olma eğilimindeydi (P = 0.064). Mel200 ve Mel140 grupları arasında sırasıyla transplantasyonda hastanede kalış süresi (P = 0.691), nötrofil engraftman süresi (P = 0.907), trombosit engraftman süresi (P = 0.234), transplantasyon sırasında febril nötropeni gelişimi (P = 1), hastanede yatış sırasında eritrosit transfüzyonu sayısı (P = 0.661), hastanede yatış sırasında trombosit transfüzyonu sayısı (P = 0.569), nakil sonrası 100. gün-deki hasta mortalite oranı (P = 0.882) ve nakil sonrası 100. gündeki hastalık durumu (P = 0.967) açısından anlamlı fark yoktu.

Sonuç: Çalışmamız, oto-HKHN sonrası ilk 100 gün sonuçlarının Mel200 ve Mel140 hazırlama rejim-lerini kullanan MM hastalarında benzer olduğunu göstermektedir. Daha kapsamlı randomize klinik çalışmalar melfalan hazırlama rejimi yoğunluğunun nakil sonrası erken dönem sonuçlarına olan etkisi-ni açıklığa kavuşturacaktır.

Anahtar Kelimeler: multiple myelom, otolog hematopoietik kök hücre nakli, melfalan, nakil sonrası erken dönem sonuçları

Introduction

High-dose chemotherapy and autologous hematopoietic stem cell transplantation (auto-HSCT) is still the standard of care up-front treatment for transplant-eligible multiple myeloma (MM) patients despite new anti-myeloma drug era (1,2). Melphalan 200 mg/m² (Mel200) is a standard accepted conditioning regimen as a high dose chemotherapy during the auto-HSCT for MM patients (3-5). But some studies revealed that using Mel200 in MM patients during the auto-HSCT was associated with increased tox-icity in older patients and in patients with renal failure (6-8). Therefore, melphalan 140 mg/m² (Mel140) has commonly been used in elderly patients and in patients with renal insufficiency in sev-eral studies (9-14). However, there are two studies to show inferior response or survival rates related to Mel140 when compared with Mel200 (13,15). In European Society for Blood and Marrow Trans-plantation (EBMT) study, Mel140 and Mel200 showed similar post-transplant outcomes, except in patients with less than a partial response to pre-transplant induction therapy (16). Similarly, the MD Anderson study revealed Mel140 had comparable efficacy to Mel200, especially in older patients and those with at least a very good partial response at the time of transplant (17).

There are conflicting results related to using reduced dose melphalan in myeloma patients at auto-HSCT in the literature as we mentioned above, and those studies generally focused on long term out-comes of MM patients after auto-HSCT. Therefore, we aimed to compare the first 100-day outcomes of the Mel140 and Mel200 conditioning after auto-HSCT in this study.

Material and Methods

Patient population

We retrospectively analyzed 69 consecutive MM patients >18 years of age who underwent their first auto-HSCT at the Adult Hematopoietic Stem Cell Transplantation Unit at Akdeniz University Hospi-tal between January 2019 and February 2023.

The diagnosis of multiple myeloma was made according to the International Myeloma Working Group (IMWG) criteria (18). The response to the treatment was based on the IMWG criteria as well (19).

Conditioning regimens and Anti-infective prophylaxis

Conditioning regimens that used in patients were Mel200 in 58 (84%) patients and Mel140 in 11 (16%) patients.

All patients received levofloxacin 500 mg/day, fluconazole 200 mg/day, and valacyclovir 500 mg/day until engraftment for anti-infective prophylaxis. After engraftment, trimethoprim-sulfamethoxazole against Pneumocystis jirovecii was started and va-

lacyclovir against herpes viruses continued to use. All patients used both of them for 6 months as an anti-infective prophylaxis.

All patients whose immunoglobulin (Ig) G level were lower than 500 mg/dL, those received 0.4 grams per kilogram intravenous immunoglobulin as a prophylactic dose for the infections.

Granulocyte colony-stimulating factor (G-CSF) 5 microgram/kg/day was started at day +1 or + 5 until the neutrophil engraftment in all patients.

Definitions and Endpoints

The neutrophil engraftment was defined as the first day for three consecutive days where the neutro-phil count was 500 cells/mm^3 or greater. The platelet engraftment was described as the first day for three consecutive days that the platelet count was 20.000/mm^3 or greater without platelet transfusion.

Disease status at transplantation was assessed to the response that obtained from previous therapies according to the IMWG response criteria (19). Comorbidity was defined presence of two or more medical conditions existing simultaneously in a patient.

The primary endpoints were both patients status (alive or death) and disease status (stringent complete response or complete response or very good partial response or partial response or minimal response or stable disease or progressive disease) at post-transplant day 100. The secondary endpoints were the duration of stay at transplant unit, neutrophil and platelet engraftment time, the number of erythro-cyte and platelet transfusions until discharge from the transplant unit and the presence of infection during the stay at transplant unit .

Statistical Analysis

All statistical analyses were performed using SPSS version 23.0 software (Chicago, USA). Descrip-tive statistics are presented as numbers and percentages for categorical variables and mean ± standard deviation, median (minimum value – maximum value) for continuous variables. Normal distribution for continuous variables were assessed with visual (histograms and probability graphics) and analytic methods (Kolmogorov-Smirnov and Shapiro-Wilk's test). Chi-squared tests were used for compari-son of categorical variables in independent groups. Mann-Whitney U test was used to compare the groups according to melphalan conditioning, and the data were presented as median (min-max) values. $p < 0.05$ was considered to be statistically significant.

Results

Patient and disease characteristics are provided in Table 1. While 41 (59.4%) of patients were male, 28 (40.6%) patients were female. The median age at auto-HSCT was 61 years old (range, 40-75), and of 69 patients, 19 (27.5%) were ≥65 years of age. 49 (71%) patients had Eastern Cooperative Oncology Group (ECOG) performance score 0, 18 (26.2%) patients had ECOG 1, 1 (1.4%) patient had ECOG 2, and 1 (1.4%) patient had ECOG 3, respectively. Glomerular filtration rate (GFR) was ≥60 ml/min in 61 (88.4%) patients and <60 ml/min in 8 (11.6%) patients. In addition to the GFR, the creatinine, which is another indicator of kidney function, was <2 mg/dL in 65 (94.2%) patients and ≥2 mg/dL in 4 (5.8%) patients.

A majority of patients (n=37, 53.6%) was in complete response before auto-HSCT, 22 (31.9%) had a very good partial response, and 8 (11.6%) had a partial response. Unfortunately, the disease status before auto-HSCT of 2 (2.9%) patients were not found. Of 69 patients, 61 (88.4%) had received first line therapy, 6 (8.7%) had received second line therapy, and 2 (2.9%) had received third line therapy prior to transplant. The number of chemotherapy cycles received before transplant was 4 in 29 (42%) patients, 5 in 17 (24.6%) patients, 6 in 9 (13%) patients, 7 in 3 (4.3%) patients, 8 in 3 (4.3%) patients, 9 in 1 (1.4%) patient, 12 in 1 (1.4%) patient, respectively. There was no information related to the number of chemotherapy cycles for 5 (7.2%) patients. The median number of chemotherapy cycles received before transplant was 5 (range, 2-12).

Of 69 patients, 64 (92.8%) patients started the G-CSF at the fifth day (+5) of stem cell infusion, and 5 (7.2%) patients started the G-CSF at first day (+1) of stem cell infusion. While 33 (47.8%) patients had no comorbidity, 16 (23.2%) patients had one chronic disease, and 20 (29%) patients had more than one chronic disease. The median hospital stay day at transplantation was 20 (range, 15-34). The median neutrophil engraftment time was 11 (range, 10-14) days. Similarly, the median time of platelet engraftment was 11 (range, 7-14) days as well. The majority of patients developed febrile neutropenia (FEN) (n=64, 92.8%) during the transplantation. The median count of infused CD34+ peripheral stem cells was 4.3x10^6/kg (range, 3.5-5.7x10^6/kg).

While the median number of erythrocyte transfusions during the stay at the stem cell transplantation unit was 1 (range, 0-6) unit, the median number of platelet transfusions was 2 (range, 1-7) units. The majority of patients in our study underwent auto-HSCT with Mel200 (n=58, 84.1%), Mel140 was used in 11 (15.9%) patients. At post-transplant day 100; of 69 patients, 63 (91.3%) patients were alive, 1 (1.4%) patient was dead, and the status of 5 (7.3%) patients were not found because of lost to follow up. The cause of death of the patient, who underwent auto-HSCT with Mel200, was Klebsiella pneumonia infection developed before engraftment occurred. The disease status

of patients at post-transplant day 100 were followed by; 31 (44.9%) patients were in complete response, 21 (30.4%) patients were in very good partial response, 6 (8.7%) patients were in partial response, respectively. Unfortunately, the disease status at post-transplant day 100 was unknown in 11 (15.9%) patients ow-ing to lost to follow up or not evaluated or death.

Comparison of Mel200 versus Mel140 group

The variables such as GFR, serum creatinine level, and the start-ing day of G-CSF were significantly different when compared with Mel200 and Mel140 groups as shown in Table 2. The ratio of patients with GFR<60 ml/min (63.6%) was significantly higher in the Mel140 group than the Mel200 group (1.7%) ($P < 0.001$). Similarly, while patients with serum creatinine≥ 2 mg/dL were 36.4% in the Mel140 group, there was not any patient with se-rum creatinine≥ 2 mg/dL in the Mel200 group ($P < 0.001$). When compared with the Mel200 and Mel140 groups, the ratio of pa-tients with the starting day of G-CSF at 5th day was significantly higher in the Mel200 group (96.6% versus 72.7%, $P = 0.026$).

However, other variables such as age ($P = 0.064$), comorbidity ($P = 0.120$), and infused CD34+ pe-ripheral stem cells ($P = 0.082$) tended to be different between the Mel200 and Mel140 groups, but those variables did not reach statistical significance.

There were not any significant difference between the Mel200 and Mel140 groups in terms of sex ($P = 0.758$), ECOG perfor-mance status ($P = 0.276$), disease status at transplantation ($P = 0.284$), treat-ment line received prior to transplant ($P = 0.424$), number of chemotherapy cycles before transplant ($P = 0.263$), hospitalisation time at transplantation ($P = 0.691$), neutrophil engraftment time ($P = 0.907$), platelet engraftment time ($P = 0.234$), febrile neutropenia during the transplantation ($P = 1$), number of erythrocyte transfusion during the hospitalisation ($P = 0.661$), number of platelet transfusion dur-ing the hospitalisation ($P = 0.569$), patient status at post-transplant day 100 ($P = 0.882$), and disease status at post-transplant day 100 ($P = 0.967$), respectively, (Table 2).

Discussion

The purpose of this single center retrospective study was to investigate the impact of melphalan dose intensity on the early term post-transplant outcomes in MM patients under-went auto-HSCT. There are few studies compared the effects of Mel140 versus Mel200 on post-transplant outcomes, and those studies generally focused on long term outcomes and designed for a specific MM population such as patients with renal impairment or elderly patients. Unlike those studies, our study included all patients who received Mel140 independent of the reason and aimed to evaluate early term outcomes af-ter auto-HSCT. To the best of our knowledge, this is the first study to compare the first 100 days results of the Mel200 and Mel140 group in MM patients after auto-HSCT.

The Mel200 is the standard conditioning regimen for MM patients without comorbidity at auto-HSCT. Reduced-dose melphalan is generally preferred for older patients and those who are fragile or with significant comorbidities. Although there are no randomised clinical trials to compare Mel200 and Mel140, several studies reported that Mel140 was feasible for MM patients, especially patients with renal impairment and older patients (6-8). Our study showed that Mel140 instead of Mel200 was statistically preferred in patients with renal suf-ficiency in our centre in line with the literature. Similar-ly, the percentage of patients ≥65 years was higher in Mel140 group than Mel200 group in the present study, but it did not reach statistical significance. This might be related to small sample size in our study. Consequently, the present study confirms Mel140 is tended to prefer in older patients and pa-tients with renal disease in our transplant center.

While platelet engraftment time was similar between the Mel140 and Mel200 groups, neutrophil en-graftment time was significantly longer in Mel140 group in the study published by Katragadda et al. In addition to, the incidence of febrile neutro-penia increased in patients with Mel140 than Mel200 patients in the same study (9). On the other hand, there were no sig-nificant differences between the Mel140 and Mel200 groups in terms of neutrophil and platelet engraftments in the EBMT and MD Anderson trials (16,17). Despite not to statistically sig-nificant, a higher percentage of patients had febrile neutrope-nia in the Mel200 group in the MD Anderson study, contrary to the study conducted by Katragadda et al. (9,17). We did not find significant differences between the Mel200 and Mel140 groups in terms of neutrophil engraftment, platelet engraft-ment, and the rate of febrile neutropenia, respectively. Our re-sults are compatible with some previous studies. But there are conflicting results related to either neutrophil engraftment time or the incidence of febrile neutropenia in the literature as we mentioned above. This could be related to the sample size of the studies, the difference between the patients included in the studies in terms of disease status at transplantation or comorbidities, and vari-able frequency of non-hematological toxicities such as mucositis.

Table 1. Disease and Patient Characteristics	
Characteristics	Total (n=69)
Sex, n (%) Female Male	 28 (40.6) 41 (59.4)
Age, year Mean±SD Median (min-max)	 59.6±8.5 61 (40-75)
Age, n (%) <65 years ≥ 65 years	 50 (72.5) 19 (27.5)
ECOG Performance Status, n (%) 0 1 2 3	 49 (71) 18 (26.2) 1 (1.4) 1 (1.4)
GFR, n (%) ≥60 ml/min <60 ml/min	 61 (88.4) 8 (11.6)
Serum creatinine, n (%) <2 mg/dL ≥2 mg/dL	 65 (94.2) 4 (5.8)
Disease status at transplantation, n (%) Complete response Very good partial response Partial response Unknown	 37 (53.6) 22 (31.9) 8 (11.6) 2 (2.9)
Treatment line received prior to transplant, n (%) 1 2 3	 61 (88.4) 6 (8.7) 2 (2.9)
The number of chemotherapy cycles received before transplant, n (%) 2 4 5 6 7 8 9 12 Unknown	 1 (1.4) 29 (42) 17 (24.6) 9 (13) 3 (4.3) 3 (4.3) 1 (1.4) 1 (1.4) 5 (7.2)
The number of chemotherapy cycles received before transplant, no Mean±SD Median (min-max)	 5±1.5 5 (2-12)
The starting day of G-CSF during the transplantation, n (%) 1st day 5th day	 5 (7.2) 64 (92.8)
Comorbidity, n (%) No 1 disease >1 disease	 33 (47.8) 16 (23.2) 20 (29)
Hospital stay period at transplantation, days Mean±SD Median (min-max)	 20.5±3.4 20 (15-34)
Neutrophil engraftment time, days Mean±SD Median (min-max)	 11.1±0.8 11 (10-14)
Platelet engraftment time, days Mean±SD Median (min-max)	 11.2±1,6 11 (7-14)
Febrile neutropenia during the transplantation, n (%) No Yes	 5 (7.2) 64 (92.8)
Infused CD34+ peripheral stem cells, 106/ kg Mean±SD Median (min-max)	 4.3±0.5 4.3 (3.5-5.7)
The number of erythrocyte transfusion during the hospitalisation, unit Mean±SD Median (min-max)	 1.2±1.5 1 (0-6)
The number of platelet transfusion during the hospitalisation, unit Mean±SD Median (min-max)	 2.6±1.4 2 (1-7)
Melphalan dose, n (%) 140 mg/m2 200 mg/m2	 11 (15.9) 58 (84.1)
Patient status at post-transplant day 100, n (%) Alive Died Lost to follow-up	 63 (91.3) 1 (1.4) 5 (7.3)
Disease status at post-transplant day 100, n (%) Complete response Very good partial response Partial response Unknown	 31 (44.9) 21 (30.4) 6 (8.7) 11 (15.9)
SD: Standard Deviation, ECOG: Eastern Cooperative Oncology Group, G-CSF: Granulocyte Colony Stimulating Factor	

Table 2. Comparison of Mel200 and Mel140 groups

Variables	Mel200 (n=58)	Mel140 (n=11)	p
Sex, n (%) Female Male	 23 (39.7) 35 (60.3)	 5 (45.5) 6 (54.5)	0.758*
Age, year Median (min-max)	 60.5 (40-73)	 66 (43-75)	0.064**
Age, n (%) <65 years ≥ 65 years	 45 (77.6) 13 (22.4)	 5 (45.5) 6 (54.5)	0.059*
ECOG Performance Status, n (%) 0 ≥1	 43 (74.1) 15 (25.9)	 6 (54.5) 5 (45.5)	0.276*
GFR, n (%) ≥60 ml/min <60 ml/min	 57 (98.3) 1 (1.7)	 4 (36.4) 7 (63.6)	<0.001*
Serum creatinine, n (%) <2 mg/dL ≥2 mg/dL	 58 (100) 0	 7 (63.6) 4 (36.4)	<0.001*
Disease status at transplantation, n (%) Complete response Very good partial response Partial response	n=57 32 (56.2) 17 (29.8) 8 (14)	n=10 5 (50) 5 (50) 0	0.284*
Treatment line received prior to transplant, n (%) 1 2 3	 50 (86.2) 6 (10.3) 2 (3.4)	 11 (100) 0 0	0.424*
The number of chemotherapy cycles received before transplant, no Median (min-max)	 4.5 (4-12)	 5.5 (2-9)	0.263**
The starting day of G-CSF during the transplantation, n (%) 1st day 5th day	 2 (3.4) 56 (96.6)	 3 (27.3) 8 (72.7)	0.026*
Comorbidity, n(%) No 1 disease >1 disease	 30 (51.8) 14 (24.1) 14 (24.1)	 3 (27.3) 2 (18.2) 6 (54.5)	0.120*
Hospital stay period at transplantation, days Median (min-max)	 20 (15-29)	 19 (17-34)	0.691**
Neutrophil engraftment time, days Median (min-max)	 11 (10-14)	 11 (10-13)	0.907**
Platelet engraftment time, days Median (min-max)	 11 (7-14)	 12 (9-14)	0.234**
Febrile neutropenia during the transplantation, n (%) No Yes	 4 (6.9) 54 (93.1)	 1 (9.1) 10 (90.9)	1.000*
Infused CD34+ peripheral stem cells, 106/ kg Median (min-max)	 4.4 (3.5-5.7)	 3.9 (3.6-4.9)	0.082**
The number of erythrocyte transfusions during the hospitalisation, unit Median (min-max)	 0.5 (0-6)	 1 (0-6)	0.661**
The number of platelet transfusions during the hospitalisation, unit Median (min-max)	 2 (1-7)	 2 (1-6)	0.569**
Patient status at post-transplant day 100, n (%) Alive Died Unknown	 53 (91.4) 1 (1.7) 4 (6.9)	 10 (90.9) 0 1 (9.1)	0.882*
Disease status at post-transplant day 100, n (%) Complete response Very good partial response Partial response	n=50 27 (54) 18 (36) 5 (10)	n=8 4 (50) 3 (37.5) 1 (12.5)	0.967*

ECOG: Eastern Cooperative Oncology Group, GFR: Glomerular Filtration Rate, G-CSF: Granulocyte Colony Stimulating Factor, Mel200: Melphalan 200 mg/m2, Mel140: Melphalan 140 mg/m2
SD: Standard Deviation, *:Chi-Square Test **: Mann-Whitney U testi

There are several studies that evaluated the duration of hospital stay at auto-HSCT in MM patients. The Mel140 and Mel200 groups were only compared in the elderly patients (>65 years) in the study of Marini et al. and the median hospital stay at auto-HSCT was similar between the Mel140 and Mel200 groups in the elderly patients (20). Similarly, Katragadda et al. reported that the median inpa-tient days during the auto-HSCT was not significantly different between the Mel140 and Mel200 groups (9). Our results were compatible with previous studies in terms of the hospital stay during the auto-HSCT, and we did not find significant difference between the Mel200 and Mel140 groups like in the literature.

In terms of transfusion support during the hospital stay at auto-HSCT, there is limited knowledge in the literature. Among the elderly patients (>65years), the need for erythrocyte and platelet transfusion was greater in the Mel200 group than the Mel140 group in the study conducted by Marine et al. But it did not reach statistically significance (20). In our study, the need for both erythrocyte and platelet transfusions was not significantly different between the Mel200 and Mel140 groups as well.

Marini et al. reported that five patients died during the first 100 days after the auto-HSCT, resulting in a transplant related mortality (TRM) of 3.8%. The deaths were related to infectious complications (20). In the EBMT study, the non-relapse mortality rate at 3 months after auto-HSCT was 0.8% and 0.5% for the Mel200 and Mel140 groups, respectively, and it was not significantly different (16). Similarly, the mortality ratio at 100 days after the auto-HSCT was 1.4% for the whole population in our study. While one patient died due to infection in the Mel200 group in the first 100 days after the auto-HSCT, nobody died in the Mel140 group. Consequently, the mortality rate at 100 days after au-to-HSCT was statistically similar between the Mel140 and Mel200 groups in our study compatible with the literature.

If we mention early response rate or disease status after the transplant, there have not been enough studies comparing the impact of Mel200 and a reduced dose of melphalan in terms of the disease sta-tus at day-100 after auto-HSCT. The disease status at 3 months after the auto-HSCT was similar be-tween the Mel140 and Mel200 groups in the MD Anderson study (17). Likewise, our study showed that the disease status at day 100 after auto-HSCT was statistically similar between the melphalan groups as well.

In conclusion, our aim was to compare the impact of Mel200 and Mel140 on short term post-transplant outcomes in MM patients who underwent first auto-HSCT. The small number of patients and retrospective nature of the study are limitations of our study. According to the first 100-day re-sults after auto-HSCT, the mortality rate, disease status, need for transfusion, febrile neutropenia ratio, engraftment time, and duration of hospitalisation were not significantly different between the Mel200 and Mel140 groups. Despite the small sample size and retrospective design, our study shows that the Mel200 and Mel140 conditioning have similar first 100-day outcomes after auto-HSCT in MM pa-tients. Further comprehensive randomised trials are needed to clarify the impact of melphalan condi-tioning intensity on early term outcomes after auto-HSCT.

Statement of Ethics

This retrospective and non-interventional study was reviewed and approved by the Institutional Ethics Board of Akdeniz University School of Medicine. The study was conducted in accordance with the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Funding Sources

There are no funding sources to declare.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author (O.K.Y.).

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Research Article

Assessment of serum glucose potassium ratio as a predictor for mortality of acute ischemic stroke

Akut iskemik inme mortalitesinin bir belirleyicisi olarak serum glukoz potasyum oranının değerlendirilmesi

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Abstract

Aim: The study aims to demonstrate the effect of changes in serum glucose/potassium ratio (GPR) which were performed in patients with acute ischemic stroke (AIS) and patient management is performed more quickly and effectively.

Material and Methods: The hemogram and biochemical parameters of patients undergoing mechanical thrombectomy (MT) for AIS have been retrospectively reviewed. Patients were divided into two groups non-survivors and survivors. The GPR was calculated, and their ability to predict mortality was statistically evaluated between the groups.

Results: A total of 173 patients, of which 131 in the survivor group and 42 in the non-survivor group, were examined. In the non-survivor group Glucose and GPR were statistically higher than the survivor group ($p<0.05$). Moreover, the sensitivity and specificity of the serum GPR were found to be 97.6% and 50.4%, respectively.

Conclusion: These findings suggest that GPR could serve as a useful parameter for predicting mortality in AIS patients undergoing mechanical thrombectomy.

Keywords: glucose-potassium ratio, acute ischemic stroke, mortality, mechanical thrombectomy

ÖZ

Amaç: Bu çalışma, akut iskemik inme (AIS) hastalarında yapılan serum glukoz/potasyum oranındaki (GPR) değişikliklerin hasta yönetiminin daha hızlı ve etkin bir şekilde yapılmasına etkisini göstermeyi amaçlamaktadır.

Gereç ve Yöntemler: AIS nedeniyle mekanik trombektomi uygulanan hastaların hematolojik ve biyokimyasal parametreleri retrospektif olarak incelendi. Hastalar non-survivor (yaşamayanlar) ve survivor (yaşayanlar) olmak üzere iki gruba ayrıldı. GPR hesaplandı ve mortaliteyi tahmin etme yetenekleri gruplar arasında istatistiksel olarak değerlendirildi.

Bulgular: Survivor grupta 131 ve non-survivor grupta 42 olmak üzere toplam 173 hasta analiz edildi. Non-survivor grubunda glukoz ve GPR, survivor grubuna göre istatistiksel olarak anlamlı şekilde yüksekti ($p<0.05$). Ayrıca, serum GPR'nin duyarlılığı ve özgüllüğü sırasıyla %97.6 ve %50.4 olarak bulundu.

Sonuç: Bu bulgular, mekanik trombektomi uygulanan AIS hastalarında mortaliteyi tahmin etmek için GPR'nin kullanışlı bir parametre olarak hizmet edebileceğini öne sürmektedir.

Anahtar Kelimeler: glukoz-potasyum oranı, akut iskemik inme, mortalite, mekanik trombektomi

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Introduction

Over 13.7 million people have a stroke annually, one in six people will experience one at some point in their lifetime, and 5.8 million people die as a result (1). In the past, the first line of treatment for acute ischemic stroke (AIS) was intravenous thrombolytic therapy. Mechanical thrombectomy (MT) for large vessel occlusions (LVO) was shown to be superior to other medical treatments in recent randomized trials (2-4). Younger age, a low baseline National Institutes of Health Stroke Scale (NIHSS) score, rapid onset of symptoms and rapid reperfusion, and a favorable baseline AlberStroke Programme Early CT Score (ASPECT) were all found to be predictive of a positive clinical outcome in recent studies (5, 6). Clinical outcomes are adversely affected by increased thrombectomy passes, intracerebral hemorrhage, and diabetes mellitus (5).

Due to an increase in catecholamines during stressful or traumatic situations, potassium levels fall, and glucose levels rise. According to the literature, patients who have subarachnoid hemorrhage, pulmonary embolism, traumatic brain injury, or blunt abdominal trauma can quickly and accurately predict their morbidity and mortality using hyperglycemia or the glucose-potassium ratio (GPR), which is calculated as glucose divided by potassium. Numerous studies demonstrate the relationship between rising blood glucose levels and critical illness and trauma-related mortality and morbidity. Comparing isolated GPR to glucose and potassium levels, isolated GPR has a better ability to predict mortality and morbidity (7-11).

In this study, the adequacy of the GPR, which is an easy and simple parameter that can be used in the clinic in predicting the mortality of patients undergoing mechanical thrombectomy for AIS, was evaluated.

Material and Methods

Study Design and Eligibility Criteria

This retrospective study was conducted at the Department of Anesthesiology intensive care unit at our hospital between 2021 March and 2023 March. Ethical approval was obtained from the Ethics Committee of KTO Karatay University (E-41901325-200-62861) on 23 June 2023. This study was carried out according to the Declaration of Helsinki or ethical rules.

The inclusion criteria are patients aged≥ 19 years undergoing mechanical thrombectomy for acute ischemic stroke. Patients with a history of diabetes mellitus or admission serum glucose level >200 mg/dL, a disease/or drug use that could induce hyperkalemia or hypokalemia, history causing hypokalemia, chronic disease history, acute renal failure, chronic renal failure, nephrological pathology, malignancy history, liver cirrhosis, age of <19 years will be excluded from the study.

The patients analyzed in the study were grouped into the survivor group and the non-survivor group.

Medical and Demographic History

On hospital admission, age, sex, and laboratory parameters were recorded: hemoglobin, hematocrit, platelet, white blood cell count (WBC), Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), blood urea nitrogen [BUN], serum creatinine, sodium, K, Glucose. In addition, GPR will be calculated using the following formulas:

GPR = glucose level/potassium level.

Outcome Measures

The primary outcome is the role of GPR in predicting mortality. The secondary outcome is GPR cut-off value for acute ischemic stroke.

Statistical Analyses

All statistical analyses will be performed using the IBM Statistical Package for the Social Sciences Statistics for Windows version 23.0 software (IBM, Armonk, NY, USA). Continuous data are reported as mean±standard deviation. The comparison of quantitative variables between the two groups was performed using the Mann–Whitney U test. Correlations between categorical variables will be evaluated using the Chi-square test. Receiver operating characteristics (ROC) analysis will be performed for the GPR and glucose for predicting mortality of acute ischemic stroke. The area under the ROC curve (AUC), cut-off values, sensitivity, specificity, positive predictive value, and negative predictive values will be calculated in order to evaluate the performance of the GPR and glucose. The level of statistical significance is set at $p<0.05$.

Results

Patient characteristics of the 358 stroke patients hospitalized during the study period and 165 with diagnosed as not meeting inclusion criteria and 20 with missing data cases were excluded. Thus, we included and analyzed data for 173 patients (83 males, 90 females; mean age, 69.8 years; range 26-97 years) (Fig 1).

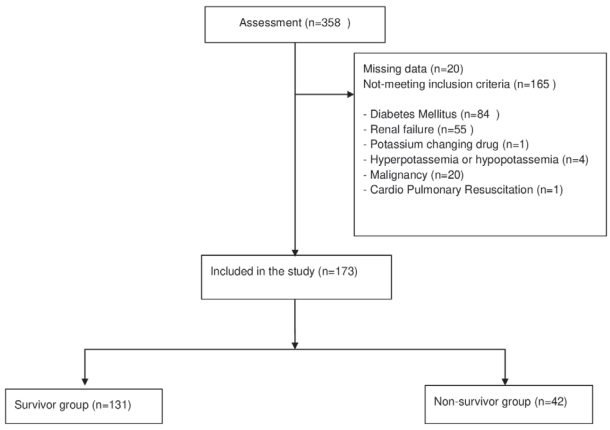

Figure 1. Consort diagram

The group stroke was defined as a survivor (group S) or non-survivor (group N) after admission to the intensive care unit. The mean patient age was 68.9 and 72.6 years, respectively, and the difference was not significant (P = 0.097). For the gender rate between groups, there were no statistical differences (p=0.077). Patients' mortality was recorded at 24.2% (n=42). Patient demographic data and laboratory parameters were compared between group S and group N (Table 1).

Table 1. Comparison of demographic data and laboratory parameters according to the mortality status

Variables	Survivor (n = 131)	Non-survivor (n = 42)	p Value
Age(years)	68.9 ±12.4	72.6 ± 11.6	0.097
Gender (Male/Female)	69/62	15/27	0.054
Hemoglobin (g/dL)	13.6 ±1.9	13.6 ± 1.8	0.750
Htc (%)	41.7 ± 5.07	42 ± 4.7	0.277
Platelet (×103/mm3)	270 ± 69	269 ± 96	0.192
WBC (x103 /mm3)	16.4 ± 2.4	12.4 ± 4.5	0.741
ALT (U/L)	17.5 ± 12.8	16.2 ±8.6	0.541
AST (U/L)	21.6 ± 9.1	23.9 ± 11.4	0.187
GGT (U/L)	29.7 ± 33.6	37.3 ± 48	0.346
BUN (mg/dL)	16.1 ± 4.6	17.3 ± 6	0.242
Creatinine (mg/dL)	0.8 ± 0.1	0.8 ± 0.1	0.191
Sodium (mmol/L)	139.3 ± 2 .7	139.4 ± 2.9	0.874
Potassium (mmol/L)	4.2 ± 0.4	4.2 ± 0.5	0.592
Glucose (mg/dL)	116 ± 18	160 ± 22	*0.001
GPR	27.6 ± 5.5	38.4 ± 7.3	*0.001
Mortality rate (%24.2)	-	-	

Htc: Hematocrit; WBC: white blood cell; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; BUN: blood urea nitrogen; GPR: glucose/potassium *p value < 0.05

We compared the GPR as a primary outcome at admission between the two groups. Median GPR at admission in the S and N groups were 27.2 (range, 15.5-45.1) and 37.6 (range, 27.2-62.1) points, respectively. The GPR was significantly correlated with the mortality rate at admission (95% confidence interval (CI): 0.851–0.949; p < 0.001).

Table 2 presented the ROC curve analysis of GPR and glucose in discriminating mortal patients among all the studied patients.

For all studied patients, the AUC for GPR was measured as 0.900, and 27.2 as a cut-off value had 97.6% sensitivity and 50.4% specificity. For glucose, the AUC was measured as 0.947, and 117.5 mg/dL as a cut-off value had 97.6% sensitivity and 47.3% specificity (Figure 2) for mortality compared between the two groups.

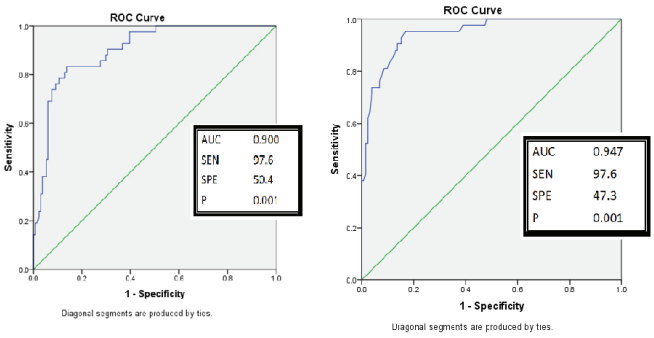

Figure 2. ROC analyses of GPR and glucose. (a) ROC curve analysis of GPR in predicting mortality. (b) ROC curve analysis of glucose in predicting mortality.

Table 2. ROC curve analysis of GPR and glucose in predicting mortality

	AUC	Cut-off value	SEN	SPE
Glucose	0.947	117.5	0.976	0.473
GPR	0.900	27.2	0.976	0.504

Discussion

This study investigated the predictive role of GPR for mortality in patients with AIS. The plasma GPR was significantly higher in non-survivors and was a predictor of mortality. Therefore, the plasma GPR was useful for predicting mortality in these AIS patients.

Intravenous thrombolytic therapy used to be the first line of treatment for acute ischemic stroke (AIS). Recent randomized trials for AIS have demonstrated that mechanical thrombectomy (MT) is superior to alternative medicinal therapies (3,4). Additionally, our hospital is the center where mechanical thrombectomy therapy has been performed successfully for many years. For this reason, the other hospitals utilize the first step of therapy as Intravenous thrombolytic therapy, and then they transfer these patients to our center. Thus, we only included the mechanical thrombectomy patients for AIS in our study.

A meta-analysis found that having excellent collaterals prior to endovascular therapy was related to better clinical results (12). Wufuer et al. demonstrated in another meta-analysis that good collaterals may contribute to positive 3-month clinical outcomes and a low mortality risk (13). Predictive favorable clinical outcomes were reduced National Institutes of Health Stroke Scale (NIHSS) scores observed at the onset of symptoms. Furthermore, it was observed that a high National Institutes of Health Stroke Scale (NIHSS) score upon admission served as an indicator of unfavorable clinical outcomes (14).

Poor clinical outcomes were predicted by elevated glucose levels. A post hoc analysis of the Solitaire Flow Restoration With the Intention for Thrombectomy (SWIFT) multicenter randomized trial revealed that a blood glucose level of >140 mg/dL was indepen-

dently linked to a lower percentage of positive clinical outcomes (15). According to Sanak et al., three months after mechanical thrombectomy for AIS, lower glucose levels may be linked to better functional results (16). The exact pathophysiological mechanism underlying the relationship between post-stroke hyperglycemia and severe neurological deficit or poor outcome in patients with AIS remains unclear. According to some research, post-stroke hyperglycemia may result from a stress response. Catecholamines, glucagon, and corticosteroids are the main hormones that control blood sugar during the hyperglycemic response (17, 18).

Potassium, which is primarily held inside of cells, is transferred by sodium/potassium adenosine triphosphatase pump (Na/K-ATPase) and active cellular absorption through the cell membrane. Catecholamine, B2 adrenergic hormones, and insulin regulate Na/K-ATPase, which can lower the levels of potassium in the blood that is circulating (19). Additionally, as previously noted, increased catecholamine output caused by AIS raises serum glucose levels; hence, insulin secretion increases, and serum potassium enters cells in this situation (20). Theoretically, as has been demonstrated in a number of prior traumatic brain injury investigations, increased serum glucose concentrations may be strongly linked with trauma severity and post-traumatic prognosis. Meanwhile, it's probable that a poor post-traumatic prognosis is linked to an increase in serum glucose and a drop in K concentration (21-23).

The mortality of patients with blood sugar levels 140 and above was shown to be statistically significant compared to those with blood sugar levels under 140 in the Leto et al. (24) study that looked at the relationships between mortality and blood glucose levels at the time of admission for hip fractures. They suggested that in individuals with hip fractures, blood glucose levels might serve as a predictive indication. According to the research done by Yendamuri et al. (25), general trauma patients with blood sugar levels greater than 200 mg/dl had a mortality rate of 34.1%. They argued that the blood glucose level at the time of admission was an independent predictor for hospital mortality in multi-trauma patients. In our study, blood glucose levels were found to be high in the mortal group at the time of admission in AIS patients. This result is similar to the above studies. But the serum GPR better reflects excessive catecholamine levels after AIS than the serum glucose concentration or serum potassium concentration alone. The use of GPR, which is quick and simple to compute and offers accurate prognostic information, has recently grown among trauma patients (10). In patients with serious brain injuries, Zhou et al.(21) investigated the value of serum GPR as a 30-day mortality prediction. The serum GPR may have a bearing on mortality in patients with severe head traumas, the study's findings indicated. Serum GPR was investigated by Fujiki et al. (26) as a clinical risk factor in individuals with aneurysmal subarachnoid hemorrhage. The study's findings revealed that the severe group's serum GPR was statistically and significantly higher than that of the control group (57.9 [22] vs. 42.3 [15.1]; $p < 0.001$). In our study, it was found that GPR in the group mortal significantly higher than alive group. Median GPR at admission in the S and N groups were 27.2 (range, 15.5-45.1) and 37.6 (range, 27.2-62.1) points, respectively. The GPR were significantly correlated with the mortality rate at admission (95% confidence interval (CI): 0.851–0.949; $p < 0.001$).

According to Jung et al. (27) the plasma GPR's AUC varied from 0.709 to 0.783. The sensitivity and specificity for predicting mortality following an aneurysmal subarachnoid hemorrhage were 90.2 and 51.0%, respectively, with a cut-off value for the GPR of 37.8. In our study, the AUC for GPR was measured as 0.900, and 27.2 as a cut-off value had 97.6% sensitivity and 50.4% specificity. For glucose, the AUC was measured as 0.947, and 117.5 mg/dL as a cut-off value had 97.6% sensitivity and 47.3% specificity for mortality compared between the two groups.

Our study has some limitations. This was a single-center and retrospective study. Another limitation was that glucagon, corticosteroid, and catecholamine hormone levels were not analyzed at the time of presentation.

Conclusion

In summary, we assessed the serum GPR as a predictor for mortality in patients undergoing mechanical thrombectomy for acute ischemic stroke. These results suggest that the serum GPR is a valuable and simple parameter that can be used in the clinic to predict mortality in patients undergoing mechanical thrombectomy for acute ischemic stroke.

Conflict of Interest

No conflict of interest was declared by the authors. In addition, no financial support was received for this study.

Author Contributions

All 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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Research Article

Paraoxonase 1 gene polymorphısms (Q192r and L55m) and associatıon wıth coronary slow flow

Paraoksonaz 1 gen polimorfizmleri (Q192r ve L55m) ve koroner yavaş akımla ilişkisi

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Abstract

Aim: Coronary slow flow (CSF) is an angiographic entity characterized by slow progression of opaque material and an early indicator of atherosclerosis. Paraoxonase 1 (PON1) protects high-density lipoprotein (HDL) and low-density lipoprotein (LDL) from oxidative modifications. PON 1 has two amino acid polymorphisms (192Q/R and 55L/M) and that affect its functioning. We aim to determine PON1 two genetic polymorphisms and relationship with CSF. As we know, our study is the first to assessment the relationship PON1 gene polymorphisms (L55M and Q192R) and CSF.

Material and Methods: We included a total of 100 patients and 2 groups as normal coronary flow (NCF) and CSF. Genomic sequences of rs854560 and rs662 polymorphisms were determined using polymerase chain reaction. The research protocol was approved by Fırat University Institutional Review Board (Approval No:16).

Results: The mean age of CSF group was 45.4±17 and NCF group was 50.5±11 years. There was the statistically difference in terms of the frequency of carrying Q and R alleles. For dual genotypes, the QQLM genotype was more common in CSF group, whereas the QRLM genotype was more common in NCF. Significant differences were found between patients with QQLM, RRLL, RRLM and QRLM genotypes and healthy individuals.

Conslusion: We found a significant relationship between the Q allele and the QQLM genotype and CSF, and we thought that these may be risk factors for CSF. In addition, the fact that the R allele and QRLM, RRLL, and RRLM genotypes were higher in the NCF group and there was a statistically significant relationship suggested that these might be protective factors for CSF.

Keywords: coronary slow flow; paraoxonase; gene polymorphism; antioxidant

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Öz

Amaç: Koroner yavaş akım (KYA), opak maddenin yavaş ilerlemesi ile karakterize anjiyografik bir antitedir ve aynı zamanda ve aterosklerozun erken bir göstergesi olduğu düşünülmektedir. İnsan paraoksonazı 1 (PON1), yüksek yoğunluklu lipoproteini (HDL) ve düşük yoğunluklu lipoproteini (LDL) oksidatif modifikasyonlardan korur. Paraoksonaz 1'in işleyişini etkileyen iki amino asit polimorfizmi (192Q/R ve 55L/M) vardır. PON1 iki genetik polimorfizmi ve koroner yavaş akım ile ilişkisini belirlemeyi amaçlıyoruz. Bildiğimiz kadarıyla çalışmamız PON1 gen polimorfizmleri (L55M ve Q192R) ile KYA ilişkisini değerlendiren ilk çalışmadır.

Gereç ve Yöntemler: Çalışmaya toplam 100 hasta dahil edildi ve normal koroner akım (NKA) ve KYA olmak üzere 2 gruba ayrıldı. rs854560 ve rs662 polimorfizmlerinin genomik dizileri polimeraz zincir reaksiyonu kullanılarak belirlendi. Araştırma protokolü Fırat Üniversitesi Kurumsal İnceleme Kurulu tarafından onaylanmıştır (Onay No:16).

Bulgular: Koroner yavaş akım grubunun yaş ortalaması 45,4±17 ve NKA grubunun 50,5±11 idi. Q ve R alellerini taşıma sıklığı açısından istatistiksel olarak fark vardı. Dual genotipler için, QQLM genotipi KYA grubunda daha yaygınken, QRLM genotipi NKA'de daha yaygındı. QQLM, RRLL, RRLM ve QRLM genotiplerine sahip hastalar ile sağlıklı bireyler arasında anlamlı fark bulundu.

Sonuçlar: Q aleli ile QQLM genotipi ve KYA arasında anlamlı bir ilişki bulduk ve bunların KYA için risk faktörleri olabileceğini düşündük. Ayrıca R aleli ile QRLM, RRLL ve RRLM genotiplerinin NKA grubunda daha yüksek olması ve istatistiksel olarak anlamlı bir ilişki bulunması bunların KYA için koruyucu faktörler olabileceğini düşündürdü.

Anahtar Kelimeler: koroner yavaş akım, paraoksonaz, gen polimorfizmi, antioksidan

Introduction

Genetic factors contribute to the risk of coronary artery disease (CAD) almost as much as environmental factors. Examining populations (patient–control) by genotyping common single-nucleotide polymorphisms within a suspected gene and its regulatory sequences is essential and provides new insights into the genetic pathways of the disease [1].

Coronary slow flow (CSF) is an important, angiographic entity characterized by the slow progression of opaque material and delayed coronary opacification without coronary artery ischemic provocative maneuvers in normal or near-normal coronary angiography. CSF was first described by Tambe et al. in 1972 and has been reported in 1–4% of patients who have undergone coronary angiography [2,3].

CSF is associated with arrhythmias, recurrent angina, and unnecessary interventions or hospitalizations. It is also thought to be an early indicator of atherosclerosis [4,5]. Pathophysiological factors, such as microvascular dysfunction, endothelial/vasomotor dysfunction, small vessel diseases, and inflammatory/neurohormonal imbalance were related to CSF. Despite all this, the underlying causes have not been precisely identified [3,6,7].

The paraoxonase gene family has three members--PON1, 2, and 3-- and is localized between q21.3 and q22.1 on the long arm of chromosome 7 [8]. Serum paraoxonase 1 (PON1) is one of the genes that plays an important role in vascular pathology and is thus considered a biomarker of CAD. Serum PON1 protects high-density lipoprotein (HDL) and low-density lipoprotein (LDL) from oxidative modification. The antioxidant activity of HDL is largely due to PON, which has the ability to metabolize lipid peroxides. Previous studies and meta-analyses have shown an association between PON1 polymorphisms and CAD [9,10].

PON1 has two amino acid polymorphisms. One is the substitution of methionine and leucine (M/L) amino acids in the 55th position, and the other is the substitution of arginine and glutamine (Q/R) amino acids at position 192 [8].

Based on the above studies and meta-analyses, we hypothesized that PON1 gene mutations might influence coronary blood flow and compared two polymorphisms of the PON1 gene in patients with CSF and normal coronary flow (NCF).

Material and Methods

This study was performed at the Cardiology Clinic of Fırat University Hospital. We included 100 patients aged 18 years or older who presented with complaints of chest pain and had undergone coronary angiography (CAG). Fifty patients with NCF served as the control group, and 50 patients with CSF served as the patient group.

Our exclusion criteria were acute coronary syndrome, unstable angina pectoris, heart failure (ejection fraction < 50%), significant valvular heart disease, and prior coronary artery bypass graft surgery. CSF was diagnosed by the joint decision of two experienced invasive cardiologists. We defined obstructive CAD as the presence of at least one major epicardial coronary artery with 40% or more stenosis.

Written informed consent was obtained from the patients for this study and is documented at our department records.

The research protocol was approved by Fırat University Institutional Review Board (Approval No:16). This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subjects.

Evaluation of Coronary Blood Flow

Coronary angiographies were performed using the standard Judkins technique with a 6F catheter. The Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) method was used for the quantitative measurement of coronary blood flow.

The first frame is when the contrast material fully opacifies the origin of the artery and starts to progress. The last frame is defined separately for each coronary artery: the distal mustache (whale's tail) for left anterior descending (LAD), the distal bifurcation of the longest branch for circumflex artery (Cx), and the emergence of the first posterolateral branch for the right coronary artery (RCA).

The normal frame counts for LAD artery are 1.7 times greater than CX and RCA.

We obtained the corrected TIMI frame count by dividing the LAD frame value 1.7.

36.2±2.6 for LAD; 22.2±4.1 for Cx; Patients with at least one coronary artery with a frame count above 20.4±3.0 for RCA were defined as CSA. For clinical practicality, the number of frames over 40 for LAD, over 25 for Cx, and over 24 for RCA were taken as coronary slow flow.

Genetic Analyses

Blood samples (5 mL) were collected in the ethylenediamine tetraacetic acid (EDTA) tubes for each patient. Genomic deoxyribonucleic acid (DNA) concentration and purity were determined by ultraviolet (UV) spectrophotometer. The absorbance ratio of a pure DNA sample at 260 nm and 280 nm was 1.8. The patient and control group DNA samples were measured, and their concentrations and purity were determined. DNA samples with values not close to 1.8 were re-isolated.

PON1 genes with rs854560 and rs662 polymorphisms were studied using the Fast Real-Time System (Applied Biosystems, Foster City, CA, USA) using TaqMan probes.

M55L: The genomic sequence of the rs854560 polymorphism is like GCCAGTCCATTAGGCAGTATCTCCA(A/T)GTCTTCAGAGCCAGTTTCTGCCCAGA. In this polymorphisym, the A-to-T transversion (ATG codon --> TTG codon), results the substitution of methionine (the 55th amino acid) by leucine.

Q192R: The genomic sequence of the Rs662 polymorphism is like TAAACCCAAATACATCTCCCAGGAT(C/T)GTAAGTAGGGGTCAAGAAAATAGTG. In these polymorphisms, the C-to-T transversion (CAA codon CGA codon) results in the substitution of glutamine (the 192nd amino acid) by arginine.

The genomic sequences of rs854560 and rs662 polymorphisms were determined using polymerase chain reaction (PCR).

After PCR, the homozygous mutant, heterozygous normal, and homozygous normal genotypes were determined according to allele 1 and allele 2 differentiation.

Statistical Analysis

Statistical evaluation was performed using the SPSS program. The relationships between the parameters were evaluated using Pearson's correlation analysis. The distribution of the patient and control groups, genotype, and allele frequencies were achieved using chi-square analysis. The Mann–Whitney U test, which is a non-parametric test, was used to evaluate the differences between the groups. P values of < 0.05 were considered statistically significant in the evaluations.

Results

The demographic and clinical characteristics of the study cohort are shown in Table 1. The mean age of the NCF group was 45.4 ± 17 years, and the mean age of the CSF group was 50.5 ± 11 years. CSF occurred more frequently in males (50% vs. 58%), but this result was not statistically significant.

Table 1. Study population baseline characteristics

Variables	CSF group (n=50)	NCF group (n=50)	p
Age (years)	50.5±11	45.4±17	0.91
Gender, male (n, %)	21 (58)	25 (50)	0.55
Diabetes mellitus (n, %)	11 (22)	4 (8)	0.51
Hypertension (n, %)	31 (62)	14 (28)	0.001**
LDL-C (mg/dL) (mean, SD)	110±36	100±22	0.09

CSF: Coronary slow flow, NCF: normal coronary flow, LDL-C, low-density lipoprotein cholesterol, **= p<0.05 (statically significant)

The number of diabetic and hypertension patients in the CSF group was higher than in the control group. This difference was not statistically significant in the diabetic patients.

In our study, 44% of all participants were hypertensive. Hypertension was detected in 62% of the CSF group, and a statistically significant difference was observed compared to the NCF group (p = 0.001). In this respect, hypertension can be considered a risk factor for or predictor of CSF. However, there was no statistically significant difference between the PON1 L55M-Q192R genotypes and hypertension in either group. Also, we did not aim to investigate the relationship between diabetes, hypertension, and CSF in our study.

In the CSF group, the mean TFC values were calculated as 46.3 ± 11.3 for LAD, 35.2 ± 15.03 for Cx, and 24.6 ± 9.55 for RCA.

PON1-55 rs854560 L/M Polymorphism Distributions in CSF and NCF Groups

There was no significant difference between the CSF and NCF groups in terms of PON1 genotype distribution and frequency or PON1 allele distribution and frequency (p = 0.7 and p = 0.8, respectively; Table 2). The genotype distribution for L55M in the NCF group was 52% for LM, 36% for LL, and 12% for MM. We found that the least common genotype was MM, and the most common genotype was LM. Our results are in line with an earlier Turkish study conducted on the L55M genotype [11].

PON1-192 rs662 Q/R Polymorphism Distributions in CSF and NCF Groups

There was no significant difference between the CSF and NCF groups in terms of PON1 genotype distribution and frequency (p = 0.53). A statistically significant difference was found between the two groups in terms of PON1 allele distribution and frequency (p = 0.012; Table 3).

In the CSF group, the QQ, QR, and RR genotype frequencies were 62%, 34%, and 4%, respectively; in the NCF group, the same frequencies were 42%, 40%, and 18%, respectively. The genotype distribution for Q192R was 42% (QQ), 40% (QR), and 18% (RR). Our results are in line with an earlier Turkish study conducted on the Q192R genotype [12]. The QQ genotype was common in both the CSF and NCF groups, and the difference was not statistically significant.

Dual Genotype Frequencies

A statistically significant difference was found between the CSF and the NCF groups in the evaluation of dual genotypes.

For the PON1 gene L55M and Q192R loci, the QQLM genotype was more common in the CSF group, whereas the QRLM genotype was more common in the NCF group.

Statistically significant differences were found between the CSF and the NCF groups regarding the QQLM (p = 0.06), RRLL (p = 0.001), RRLM (p = 0.041), and QRLM (p = 0.001) genotypes.

The QQLM genotype was the most common (40%) genotype in the CSF group. There was a significant difference between the CSF and the NCF groups in terms of the QQLM genotype, and the QRLM genotype was the most common (30%) genotype in the NCF group. There was also a significant difference between the CSF and the NCF groups in terms of the QRLM genotype. Additionally, no individuals were found in the RRMM genotypes (Table 4).

Frequencies of at Least One Q, R, L, and M Allele

We compared the frequencies of carrying at least one Q, R, L, or M allele. There was no statistically significant difference between the CSF and NCF groups in terms of the frequency of carrying the L and M alleles (approximately p = 0.05). However, we found a statistically significant difference in terms of the frequency of carrying the Q and R alleles (p = 0.001; Table 5).

The frequency of the Q allele was higher in the CSF group and was found to be statistically significant. In another study, a significant difference was found between the CAD and control groups in terms of Q allele carriage and frequency (78%) [13]. We thought that the presence of Q allele might be a risk factor for CSF and for early atherosclerosis. The L allele carriage frequency was high in the control group, but it was not statistically significant.

In terms of age, gender, hypertension, diabetes, and LDL, and considering the significant demographic characteristics of patients and relationship with the PON1 gene L55M and Q192R genotypes, no statistically significant difference was found between the CFA and NCF groups for the PON1 gene L55M and Q192R genotypes (p>0.05).

Table 2. PON1 L55M genotype and allele distribution and frequencies

Genotype Distribution and Frequencies	LL	LM	MM	Odds	Odds Ratio	CI %95	p
CSF (n=50)	18 (%36)	27 (%54)	5 (%10)	1.4	1.04	0.22-2.95	-
NCF (n=50)	18 (%36)	26 (%52)	6 (%12)	1.3			-
Allele Distribution and Frequencies	L	M					
CSF (n=50)	41 (0.82)	59 (1.18)					-
NCF (n=50)	42 (0.84)	58 (1.16)					-

- = p>0.05, CSF: Coronary slow flow, NCF: normal coronary flow

Table 3. PON1 Q192R genotype and allele distribution and frequencies

Genotype Distribution and Frequencies	QQ	QR	RR	Odds	Odds Ratio	CI %95	p
CSF (n=50)	31 (%62)	17 (%34)	2 (%4)	3.7	6.8	0.25-1.35	0.5
NCF (n=50)	21 (%42)	20 (%40)	9 (%18)	0.5			
Allele Distribution and Frequencies	Q	R					
CSF (n=50)	79 (1.58)	21 (0.42)					0.012**
NCF (n=50)	62 (1.24)	38 (1.9)					

**= p<0.05 (statically significant), CSF: Coronary slow flow, NCF:normal coronary flow

Table 4. Distribution of PON1 Q192R and PON1 L55M genotype frequencies in CSF and NCF groups

Dual genotype		CSF group (%)	NCF group (%)	p
QQ	LL	14	12	0.06
	LM	40	18	0.001**
	MM	8	12	0.3
RR	LL	4	17	0.001**
	LM	-	4	0.041**
	MM	-	-	-
QR	LL	18	10	0.7
	LM	14	30	0.001**
	MM	2	-	0.1

**= p<0.05 (statically significant), CSF: Coronary slow flow, NCF:normal coronary flow

Table 5. Frequency of at least one Q, R, L and M allele

	CSF group (%)	NCF group (%)	p
L	90	88	0.7
M	64	64	0.1
Q	96	52	0.001**
R	38	58	0.001**

**= p<0.05 (statically significant), CSF: Coronary slow flow NCF: normal coronary flow

Discussion

CSF is defined as delayed opacification of the coronary vasculature at the distal level. The pathophysiological mechanisms of CSF have not been elucidated, and it has been considered an early stage of CAD [14,15].

In cases with CSF, it has been observed using the intravascular ultrasound-IVUS- technique that the coronary arteries of these patients are not normal. On the contrary, it was showed diffuse intimal thickening, calcification, and atheroma that does not lead to luminal stenosis in the coronary arteries [16].

PON1 is located on HDL in serum and metabolizes lipid peroxides, which play a role in protecting against the accumulation of LDL and atherosclerosis. Genetic variations in the PON1 gene may affect this ability [17,18].

Several studies have shown the role of PON genes in the escalating risk of CAD (19,20). In addition, some previous studies have extensively examined the Q192R and L55M polymorphisms in PON1 in different populations [21–23].

Karakaya et al. examined the relationship between serum paraoxonase activity, phenotype distribution, and lipoproteins in patients with CAD. They found no significant difference in terms of paraoxonase genotype distribution, but they showed that low paraoxonase activity could be a risk factor for CAD [24].

Aynacıoğlu et al. showed that there was no significant relationship between PON1-Q192R polymorphism and CAD in a Turkish population [25].

Similarly, Kaman et al. could not find a significant relationship between the Q192R polymorphism and CAD in their study. However, they found a significant relationship between L55M polymorphism and CAD [11].

Our study is the first to assess the relationship between PON1 gene mutations (L55M and Q192R) and CSF. Previous studies have investigated the relationship between PON1 activity and CSF or between PON1 mutations and CAD [26,27].

In our study, the QQLM genotype was higher in the CSF group, and the difference between the two groups was significant, which suggests that the QQLM genotype may be a risk factor for CSF.

The QRLM, RRLM, and RRLL genotypes were more common in the NCF group, and the difference was statistically significant for all three groups. This suggests that the QRLM, RRLM, and RRLL genotypes may be protective factors in the case of CSF.

In our study, we found a significant relationship between the Q allele, the QQLM genotype, and CSF. We hypothesize that these may be risk factors for CSF. In addition, the fact that the R allele and the QRLM, RRLL, and RRLM genotypes were higher in the NCF group than in the CSF group and that there was a statistically significant relationship suggested that these might be protective factors in the case of CSF.

Our study was a single-center study, and the study population

was relatively small. Despite these limitations, our results are significant due to their contribution as the first study to evaluate the relationship between PON1 polymorphisms and CSF. Nevertheless, large randomized controlled studies are needed to represent this population.

Conclusion

The PON1 gene plays an important protective role in CAD and CSF. L55M and Q192R polymorphisms, which have an important place in PON1 activity, should be clarified with large-scale studies.

Pharmacological interventions that regulate PON1 activity or gene expression may play an important role in the prevention of CAD.

The authors declared that the content of the manuscript has not been presented before in any meeting. The authors have no conflicts of interest to declared.

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Research Article

Can dynamic thiol-disulfide homeostasis be an effective marker in the diagnosis of nodular goiter and thyroid cancer?

Dinamik tiyol-disülfür homeostazisi nodüler guatr ve tiroid kanseri tanısında etkili bir belirteç olabilir mi?

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Abstract

Aim: The oxidative stress has an important role in thyroid pathologies by nature of thyroid gland. Dynamic thiol-disulfide homeostasis is one of the markers of oxidative stress and its counterpart antioxidants in the body. In our study, the dynamic thiol-disulfide homeostasis was investigated in cases underwent surgery due to thyroid cancer or nodular goiter.

Material and Methods: The study included patients who underwent thyroidectomy in General Surgery Department of Keçiören Teaching and Research Hospital between 01.03.2017 and 01.06.2017. The patients were assigned into groups according to postoperative histopathological examination: group 1 included patients with benign lesion in histopathology report and group 2 included patients with malignant lesions in histopathology report. The patients who had no pathology in sonography and did not undergo surgery were assigned into group 3 as controls. In all patients, venous blood samples were drawn to evaluate dynamic thiol-disulfide homeostasis before surgery.

Results: In the study, 98 cases underwent bilateral total thyroidectomy; 77 of which had benign disease and 21 of which had malignant disease. Native thiol values (μmol/L) were 317.4±4.2, 349.9±7.9 and 299.9±7.9 (p=0) while total thiol values (μmol/L) were 353.5±4.8, 386.5±9.5 and 332.6±8.3 (p=0) and disulfide values (μmol/L) were 18.4±0.5, 20.5±0.7 and 16.7±0.6 (p=0) in group 1 (benign disease), group 2 (malignant disease) and group 3 (controls), respectively. In addition disulfide: native thiol was 5.8±0.1, 5.9±0.2 and 5.7±0.2 (p=0.8) while disulfide: total thiol was 5.2±0.1, 5.4±0.2 and 5.1±0.2 and native thiol: total thiol was 89.9±0.5, 90.7±0.5 and 90.5±1.5 (p=0.4) in group 1, 2 and 3, respectively.

Conclusion: The dynamic thiol-disulfide homeostasis can be used as a marked in the thyroid diseases; however, further studies with larger sample are needed.

Keywords: goiter, thiol-disulfide, thyroid diseases

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Öz

Amaç: Troid glandı doğası gereği troid patolojilerinde oxidatif stresin rolü önemlidir. Dinamik thiol-disulfit dengesi vücuttaki oksidatif stres ve onun dengeleyicisi antioksidanların göstergelerinden birisidir. Çalışmamızda Troid kanseri veya nodüler guatr nedeniyle opere edilen olgularda Dinamik thiol disulfit dengesi düzeylerini araştırdık.

Gereç ve Yöntemler: Keçiören Eğitim ve Araştırma hastanesi Genel Cerrahi kliniğinde 01.03.2017-01.06.2017 tarihleri arasında tiroidektomi operasyonu olan hastalar çalışmaya dahil edildi. Ameliyat sonrası patoloji sonuçları Benign gelenler Grup1, Malign gelenler Grup 2 ve Ultrasonda patoloji saptanmayan ve ameliyat edilmeyen olgular ise Grup 3 Kontrol grubuna dahil edildi. Çalışma grubundan ameliyat öncesi olmak üzere Dinamik thiol-disulfit dengesinin araştırılması için venöz kan örnekleri alındı.

Bulgular: 98 hastaya bilateral total tiroidektomi ameliyatı uygulandı; bunlardan, 77 hastanın patoloji sonuçları benign, 21 hastanın ise malign rapor edildi. Grup 1 (benign), Grup 2 (malign) ve Grup 3 (kontrol) gruplarında sırasıyla Native thiol değerleri (µmol/L) 317.4± 4.2, 349.9± 7.9 , 299.9± 7.9 (p=0), Total Thiol değerleri (µmol/L); 353.5.0±4.8, 386.5±9.5, 332.6± 8.3 (p=0), Disülfit (µmol/L); 18.4 ±0.5 20.5±0.7, 16.7±0.6 (p=0), Disulphide/native thiol 5.8.0±0.1, 5.9±0.2, 5.7± 0.2 (p=0.8), Disulphide/total thiol 5.2±0.1, 5.4±0.2, 5.1± 0.2 (p=0.7) ve Native thiol/total 89.9±0.5, 90.7±0.5, 90.5± 1.5 (p=0.4) olarak saptandı.

Sonuç: Tiroid hastalıkları tanısında Dinamik thiol-disulfit dengesi bir belirteç olarak kullanılabilir ancak geniş serili çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: guatr, tiyol-disülfür, tiroid hastalıkları

Introduction

Oxidative balance is important in the thyroid gland due to oxidative mechanisms involved in thyroid hormone synthesis; and thyroid gland is highly vulnerable against oxidative injury. The thyrocytes produces reactive oxygen metabolites (namely, hydrogen peroxide) which are important in the final step of thyroid hormone synthesis. The excessive or insufficient production of these metabolites may lead thyroid gland injury as a result of DNA strand breaks, mutations or apoptosis. Thus, it has been proposed that oxidative stress may be involved in many disorders in the thyroid gland including thyroid nodules, thyroid cancer or autoimmune thyroiditis [1-4].

In human body, there are several mechanisms to prevent free radical formation and their harmful effects. These mechanisms are generally termed as antioxidants. The antioxidants provide protection against cell damage by preventing free radical formation. There are several thiol compound containing sulfhydryl groups such as glutathione (GSH), cysteine and N-acetylcysteine. Thiols may form disulfide (RSSR) bound against oxidants by oxidation reaction. Under oxidative stress, oxidation of cysteine residues may lead mix disulfide structures between protein thiol groups and low-molecular mass thiols. The disulfides formed may be re-reduced in to thiol groups; thus, dynamic thiol-disulfide homeostasis can be maintained.

The dynamic thiol-disulfide homeostasis is one of the markers for oxidative stress which is implied in the pathogenesis of thyroid nodules and thyroid cancers and its counterpart antioxidants [4]. In this study, we intended to investigate role of dynamic thiol-disulfide homeostasis in the pathogenesis of nodular goiter and thyroid cancer.

Material and Methods

The study was approved by Ethics Committee on Clinical Research of Keçiören Teaching and Research Hospital. The study included patient who underwent surgery due to giant goiter, malignant cytology, follicular neoplasm, AUS/FUS and with cosmetic indication at General Surgery Department of Keçiören Teaching and Research Hospital between 01.03.2017 and 01.06.2017. The patients with hyperthyroidism, hypothyroidism, cardiovascular disease, diabetes mellitus chronic hepatic or renal disease and those with history of smoking and alcohol consumption were excluded. The patients who had no nodule on thyroid sonography and normal thyroid functions tests were included as controls.

In the study and control groups, the venous blood samples were drawn into EDTA tubes following 12-hours fasting in order to assess thiol-disulfide homeostasis. Plasma was obtained by

centrifugation at 1500 rpm over 10 minutes. Plasma samples were stored at -80°C until assays. During thiol-disulfide homeostasis tests, disulfide bounds were initially reduced to form free functional thiol groups. Formaldehyde was used to remove sodium borohydride unused and consumed. Total thiol (-SF+-S-S) and native thiol (-SH) levels were quantified using Ellman's and modified Ellman's reagents. The amount of native thiol was subtracted from total thiol; the difference was divided by two, indicating amount of dynamic disulfide bounds (-S-S). Using these parameters, ratios for disulfide: native thiol [(-S-S-)x100 (-SH)], disulfide total thiol [(-S-S-)x100/(-SH+-S-S-) and native thiol: total thiol [(-SH)x100/(-SH+-S-S-) were calculated.

In the study groups, total thyroidectomy or lobectomy with isthmusectomy were performed based on the diagnosis. The patients were assigned into groups according to postoperative histopathological examination: group 1 included patients with benign lesion in histopathology report and group 2 included patients with malignant lesions in histopathology report. The patient who had no pathology in sonography and did not undergo surgery were assigned into group 3 as controls.

Statistical analyses were performed using SPSS version 22. Chi-square test was used to compare groups regarding gender. The normal distribution of variables across benign and malignant groups were assessed using visual plots and analytic methods. Variables with normal distribution were compared using Student's t test. Variables with skewed distribution were compared using Mann Whitney U test. The normal distribution of variables across benign, malignant and control groups were assessed using visual plots and analytic methods. Variables with normal distribution were compared using Kruskal-Wallis test across groups. Variables with skewed distribution were compared using one-way ANOVA. The homogeneity of variance was assessed using Levene's test. In case of statistical significant across groups, binary comparisons were performed using post-hoc Tukey test. A p value<0.05 was considered as statistically significant.

Results

In the study groups underwent surgery due to thyroid gland pathology, there were 60 women (77.9%) and 17 men (22.1%) in the group 1 (benign disease) whereas 19 women (90.4%) and 2 men (9.6%) in the group 2 (malignant disease). In the control group, there were 34 women (68.0%) and 16 men (32.0%). Mean age was 51.2±1.5 years in the group 1, 48.0±3.1 years in the group 2 and 39.7±2.2 years in the group 3. There was no significant difference in gender distribution across groups. Among patients underwent surgery, histopathological examination reported as benign disease (nodular hyperplasia, benign colloidal nodule, lymphocytic thyroiditis, Hashimoto thyroiditis) in 77 (78.6%) and malignant disease in 21 (21.4%). Of 21 patients with malignant pathology, 19 (90.5%) had papillary carcinoma while 2 (9.5%) had follicular carcinoma (Table 1).

Native thiol values (µmol/L) were 317.4±4.2, 349.9±7.9 and 299.9±7.9 (p=0) while total thiol values (µmol/L) were 353.5±4.8, 386.5±9.5 and 332.6±8.3 (p=0) and disulfide values (µmol/L) were 18.4±0.5, 20.5±0.7 and 16.7±0.6 (p=0) in group 1 (benign disease), group 2 (malignant disease) and group 3 (controls), respectively. In addition disulfide: native thiol was 5.8±0.1, 5.9±0.2 and 5.7±0.2 (p=0.8) while disulfide: total thiol was 5.2±0.1, 5.4±0.2 and 5.1±0.2 and native thiol: total thiol was 89.9±0.5, 90.7±0.5 and 90.5±1.5 (p=0.4) in group 1, 2 and 3, respectively.

Table 2. Demographic characteristics of the groups

		Group 1 (Benign) (n:77)	Group 2 (Malignant) (n:21)	Group 3 (Control) (n:50)	P value
Age		51.2±1.5	48.0±3.1	39.7±2.2	0.0*
Sex	Female	60 (77.9%)	19 (90.4%)	34 (68%)	0.1**
	Male	17 (22.1%)	2 (9.6%)	16 32%)	
		Nodular hyperplasia n:32 (41.6%)	Papillary carcinoma n:19 (90.5%)		
		Benign colloidal nodule n:34 (44.2%)	Follicular carcinoma n:2 (9.5%)		
		Follicular adenoma n:4 (5.2%)			
		Lymphocytic thyroiditis n:5 (6.5%)			
		Hashimato's thyroiditis n:2 (2.6%)			

* One-way ANNOVA test
** Chi-square test

Discussion

Reactive oxygen species and free radicals play role in many metabolic processes in the human body. There is a physiological balance between ROS production and detoxification. The disruption of the balance due to internal or external factors results in oxidative stress, playing major role in the pathogenesis of many disorders. Hydrogen peroxide (H2O2) generated by NADPH oxidase is a form of ROS, which is ubiquitously produced by every single cell in the body at varying amounts. The amounts of H2O2 produced above physiological levels leads oxidative stress, resulting in DNA damage and mutations. Thyroid gland has an oxidative nature as substantial amount of ROS, particularly H2O2, is essential for thyroid hormone synthesis. It has been shown that antioxidant enzymes such as superoxide dismutase (SOD), glutathione (GSH), peroxidase (GSH-Px) and catalase as well as α- and γ-tocopherols, Co-enzyme Q and ascorbic acid have a role in the thyroid gland. Among antioxidants, peroxiredoxins (Prxs) have an unique value due its role in H2O2 elimination and prevention of H2O2-associatdd apoptosis [2, 6]. In our study, we aimed to investigate the oxidative stress and antioxidant homeostasis in the thyroid glands where oxidative stress is intense, and to clarify their role in the disease pathogenesis.

Thiol compounds containing sulfhydryl groups are involved in the thiol-disulfide homeostasis, including glutathione (GSH), cysteine or N-acetylcysteine with antioxidant effects. Thiols can form disulfide bounds (RSSR) by oxidation reaction against oxidants. Under oxidative stress, oxidation of cysteine residues may lead mix disulfide structures between protein thiol groups and low-molecular mass thiols. The disulfides formed may be re-reduced in to thiol groups; thus, dynamic thiol-disulfide homeostasis can be maintained [7]. In our study, w evaluated oxidative balance underlying thyroid pathologies through thiol-disulfide homeostasis.

Given that goiter is frequently seen with familial pattern and compatible with autosomal dominant inheritance, the genetic factors as well as environmental factors are commonly proposed as underlying mechanisms. The nodule formation is triggered by oxidative stress due to oxidative nature of thyroid hormone synthesis or induced due to factors such as iodine deficiency or smoking. If antioxidant defense system fails, this may cause nodule formation by leading DNA damage and mutations [8]. In our study, disulfide and thiol levels were significantly higher in patients with nodular goiter when compared to controls. The higher levels of disulfide compared to controls showed the role of oxidative stress in nodular goiter. However, thiol levels were also significantly higher when compared to controls. In agreement with our study, Bilginer et al. reported higher thiol levels, albeit insignificant, in benign thyroid diseases when compared to control group [13].

In cancer, redox equilibrium is also impaired; preventing antioxidant and detoxification proteins to counter oxidative stress by increasing intra- and extra-cellular ROS levels. The oxidative stress triggered leads development of malignant phenotype by inducing several processes such as angiogenesis, proliferation, invasion and apoptosis [2, 3, 9]. In the studies on oxidative state in thyroid cancers, high levels of oxidants were detected; however, antioxidant levels might vary. The

SOD activity was found to be lower when compared to normal tissues in the studies by Sugawara et al. and Durak et al. while Akıncı et al. observed a slight decrease in preoperative SOD values after surgery in patients underwent thyroidectomy [10-12]. In our study, disulfide levels as well as thiol values were found to be significantly higher when compared to controls.

In the study by Bilginer et al., 81 cases underwent surgery due to thyroid pathology and they were assigned into benign and malignant disease groups after surgery. The study groups were compared with controls. It was found that native thiol (µmol/L) was found to be 457.47 ± 62.38, 453.19 ± 63.49 and 444.81 ± 71.9 (p=0.477) while total Thiol (µmol/L) was 497.09 ± 64.78, 487.45 ± 67.87, and 474.61 ± 75.48, and disulfide (µmol/L) was 19.85 ± 11.28, 16.07 ± 9.28, 14.87 ± and 7.62 0.191 across groups. Although total thiol, native thiol and disulfide levels were found to be higher in malignant disease group when compared to benign disease and control groups, the difference did not reach statistical significance (13). In our study, native thiol values (µmol/L) were 349.9± 7.9 , 317.4± 4.2 and 299.9± 7.9 (p=0) while total Thiol values (µmol/L) were 386.5±9.5, 353.5.0±4.8, and 332.6± 8.3 (p=0) and disulfide values (µmol/L) were 18.4 ±0.5 20.5±0.7, 16.7±0.6 (p=0) in group 1, 2 and 3, respectively. In agreement with the study by Bilginer et al., total thiol, native thiol and disulfide values were found to be significantly higher in malignant group when compared to benign and control groups. This can be explained by oxidative nature of thyroid gland. Given the oxidative nature, it may result in higher antioxidant release even under oxidative stress.

In our study, there were 21 patients with thyroid cancer. Due to limited number of cases, it is difficult to draw conclusions about use thiol-disulfide homeostasis as a marker in the thyroid cancer. In addition, the mechanisms underlying thyroid pathologies are different; however, we classified these pathologies in two major groups as benign and malignant. We think that it will more appropriate to investigate thyroid pathologies separately, requiring studies with larger sample size. However, our study is valuable in clarifying role of thiol-disulfide homeostasis in thyroid pathologies.

Conclusion

Oxidative stress has an important role in the thyroid pathologies due to nature of thyroid gland. Oxidants are involved in thyroid cancer process. Thiol-disulfide homeostasis, a marker of oxidative state, can be a marker in thyroid pathologies. Further studies with larger sample size are needed in this issue.

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Research Article

Comparison of angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker treatments of patients in 3 different patient groups with proteinuria

Proteinürisi olan 3 farklı hasta grubunda hastaların anjiotensin dönüştürücü enzim inhibitörü ve/veya anjiotensin reseptör blokörü tedavilerinin karşılaştırılması

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Abstract

Aim: To evaluate the efficacy and safety of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) for proteinuria in three different patient groups with chronic kidney disease (CKD).

Material and Methods:168 patients with diabetic nephropathy, glomerulonephritis, and renal transplantation who had more than 1 gram of daily urinary protein excretion were enrolled. The patients were divided into three groups: group 1 users of ACE inhibitors, group 2 users of ARBs, and group 3 users of both ACE inhibitors and ARBs. The clinical and laboratory parameters recorded for the patients included comorbid diseases, medications, blood urea nitrogen, creatinine, potassium, 24-hour urinary protein excretion, and creatinine clearance. Laboratory tests were recorded for months 0-1-3-6-9-12-18-24. Echocardiographic changes were recorded for months 0 and 24.

Results: In all three groups, a statistically significant decrease was observed between the proteinuria levels at month 0 and all other months. Patients receiving ACE inhibitors and ARBs had significantly higher creatinine levels after the 9th month. The patients in group 1 showed a significant decrease in creatinine clearance after the 9th month of the study. In contrast, patients in group 3 showed a significant decline after the 12th month of the study. In group 2, patients using ARBs showed no significant decrease in creatinine clearance.

Conclusion: Patients with proteinuria greater than 1g per day should receive ACE inhibitors or ARB treatment, and combined therapy of ACE inhibitors and ARBs should only be used in selected patients who can be closely monitored.

Keywords: Proteinuria, ACE inhibitors, ARB, RAAS inhibitors

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Öz

Amaç: Proteinürisi olan üç farklı hasta grubunda anjiyotensin dönüştürücü enzim (ACE) inhibitörleri ve anjiyotensin reseptör blokörlerinin etkinlik ve güvenliliğini değerlendirmek

Gereç ve Yöntemler: 24 saatlik idrarda 1 gramdan fazla proteinürisi olan diyabetik nefropati, glomerülonefrit ve böbrek transplantasyonu tanısı olan 168 hasta çalışmaya alındı. Hastalar 1. grup ACE inhibitörü kullananlar, 2. grup anjiyotensin reseptör blokörü (ARB) kullananlar ve 3. grup hem ACE inhibitörü hem de ARB kullananlar olarak üç gruba ayrıldı. Hastaların eşlik eden hastalıkları, kullandığı ilaçlar ve kan üre nitrojeni, kreatinin, potasyum, 24 saatlik idrar protein atılımı, kreatinin klirensini içeren laboratuvar değerleri 0-1-3-6-9-12-18-24.aylarda kaydedildi. Hastaların çalışma başlangıcı ve takibi sonunda ekokardiyografik değişiklikleri kaydedildi.

Bulgular: Her üç grupta da 0. aydaki proteinüri değerleri ile diğer tüm aylardaki proteinüri değerleri arasında istatistiksel olarak anlamlı bir düşüş gözlendi. Hem ACE inhibitörü hem de ARB'leri kullanan grup 3 hastalarda 9. aydan itibaren kreatinin seviyeleri anlamlı derecede yükseldi. Grup 1'deki ACE inhibitörü kullanan hastalarda takibin 9. ayından sonra kreatinin klirensi değerlerinde anlamlı bir azalma saptanırken, grup 3'teki ACE inhibitörü ve ARB kullanan hastaların 12. aydan sonra kreatinin klirensleri değerlerinde istatiksel olarak anlamlı bir düşüş saptandı. Grup 2'de ARB kullanan hastalarda kreatinin klirensinde anlamlı bir azalma görülmedi.

Sonuç: 24 saatlik idrarda 1 g'dan yüksek proteinürisi olan hastalar ACEi veya ARB tedavileri almalı ve ACE inhibitörü ve anjiotensin reseptör blokörlerinin kombine tedavisi ise sadece yakından izlenebilecek seçilmiş hastalarda kullanılmalıdır.

Anahtar kelimeler: Proteinüri, ACEi, ARB, RAAS inhibitörleri

Introduction

Chronic kidney disease (CKD) is characterized by a reduction in kidney function, indicated by a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m2 or the presence of kidney damage markers, or both, for at least three months, regardless of the underlying etiology [1]. The global prevalence of CKD is estimated to range from 8% to 16% [2]. The renin-angiotensin-aldosterone system (RAAS) has been a critical therapeutic target for CKD patients with proteinuria [3-5]. Recent guidelines include using ACE inhibitors (ACEi) or angiotensin receptor blockers (ARB) as the first line of treatment. Recent studies have shown that inhibition of RAAS is effective in regulating blood pressure (BP), reducing proteinuria, decelerating the advancement of renal disease, and facilitating the prevention of cardiovascular disease (CVD) [4,6]. Reducing proteinuria may decrease the risk of disease progression.

This study aimed to evaluate proteinuria, renal function tests, GFR changes, and two-year follow-up results under ACEi and ARB treatment in different patient groups with proteinuria above 1g/day.

Material and Methods

A total of 162 patients with proteinuria of 1 g/day and above, diabetic nephropathy, glomerulonephritis, and kidney transplantation between 2009 and 2015 at the Ankara Baskent University Hospital Nephrology Department participated in the study. The 2-year data of the patients was evaluated. The study did not include patients using sirolimus due to its proteinuric effect in renal transplant recipients. Patients were divided into three groups: using ACE inhibitors (group 1), using ARB (group 2), and using ACE inhibitors and ARB (group 3). Each patient's demographic, clinical, and laboratory values were recorded retrospectively. Patients' age, gender, 0-1-3-6-9-12-18-24th months creatinine, creatinine clearance, potassium, proteinuria levels in 24-hour urine, drugs, echocardiography findings at 0 and 24 months, comorbidities, and proteinuria etiologies were recorded. The patient's 24-hour urine proteinuria was measured with the turbidimetric method. The local ethics committee approved the study.

Statistical analysis

The Statistical Package for Social Sciences version 15.0 software was used to evaluate the data. Descriptive statistical data are expressed as frequency, number, mean standard deviation, or median (min-max). The Kolmogorov-Smirnov test evaluated the distribution properties of the numeric variables. The independent-sample t-test was used for intergroup comparisons of numeric variables with a normal distribution, and Mann-Whitney's U test was used for variables without a normal distribution. Categorical data were evaluated using Fisher's Exact Test and the chi-square test. The evaluation was made with the "Monte Carlo Simulation Method" to include these frequencies in the analysis with the criteria where the

expected frequencies are less than 20%. The p <0.05 and p <0.01 values were considered statistically significant.

Results

The mean age of the patients in the study was 47.56 ± 14.37 years. Of the patients, 60.5% (n:98) were female. The patients' proteinuria was categorized based on the following etiologies: 19.1% diabetic nephropathy, 45.7% glomerulonephritis, and 35.2% renal transplant recipients. The prevalence of hypertension was 52.5%, diabetes mellitus was 32.7%, coronary artery disease was 16%, and cerebrovascular disease was 6.2% of patients. The clinical characteristics of the patients are shown in Table 1. When the causes of end-stage renal disease of the renal transplant recipients were evaluated in terms of etiology, 47% were glomerulonephritis, 21% were idiopathic, 18% were hypertension, and 14% were diabetic nephropathy.

Table 1. Clinical characteristics of the patients

		(n=162)	%
Gender	Female	98	60.5
	Male	64	39.5
Age	≤25	5	3.1
	>25 ve ≤45	75	46.3
	>45 ve ≤65	62	38.3
	>65	20	12.3
	Mean ± SD: 47.56 ± 14.37, Median: 46.0		
Other disease	Hypertension	85	52.5
	Coronary Artery Disease	26	16
	Diabetes Mellitus	53	32.7
	Previous Cerebrovascular Event	10	6.2
Proteinuria Etiology	Diabetic Nephropathy	31	19.1
	Glomerulonephritis	74	45.7
	Renal Transplantation	57	35.2

In this study, 34% of the patients (n:55) received ACE inhibitors, 36.4% (n:59) received ARBs, and 29.6% of the patients (n:48) were using both ACE inhibitors and ARBs concurrently (Table 2).

Table 2. The distribution of drug use among patients

Drug	Using		Not using		Total	
	n	%	n	%	n	%
ACEi	55	34	107	66	162	100
ARB	59	36.4	103	63.6	162	100
ACEi+ ARB	48	29.6	114	70.4	162	100
Corticosteroid	127	78.4	35	21.6	162	100
Cyclophosphamide	22	13.6	140	86.4	162	100
Cyclosporine	72	44.4	90	55.6	162	100
Azathioprine	9	5.6	153	94.4	162	100
Tacrolimus	37	22.8	125	77.2	162	100
Mycophenolate Mofetil	59	36.4	103	63.6	162	100
Beta Blocker	25	15.4	137	84.6	162	100
Calcium Channel Blocker	26	16	136	84	162	100

In all three groups, a statistically significant decrease was observed between the proteinuria levels at month 0 and the mean proteinuria levels at months 1, 3, 6, 9, 12, 18, and 24 (p <0.005). (Figure 1).

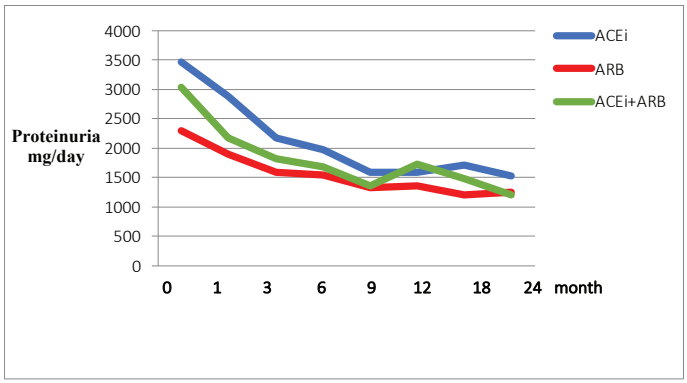

Figure 1. Change of proteinuria levels over time according to drug subgroups

When creatinine levels were evaluated in the groups, there was a statistically significant increase between the 0th and the 24th months of patients group 1 (p = 0.023). In addition, a statistically significant increase was observed in the mean creatinine levels at the 9th, 12th, and 18th months in group 3 using ACE inhibitors and ARBs. (p = 0,034, p = 0,049, p = 0,025) (Figure 2).

When the creatinine clearance of the groups was evaluated, a statistically significant decrease was observed between the creatinine clearance levels at month 0 and the mean creatinine clearance levels at months 9, 18, and 24 in group 1. (p=0.017, p=0.015, p=0.00). Also, in group 3, there was a statistically significant decrease between the creatinine clearance value at month 0 and the mean creatinine clearance value at months 12, 18, and 24. (p=0.025, p=0.015, and p=0.033). In group 2, patients using ARBs showed no significant decrease in creatinine clearance (Figure 3).

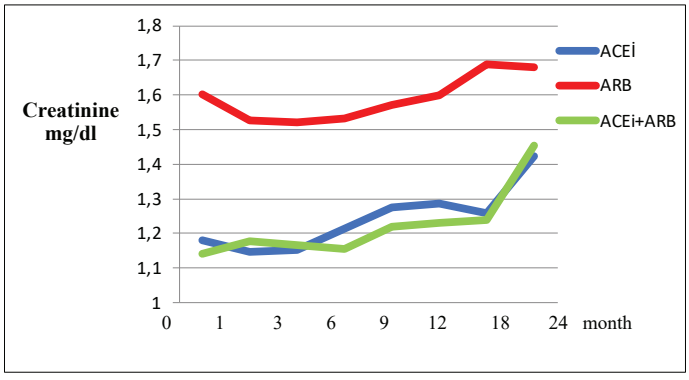

Figure 2. Change of creatinine levels over time according to drug use

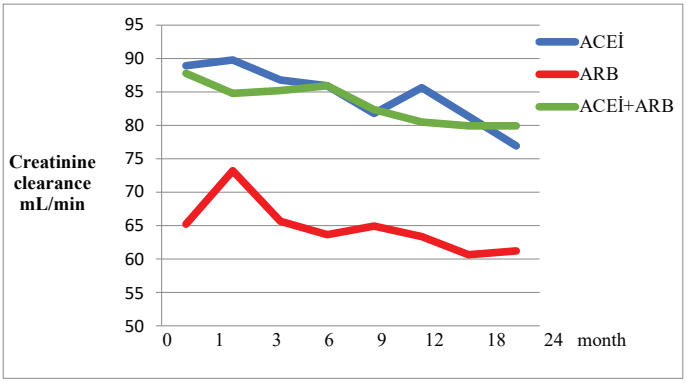

Figure 3. Change of creatinine clearance by drug groups over time

In addition, when the potassium levels were examined, a statistically significant decrease was observed in potassium levels between the 0th and 3rd months in only group 2 using ARBs (p = 0.043) (Figure 4).

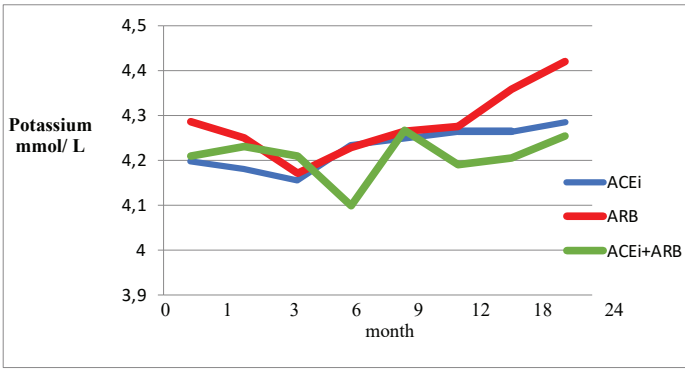

Figure 4. Change of potassium levels over time according to drug subgroups

Ejection fraction (EF) was evaluated by transthoracic echocardiography at the beginning and end of the two-year follow-up. There was no significant change in EF in the three groups. Also, there was no statistically significant difference between the groups when the groups were examined for left ventricular concentric hypertrophy (LVH) based on drug usage.

Discussion

In this study, a statistically significant decrease was observed between the proteinuria levels at month 0 and the mean control proteinuria levels in all other months in all three groups. It is known that there is a relationship between urinary protein excretion, treatment response, and progression of CKD in non-diabetic patients [7-9]. On the other hand, studies on proteinuria treatment and its effects in patients with type 2 diabetes are not sufficient [5,10]. It has been shown that antihypertensive treatments with RAS inhibitors provide more benefit than other treatments in patients with CKD with proteinuria [3]. While most of the studies in nondiabetic proteinuric patients were on ACE inhibitors, studies on the renoprotective effect of ARBs were mainly conducted on patients with diabetic nephropathy [12,13]. Although they have renoprotective effects similar to those of ACE inhibitors in nondiabetic CKD, supporting information is limited [11-13]. In this study, regardless of the primary disease, the decrease in proteinuria detected in the early period shows that ACE inhibitors and ARBs are beneficial in controlling proteinuria; combined use does not have an additive or synergistic effect. However, in selected patients with uncontrolled proteinuria with ACE inhibitors or ARBs alone, their concomitant use, even at the minimum dose, did not produce dangerous side effects. In the meta-analysis of randomized studies, there is evidence supporting the benefit of ACE inhibitors and ARBs in patients with proteinuria; the decrease in proteinuria is greater than that induced by other antihypertensive drugs. Although a meta-analysis showed that ARBs were more effective than ACEIs in reducing proteinuria in hypertensive patients, another recent meta-analysis found that treatment with ARBs and ACEIs had similar effectiveness in improving blood pressure and preventing progression of proteinuria/albuminuria. In the same way, the data we obtained in our study suggest that ARBs are at least as beneficial as ACE inhibitor treatments [14-17]. This study indicates that the treatment of ARBs is at least as beneficial as ACE inhibitors. This suggests that ARBs may be appropriate, especially in patients with severe side effects such as cough or angioedema that limit the use of ACE inhibitors.

In a meta-analysis of 1860 nondiabetic patients with CKD treated with a placebo or other antihypertensive medications, ACE inhibitors had a substantially lower progression rate of end-stage renal disease (ESRD) than other medications. RAAS blockade has an antiproteinuric effect even when the protein level mentioned in the discussion is below 1 g/day. However, its effects are more pronounced in patients with 1 g/day[18]. In our study, proteinuria levels are at least 1000 mg/day; it seems impossible to comment on the effects of ACE inhibitors and ARB use in patients with moderate proteinuria. On the other hand, at the end of the two-year follow-up, there was an increase in creatinine levels in patient group 1. This increase became statistically significant in the 9th month in the group 3. This can be interpreted as potentiating the adverse effects of both drug groups on renal function over each other. However, it should be emphasized that none of the patients developed ESRD, even in the combination group. Using an ACE in-

hibitor with an ARB, one of which is the minimal dosage, could treat persistent proteinuria. A meta-analysis of 12 studies of proteinuric patients with severe or moderately severe albuminuria confirmed that ACE inhibitors and ARBs reduce CKD progression. The incidence of ESRD is lower in treatments with ACE inhibitors and ARB treatments [19]. The 2-year follow-up period in this study may be why we did not see any patients progressing to ESRD. A 5-year follow-up of the same patient groups will provide a more appropriate interpretation of the effects on renal and patient survival.

The creatinine clearance levels of patients in group 1 decreased significantly from the 9th month, while those in group 3 receiving combined drug therapy were statistically significant from the 12th month. Group 2 patients saw no significant decrease in creatinine clearance. The study showed that GFR levels could only be maintained in group 2, even though the decline in creatinine clearance is a normal consequence of the CKD course. However, proteinuria control was achieved in all three groups.

When the patients' potassium levels were analyzed, a statistically significant decrease was observed between the patient's potassium levels in group 2 at the 0th month and the 3rd month ($p=0.04$). The fact that the patients were warned about potassium-containing foods and drinks and were followed very closely may explain the successful results in hyperkalemia. However, due to the many negative examples in the literature, patients who can be followed closely and follow a potassium-restricted diet without exception should be preferred for the combined use of ACE inhibitors and ARBs [20].

Comparing the groups for LVH according to treatment revealed no statistically significant differences. When the patients were grouped according to the diagnoses, there was no significant difference between the groups. It is known that both ACE inhibitors and ARBs have positive effects on cardiac remodeling [21,22]. Although our study did not demonstrate a significant positive impact on EF and LVH, the deterioration of cardiac functions can be prevented. We decide that the control of albuminuria, which has been independently proven to have adverse effects on cardiac functions, is the primary determinant of this condition.

In our study, no side effects were observed that could lead to the discontinuation of the treatment or exclusion of the patients from the study. This can be interpreted as the fact that most of the chronic kidney disease stages of the selected and included patients were at stage 3, and the risk of hyperkalemia was relatively low. Again, the follow-up period is limited to 2 years, which may be sufficient for the emergence of positive effects on proteinuria but insufficient for the evaluation of all kidney functions. Inadequate duration also applies to possible positive cardiac effects.

Conclusion

In conclusion, patients with proteinuria above 1g/day should initiate ACE inhibitor or ARB therapy, regardless of the underlying disease. In patients with uncontrolled proteinuria, concomitant administration of ACE inhibitors and ARBs may be safe only in a select group of compliant, closely monitored patients. Even though the use of ACE inhibitors and/or ARBs negatively affects renal function, 2-year follow-up results indicate that this negative impact does not lead to the progression of end-stage renal disease in patients.

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Authors' contributions to the article

Conception and design of the study: ZME, CBS

Generation, collection, assembly, analysis, and/or interpretation of data; ZME, CBS

Drafting or revision of the manuscript; ZME, CBS

Approval of the final version of the manuscript; ZME, CBS

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Araştırma Makalesi

Adjuvant platin bazlı tedavi verilen evre ıib-ıiıa küçük hücreli dışı akciğer kanseri hastalarında adjuvant tedaviye kadar geçen sürenin hastalıksız sağkalıma etkisi

The impact of timing adjuvant therapy on disease-free survival among patients with stage iib-iiia non-small cell lung cancer receiving platinum-based treatment

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Öz

Amaç: Küratif cerrahi rezeksiyon geçiren ve adjuvan tedavi verilen küçük hücreli dışı akciğer kanseri hastalarında adjuvan tedaviye kadar geçen sürenin hastalıksız sağ kalımla ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmamızda 2010-2020 yılları arasında küratif cerrahi rezeksiyon geçirmiş ve adjuvan tedavi alan evre IIB-IIIA hastalar retrospektif olarak değerlendirildi. Tedaviye 6 haftadan önce ve sonra başlayanlar olarak kategorize edilip radyolojik nükse kadar geçen zaman hesaplandı.

Bulgular: Toplam 89 hasta değerlendirildi. Hastaların 52'sinde adjuvan tedavi ameliyattan sonra 6 içinde başlamışken 37'sinde ise 6 haftadan sonra başladı. Tedaviye 6 haftadan sonra başlanan hastalarda hastalıksız sağkalım istatistiksel olarak anlamlı derecede daha düşük bulundu (p=0,014). Ayrıca çok değişkenli analizde ECOG performans skorunun 0 olması ve adjuvan tedaviye 6 haftadan önce başlanması bağımsız prognostik faktörler olarak bulundu (p=0,001, p=0,045)

Sonuçlar: Küratif rezeksiyon uygulanan ve adjuvan tedavi planlanan küçük hücreli dışı akciğer kanseri hastalarında tedaviye 6 haftadan sonra başlamak hastalıksız sağkalımı kısaltmıştır. Bulgularımıza göre tedaviye 6 haftadan önce başlanması önerilmektedir.

Anahtar Kelimeler: Akciğer kanseri, Adjuvan, Kemoterapi, Hastalıksız sağkalım

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Abstract

Aim: We aimed to investigate the relationship between time to adjuvant therapy and disease-free survival in patients with non-small cell lung cancer who underwent curative surgical resection and received adjuvant therapy.

Material and Methods: In our study, stage IIB-IIIA patients who underwent curative surgical resection and received adjuvant therapy between 2010 and 2020 were retrospectively evaluated. They were categorized as those who started treatment before and after 6 weeks, and the time to radiologic recurrence was calculated.

Results: A total of 89 patients were included. Adjuvant treatment was started within 6 weeks after surgery in 52 patients and after 6 weeks in 37 patients. Disease-free survival was statistically significantly lower in patients who started treatment after 6 weeks (p=0.014). In addition, ECOG performance score of 0 and starting adjuvant treatment before 6 weeks were found to be independent prognostic factors in multivariate analysis (p=0.001, p=0.045).

Conclusions: In patients with NSCLC who underwent curative resection and planned adjuvant treatment, starting treatment after 6 weeks shortened disease-free survival. According to our results, it is recommended to start treatment before 6 weeks.

Keywords: Lung cancer, adjuvant, chemotherapy, disease-free survival

Giriş

Dünya çapında, akciğer kanseri 2020'de tahmini 1,8 milyon ölüme neden olmuştur[1]. Bununla birlikte, muhtemelen tarama ve tedavideki ilerlemeler (hedefe yönelik tedaviler ve immünoterapi) nedeniyle tanı sonrası sağkalım iyileşmiştir[2]. Tedavideki olumlu gelişmelere rağmen akciğer kanseri, meme, prostat, kolorektal ve beyin tümörlerinin toplamından daha fazla ölüme neden olmaktadır[3]. Evre I, II veya III küçük hücreli dışı akciğer kanseri (KHDAK) olan hastalar, küratif cerrahi rezeksiyondan sonra bile nüks ve ölüm açısından önemli risk altındadır. Küratif tedaviye rağmen Evre IB hastaların %25'i, evre II hastaların %35-50'si ve evre III hastaların çoğunluğu nüks eder ve bu hastalık nedeniyle ölürler[4].

Modern platin bazlı rejimler kullanılarak adjuvan kemoterapi (KT) ile iyileştirilmiş sağkalım, en büyük beş çalışmadan alınan bireysel hasta verilerini birleştiren LACE meta-analizinde gösterilmiştir. Medyan takip süresi 5,2 yıl olan ve tamamen rezeke edilmiş KHDAK'li 4584 hastanın birleştirilmiş analizinde, adjuvan KT uygulanan hastalarda , KT uygulanmamasına kıyasla 5 yıllık ölüm riskinde %5,4'lük bir azalma ile ilişkilendirilmiştir (HR 0,89, %95 CI 0,82- 0.96)[5]. Sağkalım üzerindeki olumlu etki evreye göre değişmekle birlikte, istatistiksel anlamlılık yalnızca evre II ve IIIA hastalığı olan hastalarda görülmüştür.

Tamamen rezeke edilmiş evre II ve III KHDAK hastalar için, ASCO (American Society of Clinical Oncology) ve Cancer Care Ontario kılavuzları adjuvan platin bazlı ikili KT önermektedir [6, 7]. Adjuvan KT'nin optimal zamanlaması tam olarak tanımlanmamakla birlikte birçok klinisyen, cerrahi rezeksiyondan sonraki 6 hafta içinde KTye başlamayı desteklemektedir[8, 9]. Bununla birlikte, hastalar postoperatif adjuvan tedaviyi tolere etme durumları bakımından önemli ölçüde farklılık gösterebilir [10].

Hastanın performans durumu, yapılan cerrahinin tipi ve postoperatif komplikasyonlar gibi birçok faktör, postoperatif dönemde hastanın sistemik tedaviyi tolere etme yeteneğini etkileyebilir[11]. Son zamanlarda, kolon ve meme kanserinde yapılan çalışmalarda, adjuvan tedavinin gecikmesinin, tedavi başarısını düşürdüğü gösterilmiştir[12, 13]. Özellikle akciğer kanserli hastaların, ileri yaş, sigaraya bağlı akciğer hastalığı ve postoperatif komplikasyonlar nedeni ile ameliyattan sonra ameliyat öncesi performans durumlarına dönmeleri zaman almaktadır[14]. Bu nedenle, adjuvan KT'ye başlama zamanı ile etkinliği arasındaki ilişki, klinik uygulama ile oldukça önemlidir.

Çalışmamızın amacı, küratif cerrahi rezeksiyon sonrası adjuvan tedavi verilen patolojik evre IIB-IIIA KHDAK hastalarında ameliyat ile adjuvan tedavi arasındaki sürenin hastalıksız sağkalım ile arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler

Çalışmamızda, 2010-2020 yılları arasında Van Yüzüncü Yıl Üniversitesi Tıp Fakültesi Dursun Odabaşı Tıp Merkezi onkoloji kliniğinde takip ve tedavisi yapılan KHDAK hastaların dosyaları retrospektif olarak tarandı. Çalışmaya, 18 yaşından büyük, neoadjuvan tedavi almadan opere olan, metastatik olmayan, postoperatif patolojik evresi IIB-IIIA olan, KHDAK tanısı histopatolojik olarak verifiye edilen, cerrahi sınırı negatif olan ve verilerine eksiksiz ulaşılabilen hastalar dahil edildi. 18 yaşından küçük, birden fazla primer malignitesi olan, küçük hücreli akciğer kanseri tanılı, metastatik, küratif operasyon yapılmayan hastalar, adjuvan tedavi almayan, neoadjuvan tedavi alan ve verilerine ulaşılamayan hastalar hariç tutuldu.

Tümör evrelemesi; patolojik tümör, lenf nodu, metastaz (pTNM) 8. Baskısına göre yapıldı Hastalıksız sağkalım, operasyon tarihinden radyolojik nükse kadar geçen süre, genel sağkalım, hastanın ameliyat tarihinden itibaren ölüm tarihi veya son takip tarihine kadar geçen süre olarak hesaplandı.

İstatistisel Analiz

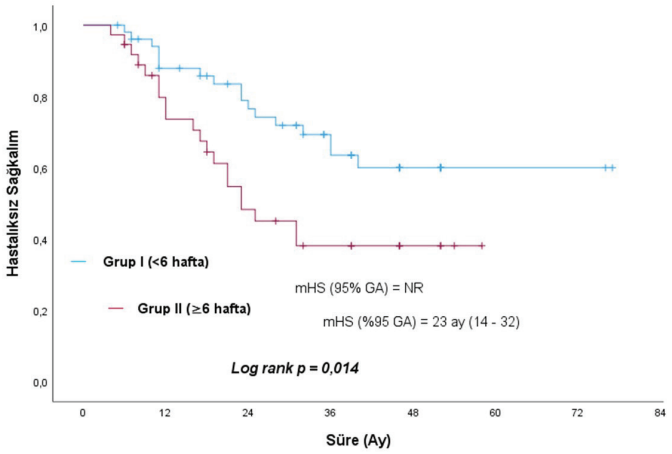
Kategorik değişkenler sayı (%), sayısal değişkenler ortalama ±standart sapma (SS) olarak gösterildi. Sayısal değişkenlerin normal dağılıma uygunluğu Kolmogorov-Smirnov, Shapiro-Wilk testleri ve histogramlar aracılığıyla değerlendirildi. Sayısal değerler normal dağılım gösterdiği için iki bağımsız grup student t testi ile karşılaştırıldı. Kategorik değişkenlerin karşılaştırmasında uygunluğa göre ki-kare ya da Fisher exact test kullanıldı. İkiden fazla kategorik değişken posthoc Bonferroni düzeltmesi ile değerlendirildi. Sağkalım süreleri adjuvan KT başlangıç tarihinden itibaren Kaplan Meier analizi ile hesaplandı ve gruplar Log-rank testi ile karşılaştırıldı. Tek değişkenli analizde p<0,20 elde edilen değişkenler çok değişkenli Cox regresyon modeline dahil edildi. P değerinin 0,05'in altında olduğu değerler istatistiksel anlamlı olarak kabul edildi. İstatistiksel analizler IBM SPSS Statistics for Windows, version 29 (IBM Corp., Armonk, N.Y., USA) ile yapıldı.

Sonuçlar

Toplam 89 hasta değerlendirildi. Hastaların tanı anındaki yaş ortalaması 57,3 ±7,8 ve çoğunluğu erkekti (%89,9). Ortalama 48 p/yıl sigara öyküsü vardı. Hastaların %92,1'inin ECOG (Eastern Cooperative Oncology Group)performans skoru (PS) 0 idi. Hastaların %51,7'si skuamöz hücreli karsinom (SCC) tanılı iken %46,1'i adenokarsinomdu. Ayrıca hastaların %31,5'i kötü diferansiye idi. Ameliyat sonrası primer tümör %3,8 pT1, %32,5 pT2, %45 pT3, %18.8 pT4 olarak, lenfatik durumu %23,5 pN0 %57,6 pN1 %18,8 pN2 olarak evrelendi. Hastaların %69,4'ünde vasküler invazyon %72,1'inde lenfatik invazyon ve %29,5'inde nöral invazyon izlendi ve hastaların %4,7'sinde perikard tutulumu, %38,7'sinde plevra tutulumu saptandı.. Takipte nüks saptanan 37 (%41,6) hastanın 14'ü lokal-bölgesel, 23'ü uzak bölgede saptandı (Tablo 1).

Tek değişkenli analizde ECOG PS ve tedaviye kadar geçen süre hastalıksız sağkalım ile ilişkili bulundu (p<0,001, p=0,018). Cinsiyeti, patoloji tanı, diferansiyasyon derecesi ve adjuvan tedavi rejimi hastalıksız sağkalım ile istatistiksel olarak ilişkili bulunmadı (p>0,05) (Tablo2). Çok değişkenli analizde ise ECOG PS'nın 0 olması ve adjuvan tedaviye kadar geçen sürenin 6 haftadan kısa olması bağımsız prognostik faktörler olarak bulundu (p=0,001, p=0,045).

Tedaviye kadar geçen sürenin 6 haftadan kısa olan grupta medyan hastalıksız sağkalıma ulaşılmamışken, 6 hafta ve daha fazla süre geçen hastaların medyan hastalıksız sağkalım süresi 23 ay (%95 GA, 14- 32 ay) bulundu. İki grup arasındaki hastalıksız sağkalım farkı istatistiksel olarak anlamlı bulundu (p=0,014) (Şekil 1).



Şekil 1. Hastalıksız sağkalım eğrileri

Tartışma

Çalışmamızda küratif rezeksiyon yapılmış evre IIB-IIIA KHDAK hastalarında adjuvan tedaviye operasyondan 6 hafta sonra başlamanın istatistiksel olarak anlamlı olacak düzeyde kısalttığını saptadık.

Literatürde ameliyat sonrası adjuvan tedaviye başlama zamanı ile ilgili net bir zaman dilimi tanımlanmamıştır. Avrupa Tıbbi Onkoloji Derneği (ESMO) kılavuzları, adjuvan tedavinin ameliyattan sonraki 42 gün içinde başlatılmasını önermektedir[15]. Ancak bu konu ile ilgili prospektif bir çalışma mevcut değildir.

Tablo 1. hasta özelikleri					
Özellikler		Toplaml n = 89 (%) mean ±SD	<6 hafta n=52 (31%) mean ±SD	≥ 6 hafta n=37 (43.1%) mean ±SD	P
Yaş		57.3 ±7.8	56.8 ±6.9	58.1 ±9.0	0.472
Cinsiyet					1.000
	kadın	9 (10.1)	5 (9.6)	4 (10.8)	
	erkek	80 (89.9)	47 (90.4)	33 (89.2)	
Patolojik tanı					0.915
	SCC	46 (51.7%)	26 (50)	20 (54.1)	
	Adenocarcinoma	41 (46.1)	25 (48.1)	16 (43.2)	
	NOS	2 (2.2)	1 (1.9)	1 (2.7)	
Grade					0.894
	1	1 (1.1)	1(1.9)	0	
	2	60 (67.4)	34 (65.4)	26 (70.3)	
	3	28 (31.5)	17 (32.7)	11 (29.7)	
Grade					0.767
	1-2	61 (68.5)	35 (67.3)	26 (70.3)	
	3	28 (31.5)	17 (32.7)	11 (29.7)	
ECOG PS					0.005
	0	82 (92.1)	50 (96.2)a	32 (86.5)a	
	1	5 (5.6)	0a	5 (13.5)b	
	2	2 (2.2)	2 (3.8)a	0a	
Cerrahi tipi					0.250
	Lobektomi	59 (66.3)	37 (71.2)	22 (59.5)	
	Pneumonektomi	30 (33.7)	15 (28.8)	15 (40.5)	
TNM evresi					0.095
	2	43 (48.2)	29 (55.8)	14 (37.8)	
	3	46 (51.7)	23 (44.2)	23 (62.2)	
Adjuvant RT					0.355
	yes	67 (75.3)	41 (78.8)	26 (70.3)	
	no	22 (24.7)	11 (21.2)	11 (29.7)	
Adjuvant KT rejimi					0.830
	Cis + vin	53 (59.6)	33 (63.5)	20 (54.1)	
	Cis + dose	17 (19.1)	9 (17,3)	8 (21.6)	
	Pacli + carbo	12 (13.5)	6 (11.5)	6 (16.2)	
	Cis + gem	7 (7.9)	4 (7.7)	3 (8.1)	
Kür sayısı					1.000
	2	1 (1.1)	1(1.9)	0	
	3	3 (3.4)	2 (3.8)	1 (2.7)	
	4	85 (95.5)	49 (94.2)	36 (97.3)	
Nüks		37 (41.6)	35 (67.3)	17 (45.9)	0.044
Nüks tipi					0.286
	bölgesel	14 (37.8)	8 (47.1)	6 (30.0)	
	uzak	23 (62.2)	9 (52.9)	14 (70.0)	
Son durum					0.016
	hayatta	69 (77.5)	45 (86.5)	24 (64.9)	
	ex	20 (22.5)	7 (13.5)	13 (35.1)	

Tablo 2. tek değişkenli ve çok değişkenli analiz

Özellikler		Tek değişkenli analiz			Çok değişkenli analiz		
		p	HR	95% CI	p	HR	95% CI
Cinsiyet	kadın*	0.548	0.726	0.256-2.060			
ECOG	0*	<0.001			0.001		
	1	<0.001	8.416	2.778-25.498	0.006	5.202	1.623-16.677
	2	0.019	5.656	1.324-24.162	0.012	7.029	1.540-32.084
Patoloji	AC*	0.506					
	SCC	0.247	1.487	0.760-2.907			
	NOS	0.920	1.109	0.146-8.443			
Grade	1-2*	0.167	0.588	0.277-1.248	0.403	0.719	0.332-1.557
Cerrahi	Lobektomi*	0.527	0.801	0.402-1.595			
TNM	2*	0.228	0.817	0.588-1.135			
Adj. RT	evet*	0.822	0.920	0.444-1.904			
Adj. CT	cis-vin*	0.783					
	cis-dose	0.338	0.643	0.260-1.589			
	pscli-carbo	0.858	1.086	0.440-2.678			
	cis-gem	0.854	0.893	0.267-2.984			
Hafta	<6 *	0.018	2.196	1.148-4.203	0.045	2.058	1.015-4.171

* referans kategori

Yapılan bir retropektif çalışmada platin dozu ile sağkalım arasında ilişki mevcut iken ameliyattan 6 hafta sonra tedaviye başlamak sağkalımla ilişkili bulunmamıştır[16]. Ayrıca Evre II KHDAK de yapılan başka bir retrospektif çalışma, adjuvan tedaviye operasyondan 42 gün sonra başlamanın sağkalım farkı yaratmadığını göstermiştir[17]. Buna ek olarak başka bir çalışmada adjuvan tedaviye operasyondan 10 hafta sonra başlamanın sağkalımla anlamlı bir ilişkisi saptanmamıştır[18]. Amerika Ulusal Kanser Veri Tabanından alınan toplam 12473 hastanın (%25'i evre I, %48'i evre II, ve %27'i evre III) retrospektif olarak değerlendirildiği çalışmada KTnin operasyon sonrası 57-127. günler arasında başlatılması mortaliteyi artırmadığı gösterilmiştir.. Ameliyat sonrası geç iyileşen hastalarda ameliyattan 4 ay sonrasında bile adjuvan KT'nin fayda gösterdiği bildirilmiştir[19].

Bununla birlikte, çelişkili sonuçlara sahip çalışmalar da mevcuttur. Bir çalışmada, cerrahiden adjuvan KT'ye kadar geçen sürenin 60 günden fazla olduğu hastaların 5 yıllık sağkalımın önemli ölçüde daha kötü olduğu gösterilmiştir[20].

Çalışmamızda tedaviye 6 haftadan sonra başlamak daha düşük hastalıksız sağkalım ile ilişkili bulunmuştur. Bu bulgular için olası teori, adjuvan KT'nin temel mantığı olan küratif cerrahi rezeksiyon sonrası kanser hücrelerinin tamamen ortadan kaldırmayabileceği olarak düşünülmektedir. Adjuvan KT ile kanser hücrelerini ortadan kaldırmak ve mikro metastazların büyümesini engellemek amaçlanmaktadır. Adjuvan KT ne kadar geç başlanırsa, geride kalan tümör hücrelerin çoğalması için fırsat o kadar artacaktır. Bu hipoteze dayanarak, adjuvan KT ameliyattan sonra mümkün olan en kısa sürede başlanmalıdır. Ayrıca tedaviye geç başlanması çoğunlukla hastalarda komorbid hastalıklar bulunmasına ve pulmoner cerrahinin komplikasyonlar ile ilişkili olabileceği için bu hastaların KT öncesi performansları daha düşük saptanabilir.. Çalışmamızda adjuvan tedavisi geciken hastalarda, istatistiksel anlamlı olmamakla birlikte oransal olarak pulmonektomi yapılan hastalar daha fazla görülmüştür. Ayrıca hastaların KT öncesi performans skoru hastalıksız sağkalım açısından bağımsız prognostik faktör olarak bulunmuştur.

İncelediğimiz kadarıyla literatürde ameliyat ile adjuvan KT arasındaki sürenin önemini araaştıran çalışmalar oldukça sınırlıdır. Optimum sürenin net olarak tanımlanmamış olması ve önerilerin kısıtlı sayıdaki literatüre dayanması nedeniyle, bulgularımızın literatüre önemli bir katkı sağlayacağını düşünmekteyiz. Bununla birlikte, çalışmamızın tek merkezli olması,tedavi ve takip prosedürlerin benzer olması nedeniyle hasta homojenitesine katkı sağlamıştır..

Çalışmamızın birkaç kısıtlayıcı özelliği bulunmaktadır. Çalışmanın retrospektif tasarım ve nispeten düşük örneklem sayısı nedeniyle muhtemel bias barındırabileceği için

bulgularımız yorumlanırken dikkatli olmak gerekmektedir. Buna ek olarak hastaların komorbid hastalıklarının ve moleküler analiz sonuçlarının detaylıca raporlanmaması ve sağkalım verilerinin yeterince olgunlaşmamış olması çalışmayı sınırlandıran özelliklerdendir.

Sonuç olarak küratif rezeksiyon uygulanan adjuvan tedavi alması gereken evre IIB-IIIA KHDAK hastalarında tedaviye 6 haftadan sonra başlamak hastalıksız sağkalım süresini olumsuz etkilemiştir. Bulgularımıza göre tedavi gereksinimi olan hastalarda 6 haftayı geçirmeden tedaviye başlanması gerektiği sonucuna vardık. Adjuvan KT başlama zamanı ile hastalıksız sağkalım ve genel sağkalım arasındaki ilişkiyi net bir şekilde tanımlanması ve bulgularımızın doğrulanması için daha büyük ölçekli, prospektif, iyi tasarlanmış çalışmalara ihtiyaç bulunmaktadır.

Etik kurul

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Research Article

Background of the need for targeted therapy options and platinum-based therapy responses in EGFR and ALK-mutated lung adenocarcinoma

EGFR ve ALK mutasyonu taşiyan akciğer adenokarsinomlarinda platin bazli tedavi yanitlari ve hedefe yönelik tedavi ihtiyacinin arka plani

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Abstract

Aim: To present our experience in EGFR and EML-4/ALK-mutated lung adenocarcinoma patients.

Material and Methods: 2580 patients were retrospectively evaluated. Only stage-4 lung adenocarcinoma patients who treated with at least 2-cycles of platinum-based regimens at frontline were included.

Results: Among 105 eligible patients, EGFR and EML-4/ALK mutations was detected in 14 and 4 patients. 75 were wild-type for both mutations. The median age and age of diagnose was 61 and 58.5, respectively. 81% was male and 78% was smoker. EGFR and EML-4/ALK-mutant patients were predominantly female and non-smoker (EGFR; p=0.025 and 0.002, EML-4/ALK; p=0.003 and 0.012,respectively). EML-4/ALK- mutant patients were significantly younger than EML-4/ALK wild-type (p=0.02) (Table 1). EGFR exon-19, 20 and 21 mutations were associated with liver, bone and pleural metastases, respectively (p=0.046, 0.05 and 0.035,respectively). After firstline platinum-based chemotherapy, complete remission (CR) and partial remission (PR) rates were 4.7% and 24.6%,respectively. Concurrent radiotherapy and absence of bone metastases at diagnosis were significant factors influencing firstline platinum-based therapy responses (p=0.004 and p=0.046,respectively). EGFR or EML-4/ALK mutation status didn't show significant difference in terms of platinum-based treatment response (p=0.933 and 0.184,respectively). Median progression-free survival (PFS) was 10 months. The observed effect of concurrent radiotherapy and the presence of bone metastases on treatment response didn't reflected in the PFS results (p=0.079 and 0.285,respectively).

Conclusion: The presence of EGFR and ALK mutations does not effect the treatment response of platinum-based regimens. The association of EGFR exon subsets with metastasis points is worth investigating.

Keywords: EGFR, EML-4/ALK, ALK, platinum, lung adenocarcinoma

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Öz

Amaç: EGFR ve EML-4/ALK mutasyonlu akciğer adenokarsinomu hastalarındaki deneyimlerimizi sunmak.

Gereç ve Yöntemler: 2580 hasta retrospektif olarak değerlendirildi. Çalışmaya yalnızca evre 4 akciğer adenokarsinomu olup ilk sıra en az 2 siklus platin bazlı rejimlerle tedavi edilen hastalar dahil edilmiştir.

Bulgular: Çalışmaya uygun 105 vakanın 14'ü EGFR, 4'ü EML-4/ALK mutant iken 75 vaka her iki mutasyonu da taşımıyordu. Medyan yaş ve tanı yaşı sırasıyla 61 ve 58.5 idi. %81'i erkekti ve %78'i sigara içiyordu. EGFR ve EML-4/ALK-mutant hastalar ağırlıklı olarak kadındı ve sigara içmiyordu (sırasıyla EGFR; p=0.025 ve 0.002, EML-4/ALK; p=0.003 ve 0.012). EML-4/ALK-mutant hastalar, bu mutasyonu taşımayanlara göre daha gençti (p=0,02) (Tablo 1). EGFR ekson-19, 20 ve 21 mutasyonları sırasıyla karaciğer, kemik ve plevral metastazlarla ilişkiliydi (sırasıyla p=0.046,

0.05 ve 0.035). Birinci basamak platin bazlı kemoterapiden sonra tam remisyon ve kısmi yanıt oranları sırasıyla %4,7 ve %24,6 idi. Eşzamanlı radyoterapi ve tanı sırasında kemik metastazlarının olmaması birinci basamak platin bazlı tedavi yanıtlarını etkileyen faktörlerdi (sırasıyla p=0.004 ve p=0.046). EGFR veya EML-4/ALK mutasyon durumu platin bazlı tedavi yanıtı açısından anlamlı fark göstermemiştir (sırasıyla p=0,933 ve 0,184). Medyan progresyonsuz sağkalım 10 ay iken eşzamanlı radyoterapi ve kemik metastazının tedavi yanıtı üzerinde gözlenen etkisi PFS sonuçlarına yansımamıştır (sırasıyla p=0,079 ve 0,285).

Sonuçlar: EGFR ve ALK mutasyonlarının varlığı, platin bazlı rejimlerin tedavi yanıtını etkilememektedir. EGFR ekson alt gruplarının metastaz noktaları ile ilişkisi araştırılması gereken bir nokta olarak saptanmıştır.

Anahtar Kelimeler: EGFR, EML-4/ALK, ALK, platin, akciğer adenokarsinomu.

Introduction

Primary lung cancer is the second most common malignancy after non-melanoma skin cancer and is the most common cause of malignancy related death. Non-small cell lung cancers constitute 80-90% of primary lung cancers and due to the decrease in tobacco use in recent years, the frequency of squamous cell type has decreased while the adenocarcinoma type has become dominant [1]. Frontline platinum-based therapy response rates for lung adenocarcinoma have been reported to range from 30 to 40%. [2]. To increase these low response rates, EGFR and ALK gene mutations have emerged as important focal points in the development of targeted therapies.

Increased tyrosine kinase activity resulting from mutations effecting the tyrosine kinase domain of EGFR and inversion of the short arm of the chromosome 2, which causes the fusion of the ALK gene with the EML-4 gene, play an important role in the etiopathogenesis of non-small cell lung cancer. Therefore, current guidelines recommend routine screening of these genes regardless of the clinical status [1,3].

In this study, based on the rarity of these mutations and studies with limited number of patients, we aimed to present our single center experience and make a contribution to the literature.

Material and Methods

2580 lung cancer patients who applied to our clinic between 2007 – 2016 were retrospectively evaluated for the study. Only stage 4 lung adenocarcinoma patients who treated with at least 2 cycles of platinum-based regimens as firstline therapy and investigated for EGFR Exon 18-19-20-21 mutations and/or the EML-4/ALK transfusion gene were included in the study. Patients treated with regimens other than platinum-based or without interim and/or end-of-treatment PET-CT imagining results were excluded. 12 patients were negative for EGFR mutations but their ALK mutation status was unknown. These patients also excluded from EGFR and EML-4/ALK wild-type group during statistical analysis.

The presence of activating mutations of the EGFR gene was investigated with the Enterogen EGFR Mutation Analysis Kit in the ABI7500 Real-time PCR device after DNA isolation from the slides of the tumor tissue. The exon 18 codon 719 region, exon 19 deletions, exon 20 insertions and codon 768 and 790 regions, exon 21 codon 858 and 861 regions of the EGFR gene were analyzed. The presence of EML-4/ALK gene translocation was examined immunohistochemically using CST D5F3 antibody. FISH analysis were also performed using the FDA-approved Abbott-Vysis LSI ALK Break Apart Rearrangement probe.

In evaluation of treatment response, evaluation was made according to RECIST v1.1 (Response Evaluation Criteria in Solid Tumors) criteria for computed tomography. PERCIST (Positron Emission Tomography Response Criteria In Solid Tumors) criteria were used for response evaluations with PET-CT. In the light of these criteria, patients who showed complete remission and partial remission after firstline treatment were considered to have responded to treatment. Patients with stable disease and progression were considered unresponsive to treatment.

While evaluating the findings obtained in the study, SPSS 21.0 statistical package program was used for statistical analysis. Pearson Chi-Square test and Fisher Exact test were used to compare qualitative data. The effect of risk factors on survival was analyzed by Kaplan-Meier and Log-rank tests. The results were evaluated at the 95% confidence interval, at the $p<0.05$ significance level.

This study is approved by Istanbul University Clinical Research Ethics Committee with the decision numbered 83045809/604.01/02.381409 dated 3 December 2015 and conducted in accordance with the Helsinki Principles Declaration.

Results

Among 105 eligible patients, 14 patients harbored EGFR gene mutations while EML-4/ALK transfusion was detected in 4 patients. 75 patients were wild-type for both mutations. Median age of entire cohort was 61 while median age of diagnose was 58.5. 81% was male and 78% was smoker. The most frequent metastasis sites were bone (38%), brain (35%) and contralateral lung (32%) (Table 1).

Table 1. Demographic and clinical results (WT/WT: Wild-type for EGFR and EML4/ALK mutations). All p values belong to the comparisons of the cases carrying gene mutations with the WT/WT group.

		Total Cohort (n=105)	*EGFR* (n=14)		*ALK* (n=4)		WT/WT (n=75)
				p		p	
Age (y)		61	60	0,79	48	**0,026**	61
Age at Diagnosis (y)		58,5	58,5	0,93	47	**0,028**	60
Gender (n)	F	20	6	**0,025**	3	**0,020**	10
	M	85	8		1		65
Tobacco Use (n)		82	6	**0,002**	1	**0,037**	65
Metastasis Sites (n)							
Brain		37	2	0,06	2	0,40	28
Bone		40	7	0,24	3	0,13	25
Liver		8	2	0,29	1	0,31	5
Pleura		12	3	0,2	0	0,56	9
Contralateral Lung		34	7	0,11	1	0,57	23
Soft Tissue		4	2	0,51	0	0,87	2
Adrenal Gland		19	1	0,44	1	0,56	14

EGFR and EML-4/ALK mutant patients were predominantly female and non-smoker compared to wild-type patients (EGFR; p=0.025 and 0.002, EML-4/ALK; p=0.003 and 0.012, respectively). Additionally, EML-4/ALK mutant patients were significantly younger than EML-4/ALK wild-type (p=0.02) (Table 1). Although metastasis sites did not differ according to EGFR mutation status, when subgroup analysis was performed, exon 19, 20 and 21 mutations significantly appeared to be associated with liver, bone and pleural metastases, respectively (p=0.046, 0.05 and 0.035, respectively).

After firstline platinum-based chemotherapy, complete remission (CR) and partial remission (PR) rates were 4.7% and 24.6%, respectively. Stable disease status was observed in 4.7% while 66% of patients showed progression. Concurrent radiotherapy (RT) and absence of bone metastases at diagnosis were statistically significant factors influencing firstline platinum-based therapy responses. Concurrent radiotherapy with platinum based chemotherapy (n=35) showed significantly superior treatment response rates comparing patients who did not recieve radiotherapy (p=0.004). Relaps rates of patients with and without bone metastasis were %77.5 and. %58.5 after platinum based therapy, respectively (p=0.046). EGFR or EML-4/ALK gene mutation status did not able to show any significant difference in terms of platinum-based treatment response (p=0.933 and 0.184, respectively). The effect of EGFR exon mutations on treatment response or survival results did not performed due to low numbered subgroups.

Median progression-free survival (PFS) duration of entire cohort was 10 months. Median PFS durations of EGFR, EML-4/ALK and WT/WT groups were also comparable which were 10.8, 12 and 10.2 months, respectively (p=0.506) (Figure 1). The observed effect of concurrent radiotherapy and the presence of bone metastases on treatment response is not reflected in the PFS results (p=0.079 and 0.285, respectively). Brain metastasectomy was performed in 8 (21.6%) of 37 cases with brain metastases and no positive effect was detected in terms of PFS and treatment response rates (p=0.127 and p=0.465). Estimated overall survival (OS) rate of entire cohort was 17% at first year.

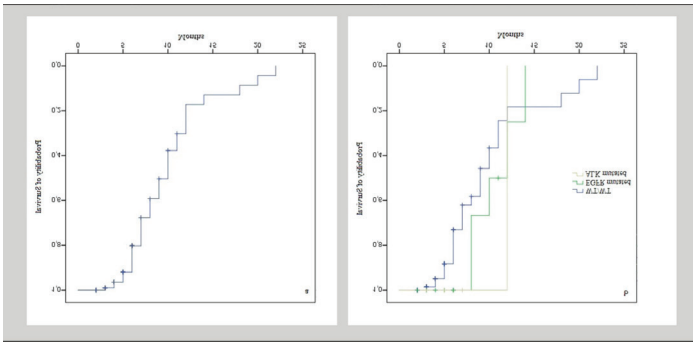

Figure 1. Cumulative PFS of entire cohort (a) and mutation groups (b).

Discussion

Lung cancer is still among the most common cancers but with the decrease in tobacco use and the addition of targeted therapy agents to conventional chemotherapy regimens, a halving of incidence and mortality rates has been observed in the last two decades [12]. As the details of the cancer development process are clarified, new possibilities for treatments emerge. Point mutations in exon 18 and 21, Exon 19 deletion and Exon 20 insertion of the EGFR gene effect the receptor tyrosine kinase domain of the transmembrane cell receptor protein. Similarly, translocation of the ALK gene on the short arm of chromosome 2 with the EML-4 gene causes an increase in intracellular tyrosine kinase activity and this pathway plays a critical role in cancer pathogenesis. Targeted therapies for EGFR and ALK genes, which have been shown to be important in lung non-small cell cancer, are among the most important developments in this regard.

Frequencies of EGFR and EML-4/ALK transfusion gene mutations in lung adenocarcinoma were reported as 10-20% and 2-5%, respectively [1]. Patients harbouring these mutations are presenting a different clinical profile compared to wild types. Most

studies showed that, EGFR and EML-4/ALK-mutated lung adenocarcinoma patients are mostly non-smoker females and also EML-4/ALK positive patients are significantly younger [4-6,7]. Results of our cohort were consistent with these findings.

In our study, EGFR mutant patients were unable present significant difference regarding response to platinum-based chemotherapy, PFS or OS comparing EGFR wild-type patients. The only significant factors improving platinum-based treatment results were concomittant RT and absence of bone metastasis at diagnose (p=0.004 and 0.046, respectively). Also some other studies evaluating platinum-based chemotherapy response from the perspective of EGFR gene mutation also declared ~30% treatment response, but no statistically significant difference was found in treatment response, PFS and OS between mutated and wild-type patients [13-15].

In the study published by Capuzzo et al. [2], 185 cases were examined and EGFR gene mutations were found in 24 cases (15 Exon 19 mutated, 2 Exon 20 mutated and 7 Exon 21 mutated). In patients who received platinum-based chemotherapy as frontline therapy, the response rates were 37% vs. 32.8% in EGFR-mutated and wild-type group, respectively (p=0.6). PFS and OS durations of EGFR-mutated and wild-type groups were also comparable (PFS: 8.1 vs. 4.1 mo., p=0.1; OS: 28.5 vs. 14.8 mo., p=0.07, respectively). But when EGFR subgroups were examined, it was observed that only patients with Exon 19 mutations responded to platinum-based chemotherapy (46.6%), while no treatment response was obtained in Exon 20 and 21 groups (p=0,02) [2].

In another article evaluating 162 lung adenocarcinoma patients [8], of which 40 were EGFR-mutated, platinum-based frontline therapy responses were comparable between EGFR- mutated and wild-type groups (43.5% vs. 23.9%, p=0.072). PFS and OS durations of EGFR- mutated and wild-type patients were also did not able to show significant difference between groups (p=0.69 and p=0.069, respectively). In this study only 9 patients were carrying classical EGFR mutations (exon 18, 19 and 21 mutations) while remaining 31 patients were positive for other EGFR mutations. Subanalysis of classical EGFR-mutated patients showed similar PFS duration (p=0.81) but better platinum-based therapy response (p=0.021) and improved OS duration (p=0.028) comparing wild-type patients. Although the small number of patients, the presence of EGFR gene mutation was declared as an independent favorable prognostic factor for platinum-based treatment response and overall survival [8].

EGFR gene mutation was found to be associated with brain, bone and pleural metastases in the REASON study [5] from Germany, which consisted of 432 EGFR gene mutation-positive cases. We also found a possible correlation between Exon 19, 20 and 21 mutations with liver, bone and pleural metastases, respectively. However, it was impossible to make a definitive interpretation due to the insufficient number of patients.

The presence of EML-4/ALK transfusion stands out as a negative factor for patients. In the study of Mayo Clinic [6], 266 EML-4/ALK negative non-small cell lung cancer cases compared to 34 EML-4/ALK-mutated patients and EML-4/ALK positivity declared as a negative predictive factor for progression/relapse-free survival [6]. Koh et al. [9] examined 221 lung adenocarcinoma patients, of which 45 were harboring EML-4/ALK transfusion and

46 were EGFR mutants, 170 cases were treated with platinum-based chemotherapy in frontline therapy. The treatment response rates were 18.8% in the EML-4/ALK group, 37.5% in the EGFR group and 40.4% in the EGFR and EML-4/ALK wild-type group (p=0.091). Progression-free survival durations were 6.2, 5.4 and 7.3 months, respectively (p=0.348). In patients treated with tyrosine kinase inhibitors (TKIs), the treatment response rate reached to 50% and PFS duration improved to 19.6 months in EGFR group. Due to low response rate to

platinum-based chemotherapy, EML-4/ALK transfusion gene positivity was declared as a poor prognostic factor [9].

Shaw et al. [7] obtained comparable results in response rates to platinum-based treatment in a cohort consisted of 19 EML-4/ALK positive, 31 EGFR positive and 91 WT/WT patients. But as expected, EGFR-mutated group's frontline TKI response rate was significantly superior than EML-4/ALK and WT/WT groups ($p<0.001$). PFS duration of EGFR group after TKI treatment was 16 months which was significantly longer than EML- 4/ALK-mutated (5 months) and WT/WT patients (6 months) ($p=0.004$). The presence of EML- 4/ALK transfusion gene was strongly related to TKI resistance [7].

Current guidelines recommend TKIs and ALK inhibitors as first-line therapy for patients with these mutations [1,3]. Although additional 20% increase in firstline therapy responses and approximately 12 months of PFS with targeted therapies for EGFR and ALK mutations, this improvement was not reflected in overall survival results.

First generation TKIs, gefitinib and erlotinib, were unable to show significant OS benefit with over platinum-based regimens but OR and PFS rates were significantly improved [1]. In the light of these results, and with their safe use even in patients with low performance scores, TKIs have become the backbone of EGFR-mutated lung adenocarcinoma patients. Following these agents, afatinib and dacomitinib emerged to the market as second generation TKIs. Osimertinib, third-generetion TKI, proved itself in the FLAURA study [11] with its PFS contribution against 1st generation TKIs and its superior response results in cases with CNS metastasis. Moreover, with the statistically significant contribution to OS (38.6 vs 31.8 months, $p=0.046$), the current guidelines are recommending asimertinib as preferred therapy in firstline treatment of patients with sensitizing EGFR mutations [1,3]. Crizotinib was the first targeted therapy improving OR and PFS rates of EML-4/ALK rearranged patients comparing platinum-based therapies. Ensuing ALK inhibitors, ceritinib, alectinib and brigatinib took these results to an even better point. In the ALTA-1L study [10], the estimated 1-year PFS rate for brigatinib was a remarkable success compared to crizotinib (67% vs 43%, $p<0,001$). Ensartinib and lorlatinib also stand out as ALK inhibitors whose phase 3 studies are ongoing and are expected to be included in daily clinical practice in the near future [1].

Although targeted therapies have considerably increased the OR and PFS results compared to platinum-based therapies, there is still a need for new agents to prolong the duration of OS.

Conclusion

The presence of EGFR and ALK mutations does not effect the treatment response of platinum-based regimens according to current literature and our study. Retrospective study design and low numbered subgroups in EGFR and EML-4/ALK mutated patients are the limitations of our study. Although these limitations, the association of EGFR exon subsets with metastasis points is worth investigating, as demonstrated in REASON study [5].

Disclosure

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Olgu Sunumu

Erişkinde multipl nuck kanal kisti; olgu sunumu

Multipl nuck canal cyst in adult; a case report

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Öz

Nuck kanal kisti kız çocuklarında prosesus vajinalisin(PV) kapanma defekti sonucu oluşan seyrek görülen bir patolojidir. Literatürde fazla rastlanmayan bir patoloji olması dolayısıyla biz de 27 yaşında sağ inguinal bölgede ağrı ve şişlikle başvuran kadın hastada tespit ettiğimiz Nuck kanal kistini sunmayı amaçladık.

Anahtar kelimeler: nuck kanal kisti;inguinal hernia;prosesus vajinalis

Abstract

Nuck canal cyst is a rare pathology that occurs as a result of closure defect of the processus vaginalis in girls. Since it is a rare pathology in the literature, we aimed to present the Nuck canal cyst, which we detected in a 27-year-old female patient who presented with pain and swelling in the right inguinal region.

Keywords: nuck canal cyst;inguinal hernia;processus vaginalis

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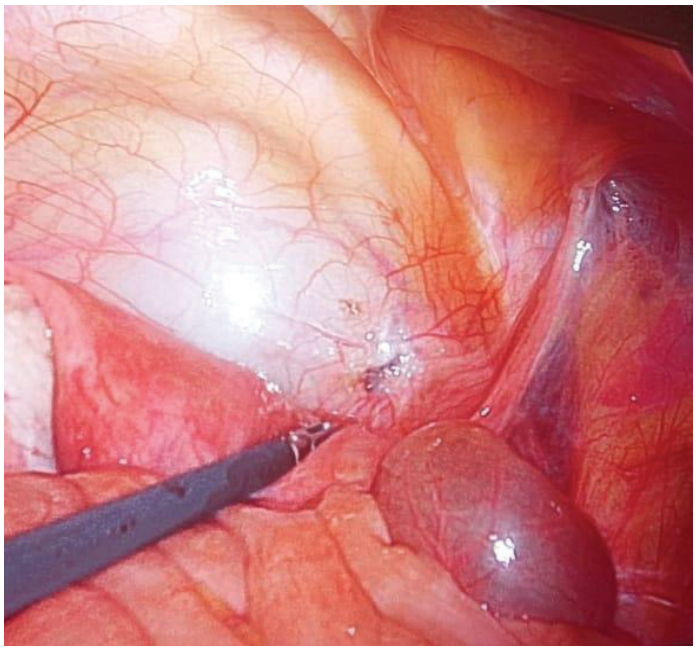
Giriş

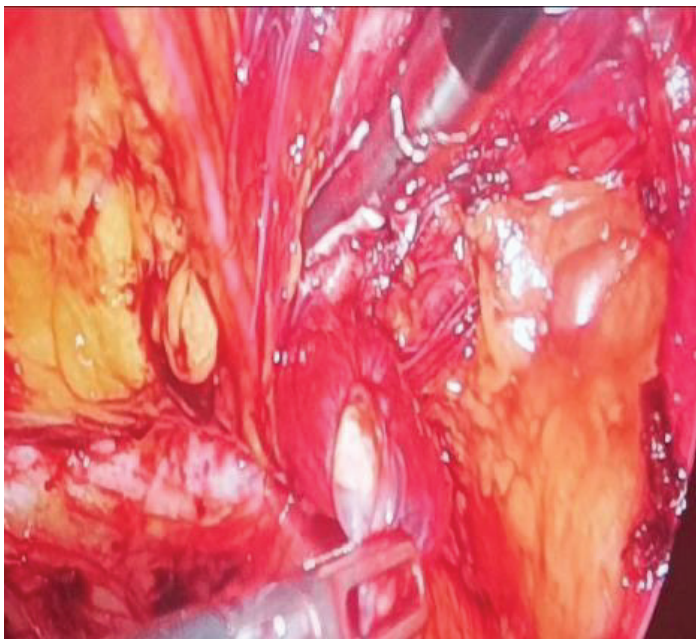
Nuck kanalı erkeklerdeki prosesus vajinalisin kadınlardaki benzeridir. Doğumdan sonraki ilk yıllarda kapanarak peritonla bağlantısı kesilir. Bu kanal kapanmayıp gerilemezse Nuck kanal kisti veya hidrosele neden olur. Daha çok pediatrik yaş grubunda ve erkeklerde görülen bu durum, kadınlarda görülürse Nuck kanal kisti, Nuck kanal hidroseli veya kadın hidroseli olarak adlandırılır(1). Eğer prosesus vajinalis, yalnız sıvı geçişine izin verecek kadar küçükse hidrosel veya kordon kisti gibi patolojiler, eğer abdominal organların geçişine izin verecek kadar büyükse inguinal herniler meydana gelir(2). Nuck kanal kisti ilk olarak 1650 yılında Anton Nuck tarafından tanımlanmıştır(3). Nadir görülen ve ayırıcı tanıda göz önünde bulundurulması gereken bir patoloji olarak , literatür eşliğinde kadın olgumuzu sunarak bilgilerimizi tazelemeyi amaçladık.

Olgu

28 yaşında kadın hasta yıllardır devam eden ,sağ kasığında ağrı ve çok hissedilmeyen kitle şikayetiyle polikliniğe başvurdu. Bulantı, kusma, karın ağrısı yoktu. Muayenesinde inguinal bölgede hafif hassasiyet saptandı. Belirgin bir kitle saptanmadı. Valsalva manevrasında inguinal bölgede belirginleşen bir şişlik yoktu. Kan tetkiklerinde anormal bir değer tespit edilmedi. Yapılan ultrasonografisinde sağ inguinal kanal içinde 3x2 cm lik kistik kitle ve batın içinde iliak damarlar üzerinde 5 cm lik kistik kitle saptandı. Herni saptanmadı. Hastaya kanal içindeki kistik kitle için açık ameliyat planlanacaktı fakat batın içinde iliak damarlar üzerinde de kistik kitleden bahsedildiğinden laparoskopik ameliyat planlandı. Hastaya umblikus üzerinden 10 luk ve umblikus hizasından midklavuküler hattan 5 lik trokarlarla laparoskopik olarak batına girildi. Yapılan eksplorasyonda iliak damarlar üzerindeki kistik lezyon görüldü. İnguinal kanal içindeki kistlere ulaşılamayınca periton, transabdominal preperitoneal(TAPP) herni ameliyatındakine benzer şekilde spina iliaka anterior süperiordan başlayarak medial umblikal ligamente kadar transvers olarak açıldı. Ligamentum Rotundum(Round ligaman) ortaya kondu. Batın içindeki peritona yapışık kistik lezyon eksize edildi. (Resim1) Daha sonra Round ligaman çekilerek inguinal kanal içindeki Nuck kanal kistine ulaşıldı.(Resim 2) Kist izole olarak çıkartılamadı. Round ligaman eksize edilerek kistle beraber çıkartıldı. Potansiyel herni gelişimine engel olmak için myopektineal orifisi içine alacak şekilde 10x15 cm lik poliprolen yama yerleştirildi. Periton kapatılarak ameliyat sonlandırıldı. Hasta postoperatif sorunsuz olarak takip edilip, cerrahi şifa ile taburcu edildi. Patoloji sonucu Nuck kanal kisti ile uyumlu olarak raporlandı.



Resim 1



Resim 2

Tartışma

Nuck kanal kisti Hollandalı bir anatomist olan Anton Nuck Van Leiden tarafından 1650 yılında inguinolabial kist olarak tarif edilmiştir(2). Nuck kanalı ile ilgili patolojiler PV kapanmasındaki defektlere bağlı olarak ortaya çıkmaktadır ve çok sık rastlanan bir durum değildir. Wei ve ark. (3) 2002 yılına kadarki olguları kapsayan çalışmalarında 400 civarında vaka bildirmişlerdir. Hastalar klinik olarak inguinolabial bölgede ağrısız, batına redükte edilemeyen, hareketli, genellikle 3 cm'yi geçmeyen

olmayan kitle şikayeti ile başvururlar.(5) Uterus, ligamentum teres uteri bağlantısıyla pelvik yan duvara bağlanır. Normalde uterin destek görevi olmayan bu ligament (round ligament) inguinal kanaldan geçerek daha ince liflere ayrılır ve labium majus içerisinde dağılır. Round ligament internal inguinal kanaldan geçtikten sonra proksimal kısımdaki parietal periton çok distale uzanmadan sonlanır. Bu küçük fizyolojik periton invajinasyonuna Nuck Kanalı adı verilmektedir ve erkekteki prosesus vajinalisin eşdeğeridir.(6) Hayatın ilk yılında Nuck kanalının oblitere olmaması Nuck Kanalı kisti veya indirekt herniye yol açabilir. Nuck kanal kisti labium majusa herniye olursa hidrosel olarak adlandırılır. Nuck kanal kistleri inguinal kanalın labium seviyesinde , kanal içinde veya batın içinde herhangi bir yerde oluşabilir. Ultrasonografik inceleme önemli bir tanı aracıdır, inguinal ligament altında hipoekoik, bazen de kistik mural nodüller içerebilen, fuziform şekilli lezyonalarda Nuck Kanal kistinden şüphelenilmelidir. (7) Tanının şüpheli olduğu durumlarda kitlenin intraabdominal bağlantısı, diğer organlarla ilişkisi açısından manyetik rezonans görüntüleme yapılabilir (8). Ayrıcı tanıda inguinal indirekt herni, kistik lenfanjiomlar, inflammatuvar ya da malign lenfadenopati, abse formasyonu, ve vasküler oluşumlar (anevrizma) gelmelidir. Son tanı cerrahi ve sonrasında patolojik inceleme sonrası kesinleşecektir. Cerrahi tedavide kistin eksize edilerek prosesus vajinalisin ligate edilmesi rekürrensleri azaltacaktır. Fakat potansiyel olarak rekürrensin öngörüldüğü olgularda polipropleN cerrahi meş kullanımı cerrahi başarıyı artıracaktır. Ayrıca kistin labiumda olmadığı kanal içinde veya batında olduğu vakalarda bizim de uygulamış olduğumuz laparoskopik yaklaşım kullanılabilir.

Sonuç

İnguinal ya da vulvar kitleyle başvuran kadınlarda ayırıcı tanıda Nuck Kanal kisti düşünülmeli ve bu hastalara mutlaka ultrasonografik inceleme yapılmalıdır. Semptomatik hastalarda kistin eksizyonu ve kanalın obliterasyonu yeterli olurken, nüksün yüksek ihtimal olduğu vakalarda cerrahi meshler kullanılmalıdır.

Etik Kurul Onayı

Görsellerin kullanımı için kurum onayı alınmıştır. Hasta Onamı: Yazılı onamı bu çalışmaya katılan hastadan alınmıştır. Hakem Değerlendirme Süreci: Dışarıdan hakemli.

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Case Report

Attention to the differential diagnosis of Covid-19: Salmonellosis

Covid-19'un ayırıcı tanısına dikkat: Salmonelloz

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Abstract

In this case series, three patients who were hospitalized with suspected COVID-19 infection and received treatment were diagnosed with Salmonellosis and discharged with recovery. Elderly patients with pre-diagnosed COVID-19, with a history of chronic disease, and who are considered to be in the risky group are immediately hospitalized and followed up. The frequent occurrence of symptoms such as fever, cough, respiratory distress, weakness as well as nausea, vomiting, abdominal pain, and diarrhea in patients with COVID-19 pre-diagnosis, increases the importance of anamnesis and physical examination in the differential diagnosis.

Keywords: COVID-19, salmonellosis, enteric fever, differential diagnosis

Öz

Bu vaka serisinde, COVID-19 enfeksiyonu şüphesiyle hastaneye yatırılan ve tedavi gören üç hasta Salmonelloz tanısı almış ve iyileşerek taburcu edilmiştir. COVID-19 ön tanısı almış, kronik hastalık öyküsü olan ve riskli grupta olduğu düşünülen yaşlı hastalar derhal hastaneye yatırılarak takip edilmektedir. COVID-19 ön tanılı hastalarda bulantı, kusma, karın ağrısı ve ishalin yanı sıra ateş, öksürük, solunum sıkıntısı, halsizlik gibi belirtilerin sık görülmesi, ayırıcı tanıda anamnez ve fizik muayenenin önemini artırmaktadır.

Anahtar Kelimeler: COVID-19, salmonelloz, enterik ateş, ayırıcı tanı

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Introduction

Although vaccination and mutations have reduced the effectiveness of the new coronavirus (COVID-19), the disease has had a high mortality potential since its first appearance in December 2019 [1]. Although respiratory tract infection symptoms such as sore throat and cough accompanying fever are often present in the COVID-19 clinic, gastrointestinal system infection symptoms such as nausea, vomiting and diarrhea can also be seen [2]. The condition can produce characteristics comparable to the clinical signs of other infectious disease agents, and therefore the diagnosis and management can be challenging.

Salmonellosis is an infectious disease that threatens public health and can cause epidemics. Salmonella strains are gram-negative, facultative anaerobic bacilli that belong to the Enterobacteriaceae family [3]. Salmonella typhi (typhoid) and Salmonella paratyphi A, B, and C (paratyphoid) strains are the ones that cause enteric fever. The typical clinical picture manifests within 12–72 hours of consuming bacteria-contaminated foods and drinks (meat and meat products, raw eggs, unpasteurized milk, etc.) or coming into contact with people and animals carrying the disease. Common symptoms are fever, diarrhea, nausea, vomiting, and abdominal pain. Older people, infants and immunocompromised individuals are at greater risk of experiencing the symptoms more severely. Even rarely, pulmonary involvement can be seen [4]. In this case series, we report on three patients admitted to the hospital with a suspected COVID-19 infection and treated but later diagnosed with salmonellosis and discharged.

Case I

A 90-year-old female patient with a history of congestive heart failure (CHF), hypertension (HT), and asthma was admitted to the emergency department with a sudden onset of nausea, vomiting, abdominal pain, accompanied fever, and dyspnea. Upon arrival, vital signs were documented: arterial blood pressure: 136/80 mmHg, pulse: 107/min, oxygen saturation: 78%, fever: 39.0 °C (Table 1). The physical examination revealed minimal abdominal tenderness with palpation and no defense or rebound. Other system examinations revealed no evidence of pathology. Cardiothoracic computed tomography (CT) and posterior-anterior (PA) chest X-ray revealed an increase in the cardiothoracic ratio, left ventricular dominancy, cardiomegaly, calcified atheroma plaques on the thoracic aortic wall, an increase in the anteroposterior thoracic diameter, emphysematous lung hyperinflation, and increased pulmonary vascular distribution and coarsening. No significant pathology in the lung parenchyma was reported. These findings were interpreted to be an age-related, chronic change in the patient. The patient's laboratory findings are shown in Table 2.

Table 1. Vital signs of the cases

	Case-I	Case-II	Case-III
Fever (°C)	39.0	39.0	37.6
Pulse/min	107	98	88
Arterial Blood Pressure (mmHg)	136/80	90/50	110/70
O2 Saturation (%)	78	94	97

Table 2. Laboratory results of the cases

	Case I	Case II	Case III
Wbc (109 /l)	10.5	14.2	10.9
Neutrophil (109 /l)	9.69 (92.7%)	13.4 (94.6%)	5.8 (53.5%)
Lenfosite (109 /l)	0.3 (2.8%)	0.3 (2.29%)	3.2 (29.1%)
Hgb (gr/dl)	13.1	13.6	12.4
Htc (%)	37.7	39.7	37.2
Plt (/mm3)	124000	220000	330000
CRP (mg/L)	89.7	189	32
AST (u/l)	43	44	28
ALT (u/l)	29	24	24
Glucose (mg/dl)	124	108	165
Urea (mg/dl)	121	53	20
Creatinine (mg/dl)	1.8	1.3	0.7
ESR (/h)	31	29	18
Troponin-I (ng/ml)	0.445	0.430	0.356
CK-MB (ng/ml)	4.37	5.73	6.72
Fibrinogen (ng/ml)	462	452	418
Procalsitonin (ng/ml)	3.83	1.8	2.1

White blood cell: Wbc, Hemoglobin: Hgb, Hematocrit: Htc, Platelet: Plt, C reactive peptide: Crp, Aspartate Aminotransferase: Ast, Alanine Aminotransferase: Alt.

Depending on these symptoms and clinical findings, supportive treatment was initiated, a swab sample was taken, and the patient was hospitalized, considering the pre-diagnosis of COVID-19. COVID-19 was negative in two swab samples obtained for two consecutive days. The patient had a complaint of diarrhea on the first day. Therefore, in the stool examination requested on the 4th day, it was observed that the stool was macroscopically green, watery, and mucoid, occasionally bloody, and microscopic analysis revealed 1-2 erythrocytes and abundant leukocytes in the fields. No parasite cysts or eggs were found in the stool test. The occult blood test in stool was positive. The Entamoeba histolytica adhesin

test was negative. In the stool culture sent the next day, Salmonella enteritidis growth was detected in the bacterial identification made on the VITEK 2 (Biomerioux, France) automated system from colonies with a lactose-negative appearance on Salmonella Shigella (SS) agar medium. The patient was transferred to another ward, and ciprofloxacin treatment was administered according to the antibiogram tests. The patient was discharged with full recovery on the 7th day of hospitalization.

Case II

A 70-year-old male patient with a history of HT, diabetes mellitus (DM), and coronary artery disease (CAD) was admitted to the emergency department with fever, nausea, and diarrhea. On arrival, vital signs were noted: arterial blood pressure: 90/50 mmHg, pulse: 98/min, oxygen saturation: 94%, fever: 39.0 °C (Table 1). The physical examination revealed no prominent pathological findings. The PA chest X-ray and thorax CT were interpreted as atypical concerning the infectious process and viral pneumonia. The patient's laboratory findings are shown in Table 2.

As we were in the pandemic period, it was considered that existing diarrhea and fever could be seen during COVID-19. After collecting PCR swab samples, blood cultures, urine cultures, and stool cultures, the patient was isolated and admitted to the hospital with a pre-diagnosis of COVID-19.

Supportive treatment was initiated for the patient. The PCR test was negative, whereas Salmonella enteritidis growth was detected in stool culture. Ciprofloxacin, found to be sensitive on the antibiogram tests, was added to the patient's treatment, and the patient was discharged with complete recovery.

Case III

An otherwise healthy 57-year-old female patient was admitted to the emergency department with fever, nausea, vomiting, and diarrhea. Patient vital signs were noted: arterial BP: 110/70 mmHg, pulse 88/min, oxygen saturation 97%, fever: 37.6 °C (Table 1). Although auscultation revealed bibasilar rhonchi, PA chest X-ray findings were within normal limits. On the thorax CT, changes in the lower lung lobes were interpreted as having a suspicious "ground glass" appearance.

After collecting a stool culture and PCR swab sample, supportive care was initiated. A control swab was taken from the patient, whose initial PCR was negative. Salmonella enteritidis was detected in the stool culture of the patient whose control PCR was negative. The insulting microorganisms were found to be sensitive to Ciprofloxacin in the antibiogram. Thus Ciprofloxacin was added to the patient's medication, and the patient was eventually discharged with a complete recovery.

Discussion

COVID-19 can present many symptoms, including fever, respiratory distress, cough, weakness, headache, abdominal pain, nausea, vomiting, and diarrhea [5]. Advanced age and presence of additional disease are parameters that predict a serious clinical course for COVID-19 [6]. In addition, it is known that the clinical course of COVID-19 is more serious in COVID-19 patients who present with diarrhea [2]. However, despite the presence of diarrhea symptoms in our patients, COVID-19 was not detected. Further investigations revealed that diarrhea was caused by Salmonellosis. Fever, headache, rash, weakness, and abdominal pain are typical clinical signs of salmonellosis (typhoid), which can mimic the clinical features of COVID-19. Typhoid fever is transmitted by ingesting contaminated water and food with infected human feces. [7]. The subjects in this case series also had fever, fatigue, nausea, and vomiting, which may be typical of both diseases. In a study by Aleena Haqqi et al., the co-occurrence of COVID-19 and Salmonella typhi has been described as a significant medical issue. It has also been suggested that this situation makes the task of healthcare professionals struggling with COVID-19 even more challenging [8]. In addition, in the conditions of the pandemic, especially in developing countries, all patients may not be able to receive care at once due to limited financial and health resources. This can result in serious public health problems by increasing mortality.

Conclusion

Patients with a history of the concomitant disease, are elderly, and have a pre-diagnosis of COVID-19 are often hospitalized and followed up. The frequent complaints such as fever, cough, respiratory distress, weakness, nausea, vomiting, abdominal pain, and diarrhea in patients with a pre-diagnosis of COVID-19 increase the importance of anamnesis and physical examination in the differential diagnosis. A detailed clinical evaluation of the patient regarding possible bacterial and viral infections is essential, especially in patients with negative PCR tests.

Presented at a meeting

Yes (only one case presented in 5th International Medicine and Health Sciences Researches Congress)

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No

Conflicts of Interests Statement

The authors declare that they have no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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Etik kurallar: Klinik araştırmaların protokolü etik komitesi tarafından onaylanmış olmalıdır. İnsanlar üzerinde yapılan tüm çalışmalarda, "Yöntem ve Gereçler" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın Helsinki İlkeler Deklerasyonuna (www.wma.net/e/policy/b3.htm) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır. Çalışmaya dahil edilen tüm insanların bilgilendirilmiş onam formunu imzaladığı metin içinde belirtilmelidir. Turkish Journal of Clinics and Laboratory gönderilen yazıların Helsinki Deklarasyonuna uygun olarak yapıldığını, kurumsal etik ve yasal izinlerin alındığını varsayacak ve bu konuda sorumluluk kabul etmeyecektir.

Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntemler bölümünde Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) prensipleri doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır.

Teşekkür yazısı: Varsa kaynaklardan sonra yazılmalıdır.

Maddi destek ve çıkar ilişkisi: Makale sonunda varsa çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve varsa bu kuruluşların yazarlarla olan çıkar ilişkileri belirtilmelidir. (Olmaması durumu da "Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların herhangi bir çıkar dayalı ilişkisi yoktur" şeklinde yazılmalıdır.

Kaynaklar: Kaynaklar makalede geliş sırasına göre yazılmalıdır. Kaynaktaki yazar sayısı 6 veya daha az ise tüm yazarlar belirtilmeli, 7 veya daha fazla ise ilk 3 isim yazılıp ve ark. ("et al") eklenmelidir. 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. Kaynak sayısının araştırmalarda 25 ve derlemelerde 60, olgu sunumlarında 10, editöre mektupta 5 ile sınırlandırılmasına özen gösterilmelidir. Kaynaklar metinde cümle sonunda nokta işaretinden hemen önce köşeli parantez kullanılarak belirtilmelidir. Örneğin [4,5]. Kaynakların doğruluğundan yazar(lar) sorumludur. Yerli ve yabancı kaynakların sentezine önem verilmelidir.

Şekil ve tablo başlıkları: Başlıklar kaynaklardan sonra yazılmalıdır.

4. Şekiller: Her biri ayrı bir görüntü dosyası (jpg) olarak gönderilmelidir.

Makalenin basıma kabulünden sonra "Dizginin ilk düzeltme nüshası" sorumlu yazara e-mail yoluyla gönderilecektir. Bu metinde sadece yazım hataları düzeltilecek, ekleme çıkartma yapılmayacaktır. Sorumlu yazar düzeltmeleri 2 gün içinde bir dosya halinde e-mail ile yayın idare merkezine bildirecektir.

Kaynak Yazım Örnekleri

Dergilerden yapılan alıntı;

Özpolat B, Gürpınar ÖA, Ayva EŞ, Gazyağcı S, Niyaz M. The effect of Basic Fibroblast Growth Factor and adipose tissue derived mesenchymal stem cells on wound healing, epithelization and angiogenesis in a tracheal resection and end to end anastomosis rat model. Turk Gogus Kalp Dama 2013; 21: 1010-19.

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, ulaşım tarihi detaylı olarak verilmelidir.

DOI numarası vermek;

Joos S, Musselmann B, Szecsenyi J. Integration of Complementary and Alternative Medicine into Family Practice 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.

Bilimsel sorumluluk beyanı: Kabul edilen bir makalenin yayınlanmasından önce her yazar, araştırmaya, içeriğinin sorumluluğunu paylaşmaya yetecek boyutta katıldığını beyan etmelidir. Bu katılım şu konularda olabilir:

a. Deneylerin konsept ve dizaynlarının oluşturulması, veya verilerin toplanması, analizi ya da ifade edilmesi;

b. Makalenin taslağının hazırlanması veya bilimsel içeriğinin gözden geçirilmesi

c. Makalenin basılmaya hazır son halinin onaylanması.

Yazının bir başka yere yayın için gönderilmediğinin beyanı: "Bu çalışmanın içindeki materyalin tamamı ya da bir kısmının daha önce herhangi bir yerde yayınlanmadığını, ve halihazırda da yayın için başka bir yerde değerlendirilmede olmadığını beyan ederim. Bu, 400 kelimeye kadar olan özetler 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 listesi:

1. Editöre sunum sayfası (Sorumlu yazar tarafından yazılmış olmalıdır)

2. Başlık sayfası (Makale başlığı/kısa başlık Türkçe ve İngilizce, Yazarlar, kurumları, sorumlu yazar posta adresi, tüm yazarların e-mail adresleri, sorumlu yazarın telefon numarası)

3. Makalenin metin sayfası (Makale başlığı/kısa başlık Türkçe ve İngilizce, Özet/anahtar kelimeler, Summary/keywords, makale metni, kaynaklar, tablo ve şekil başlıkları, tablolar, şekiller)

4. Tablo ve grafikler metin içinde olmalıdır.

5. Şekiller (En az 300 dpi çözünürlükte) ayrı bir veya daha fazla dosya halinde gönderilmelidir.

TURKISH JOURNAL of CLINICS and LABORATORY

Türk Klinik ve Laboratuvar Dergisi

Turkish Journal of Clinics and Laboratory - Türk Klinik ve Laboratuvar Dergisi

Tıp dergilerine gönderilecek makalelerin standart gereksinmeleri ile ilgili tüm bilgileri www.icmje.org internet adresinde bulabilirsiniz

Amaç ve kapsam: "Turkish Journal of Clinics and Laboratory", hakemli, açık erişimli ve periyodik olarak çıkan, DNT Ortadoğu Yayıncılık A.Ş. ye ait bir dergidir. Hedefimiz uluslararası bir tabanda hastalıkların teşhis ve tedavisinde yenilikler içeren yüksek kalitede bilimsel makaleler yayınlamaktır. Yılda dört kez çıkan bir bilimsel bir tıp dergisidir. Hakemli bir dergi olarak gelen yazılar konsültanlar tarafından, öncelikle, biyomedikal makalelere ait Uluslararası Tıp Dergileri Editörleri Komitesi (www.icmje.org adresinden ulaşılabilir) tarafından tanımlanan standart gereksinimler ile ilgili ortak kurallara uygunluğu açısından değerlendirilir. Tıbbın her dalı ile ilgili retrospektif/prospektif klinik ve laboratuar çalışmalar, ilginç olgu sunumları, davet üzerine yazılan derlemeler, editöre mektuplar, orijinal görüntüler, kısa raporlar ve cerrahi teknik yazılarıları yayımlayan bilimsel, uluslar arası hakemli bir dergidir. Başka bir dergide yayımlanmış veya değerlendirilmek üzere gönderilmiş yazılar veya dergi kurallarına göre hazırlanmamış yazılar değerlendirme için kabul edilmez.

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Açık erişim politikası: Turkish Journal of Clinics and Laboratory açık erişimi olan bir dergidir. Kullanıcı lar yazıların tam metnine ulaşabilir, kaynak gösterilerek tüm makaleler bilimsel çalışmalarda kullanılabilir.

Aşağıdaki rehber dergiye gönderilen makalelerde aranan standartları göstermektedir. Bu uluslararası format, makale değerlendirme ve basım aşamalarının hızla yapılmasını sağlayacaktır.

Yazarlara Bilgi: Yazıların tüm bilimsel sorumluluğunu yazar(lar)a aittir. Editör, yardımcı editör ve yayıncı dergide yayınlanan yazılar için herhangi bir sorumluluk kabul etmez.

Dergi adının kısaltması: Turk J Clin Lab

Yazışma adresi: Yazılar e-mail yoluyla sorumlu yazar tarafından, Dergipark ta yer alan Turkish Journal of Clinics and Laboratory linkine girip kayıt olduktan sonra gönderilmelidir.

Makale dili: Makale dili Türkçe ve İngilizcedir. İngilizce makaleler gönderilmeden önce profesyonel bir dil uzmanı tarafından kontrol edilmelidir. Yazıdaki yazım ve gramer hataları içerik değişmeyecek şekilde İngilizce dil danışmanı tarafından düzeltilebilir. Türkçe yazılan yazılarda düzgün bir Türkçe kullanımı önemlidir. Bu amaçla, Türk Dil Kurumu Sözlük ve Yazım Kılavuzu yazım dilinde esas alınmalıdır.

Makalenin başka bir yerde yayımlanmamıştır ibaresi: Her yazar makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, editöre sunum sayfasında belirtmelidirler. 400 kelimeden az özetler kapsam dışıdır. 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.

Değerlendirme: Dergiye gönderilen yazılar format ve plagiarism açısından değerlendirilir. Formata uygun olmayan yazılar değerlendirilmeden sorumlu yazara geri gönderilir. Bu tarz bir zaman kaybının olmaması için yazım kuralları gözden geçirilmelidir. Basım için gönderilen tüm yazılar iki veya daha fazla yerli/yabancı hakem tarafından değerlendirilir. Makalelerin değerlendirilmesi, bilimsel önemi, orijinalliği göz önüne alınarak yapılır. Yayıma kabul edilen yazılar editörler kurulu tarafından içerik değiştirilmeden yazarlara haber verilerek yeniden düzenlenebilir. Makalenin dergiye gönderilmesi veya basıma kabul edilmesi sonrası isim sırası değiştirilemez, yazar ismi eklenip çıkartılamaz.

Basıma kabul edilmesi: Editör ve hakemlerin uygunluk vermesi sonrası makalenin gönderim tarihi esas alınarak basım sırasına alınır. Her yazı için bir doi numarası alınır.

Yayın hakları devri: http:/www.dergipark.ulakbim.gov.tr/tjclinlab adresi üzerinden online olarak gönderilmelidir. 1976 Copyright Act'e göre, yayımlanmak üzere kabul edilen yazıların her türlü yayın hakkı yayıncıya aittir.

Makale genel yazım kuralları: Yazılar Microsoft Word programı (7.0 ve üst versiyon) ile çift satır aralıklı ve 12 punto olarak, 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. Türkçede ondalık sayılarda virgül kullanılmalı (55,78) İngilizce yazılarda nokta (55.78) kullanılmalıdır. Derleme 4000, orijinal çalışma 2500, olgu sunumu 1200, editöre mektup 500 kelimeyi geçmemelidir. Özet sayfasından sonraki sayfalar numaralandırılmalıdır.

Yazının bölümleri

1. Sunum sayfası: Yazının Turkish Journal of Clinics and Laboratory 'de yayınlanmak üzere değerlendirilmesi isteğinin belirtildiği, makalenin sorumlu yazarı tarafından dergi editörüne hitaben gönderdiği yazıdır. Bu kısımda makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, maddi destek ve çıkar ilişkisi durumu belirtmelidir.

2. Başlık sayfası: Sayfa başında gönderilen makalenin kategorisi belirtilmedir (Klinik analiz, orijinal çalışma, deneysel çalışma, olgu sunumu vs).

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Türkçe ve İngilizce yazılmalı ve kısa başlık (runing title) Türkçe ve İngilizce olarak eklenmelidir. Tüm yazarların ad ve soyadları yazıldıktan sonra üst simge ile 1'den itibaren numaralandırılıp, unvanları, çalıştıkları kurum, klinik ve şehir yazar isimleri altına eklenmelidir.

Bu sayfada "sorumlu yazar" belirtilmeli isim, açık adres, telefon ve e-posta bilgileri eklenmelidir.

Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir.

3. Makale dosyası: (Yazar ve kurum isimleri bulunmamalıdır)

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Türkçe ve İngilizce yazılmalı ve kısa başlık (runing title) Türkçe ve İngilizce olarak eklenmelidir.

Özet: Türkçe ve İngilizce yazılmalıdır. Orijinal çalışmalarda özetler, Amaç (Aim), Gereç ve Yöntemler (Material and Methods), Bulgular (Results) ve Sonuçlar (Conclusion) bölümlerine ayrılmalı ve 250 sözcüğü geçmemelidir. Olgu sunumları ve benzerlerinde özetler, kısa ve tek paragraflık olmalıdır (150 kelime), Derlemelerde 300 kelimeyi geçmemelidir.

Anahtar kelimeler: Türkçe ve İngilizce özetlerin sonlarında bulunmalıdır. En az 3 en fazla 6 adet yazılmalıdır. Kelimeler birbirlerinden noktalı virgül ile ayrılmalıdır. İngilizce anahtar kelimeler "Medical Subject Headings (MESH)" e uygun olarak verilmelidir. (www.nlm.nih.gov/mesh/MBrowser.html). Türkçe anahtar kelimeler "Türkiye Bilim Terimleri' ne uygun olarak verilmelidir (www.bilimterimleri.com). Bulunamaması durumunda birebir Türkçe tercümesi verilmelidir.

Metin bölümleri: Orijinal makaleler; Giriş, Gereç ve Yöntemler, Bulgular, Tartışma olarak düzenlenmelidir. Olgu sunumları; Giriş, Olgu sunumu, Tartışma olarak düzenlenmelidir. Şekil, fotoğraf, tablo ve grafiklerin metin içinde geçtiği yerler ilgili cümlenin sonunda belirtilmeli metin içine yerleştirilmemelidir. 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. Tablolar metin sonuna eklenmelidir. Resimler/fotoğraf kalitesi en az 300dpi olmalıdır.