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EDITORIAL

Our dear readers,

We are happy to publish the first issue of our journal in 2022. Although the COVID-19 pandemic is still goes on, we still eager to prominent our scientific quality. We would like to thank all our writers who gave us strength with their articles and scientific support, even though we are in the pandemic process. As time progresses, we are followed by a wider audience. Principally; we want to contribute to the international literature at an increasing level by entering more international indexes and raise the success bar of our journal. In this context, our work continues rapidly. We hope this issue will be useful to our readers.

Kind regards,

Prof. Alpaslan TANOĞLU, MD, PhD
Editor-in-Chief

EDİTÖRDEN

Çok değerli okuyucularımız,

Dergimizin 2022 yılının ilk sayısını yayımlamaktan mutluluk duyuyoruz. COVID-19 pandemisi devam etse de bilimsel kalitemizi öne çıkarmaya devam ediyoruz. Pandemi sürecinde olmamıza rağmen makaleleri ve bilimsel destekleriyle bizlere güç veren tüm yazarlarımıza teşekkür ederiz. Zaman geçtikçe daha geniş bir kitle tarafından takip ediliyoruz. Prensip olarak; daha fazla uluslararası indekse girerek uluslararası literatüre artan oranda katkı sağlamak ve dergimizin başarı çıtasını yükseltmek istiyoruz. Bu kapsamda çalışmalarımız hızla devam etmektedir. Bu sayının okuyucularımız için faydalı olacağını umuyoruz.

Saygılarımla

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MEDICINE PALLIATIVE CARE

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The role of chest tomography in the diagnosis of COVID-19

COVID-19 tanısında göğüs tomografisinin rolü

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ABSTRACT

Aim: We aimed to examine the diagnostic power of chest computerized tomography (CT) comparing with 'Clinical Decision' and RT-PCR results among the patients admitted to the hospital with COVID-19 disease suspicion.

Material and Method: This study included 162 patients who applied to the pandemic outpatient clinic between March 11 and April 11, 2020, suspected of new coronavirus infection, and had chest CT and RT-PCR tests at the same time. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and positive odds ratio of RT-PCR and chest CT imaging are investigated for the diagnosis of COVID-19.

Results: It was found that 56.8% (92 patients) of chest CT scans taken at admission were compatible with viral pneumonia. With the 'Clinical Decision', which we accept as the gold standard diagnostic method, 61.1% of the patients (99 patients) were evaluated as COVID-19 positive and treatment was started. According to clinical decision, sensitivity of chest CT was 92.9%.

Conclusion: COVID-19 pneumonia is a serious life-threatening condition. Rapid diagnosis and early treatment are very important in terms of reducing mortality and morbidity. The chest CT might create an early diagnosis and treatment opportunity.

Keywords: COVID-19, coronavirus, pneumonia, chest, computerized tomography

ÖZ

Amaç: COVID-19 hastalığı şüphesiyle hastaneye başvuran hastalarda göğüs bilgisayarlı tomografi (BT)'sinin 'Klinik Karar' ve RT-PCR sonuçları ile karşılaştırmalı olarak tanısal gücünü incelemeyi amaçladık.

Gereç ve Yöntem: Bu çalışmaya 11 Mart - 11 Nisan 2020 tarihleri arasında pandemi polikliniğine başvuran, yeni koronavirüs enfeksiyonu şüphesi olan ve aynı anda göğüs BT ve RT-PCR tetkikleri yapılan 162 hasta dahil edildi. COVID-19 tanısı için RT-PCR ve göğüs BT görüntülemenin duyarlılığı, özgüllüğü, pozitif öngörü değeri (PPV), negatif öngörü değeri (NPV), doğruluğu ve pozitif olasılık oranı araştırılmaktadır.

Bulgular: Başvuru sırasında çekilen akciğer tomografilerinin %56,8'inin (92 hasta) viral pnömoni ile uyumlu olduğu bulundu. Altın standart tanı yöntemi olarak kabul ettiğimiz 'Klinik Karar' ile hastaların %61,1'i (99 hasta) COVID-19 pozitif olarak değerlendirildi ve tedaviye başlandı. Klinik karara göre göğüs BT'nin duyarlılığı %92,9 idi.

Sonuç: COVID-19 pnömonisi hayatı tehdit eden ciddi bir durumdur. Hızlı tanı ve erken tedavi, mortalite ve morbiditeyi azaltmak açısından çok önemlidir. Göğüs BT erken tanı ve tedavi fırsatı yaratabilir.

Anahtar Kelimeler: COVID-19, coronavirüs, pnömoni, göğüs, bilgisayarlı tomografi

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INTRODUCTION

COVID-19 infection can occur in a wide spectrum of asymptomatic disease, mild upper respiratory tract infection, respiratory failure and severe viral pneumonia that can result in death (1). The most common symptoms are nonspecific findings such as shortness of breath, cough, fever, headache, muscleaches and weakness (2). Approximately 20% of cases are severe and mortality is about %3 (3).

Since there is no specific treatment for COVID-19, it is important to detect infected people early and isolate them from the healthy population. In the differential diagnosis of COVID-19 pneumonia, imaging tests should also be used in addition to the patient's history, clinical, laboratory findings and coronavirus specific diagnostic tests (4). In literature, the diagnostic value of chest x-ray is relatively low as 30–60% in COVID-19 pneumonia. Although it is possible to see some abnormalities in viral pneumonia on chest x-rays, it cannot be excluded the disease if the chest x-ray is normal (5). Non contrast chest computed tomography (CT) should be considered for early diagnosis of viral disease in suspected patients with normal chest x-ray (6).

RT-PCR means that many COVID-19 patients can not be detected at the first admission and can not receive appropriate treatment on time. Such patients pose a risk to infect a larger population, given the highly infectious nature of the virus (7). Chest CT, a routine thorax imaging tool for the diagnosis of pneumonia, is a relatively easy and fast imaging method. Typical chest CT radiographic features in almost all COVID-19 patients are pathchy subpleural ground glass densities, multifocal irregular consolidation and / or interstitial changes with peripheral distribution (**Figure 1**) (8,9). These typical radiological findings have also been observed in patients with negative RT-PCR results, but with clinical symptoms (10).

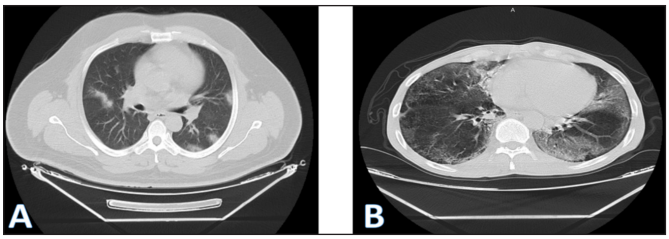

Figure 1. Chest CT image. **A.** Chest CT image of a 48-years-old RT-PCR negative male patient; irregular subpelural nodular infiltrations **B.** Chest CT image of a 45-years-old RT-PCR negative male patient; subpleural groundglass infiltrations with crazy paving in lower and middle zones

In this study, we aimed to examine the diagnostic power of chest CT by expert compatibility and RT-PCR in 162 patients admitted to the hospital with suspicion of COVID-19.

MATERIAL AND METHOD

The study was carried out with the permission of Yıldırım Beyazıt University Faculty of Medicine Clinical Research Ethics Committee (Date; 09.09.2020, Decision No: 72). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients and Study Design

The study included 162 patients who applied to the pandemic outpatient clinics between March 11 and April 11, 2020, suspected of new coronavirus infection, and had chest CT and RT-PCR tests at the same time. Because our study was retrospective, informed consent was not obtained.

Patients over 18 years of age who applied to the COVID polyclinic and underwent chest CT scan and nasopharyngeal swab RT-PCR were included in this study. Patients under the age of 18 were excluded from the study.

Especially in patients with COVID-19 pneumonia, advanced age and comorbidity require rapid diagnosis and treatment. False negative results and late diagnosis may be fatal in these patients. In patients with negative RT-PCR tests, 1 pulmonologist (MD), 2 infectious diseases specialists (TUU, SSG) and 1 radiologist (MEA) experienced in the field of all patients to identify COVID-19 with higher sensitivity blindly evaluated by RT-PCR test results. All physicians had access to patients' exposure history, clinical symptoms, and CT images. Regardless of RT-PCR results, patients were reported as COVID-19 compatible or not with expert opinion. Considering the rapidly spreading COVID-19 epidemic with Clinical Decision, our aim in our study was to detect especially mortal COVID-19 pneumonias, isolate patients and apply appropriate treatment quickly.

The Chest CT Assessment

Chest CT examinations were performed using a 16-channel multi-detector CT device (GE Brightspeed). CT specification: tubevoltage, 120 kVp; tubecurrent, standard (reference mAs, 80–180); slicethickness, 1.25 mm; reconstructionrange is 0,625 mm. All chest CT images were obtained with full inspiration in the patient's supine position and without contrast material. All chest CT evaluation performed by an experienced radiologist.

RT-PCR test

The COVID-19 respiratory samples in patients matching to the probable case definition of SARS-CoV-2 has been evaluated by Turkey General Directorate of Public Health (GDPH) Microbiology Reference Laboratory. Nucleic acid amplification tests (NAAT) for SARS-CoV-2 virus and routine confirmation of COVID-19 cases based

on detection of specific sequences of virus RNA with a NAAT test such as real-time reverse transcription-polymerase chain reaction (rRT-PCR) and when necessary verification by sequence analysis method.

Statistical Analysis

As a result of post-hoc power analysis, the power calculated by considering the frequency of diagnosis with both tests (57% vs 22%) was found to be 100% at a confidence interval of 95%.

Statistical Package for Social Sciences (SPSS), version 22.0 (SPSS Inc. Chicago, USA) computer package program was used for statistical analysis of the research data.

Categorical variables were shown as numbers and percentages, and continuous variables were presented with mean±standard deviation (SD) and median (min-max) for descriptive analysis. A Chi-square test was used in comparison analysis for categorical variables.

In this study, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and positive probability ratio of the RT-PCR, and chest CT imaging in the application to diagnose COVID-19 were presented. In addition, the consistency of both tests according to the expert opinion is presented with the value of kappa and its p-value. Consistency between observations for CT and RT-PCR was evaluated with the kappa value and its p-value.

RESULTS

One hundred sixty two COVID-19 suspicious patients with an average age of 48.42 ±17.98 (range 18-90) years were included in the study. 23,5% (38 patients) of the patients are 65 years and older, 54,9%(89 patients) are male. It was found that 56,8% (92 patients) of the chest CT obtained up on admission were compatible with viral pneumonia (**Table 1**).

Table 1. Baseline demografics

Age, year	
Mean±sd	48.42 ±17.98
Median (min-max)	46.0 (18-90)
Age, n (%)	
<65 years	124 (76.5)
≥65 years	38 (23.5)
Sex, n (%)	
Female	73 (45.1)
Male	89 (54.9)
Chest CT scan, n (%)	
Consistent with viral pneumonia (positive)	92 (56.8)
No CT findings of viral pneumonia	70 (43.2)
Clinical decision, n (%)	
COVID-19 positive	99 (61.1)
COVID-19 negative	63 (38.9)

Thoracic ground glass density/consolidation, multifocal opacities were observed in the early period (after the onset of symptoms, days 0-4). In the interim period (days 5-13), new progressive consolidation and bilateral-multi lobar involvement were observed. Regression of late period (>14 days) lesions were detected, but complete resorption was not seen until day 26.

Treatments of COVID-19 patients were initially started as Triple therapy: Azithromycin + Oseltamivir + Hydroxychloroquine, according to the COVID-19 treatment recommendations of the Ministry of Health of the Republic of Turkey. Treatment of patients whose clinical, radiological or laboratory deteriorated despite initial therapy was continued Quadruple therapy: Azithromycin + Oseltamivir + Hydroxychloroquine + Favipiravir and MV (Mechanical Ventilation) as needed (**Figure 2**). According to the clinical decision, 61,1% (99 patients) of the admitted patients were evaluated as COVID-19 positive and treatment were started. According to the clinical decision, 61.1% of the patients (99 patients) were evaluated as COVID-19 positive and treatment was started. Triple therapy treatment was started in 79.8% (79) of COVID-19 patients. The mean age was 52.87±18.70 (range 18-90) years and 51.5% (51) of them were male. When the treatments received by the patients were analyzed according to age groups, a significant difference was found (p=0.004). It was determined that patients over 65 years old received quadruple therapy (26.7%) and quadruple therapy+MV treatments (13.3%) more than patients under 65 years of age (**Figure 1**).

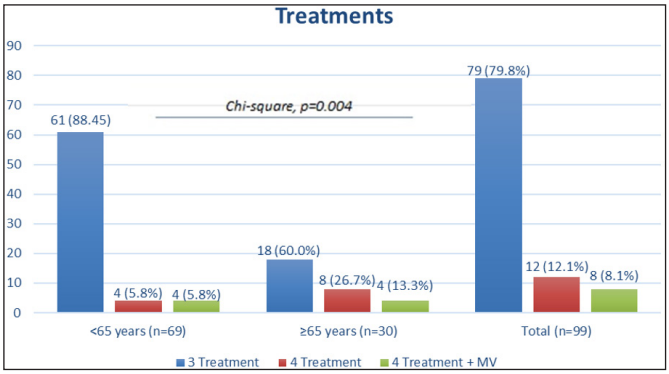

Figure 2. Treatments of COVID-19 patients Triple Treatment: Azithromycin + Oseltamivir + Hydroxychloroquine, Quad Treatment: Azithromycin + Oseltamivir + Hydroxychloroquine + Favipiravir, MV: Mechanical Ventilation).

According to the clinical decision, 57% (62 patients) of the patients were diagnosed with a true positive diagnosis by chest tomography, a true negative diagnosis was made for 39% (63 patients), and a false negative diagnosis was made for 4% (7 patients). The sensitivity (92.9%), specificity (100%), PPD (100%) and NPD I (90%), accuracy (95.7%) and kappa value (0.911) of chest tomography were found to be high. When the age groups

were evaluated separately, it was noted that the sensitivity of thorax tomography decreased to 89.9% in the group under 65 years of age (**Table 2**).

According to the clinical decision, 50% (62 patients) of 124 patients under the age of 65 years included in the study had a correct positive diagnosis by chest tomography, 44% (55 patients) had a negative diagnosis and 6% (7 patients) had a false negative diagnosis. None of the patients under 65 years of age have been diagnosed false positive by chest tomography (**Table 2**).

The compliance of chest CT with PCR test in clinical diagnosis is evaluated in **Table 3.** There were 28 patients, both of whom evaluated as COVID-19 positive, and 63 patients, which evaluated as COVID-19 negative, and the kappa value of both diagnostic methods was calculated as 0.186 (p=0.056). In **Figures 3** and **4**; the results of 162 patients who underwent PCR test and chest CT, and the treatments they received were evaluated according to the expert clinical opinion. While with chest CT 56.8%(92)of the 162 patients were diagnosed as COVID-19, with the PCR test 21.6% (35) patients were diagnosed. According to the clinical expert opinion, 78. 3% (72) of the 92 patients diagnosed with CT got triple therapy, 13% (12), quad therapy, and 8,7% (8), quad therapy and mechanical ventilation support. 40.1(51) % of 127 patients, PCR test COVID-19 negative got triple therapy, 7.1% (9) quad therapy, and 3.1(4) % quad therapy and mechanical ventilation support.

Table 2. Diagnostic value of Torax CT scan according to clinical decision

	<65 years n=124	≥65 years n=38	Total n=162
TP, n (%)	62 (50)	30 (79)	92 (57)
FP, n (%)	0	0	0
TN, n (%)	55 (44)	8 (21)	63 (39)
FN, n (%)	7 (6)	0	7 (4)
Sensitivity, %	89.9	100	92.9
Specifity, %	100	100	100
PPV, %	100	100	100
NPV, %	88.7	100	90
Accuracy, %	94.3	100	95.7
Kappavalue (p)	0.887 (p=0.041)	1.00 (p<0.001)	0.911 (p=0.033)

TP indicates true-positive; FP, false-positive; TN, true-negative; FN, false-negative
PPV: Positive Predictive Value, NPV: Negative Predictive Value

Table 3. Torax CT scan and RT-PCR consistency in diagnosis

	<65 years n=124	≥65 years n=38	Total n=162
CT + PCR +, n (%)	19 (15)	9 (24)	28 (17)
CT + PCR -, n (%)	43 (35)	21 (55)	64 (40)
CT - PCR +, n (%)	7 (6)	0	7 (4)
CT - PCR -, n (%)	55(44)	8 (21)	63 (39)
Accuracy, %	60	45	56
Kappa value (p)	0.194 (p=0.072)	0.153 (p=0.066)	0.186 (p=0.056)

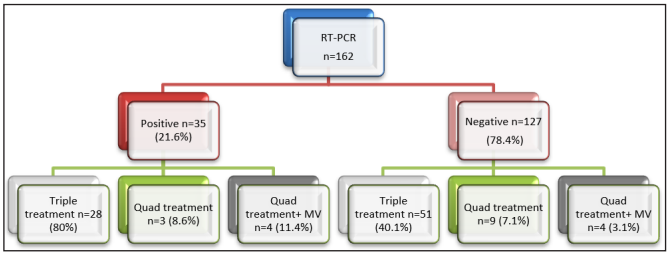

Figure 3. Treatment Distributions Based on Pcr Results. (Triple Treatment: Azithromycin + Oseltamivir + Hydroxychloroquine, Quad Treatment: Azithromycin + Oseltamivir + Hydroxychloroquine + Favipiravir, MV: Mechanical Ventilation).

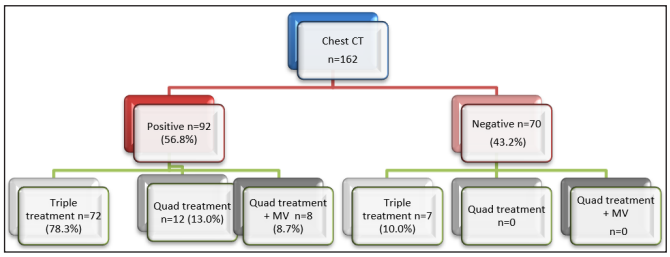

Figure 4. Treatment Distributions According to Chest CT Results. (Triple Treatment: Azithromycin + Oseltamivir + Hydroxychloroquine, Quad Treatment: Azithromycin + Oseltamivir + Hydroxychloroquine + Favipiravir, MV: Mechanical Ventilation).

DISCUSSION

Our study results showed that diagnosis can be missed with RT-PCR and chest X-ray in patients with COVID-19 pneumonia. When the diagnosis was confirmed with lung tomography in patients with high clinical suspicion, radiological findings of COVID-19 were found in patients who were falsely diagnosed with chest X-ray and RT-PCR. Early and accurate diagnosis of COVID-19 has a very important role in ensuring rapid isolation and consequently pandemic control. Also, starting the treatment of patients in a short time will contribute to the reduction of mortality. In a study conducted by Chen N et al. (11) with 99 patients, the mean age was 55,5 years and 67% of the patients were male, and the probability of infection with COVID-19 was higher in older men. In another study involving 1049 patients in China, the average age was 51 years, while 54% were reported as women (12). RT-PCR and chest CT were taken simultaneously in this study. COVID-19 suspicious patients are included. All patients with COVID-19 symptoms compatible with RT-PCR positive or chest CT compatible with viral pneumonia have been accepted as COVID-19 and treatment has been started. According to the results, the average age of patients with COVID 19 was 52,6±18.7 years, while 51.5% were male patients.

The number of patients with viral pneumonia on chest CT was 92 (56,8%) and the sensitivity of CT was found to be high with 92.9% according to the expert view. This rate was 76% in the study of Zhong et al (13). The false-negative rate of chest CT was only 7 (6%). All of these

patients received triple therapy and the clinics of patients were in good conditions. In a study conducted by Tao Ai et al. (12) in 1014 patients, the number of patients with RT-PCR positive but without CT findings in chest CT was reported as 21 (3%), while chest CT of 888 (87.5%) patients was found to be compatible with viral pneumonia. In a study in which Xingzhi Xie et al. (14) examined 167 patients, the false negativity rate of chest CT was reported as only 7 (4%) and in another study involving 99 patients, it was reported as 2%. This result may show that the number of COVID-19 patients with a mild clinical course without pneumonia is low. It can also be attributed to the high false-negative rate of RT-PCR results in this patient group. In the study conducted by Ai T et al (12), the rate of false negativity was reported as 30.8%. This may be due to the RT-PCR result being dependent on external factors such as the sampling, preservation, the stage of the disease and the reliability of the test kits. These results showed that when acting only according to the PCR result, a significant number of patients would remain untreated and would pose a major problem in terms of isolation and pandemic control. Kesmez et al (7),311 RT-PCR positive Chest CT findings of 21.9% of the patients were evaluated as normal. In our study, the rate of chest CT performed in RT-PCR positive patients was 45.7%. Chunqin Long et al (16), diagnosed a total of 36 cases of COVID-19 pneumonia. Thirty-five patients had abnormal CT findings at presentation and only one patient had a normal chest CT. 30 cases were detected positive by RT-PCR and 6 cases were initially missed. Of these 6 missed cases, 3 tested positive in the second RT-PCR test and the other 3 were positive in the third round of RT-PCR evaluations. While the sensitivity of CT scans at admission was 97.2%, the sensitivity of first-round rRT-PCR was 84.6%. In our study, the sensitivity (92.9%) and specificity (100%) of chest tomography were found. When the age groups were evaluated separately, it was noted that the sensitivity of thorax tomography decreased to 89.9% in the group under 65 years of age. In a case of Hao Feng et al (17), a 34-year-old male patient had a negative RT-PCR test on four consecutive pharyngeal swabs. Chest CT showed findings consistent with COVID-19 at admission. However, the fifth RT-PCR test gave a positive result on the fifth day after admission. It is difficult to distinguish COVID-19 pneumonia from other viral pneumonias by CT findings alone; however, they highlight the usefulness of chest CT for early detection of COVID-19 when RT-PCR tests show negative results. These results are consistent with our study, for early diagnosis and treatment, false negative RT-PCR should be kept in mind in case of clinical suspicion, and tomography should be performed when necessary. The study of Joseph V Waller et al.(18) emphasized that CT has limited sensitivity and lower specificity than RT-PCR testing for COVID-19, but the importance of Chest CT as a complementary diagnostic tool, especially in symptomatic patients. In a case series study by Eric D. Tenda et al (19); Strongly recommends the use of non-contrast chest CT to diagnose COVID-19 in patients with RT-PCR negative, chest X-ray non-diagnostic and moderate symptoms.

Chest CT showed that it has a very important tool in the diagnosis of COVID-19 with an accuracy of 95,7%. In addition, while chest CT results immediately, RT-PCR results require several hours. In a study involving 53 positive patients, 37 (69,8%) reported that early diagnosis was made with the result of thoracic CT, lung imaging findings were detected before symptoms occurred, and laboratory tests were concluded approximately 3 days later (20).

This study has some limitations. First this study was retrospective an single center. In the application, recurrent PCR results of patients who were negative for PCR were not expected, only PCR results at the time of application were evaluated. But this is also the hypothesis of this study because we advocated that simultaneous chest CT use with PCR test to the patients is a reliable and confirmatory approach, especially in order not to miss or delay the diagnosis of the patients during admission.

CONCLUSION

COVID-19 pneumonia is a serious, life-threatening condition. Rapid diagnosis and early treatment are very important in terms of reducing mortality and morbidity. In addition, early diagnosis is important for more efficient use of hospital resources. It is very important to use diagnostic methods with high sensitivity and specificity in order to reach a rapid diagnosis. Therefore, chest CT application may be appropriate in patients with clinically negative COVID-19 pneumonia, chest X-ray and RT-PCR test. Chest CT can be life-saving with early diagnosis, especially in elderly patients. Further studies with larger series are needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Yıldırım Beyazıt University Faculty of Medicine Clinical Research Ethics Committee (Date; 09.09.2020, Decision No: 72).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Evaluation of clinicopathological and prognostic significance of RDW in gastric cancer

RDW'nin mide kanserinde klinikopatolojik ve prognostik öneminin değerlendirilmesi

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ABSTRACT

Objective: We aimed to reveal possible relationships between pre-operative RDW values and clinicopathological features of gastric cancer (GC) and to evaluate its predictive impact on progression and prognosis of GC.

Material And Method: A total of 92 patients who underwent curative surgery were retrospectively included the study. GC patients were divided into two groups: high-RDW group (>14.5%, n=58) and low-RDW (<14.5%, n=34).

Results: The optimal pre-operative RDW cut-off value to predict mortality in GC patients was 14.5% (AUC=0.690, p=0.010). Increased tumor size and decreased albumin and hemoglobin values were found in the high-RDW group (p=0.036, 0.003 and <0.001, respectively). The 5-year overall survival (OS) rates were 17.6±5% in patients with high-RDW and 44.5±9% in the low-RDW group (p<0.001). Cox regression analysis showed perineural invasion, surgical margin positivity, N3 stage, leakage and high RDW were independent prognostic factors for mortality.

Conclusion: Our results indicate that RDW is associated with GC pathogenesis and tumor progression. Pre-operative RDW may be a non-invasive, easily accessible and reliable indicator to predict survival in patients with GC.

Keywords: Gastric cancer, red cell distribution width, RDW, prognosis, overall survival

ÖZ

Amaç: Preoperatif RDW değerleri ile mide kanseri (MK)'nin klinikopatolojik özellikleri arasındaki olası ilişkileri ortaya koymayı ve MK'nin progresyonu ve prognozu üzerindeki prediktif etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Küratif cerrahi uygulanan toplam 92 hasta retrospektif olarak çalışmaya dahil edildi. MK hastaları iki gruba ayrıldı: yüksek RDW grubu (>%14,5, n=58) ve düşük RDW (<%14,5, n=34).

Bulgular: MK hastalarında mortaliteyi öngörmek için optimal preoperatif RDW eşik değeri %14,5 idi (AUC=0,690, p=0,010). Yüksek RDW grubunda tümör boyutunda artış, albümin ve hemoglobin değerlerinde azalma saptandı (sırasıyla p=0,036, 0,003 ve <0,001). Yüksek RDW'li hastalarda 5 yıllık genel sağkalım (OS) oranları %17,6±%5 ve düşük RDW grubunda %44,5±%9 idi (p<0,001). Cox regresyon analizi perinöral invazyon, cerrahi sınır pozitifliği, N3 evresi, sızıntı ve yüksek RDW değerinin mortalite için bağımsız prognostik faktörler olduğunu gösterdi.

Sonuç: Sonuçlarımız, RDW'nin MK patogenezinde ve tümör progresyonunda rol oynadığını göstermektedir. Preoperatif RDW, MK'li hastalarda sağkalımı öngörmek için invazif olmayan, kolay erişilebilir ve güvenilir bir gösterge olabilir.

Anahtar Kelimeler: Mide kanseri, eritrosit dağılım genişliği, RDW, prognoz, genel sağkalım

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INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies worldwide, with almost one million new cases reported annually (1). Despite the global decline in incidence and mortality, as well as recent improvements in the management modalities of GC, treatment options still not promising enough and it remains the third leading cause of cancer-related death (2). Because GC is either asymptomatic or presents with non-specific signs and symptoms at early stages, most patients are usually diagnosed at an advanced stage. Most cases have regional or distant metastases at presentation, and overall 5-year survival is often less than 30% after surgical intervention with lymph node dissection and chemotherapy and radiotherapy administration(3). Therefore, identifying independent prognostic determinants may help predict and improve long-term outcomes in GC patients. Although several factors have been determined to stratify patient survival in different cohorts of GC patients, there is a still need for non-invasive, low-cost, and reliable predictors to establish prognostic models (4).

Accumulating evidence indicates that both systemic and local inflammatory responses play important roles in tumor progression by inducing invasion, migration, angiogenesis and metastasis, and are related with the prognosis of GC (5). Red blood cell distribution width (RDW) is a routine laboratory parameter and it is widely used to differentiate anemia in clinical settings (6). Previous studies also reported that elevated RDW value is related with systemic inflammation, malnutrition and cancer pathophysiology -including its development, progression and prognosis (7). Although, the prognostic value of the pre-operative RDW value for gastric cancer is still unclear.

The aim of this study was to evaluate the relationship between pre-operative RDW values and clinicopathological characteristics of GC and to investigate its prognostic significance in GC patients who underwent surgical treatment.

MATERIAL AND METHOD

The study was carried out with the permission of Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee (Date: 15.06.2021, Decision No: 03). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was designed as a single center retrospective study and was carried out from January 2011 to January 2016 in General Surgery Department of Eskişehir Osmangazi University Hospital. A total of 92 patients (after exclusion) who underwent curative surgical intervention for histopathologically-diagnosed GC were included the study. Patients were randomly selected and only those with confirmed histopathological diagnosis, complete demographic, clinicopathological and follow-up data, and those in which complete blood counts had been perfromed before surgical intervention were included in the study. Patients with recurrent gastric cancer, synchronous or metachronous cancer, anemia, cirrhosis, clinical sign of infection, autoimmune diseases, hematological disorders, those who received neoadjuvant therapy or an emergency gastrectomy for bleeding or perforation, those using corticosteroids in the last 6 months, and patients with incomplete data were excluded from the study. A total of 20 patients had been excluded due to exclusion criteria. Since the study was designed as a retrospective evaluation, written informed consent from patients was waived.

Demographic features and clinicopathological characteristics, including type of surgical procedure, the size, histology, differentiation and primary location of tumor, Lauren classification, the number of lymph nodes and metastatic lymph nodes, perineural invasion, lymphovascular invasion, extracapsular invasion, surgical margin positivity, tumor stage, the length of hospitalization, the presence of leakage or infection, the recurrence status, and the final status were obtained from hospital records each patient. The tumor stage of patients was determined in accordance with the pathological classification criteria of the American Joint Committee on Cancer Staging / UICC-TNM for GC (8). Patients were divided into three main groups: diffuse, intestinal and mixed according to Lauren classification criteria (9). All patients were followed regularly with clinical and radiological evaluation every 3 to 6 months. Causes of death and recurrence status were assessed by reviewing medical records or by direct questioning of close relatives. The last follow-up evaluations were performed in September 2021. Overall survival (OS) was determined as the duration from the date of surgical procedures to the date of death or the last follow-up.

All analyses were performed on SPSS v21 (IBM, Armonk, NY, USA). Histograms and Q-Q plots were used to determine whether variables were normally distributed. Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. The best cut-off for RDW to predict mortality was determined by using Receiver Operating Characteristics (ROC) curve analysis and the Youden J statistic. Continuous variables were analyzed with the independent samples t-test or the Mann-Whitney U test depending on normality of distribution. Categorical variables were analyzed with Pearson chi-square or Fisher's exact test. Survival times were calculated with the Kaplan-Meier

method. Between-group comparisons of survival times were performed with the Log rank test. Cox regression analysis (forward conditional method) was performed to determine significant prognostic factors. p<0.05 values were accepted as statistically significant results.

RESULTS

Demographic characteristics, laboratory results and clinicopathological data of GC patients are given in **Table 1**. The mean age of patients was 63.9±14.1 years and most of them were male (n:60, 65.22%). In the pathological evaluation, gastric adenocarcinoma was diagnosed in 60 (65.22%) patients, signet ring cell adenocarcinoma in 30 (32.61%) patients, and mucinous adenocarcinoma in 2 (2.17%) patients. Surgical intervention was applied to 66 (71.74%) patients as total gastrectomy, 25 (27.17%) patients as subtotal gastrectomy and 1 (1.09%) patient underwent laparoscopic total gastrectomy. According to the Lauren classification, diffuse type was present in 43 (46.74%) patients, intestinal type in 38 (41.3%) patients, and mixed type cancer in 11 (11.96%) patients. The tumor was located in the proximal third in 28 (30.43%) patients, in the central third in 26 (28.26%) patients, and in the distal third in 31 (33.7%) patients, while 7 (7.61%) patients had linitis plastica. According to TNM stage evaluation, 27 (29.35%) patients presented at stage 3A, 14 (15.22%) patients at stage 3B, 21 (22.83%) patients at stage 3C, and 2 (2.17%) patients at stage 4. During the follow-up period, recurrence was observed in 35 (38.04%) patients and 72 (78.26%) patients died. While mean hemoglobin values were 12.02±1.98 g/dL in GC patients, mean albumin levels were 4±0.57 g/dL. The median RDW values were 15.1 (13.95-16.9) %.

ROC analysis indicated that the optimal pre-operative RDW cut-off value for mortality prediction was 14.5 (AUC=0.690, p=0.010) in GC patients (**Table 2**, **Figure 1**). Therefore, GC patients were divided into two groups: high pre-operative RDW group (>14.5, n=58) and low pre-operative RDW (<14.5, n=34) (**Table 3**). Increased tumor size and decreased albumin and hemoglobin values were present in patients with high pre-operative RDW (p=0.036, 0.003, <0.001, respectively). The number of patients in the N0 stage was lower in the high pre-operative RDW group (p=0.013).

Table 2. Performance of the RDW to predict mortality

Cut-off	≥ 14.5
Sensitivity	72.22%
Specificity	70.00%
Accuracy	71.74%
PPV	89.66%
NPV	41.18%
AUC (95.0% CI)	0.690 (0.533-0.846)
p value	0.010

RDW: Red cell distribution width, PPV: Positive Predictive Value, NPV: Negative Predictive Value, AUC: Area Under ROC Curve, CI: Confidence Intervals

Table 1. The demographic features and tumor characteristics of patients

Age, years	63.85±14.06
Gender	
Female	32 (34.78%)
Male	60 (65.22%)
Time between diagnosis and operation, days	16 (9-26)
Surgical Procedure	
Subtotal	25 (27.17%)
Total	66 (71.74%)
Laparoscopic subtotal	0 (0.00%)
Laparoscopic total	1 (1.09%)
Differentiation	
Poor	55 (59.78%)
Moderate	24 (26.09%)
Well	13 (14.13%)
Histology	
Adenocarcinoma	60 (65.22%)
Signet ring cell adenocarcinoma	30 (32.61%)
Mucinous adenocarcinoma	2 (2.17%)
Lauren classification	
Intestinal	38 (41.30%)
Diffuse	43 (46.74%)
Mixed	11 (11.96%)
Location	
Proximal 1/3	28 (30.43%)
Central 1/3	26 (28.26%)
Distal 1/3	31 (33.70%)
Linitis plastica	7 (7.61%)
Tumor size, mm	50 (30-80)
Number of lymph nodes	20 (13-32)
Number of metastatic lymph nodes	4 (1-13.5)
Extracapsular invasion	39 (42.39%)
Lymph node dissection	
D1	18 (19.57%)
D2	47 (51.09%)
D1+	2 (2.17%)
D2+	25 (27.17%)
Perineural invasion	67 (72.83%)
Lymphovascular invasion	61 (66.30%)
Surgical margin positivity	12 (13.04%)
T stage	
T1	12 (13.04%)
T2	5 (5.43%)
T3	36 (39.13%)
T4	39 (42.39%)
N stage	
N0	21 (22.83%)
N1	16 (17.39%)
N2	24 (26.09%)
N3	31 (33.70%)
M stage	
M0	90 (97.83%)
M1	2 (2.17%)
TNM stage	
Stage 1A	9 (9.78%)
Stage 1B	3 (3.26%)
Stage 2A	8 (8.70%)
Stage 2B	8 (8.70%)
Stage 3A	27 (29.35%)
Stage 3B	14 (15.22%)
Stage 3C	21 (22.83%)
Stage 4	2 (2.17%)
Adjuvant chemotherapy	77 (83.70%)
Adjuvant radiotherapy	57 (61.96%)
Length of hospitalization, days	9 (6-12)
Leakage	16 (17.39%)
Infection	27 (29.35%)
Recurrence	35 (38.04%)
Albumin, g/dL	4.00±0.57
Hemoglobin, g/dL	12.02±1.98
RDW, %	15.10 (13.95-16.90)
Final Status	
Exitus	72 (78.26%)
Alive	20 (21.74%)

RDW: Red cell distribution width, Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage)

Table 3. Patient characteristics and clinicopathological features with regard to RDW level

	RDW		p
	< 14.5 (n=34)	≥ 14.5 (n=58)	
Age, years	61.21±15.39	65.40±13.11	0.169
Gender			0.882
Female	11 (32.35%)	21 (36.21%)	
Male	23 (67.65%)	37 (63.79%)	
Surgical Procedure			0.733
Subtotal	9 (26.47%)	16 (27.59%)	
Total	25 (73.53%)	41 (70.69%)	
Laparoscopic subtotal	0 (0.00%)	0 (0.00%)	
Laparoscopic total	0 (0.00%)	1 (1.72%)	
Differentiation			0.735
Poor	20 (58.82%)	35 (60.34%)	
Moderate	8 (23.53%)	16 (27.59%)	
Well	6 (17.65%)	7 (12.07%)	
Histology			0.454
Adenocarcinoma	24 (70.59%)	36 (62.07%)	
Signet ring cell adenocarcinoma	10 (29.41%)	20 (34.48%)	
Mucinous adenocarcinoma	0 (0.00%)	2 (3.45%)	
Lauren classification			0.626
Intestinal	12 (35.29%)	26 (44.83%)	
Diffuse	17 (50.00%)	26 (44.83%)	
Mixed	5 (14.71%)	6 (10.34%)	
Location			0.287
Proximal 1/3	13 (38.24%)	15 (25.86%)	
Central 1/3	11 (32.35%)	15 (25.86%)	
Distal 1/3	9 (26.47%)	22 (37.93%)	
Linitis plastica	1 (2.94%)	6 (10.34%)	
Tumor size, mm	35 (27±75)	60 (40±80)	0.036
Number of lymph nodes	21 (15±29)	19 (13±34)	0.971
Number of metastatic lymph nodes	2.5 (0±11)	4.5 (2±17)	0.102
Extracapsular invasion	12 (35.29%)	27 (46.55%)	0.403
Lymph node dissection			0.240
D1	7 (20.59%)	11 (18.97%)	
D2	21 (61.76%)	26 (44.83%)	
D1+	0 (0.00%)	2 (3.45%)	
D2+	6 (17.65%)	19 (32.76%)	
Perineural invasion	22 (64.71%)	45 (77.59%)	0.272
Lymphovascular invasion	20 (58.82%)	41 (70.69%)	0.350
Surgical margin positivity	4 (11.76%)	8 (13.79%)	1.000
T stage			0.688
T1	5 (14.71%)	7 (12.07%)	
T2	3 (8.82%)	2 (3.45%)	
T3	12 (35.29%)	24 (41.38%)	
T4	14 (41.18%)	25 (43.10%)	
N stage			0.013
N0	14 (41.18%)	7 (12.07%)	
N1	4 (11.76%)	12 (20.69%)	
N2	6 (17.65%)	18 (31.03%)	
N3	10 (29.41%)	21 (36.21%)	
M stage			0.529
M0	34 (100.00%)	56 (96.55%)	
M1	0 (0.00%)	2 (3.45%)	
TNM stage			0.069
Stage 1A	5 (14.71%)	4 (6.90%)	
Stage 1B	2 (5.88%)	1 (1.72%)	
Stage 2A	6 (17.65%)	2 (3.45%)	
Stage 2B	2 (5.88%)	6 (10.34%)	
Stage 3A	8 (23.53%)	19 (32.76%)	
Stage 3B	2 (5.88%)	12 (20.69%)	
Stage 3C	9 (26.47%)	12 (20.69%)	
Stage 4	0 (0.00%)	2 (3.45%)	
Adjuvant chemotherapy	30 (88.24%)	47 (81.03%)	0.542
Adjuvant radiotherapy	21 (61.76%)	36 (62.07%)	1.000
Length hospitalization, days	9 (7±11)	10 (6±13)	0.630
Leakage	3 (8.82%)	13 (22.41%)	0.169
Infection	8 (23.53%)	19 (32.76%)	0.483
Recurrence	12 (35.29%)	23 (39.66%)	0.847
Albumin, g/dL	4.22±0.43	3.86±0.60	0.003
Hemoglobin, g/dL	13.16±1.69	11.35±1.83	<0.001
Final Status			0.001
Exitus	20 (58.82%)	52 (89.66%)	
Alive	14 (41.18%)	6 (10.34%)	

RDW: Red cell distribution width. Data are given as mean±standard deviation or median (1st quartile±3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage)

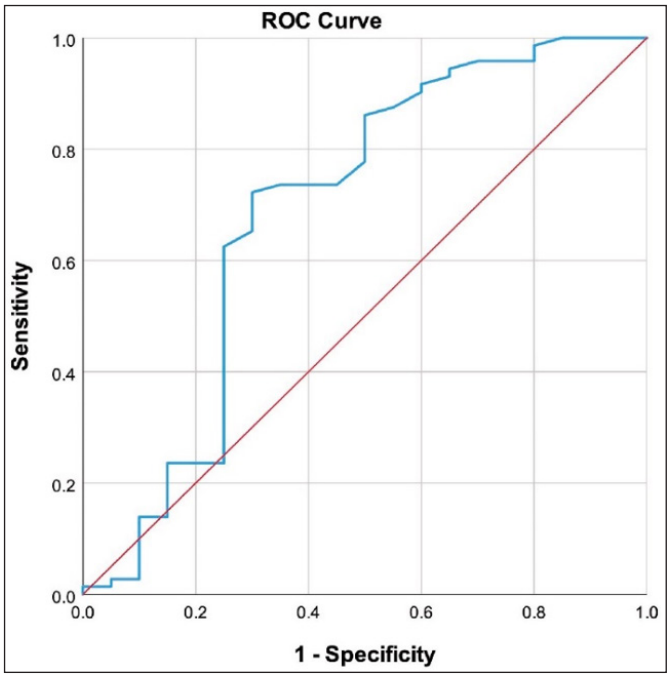

Figure 1. ROC curve of the RDW to predict mortality

Five-year OS rates were examined with Kaplan-Meier method and comparisons were performed with the Log rank test (**Table 4**). Overall, 5-year OS was 27.2±4.8 %. Intestinal type GC showed significantly higher OS rates than diffuse type GC (p=0.020). Patients with linitis plastica demonstrated significantly lower OS rate compared to other locations (p=0.006). Lower OS rates were observed in GC patients with extracapsular invasion, perineural invasion, lymphovascular invasion, leakage, infection, and recurrence, as well as in those with surgical margin positivity and higher RDW values (all, p<0.05). T4 and also N3 stage showed decreased OS rates than the other stages (all, p=<0.001). Lower OS rates were found in stage 3&4 compared to stage 1 and 2 (p=<0.001). The OS rates were 17.6±5% in patients with high-RDW and 44.5±9% in the low-RDW group (p=<0.001).

We performed Cox regression analysis to determine the best prognostic factors associated with mortality (**Table 5**). We found perineural invasion, surgical margin positivity, N3 stage, leakage and high RDW as poor prognostic factors. Patients with perineural invasion had 2.395-fold higher risk of death than those without (HR: 2.395, 95% CI: 1.268-4.526, p=0.007) (**Figure 2**). Patients with positive surgical margin presented 2.220-fold higher risk of death than those without (HR: 2.220, 95% CI: 1.040-4.740, p=0.039) (**Figure 3**). Patients with N3 stage tumor showed 3.223-fold higher risk of death than those without (HR: 3.223, 95% CI: 1.763-5.893, p<0.001) (**Figure 4**). Patients with leakage demonstrated 5.112-fold higher risk of death compared to those without leakage (HR: 5.112, 95% CI: 2.679-9.755, p<0.001) (**Figure 5**). Patients

with high RDW (≥ 14.5) had 1.978-fold higher risk of death than patients classified in the low RDW group (HR: 1.978, 95% CI: 1.166-3.357, p=0.011) (**Figure 6**). Other variables included in the model were non-significant, including Lauren classification (p=0.364), location (p=0.577), extracapsular invasion (p=0.991), lymphovascular invasion (p=0.106), T stage (p=0.165), TNM stage (p=0.293), infection (p=0.079), recurrence (p=0.547), time between diagnosis and surgery (p=0.229), tumor size (p=0.248), total number of lymph nodes (p=0.613), number of metastatic lymph nodes (p=0.500), albumin (p=0.182) and hemoglobin (p=0.803).

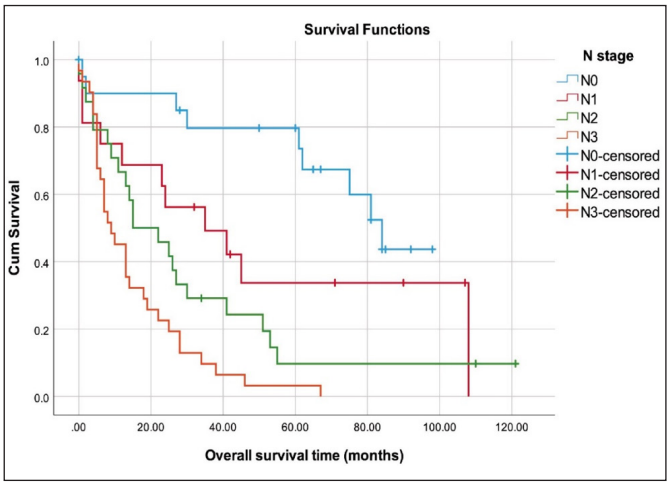

Figure 4. Overall survival plot with regard to N stage

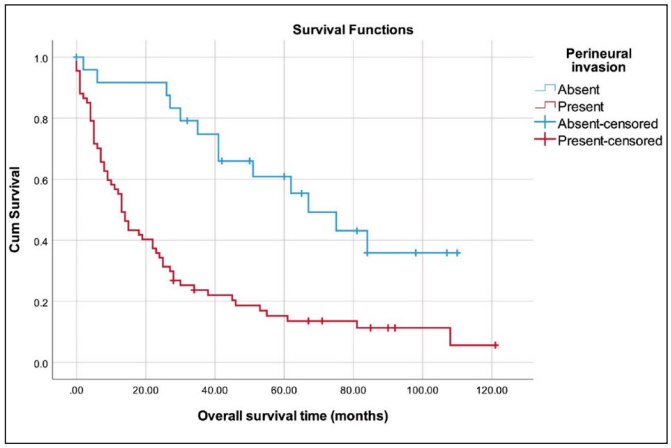

Figure 2. Overall survival plot with regard to perineural invasion

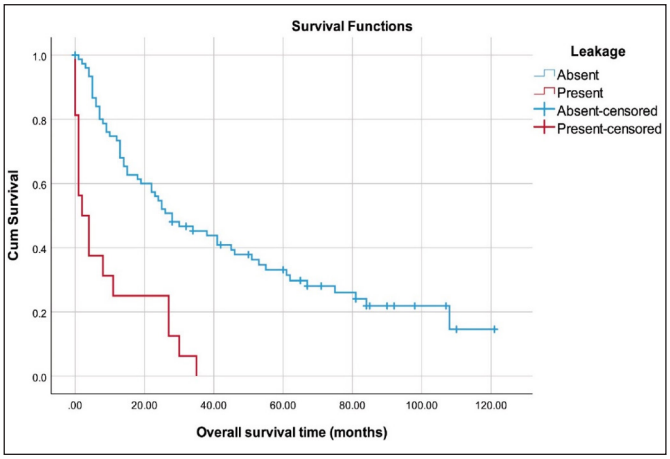

Figure 5. Overall survival plot with regard to leakage

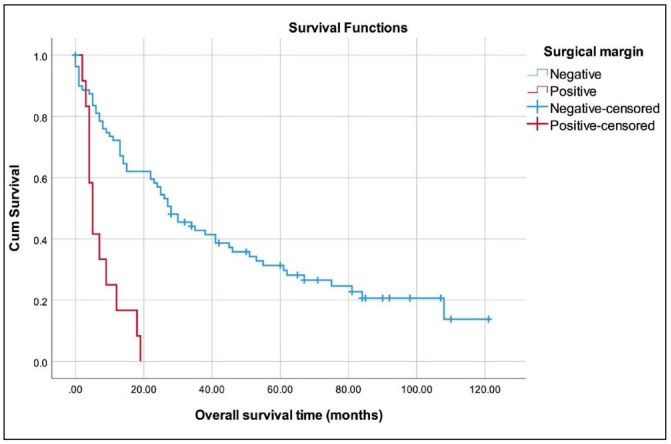

Figure 3. Overall survival plot with regard to surgical margin positivity

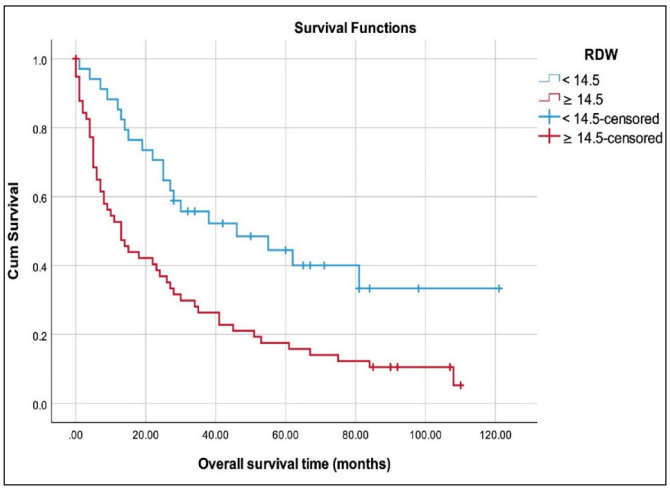

Figure 6. Overall survival plot with regard to RDW level

Table 5. Significant prognostic factors of the mortality, Cox regression analysis

	β Coefficient	Std Error	p	Exp(β)	95.0% CI for Exp(β)	
Perineural invasion	0.873	0.325	0.007	2.395	1.268	4.526
Surgical margin positivity	0.798	0.387	0.039	2.220	1.040	4.740
N3 stage	1.170	0.308	<0.001	3.223	1.763	5.893
Leakage	1.632	0.330	<0.001	5.112	2.679	9.755
RDW (≥ 14.5%)	0.682	0.270	0.011	1.978	1.166	3.357

CI: Confidence interval, RDW: Red cell distribution width

Table 4. Survival times (months) with Kaplan Meier method and comparisons of groups with Log rank test

	n	Exitus	Mean (95.0% CI)	Median (95.0% CI)	5-years survival rate (%)	p
Overall survival	92	72	40.11 (31.32±48.90)	24 (13.81±34.19)	27.2±4.8	N/A
Age						0.214
< 65 years	46	34	45.59 (32.60±58.59)	26 (19.35±32.65)	32.0±7.0	
≥ 65 years	46	38	33.84 (23.04±44.64)	15 (7.12±22.88)	22.8±6.5	
Gender						0.367
Female	32	26	32.00 (20.65±43.34)	18 (4.92±31.08)	24.7±7.9	
Male	60	46	43.04 (31.75±54.32)	25 (16.33±33.68)	28.5±6.0	
Surgical Procedure						0.087
Subtotal	25	17	51.05 (34.37±67.73)	41 (9.95±72.05)	41.7±10.1	
Total	67	55	35.11 (25.45±44.78)	19 (8.69±29.31)	21.6±5.3	
Differentiation						0.175
Poor	55	46	34.56 (24.29±44.84)	19 (7.70±30.31)	20.8±5.7	
Moderate	24	18	38.47 (21.57±55.37)	15 (0.00±30.36)	26.8±9.5	
Well	13	8	54.17 (35.69±72.64)	62 (11.14±112.86)	52.7±14.1	
Histology						0.145
Adenocarcinoma	60	45	40.91 (31.08±50.74)	27 (21.42±32.58)	28.8±6.1	
Signet ring cell adenocarcinoma	30	25	31.25 (16.50±46.00)	9 (1.49±16.52)	18.8±7.3	
Lauren classification						0.020
Intestinal	38	25	52.49 (38.62±66.35)[a]	41 (6.33±75.67)	45.2±8.3	
Diffuse	43	38	27.82 (17.49±38.15)[b]	14 (5.01±22.99)	11.5±5.2	
Mixed	11	9	39.55 (12.97±66.12)[ab]	19 (3.90±34.11)	24.2±13.8	
Location						0.006
Proximal 1/3	28	24	29.44 (15.78±43.10)[a]	22 (11.63±32.37)	10.9±6.6	
Central 1/3	26	19	46.79 (30.35±63.23)[a]	27 (3.79±50.21)	37.3±9.7	
Distal 1/3	31	22	48.17 (32.93±63.41)[a]	41 (8.91±73.09)	39.1±9.0	
Linitis plastica	7	7	9.71 (5.85±13.58)[b]	11 (0.00±26.40)	0.0±0.0	
Extracapsular invasion						<0.001
Absent	53	35	53.22 (41.64±64.80)	51 (26.38±75.62)	44.1±7.1	
Present	39	37	19.64 (11.42±27.86)	12 (7.11±16.89)	5.1±3.5	
Lymph node dissection						0.112
D1 & D1+	20	14	51.54 (33.72±69.36)	35 (10.90±59.11)	39.4±11.1	
D2	47	35	40.84 (27.75±53.93)	22 (9.67±34.33)	29.0±6.9	
D2+	25	23	28.54 (15.64±41.45)	18 (3.31±32.69)	14.4±7.3	
Perineural invasion						<0.001
Absent	25	13	69.19 (53.85±84.53)	67 (43.88±90.12)	60.9±10.3	
Present	67	59	28.51 (19.89±37.14)	13 (9.99±16.01)	15.2±4.5	
Lymphovascular invasion						<0.001
Absent	31	16	68.12 (52.75±83.48)	81 (40.09±121.91)	58.2±9.3	
Present	61	56	25.22 (17.28±33.16)	13 (9.72±16.28)	12.3±4.3	
Surgical magrin						<0.001
Negative	80	60	45.04 (35.39±54.7)	28 (19.40±36.60)	31.3±5.4	
Positive	12	12	7.67 (4.41±10.92)	5 (3.33±6.67)	0.0±0.0	
T stage						<0.001
T1 & T2	17	9	65.08 (49.01±81.16)[a]	75 (43.65±106.35)	61.9±12.3	
T3	36	28	44.54 (30.52±58.57)[a]	27 (19.76±34.24)	31.2±8.1	
T4	39	35	21.06 (12.46±29.67)[b]	12 (5.88±18.12)	9.0±4.8	
N stage						<0.001
N0	21	9	72.49 (58.08±86.90)[a]	84 (69.59±98.41)	79.7±9.1	
N1	16	11	49.78 (26.50±73.06)[ab]	35 (4.93±65.07)	33.8±12.6	
N2	24	21	30.90 (17.02±44.79)[b]	15 (1.80±28.20)	9.7±6.4	
N3	31	31	15.13 (9.84±20.42)[c]	9 (4.76±13.24)	3.2±3.2	
TNM stage						<0.001
Stage 1	12	5	77.42 (62.70±92.14)[a]	84 (62.79±105.21)	81.8±11.6	
Stage 2	16	10	60.46 (38.64±82.28)[a]	61 (22.11±99.89)	53.7±13.0	
Stage 3 & 4	64	57	26.39 (18.00±34.78)[b]	13 (9.52±16.48)	10.9±4.1	
Adjuvant chemotherapy						0.202
Absent	15	13	27.68 (12.53±42.84)	10 (0.00±27.99)	25.0±11.6	
Present	77	59	42.24 (32.43±52.06)	25 (16.46±33.54)	27.8±5.3	
Adjuvant radiotherapy						0.502
Absent	35	26	41.46 (29.05±53.86)	30 (16.15±43.86)	37.1±8.5	
Present	57	46	37.48 (26.54±48.42)	19 (8.43±29.57)	21.3±5.6	
Leakage						<0.001
Absent	76	56	46.70 (36.72±56.69)	28 (14.15±41.85)	33.1±5.6	
Present	16	16	9.50 (3.35±15.65)	2 (0.00±5.92)	0.0±0.0	
Infection						0.001
Absent	65	47	48.01 (37.27±58.76)	30 (15.07±44.93)	33.9±6.1	
Present	27	25	19.32 (8.84±29.79)	10 (0.00±20.18)	11.1±6.0	
Recurrence						0.011
Absent	57	38	50.24 (37.18±63.31)	30 (0.00±77.83)	43.9±6.7	
Present	35	34	24.40 (18.53±30.27)	22 (15.05±28.95)	2.9±2.8	
RDW						0.001
<14.5%	34	20	61.21 (44.65±77.77)	46 (7.54±84.46)	44.5±9.0	
≥14.5%	58	52	28.57 (19.76±37.38)	13 (6.67±19.33)	17.6±5.0	

CI: Confidence interval, RDW: Red cell distribution width

DISCUSSION

This study aimed to reveal the associations between pre-operative RDW values and clinicopathological features of GC and to evaluate its predictive impact on progression and prognosis of GC. We found that pre-operative RDW was associated with tumor size, N stage, and pre-operative albumin and hemoglobin values in patients with GC. The cut-off value for pre-operative RDW (>14.5) could be used to predict mortality in GC patients. We also demonstrated that perineural invasion, surgical margin positivity, N3 stage, leakage and high RDW value may be used as independent prognostic indicators for OS in GC patients.

Recent studies have drawn attention to the link between inflammation and malignancies, and have shown that cancer can act as a cause or consequence of chronic inflammation. Additionally, cancer-related inflammation plays a substantial role in tumor pathogenesis, including GC, which involves initiation, progression, metastasis and clinical prognosis (10). Chronic inflammation may cause poor response to chemotherapy, resulting in a worse prognosis for cancer patients (11). Possible links may also exist with aberrant triggering of multiple signaling pathways, including angiogenesis, abnormal apoptosis, increased cytokine production, inappropriate immune cell proliferation/differentiation, epithelial transformation, and nutritional factors (10). Although clinicopathological factors of GC, such as TNM stage, lymph node metastases and lymphatic vessel invasion, are utilized to aid patient risk classification and treatment approaches, the complexity of the pathogenesis of GC prompts researchers to investigate more suitable indicators in order to assess patients' clinical status for prognostic and therapeutic purposes (12).

RDW is a biomarker routinely analyzed in clinical laboratories to demonstrate heterogeneity in the size of circulating erythrocytes, and may reflect nutritional insufficiencies (folate, vitamin B12 or iron deficiency) which are often detected in GC patients, and can lead to significant decline in the emotional and physical status of GC patients (13). Recent studies have shown that increased RDW is related with oxidative stress and inflammation, and correlates with overall and disease-specific survival in diseases with progressive features or chronic inflammation (12, 14). In addition, RDW has received increasing attention in recent years in terms of malignancy pathogenesis and it has been found that elevated RDW value is related with diagnosis and survival in many cancer types, including esophageal, colorectal, pulmonary, hepatocellular, prostate, and breast cancers (15). Zhou et al. (6) reported in a meta-analysis of 13 studies involving 3509 patients with gastrointestinal cancer that patients with elevated RDW tended to have shorter OS and cancer-free survival compared to patients with low RDW. They also demonstrated that increased RDW was related with larger tumor size, deeper invasion, worse differentiation, more advanced clinical stage and earlier lymph node metastasis. Increased pre-operative RDW reported in cancer patients may be due to elevated inflammatory mechanisms induced by tumor cells and their microenvironment (16). High levels of secreted pro-inflammatory cytokines, such as IL-6, TNF-α and CRP, can inhibit erythropoietic activity on bone marrow erythrocyte stem cells and impair iron metabolism and homeostasis, and also shorten red blood cell survival, resulting in the release of more immature red blood cells into peripheral blood circulation and elevation of pre-operative RDW (17). It is also thought that RDW regulates cancer progression by inducing the glycolytic process of tumor cells, and that elevated RDW may be a surrogate indicator of advanced glucose metabolism, which is significant for the survival of GC patients (18). RDW is also related with impaired nutritional status, which has been reported to be associated with a lower response to management, worse prognosis, and quality of life in cancer patients (19).

Taking these relationships into account, we aimed to look over the prognostic value of RDW in GC patients. We found a significant cut-off value for pre-operative RDW that could identify mortality in GC patients (>14.5). Consistent with our results, Sakin et al. (20) demonstrated an RDW threshold of 14.1, with 61.3% sensitivity and 64% specificity in predicting the presence of GC in a large study including 330 GC patients and 330 healthy controls. Shota et al. (21) reported in 221 GC patients who underwent curative surgery that the optimal cut-off value for RDW was 14.85 pre-operatively and 14.05 post-operatively. Our result indicates that pre-operative RDW could be used as an indicator for predicting mortality in patients with GC. We then divided GC patients into two groups according to the cut-off value for RDW. We found that pre-operative RDW was associated with tumor size, lymph node stage as well as pre-operative albumin and hemoglobin. Similarly, Hirahara et al. (22) demonstrated a positive relationship between RDW and tumor size, lymph node metastasis, pathological stage, serum albumin and CRP levels in 366 GC patients. Yazici and colleagues (23) revealed that RDW is correlated with preoperative hemoglobin, tumor stage, tumor diameter and metastatic lymph nodes. Yuksel et al. (14) showed in 411 operated GC patients that elevated pre-operative RDW was present in patients with advanced TNM stage, advanced T stage, node positivity, hypoalbuminemia, more metastatic lymph nodes and increased age. Cheng et al. (12) reported that a higher RDW was related with

advanced age, deeper tumor infiltration, larger tumor size and lymph node metastasis. Our results suggest that RDW is involved in GC pathogenesis and tumor progression. We support the idea that increased RDW reflects tumor-associated systemic inflammation and impaired nutritional status.

In the present study, we found that high preoperative RDW, presence of extracapsular invasion, perineural invasion, lymphovascular invasion, leakage, infection and recurrence, T4 or N3 stage, linitis plastica, intestinal type GC, and surgical margin positivity were associated with worse OS in patients with GC. The OS rates were 17.6±5% in high-RDW patients and 44.5±9% in the low-RDW group. Similar to our result, Sakin et al. (20) found the 5-year OS rate was 57.7% in GC patients with high RDW and 74.4% low-RDW group, with an RDW value of >15.5 associated with 5.7-fold greater risk for recurrence. Shota et al. (21) demonstrated that 5 years OS rates differed significantly in the GC group with high RDW (>14.85 for RDW) (52.4%) compared to the low-RDW group (<14.85) (78%). In addition, after adjusting for other confounding factors, we performed Cox regression analysis to determine prognostic variables associated with mortality. We demonstrated that a high RDW value, perineural invasion, surgical margin positivity, N3 stage, and the presence of leakage were independent prognostic factors for mortality in GC patients who underwent surgical resection. These factors were significantly associated with postoperative mortality and disease prognosis. This was consistent with the literature (12, 20, 21). Our results indicate that RDW was a powerful prognostic factor that could be used to classify patients with high mortality risk.

Several limitations should be acknowledged. First, our study was a retrospective, single-center study including few patients, which may have led to various types of bias. Secondly, we could not identify those who died from non-GC causes due to long follow-up and data loss, leading to lack of disease-specific analyses.

CONCLUSION

Our results indicate that RDW is associated with GC pathogenesis and tumor progression. The pre-operative RDW cut-off value of 14.5 could be used to predict mortality in GC patients. A high RDW value, perineural invasion, surgical margin positivity, N3 stage, and the presence of leakage may be used as independent prognostic indicators of OS in GC patients. The fact that RDW measurement is non-invasive, easily accessible and fast will provide convenience to physicians in predicting GC patients at high risk for mortality..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee (Date: 15.06.2021, Decision No: 03).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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The impact of F-18 FDG PET/CT in the restaging of colorectal cancer in patients with suspected recurrence

Kolorektal kanserlerin yeniden evrelemesinde F-18 FDG PET/BT'nin önemi

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ABSTRACT

Aim: The aim of the present study is to investigate the impact of F-18 FDG PET/CT in the restaging of colorectal cancer in patients with suspected recurrence. Thus, PET/CT findings were compared with that of CT. In addition, the correlation between serum CEA levels and PET/CT and CT findings was investigated. Furthermore, the role of PET/CT in treatment response among patients who were treated after restaging was assessed.

Material and Method: In this retrospective study, a total of 102 patients operated for colorectal cancer (63 female, 39 male, mean age 65.81±4.63 years) were investigated. F-18 FDG PET/CT scans were acquired in all patients. The findings of PET/CT were compared with that of concurrent CT, and also with CEA levels.

Results: In the study, the success rates of PET/CT and CT in detecting pathologic lesions in colorectal cancer cases with suspected recurrence were 98% and 64.7%, respectively. In 34 cases, pathologic lesions were detected with PET/CT, while CT showed no recurrence. The lesions of 68 cases out of 70 with high CEA levels were localized by means of PET/CT, whereas pathology was observed by CT in only 45 cases. Thus, PET/CT was considered more successful than CT in detecting recurrence. In the liver where lesion was localized the most, the sensitivity and specificity of PET/CT were 88% and 92%, respectively, while the sensitivity and specificity of CT were 80% and 76%, respectively.

Conclusion: In the light of findings, our study suggested PET/CT as a valuable imaging tool for restaging and treatment response assessment in colorectal cancer cases with suspected recurrence.

Keywords: Colorectal cancer, F-18 FDG PET/CT, CT, restaging

ÖZ

Giriş: Bu çalışmada, kolorektal kanserli hastalarda, uygulanan cerrahi, kemoterapi, radyoterapi sonrası takip döneminde hastalığın nüksünü düşündürür belirti ve bulgu varlığında nüksü doğrulamak ve hastalığın yayılım bölgelerini saptamak için yapılan yeniden evrelemede F-18 FDG PET/BT'nin öneminin saptanması amaçlanmıştır. Bunun için PET/BT görüntüleri, BT görüntüleri ile karşılaştırılmış ve serum CEA düzeyi ile görüntüleme yöntemlerinin uyumu incelenmiştir. Ayrıca, yeniden evrelemede patolojik bulgu saptanan hastalarda uygulanan tedavi sonrası tedaviye cevabın belirlenmesinde PET/BT'nin rolü de araştırılmıştır.

Gereç ve Yöntem: Retrospektif olarak yapılan bu çalışmaya, 102 hasta dahil edilmiştir. Tüm hastalara yeniden evrelendirme amacıyla F-18 FDG ile PET/BT görüntülemesi yapılmış olup PET/BT sonuçları, eş zamanlı olarak yapılan BT, serum CEA düzeyi ve klinik, eğer varsa histopatolojik incelemenin sonuçları ile karşılaştırılmıştır.

Bulgular: Çalışmada, nüks şüphesi olan kolorektal kanserli olgularda, PET/BT'nin patoloji saptama oranı %98, BT'nin ise %64,7 olarak hesaplanmıştır. BT'de patoloji izlenmeyen 34 hastada PET/BT ile patolojik lezyonların görüntülenebildiği, serum CEA düzeyi normal olan 70 hastanın 68'inde PET/BT ile, 45'inde ise BT ile patolojik lezyonun lokalize edildiği görülmüştür. Yapılan değerlendirmede, nüks hastalığın saptanmasında PET/BT'nin BT'den daha başarılı olduğu sonucuna ulaşılmıştır.

Sonuç: Bu bilgiler ışığında, takip döneminde nüks şüphesi olan kolorektal kanserli olguların yeniden evrelemesinde ve sonrasında yapılan tedavinin etkinliğinin değerlendirilmesinde F-18 PET/BT'nin yararlı olduğu sonucuna ulaşılmıştır.

Anahtar Kelimeler: Kolorektal kanser, PET/BT, BT, yeniden evreleme

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INTRODUCTION

Colon and rectum cancers classified as colorectal cancers are substantial health problems, mostly seen in developed countries, which result in severe morbidity and mortality. In general, colorectal cancer is diagnosed between 50-75 years of age, and aging is a major risk for the disease. Lymphatic dissemination is the most common way of metastatic spread and the most common sites of metastasis are the liver (60%), the lung (50%), the bone (15%), and the peritoneum (15%) (1-3).

The treatment of colorectal cancer depends on tumor location and size, and the overall health condition of the patient. The standard treatments are surgery, chemotherapy, and radiotherapy. Recurrence in colorectal cancer occurs in the first 4 years after surgery, generally with liver occupancy (4-10). In case of the presence of pathological focus or signs and symptoms for suspected recurrence, restaging is important in order to decide on the treatment plan and to determine the extent of the disease (3-7).

PET/CT is a widely preferred hybrid imaging modality for restaging in oncological patients. The superiority of PET/CT over other imaging modalities lies in its ability to spot metabolic/functional changes at early stages in the absence of morphological changes. Early detection of tumors with PET/CT scan leads to early treatment and prolonged survival (8-14).

F-18 FDG PET/CT is commonly used for staging, restaging, treatment response assessment, radiotherapy planning, and chemosensitivity assessment in many types of cancer (14-19).

The present study aims to investigate the impact of F-18 FDG PET/CT in the restaging of colorectal cancer in patients with suspected recurrence, as well as determining the extent of the disease.

MATERIAL AND METHOD

Patients

A total of 102 patients with colorectal cancer who were referred to Başkent University Adana Research Hospital Nuclear Medicine Department between January 2007 and December 2011 for restaging PET/CT scan due to suspected recurrence were included in the study. Data were retrospectively collected from the medical records of these patients.

PET/CT results were compared with that of CT, which is also widely used in the diagnosis, and follow-up evaluation of oncologic patients. The correlation between serum CEA levels and the imaging modalities was also investigated. The results were confirmed with histopathological data where available (n=30), or, alternatively, with clinical follow-up.

In the presence of pathological evidence on the restaging imaging, the importance of PET/CT in treatment response was assessed. Changes in the SUV levels of lesions were also noted in this regard.

Due to the regulations and the requriements which are subject to our study at the date of appication did not enforce seperate ethical approval for retrospective studies. Our study was approved by Başkent University Medicine and Health Sciences Research Board of the institution within these circumstances that are explanied above (Date: 02.08.2011, Decision No: KA11/166). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

PET/CT Imaging

Blood glucose levels were checked before the procedure. Patients whose blood glucose levels less than 200 mg/dl were administered 9-15 mCi F-18 FDG via the intravenous route. Then, the patients rested for approximately an hour in a calm environment without speaking or chewing anything until the imaging procedure.

The scanner used in the study was GE Discovery STE 8 Slice PET/CT (General Electric Company, Milwaukee, Wisconsin, USA) with retractable septa and a 17 cm field-of-view (FOV). Trans-axial resolution was 5.47 mm in 2D mode and 6 mm in 3D mode. Imaging was performed while patients were in the supine position with their arms up or next to the body and asked to breathe normally. After topographic CT imaging, vertex-to-upper-thigh CT images were acquired with 80mA chamber current and 140kV chamber voltage at 0.8-second rotation speed. Immediately following CT imaging, PET imaging was performed for 3-4 minutes per bed position. Scatter and attenuation correction of both CT and PET images were done. Maximum Intensity Projection (MIP), and PET, CT, and PET/CT fusion images were acquired.

F-18 FDG PET/CT images were examined in the light of diagnosis, administered treatment history, results and other imaging scans where available, and laboratory findings. In addition, the presence of focal lesion with increased FDG uptake, and the size and presence of a CT counterpart of the lesion were investigated. Lesions were examined for malignancy by considering physiological uptakes, typical presentation characteristics of benign formations, and fusion images. In the semi-quantitative assessment of lesions, the standard uptake value (SUV) of FDG was used.

Statistical Analysis

Statistical analysis was performed with SPSS version 15.0 (Statistical Package for Social Sciences, IBM Company). Descriptive statistics were used. Chi-squared and

Fischer's exact tests were conducted for comparisons between groups. The results were presented in 2 by 2 tables. P < 0.05 was considered as statistically significant.

A total of 102 patients with colorectal cancer were included in the study; 39 (38.2%) were male and 63 (61.8%) were female. The mean age of the patients was 65.81±4.63 years. All patients had undergone surgery following the diagnosis, and staging steps and chemotherapy was administered. The follow-up time was 11 to 50 months. During the follow-up period, all patients underwent restaging in order to determine the dissemination of the disease, as there were signs and symptoms suggesting recurrence. The time to recurrence was 6 months to 2 years. For restaging, all 102 patients underwent PET/CT, and 101 had a CT scan.

PET/CT and CT Results and Restaging

The pathologic lesion detection rate of PET/CT for restaging purposes was determined as 98%. Upon the examination of results, activity uptake was found in the liver (n=45), lung (n=41), pelvic lymph nodes (n=27), rectosigmoidal lymph nodes (n=25), surgical site (n=23), mediastinum (n=21), abdomen (n=19), mesenteric lymph nodes (n=13), head and neck (n=11), reptoperitoneal lymph nodes (n=11), bone (n=9), supraclavicular lymph nodes (n=7), suprarenal gland (n=4), kidney (n=2), para-aortic lymph nodes (n=2), gastric lymph nodes (n=2), hilus (n=1), anal area (n=1) and peritoneum (n=1). Localization of pathology detected sites with PET/CT and avarage SUV values are repsented in **Table 1**. PET/CT and CT agreement for lung, liver and surgery area are presented in **Table 2**.

Table 1. Localization of pathology detected sites with PET/CT and average SUV values

Localization	PET/CT (n=102)	SUV* (avr±SD)
Mediastinum	20.6% (n=21)	3.71±2.51
Hilus	1% (n=1)	5
Lung	40.2% (n=41)	6.96±3.56
Liver	44.1% (n=45)	9.80±7.29
Gastric LN†	2% (n=2)	9.50±3.54
Retroperitoneal LN†	10.8% (n=11)	5.91±4.25
Pelvic LN†	26.5% (n= 27)	6.33±3.83
Mesenterik LN†	12.7% (n=13)	4.77±2.95
Bone	8.8% (n=9)	6.33±6.23
Abdomen	18.6% (n=19)	5.47±3.96
Head&Neck	10.8% (n=11)	4.73±3.49
Supraclaviculer LN†	6.9% (n=7)	5.7±3.05
Kidney	2% (n=2)	7.07±5
Paraaortic LN†	2% (n=2)	5.50±3.54
Anal canal	1% (n=1)	11
Rektosigmoid	24.5% (n=25)	16.12±8.31
Peritonitis carsinomotoza	1% (n=1)	22
Surrenal gland	3.9% (n=4)	3.75±2.87
Surgery area	22.5% (n=23)	12.48±5.01

* Standart uptake value; † Lymph node

Table 2. Agreement of PET/CT and CT on detection of pathology

a) Lung		
	CT	
PET/CT	Normal	Pathologic
Normal	59.8% (n=61)	0.0% (n=0)
Pathologic	33.3% (n=34)	6.9% (n=7)
Total	93.1% (n=95)	6.9% (n=7)
$\chi2$=11.2, p=0.001†, † Fischer's exact test value.		
b) Liver		
	CT	
PET/CT	Normal	Pathologic
Normal	53.9% (n=55)	2.0% (n=2)
Pathologic	14.7% (n=15)	29.4% (n=30)
Total	68.6% (n=70)	31.4% (n=32)
$\chi2$=46.6, p<0.001†, † Fischer's exact test value.		
c) Surgery area		
	CT	
PET/CT	Normal	Pathologic
Normal	75.5% (n=77)	2.0% (n=2)
Pathologic	14.4% (n=13)	9.8% (n=10)
Total	88.2% (n=90)	11.8% (n=12)
$\chi2$=28.8, p<0.001†, † Fischer's exact test value.		

Relationship between serum CEA levels and imaging modalities

Serum CEA levels were examined in 97 of the 102 patients and were found elevated in 27 (11.3-945 ng/ml) and normal in 70. Pathologic lesion was detected with PET/CT in 68 of the 70 patients with normal CEA levels. PET/CT results were normal in the remaining 2 patients.

CT was evaluated as 'pathologic' in 16 of the 27 patients with elevated CEA levels. Pathologic lesion was detected with CT in 45 of the 70 patients with normal CEA levels, and no lesion was detected in 20 patients.

Detection of Liver Metastasis of Colorectal Cancer with PET/CT and CT

The investigation included 30 patients whose liver biopsy, CT, and PET/CT data were available. For PET/CT, the sensitivity and specificity for the detection of liver metastasis were 88% and 92%, respectively. For CT, the sensitivity and specificity were 80% and 76%, respectively.

Assessment of Treatment Response after Restaging with PET/CT

An assessment of the treatment choice after restaging with PET/CT revealed that all patients were administered chemotherapy with a mean of 6.34±2.95 cycles. The rate of the patients who underwent radiotherapy was 16.7%, radiofrequency ablation 2.9%, and surgery 45.1%.

According to the SUV values, 95% of the patients partially responded to treatment, while 3.9% completely responded. The remaining 1.1% failed to respond.

Evaluation of PET/CT images after treatment revealed the responsive regions as mediastinum, lung, liver,

retroperitoneal lymph node, pelvic lymph node, bone, abdomen, head and neck, supraclavicular lymph node, kidney, para-aortic lymph node, anal area, rectosigmoid, and surgical site. Assessment of treatment response for lung, liver and surgery area are presented in **Table 3**.

Table 3. Treatment response assessment with FDG PET/CT

a) Lung		
	Post-treatment FDG PET/CT	
Pre-treatment FDG PET/CT	Normal	Pathologic
Normal	52.9% (n=54)	6.9% (n=7)
Patolojik	18.6% (n=19)	21.6% (n=22)
Total	71.6% (n=73)	28.4% (n=29)
$\chi 2$=21.4, p<0.001†, † Fischer's exact test value.		
b) Liver		
	Post-treatment FDG PET/CT	
Pre-treatment FDG PET/CT	Normal	Pathologic
Normal	49.0% (n=50)	6.9% (n=7)
Patolojik	16.7% (n=7)	27.5% (n=28)
Total	65.7% (n=67)	34.3% (n=35)
$\chi 2$=27.8, p<0.001†, † Fischer's exact test value.		
c) Surgery area		
	Post-treatment FDG PET/CT	
Pre-treatment FDG PET/CT	Normal	Pathologic
Normal	74.5% (n=76)	2.9% (n=3)
Patolojik	13.7% (n=14)	8.8% (n=9)
Total	88.2% (n=90)	11.2% (n=12)
$\chi 2$=21.4, p<0.001†, † Fischer's exact test value.		

DISCUSSION

Colorectal cancer is the most common type of gastrointestinal cancer. It is a significant cause of mortality and morbidity around the world, with more than 1 million people estimated to develop the disease per year (1-5). In Turkey, colorectal cancer ranks third after lung and breast cancers, and the incidence of the disease is 7.7% with a distribution of 59% male patients and 41% female. In the present study with a population of 102 patients, 38.2% were male and 61.8% were female.

Recurrence after treatment is common in colorectal cancer (15-19). In a study by Willkomm et al. (26), recurrence was reported to be seen within 3 years after primary tumor resection. Another study by Farrokh indicated the time to recurrence to be within the first 2 years after initial treatment (16). In the present study, the follow-up time was 11 to 50 months and the time to recurrence was 6 to 24 months.

Conventional imaging modalities such as USG, MRI, and CT are routinely used for determining the dissemination of disease and restaging when there are suspicious signs and symptoms suggesting recurrence in patients with colorectal cancer. Because these modalities have limitations in differentiating between inflammation/scar tissue occurring after surgery/radiotherapy and recurrence or metastasis, they are considered to have low sensitivity for restaging. CT also has limitations in detecting liver lesions, small-sized metastatic lymph nodes, and small-sized peritoneal malignancy (3-9).

F-18 FDG PET/CT is commonly used for diagnosis, staging, treatment response assessment, radiotherapy planning, and chemosensitivity assessment in many types of cancer (21-23). Higher glucose metabolism in cancer cells compared to normal cells results in increased FDG uptake, and, thus, tumor localization can easily be achieved. The superiority of PET/CT over other imaging modalities lies in its ability to demonstrate metabolic/functional changes at early stages in the absence of morphological change. Early detection of tumors with PET/CT imaging leads to early treatment and improved morbidity (20-23).

In a retrospective study of 50 patients by Metser et al. (17), FDG PET/CT and CT were compared with regard to the restaging of colorectal cancer. Based on the analysis of tumor presence, the sensitivity and specificity of PET/CT were reported as 98.1% and 75%, respectively, whereas those of CT were 66.7% and 62.5%, respectively. In the present study, recurrence at the pre-sacral area, lymph node <1cm, and liver metastasis around radiofrequency ablation focus were correctly identified with PET/CT, while missed by CT. In a study by Huebner et al. (23), the sensitivity and specificity of PET/CT for restaging was reported as 97% and 76%, respectively. In another study by Czerni et al. (2), the sensitivity of PET/CT for restaging was indicated as 88% . In the present study, the calculations of sensitivity and specificity of PET/CT and CT for restaging were not performed due to the lack of histopathology data for all patients. The pathologic lesion detection rates of PET/CT and CT for restaging purposes were determined as 98% and %64.7, respectively. In line with previous studies, our investigation corroborated the superiority of PET/CT in detecting tumor recurrence.

It is known that the most common site of metastasis for colorectal cancer is the liver. Synchronous liver metastasis rate during primary tumor resection is 10-25%. Liver metastasis rate within 2 years following tumor resection without synchronous metastasis was reported to be 20-50% (20,21). In our investigation, liver pathology was present in 44%, which was similar to previous studies. In a study by Wiering et al. (3), the sensitivity and specificity of PET/CT in detecting liver metastasis were 79.9% and 92.3%, respectively, whereas those of CT were 82.7% and 84.1%, respectively. In another study by Schlag et al. (17), the sensitivity and specificity of FDG PET/CT in detecting liver metastasis were 91% and 100%, respectively, whereas those of CT were 74% and 85%, respectively. The study of Niekel et al. (27) reports both parameters as 97% for PET/CT, 88% and 93% for MRI,

respectively, and 84% and 95% for CT, respectively. In the present study, the sensitivity and specificity of PET/CT in detecting liver metastasis of colorectal cancer was 88% and 92%, respectively, whereas that of CT were 80% and 76%, respectively. These figures were in line with previous studies indicating a higher sensitivity and specificity for PET/CT.

The lung is the site where PET/CT is the most effective in detecting extra-hepatic metastases of colorectal cancer. Recent studies have shown that PET/CT can detect all lesions in the lung while CT can only detect 20%. The sensitivity of CT in detecting para-aortic and portal lymph node metastasis is 46% while that of PET/CT is 77%. The reliability of CT and PET/CT is much lower for bone and peritoneal metastasis, and laparoscopy is the best option to assess peritoneal metastasis before laparotomy (18,19-21). In many cases, local recurrence at the primary site of colorectal cancer cannot be identified due to the prior surgery and, sometimes, postoperative changes. Studies have shown that PET/CT is 93% successful in detecting the local recurrence of colorectal cancer, while CT is 50%. PET/CT's limitation lies in not differentiating increased FDG uptake due to chronic infection and tumors.

In the present study, a localization-based comparison of PET/CT and CT revealed that PET/CT is significantly superior to CT in detecting lesions in the mediastinum, lung, rectosigmoid, peritoneum, suprarenal gland, and the surgical site. PET/CT is important in the detection of small lymph nodules, early osseous deposits and inflammatory changes due to treatment. But, PET/CT has imitations on detecting subcentimetric hepatic and lung nodules (28).

Elevated serum CEA levels are observed in approximately two-thirds of the patients with colorectal cancer, meaning that it is the earliest sign to suggest the disease or its recurrence among other diagnostic symptoms. The sensitivity of CEA in detecting recurrence is 70-80%, but lesion-based examination has revealed that CEA has lower accuracy in detecting local recurrences and lung metastases. Conventional imaging modalities such as CT and MRI can localize recurrence 3-9 months after the increase in CEA levels (10,29-32). With its functional imaging capabilities, FDG PET/CT is more sensitive compared to other modalities when CEA levels are increased. FDG PET/CT has 65-75% diagnostic accuracy in cases suggesting recurrence with elevated CEA levels despite negative results with conventional imaging (32). Recent studies have reported its positive predictive value as 89-95% and negative predictive value as 85-100% in patients with high CEA levels (10). In any case, PET/CT is recommended as a more accurate diagnostic tool in patients with normal CEA levels. In a retrospective study, Sarıkaya et al. (11) examined the PET findings of colorectal patients with normal CEA levels and reported a positive predictive value of 88.8% for PET/CT, particularly in liver metastasis. In the present study, serum CEA levels data of 92 among the 102 total patients were available, and 70 (72.2%) of these were within the normal range whereas 27 (27.8%) were elevated. Pathologic lesion was detected via PET/CT in 68 of the 70 patients with normal CEA levels, suggesting that PET/CT is superior in detecting colorectal cancer or its recurrence, which was in line with previous studies. The comparison of CEA levels and CT results in the present study showed that CT detected pathology in 25 of the 70 patients with normal CEA levels, and in 16 of the 27 patients with elevated CEA levels. Our investigation yielded no significant difference between CT and serum CEA with regard to detecting recurrence.

Anatomic imaging modalities such as CT and MRI often fail to assess treatment response after restaging due to conditions such as treatment-induced necrosis and inflammation. FDG PET/CT is successful in this regard. However, the accuracy of PET/CT imaging depends on allowing sufficient time for the disappearance of benign metabolic activity, which can develop after treatment. The longer the time allowed prior to the imaging, the specificity of FDG PET/CT is higher.

Our study suggested FDG PET/CT is considered a more accurate diagnostic tool compared to other imaging modalities for restaging and treatment response assessment in cases of colorectal cancer with suspected recurrence on follow-up after treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: Due to the regulations and the requriements which are subject to our study at the date of application did not enforce seperate ethical approval for retsospective studies. Our study was approved by Başkent University Medicine and Health Sciences Research Board of the institution within these circumstances that are explanied above (Date: 02.08.2011, Decision No: KA11/166).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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A retrospective, observational study: early versus late favipiravir in COVID-19 pneumonia

COVID-19 pnömonisinde erken ve geç dönemde favipiravir: retrospektif gözlemsel bir çalışma

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ABSTRACT

Aim: Positive results have been reported regarding the early use of favipiravir,a RNA-dependent RNA polymerase inhibitor,in the COVID-19 pandemic. In our study, we aimed to understand the potential role of favipiravir in controlling COVID-19 pneumonia and sepsis by comparing the early use of favipiravir with the late using.

Material and Method: Treatments are carried out in line with the guidelines constantly updated by the Ministry of Health in Turkey. Following the guide published on April 14,2020,we examined 18 patients who received favipiravir as the last treatment option in the late period and 17 patients who received favipiravir in the early period in two different groups.We recorded the demographic characteristics,co morbidities,APACHE-II scores,consecutive SOFA scores and mortality status of the patients in both groups.

Results: The difference between groups in terms of gender and age was not statistically significant.The difference between groups in terms of APACHE-II score was statistically significant.(p=0.018)The late group also had higher APACHE-II scores.The difference between groups in terms of exitus was not statistically significant but lower in the group using favipiravir early.

Conclusion: In studies with a limited number of patients, favipiravir has been shown to have a significant advantage over lopinavir/ritonavir in viral clearance as well as a significant reduction in viral load when used in the early period.Similarly,in our study,patients who used favipiravir in the late period came to us more seriously and the mortality rate was higher. We think that favipiravir had a significant effect even in studies with a small number of patients, and larger studies are needed in this area.

Keywords: COVID-19, favipiravir, pneumonia

ÖZ

Amaç: COVID-19 pandemisinde RNA bağımlı bir RNA polimeraz inhibitörü olan favipiravirin erken kullanımına ilişkin olumlu sonuçlar bildirilmiştir. Çalışmamızda favipiravirin erken kullanımı ile geç kullanımı karşılaştırarak COVID-19 pnömonisi ve sepsis kontrolünde favipiravirin potansiyel rolünü anlamayı amaçladık.

Gereç ve Yöntem: Türkiye'de Sağlık Bakanlığı tarafından sürekli güncellenen kılavuzlar doğrultusunda tedaviler yürütülmektedir.14 Nisan 2020 tarihinde yayınlanan rehberin ardından geç dönemde son tedavi seçeneği olarak favipiravir almış 18 hastayı ve erken dönemde almış olan 17 hastayı iki farklı grupta inceledik. Her iki gruptaki hastaların demografik özellikleri, komorbiditeleri, APACHE-II skorları, ardışık SOFA skorları ve mortalite durumları kaydedildi.

Bulgular: Gruplar arası cinsiyet ve yaş farkı istatistiksel olarak anlamlı değildi. Gruplar arası APACHE-II puanı açısından fark istatistiksel olarak anlamlıydı (p=0.018). Geç dönemde kullanan grubun APACHE-II puanları daha yüksekti. Gruplar arasında mortalite oranı favipiraviri erken kullanan grupta istatistiksel olarak anlamlı olmasa da numerik olarak daha düşüktü.

Sonuç: Sınırlı sayıda hasta ile yapılan çalışmalarda, favipiravirin erken dönemde kullanıldığında viral klirenste lopinavir/ritonavire göre belirgin bir avantaj sağladığı ve viral yükte önemli bir azalma sağladığı gösterilmiştir. Favipiraviri geç dönemde kullanan grup bize daha ciddi geldi ve mortalite oranı daha yüksekti. Favipiravir az hasta sayılı çalışmalarda bile anlamlı bir etki yaptığı ve bu konuda yapılacak daha büyük çalışmalara ihtiyaç olduğunu düşünüyoruz.

Anahtar kelimeler: COVID-19, favipiravir, pnömoni

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INTRODUCTION

The coronavirus infection that started in Wuhan, China at the end of 2019 quickly surrounded the world and was declared as a pandemic by the World Health Organization (WHO) as of March 12, 2020 (1,2).

There is no specific drug that has a specially developed license against COVID-19. Testing available drugs provided an emergency treatment opportunity in the pandemic.Treatment options are very limited all over the world; Different combinations of 7 drugs thought to be effective have been genereally tried. (hydroxychloroquine, lopinavir/ritonavir, darunavir/ritonavir, oseltamivir, remdesivir, favipiravir) (1,3).

Favipiravir is a purine analog that inhibits RNA-dependent RNA polymerase (RdRP), which is required for viral replication in human cells. The drug is converted intracellularly into its active phosphorylated form and recognized as a substrate by the viral RdRP. When this enzyme which is necessary for the replication of viruses, is inhibited, a decrease in viral load occurs (4,5).

Tanaka et al. (6) demonstrated the beneficial effects of favipiravir use such as decrease in pulmonary viral load and decrease in tumor necrotizing factor (TNF) alpha levels in their study on influenza infections.

In a metanalysis investigating the side effects and safety profile of favipiravir, it was emphasized that it has a positive safety profile, it is well tolerated especially in short-term use, large-scale studies are needed to determine its long-term effects (7). It is necessary to be careful in terms of teratogenicity potential and hyperuricemia and QTc prolongation (8,9).

There are studies showing that the use of favipiravir as the first option in the early period in COVID-19 pneumonia is more effective in reducing the severity of sepsis and its response in late use is not effective (10).

In our study, we aimed to understand the potential role of favipiravir in the control of COVID-19 pneumonia and sepsis by comparing early and late period using

MATERIAL AND METHOD

The study was carried out with the permission of Eskişehir Osmangazi University Faculty of Medicine Non-Interventional Clinical Researchs Ethics Committee (Date: 14.07.2020, Decision No: 26). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Following the approval of the ethics committee and the Ministry of Health commission, polymerase chain reaction (PCR) positive COVID-19 pneumosepsis patients who were followed and treated in the Anesthesiology and Reanimation Intensive Care Unit during the pandemic period between 11.03.2020-01.06.2020 were included in the study. The patients in Turkey were treated in algorithms prepared by the ministry of health and continuously updated (11). In the first scientific committee guidelines, favipiravir is recommended for use in the relatively late period (as an alternative to lopinavir / ritanavir therapy) only in patients with severe pneumonia who do not respond to initial treatment regimens (hydroxychloroquine + oseltamivir + azithromycin (according to physician judgment)); It was included in the guide dated April 14, 2020 as the first treatment option in the early period in pneumonia cases. Patients before 14 April were included in the favipiravir-late group and after 14 April patients were included in the favipiravir-early group. In both groups, patients' ages, demographic data, comorbidities, acute physiology and chronic health evaluation-II (APACHE-II) scores, outpatient or hospital admission status, starting days of favipiravir treatment, number of days they received favipiravir treatment, adverse effects of favipiravir,discharge and mortality status were recorded. The consecutive sequential organ failure assessment (SOFA) scores of all patients were recorded and the effect of favipiravir on the treatment process and the severity of sepsis was evaluated. Patients with no consecutive SOFA scores were excluded from the study. Of the 52 patients who came with the suspicion of respiratory distress and coronavirus pneumonia, 17 patients with negative PCR tests were excluded, and the data of 35 patients in total were analyzed.

Statistical Analysis

Continuous variables are given by using; Mean, Standard deviation, Median, Minimum and Maximum values and categorical variables are shown by giving numbers and percentages. In the comparison of continuous varibles in 2 groups, Mann-Whitney-U test was used for non-normal distribution. Wilcoxon test was used to compare the values measured at 3 different times in the groups. Group comparisons of categorical variables were analyzed using crosstabs statistics (Chi-square tests: Pearson Chi-square. The values of the continuous variables measured at 3 different times were analyzed by General Linear Model in 2 groups. The statistical significance level was taken as $p < 0.05$.

RESULTS

Data of a total of 35 patients were analyzed, with data of 18 patients as late group and 17 patients as early group. The difference between groups in terms of gender and age was not statistically significant. The mean age was 74.14±12.55 ($p=0.577$). The difference between groups in terms of APACHE-II score was statistically significant. ($p=0.018$) The late group also had higher APACHE-II

scores. Only the difference between the groups in terms of hypertension was statistically significant and in the early group was seen at a higher rate ($p<0.05$). The difference between groups in terms of malignancy and DM was not statistically significant (**Table 1**). The difference between groups in terms of exitus was not statistically significant but lower in the group using favipiravir early (**Table 2**). Consecutive SOFA scores between favipiravir groups were not found to be statistically significant (**Table 3**). The most common adverse effect was hyperuricemia with 17 patients (%48.5).

Table 1 . Demographic characteristics of COVID-19 patients

	Patients, no. (%)All (35)	Favipiravir late group (n=18)	Favipiravir early group(n=17)	P value
Age, mean±SD, y	74.14±12.55	76.50±13.40	72.00±9.70	0.577
Gender	0.600			
Male	19	9	10	
Female	16	9	7	
Coexisting disorders				
Hypertension	23	9	14	0.044
Diabetes Mellitus	13	6	7	0.631
Malignancy	19	10	9	0.877
APACHE II	18.91±8.15	22.0±7.40	12.00±8.10	0.018

Table 2. Mortality status of COVID-19 patients

	Patients, no. (%) All (35)	Favipiravir late group (n=18)	Favipiravir early group(n=17)	P value
Mortality status	-	-	-	0.053*
Ex	24	15	9	-
Discharge	11	3	8	-

* Pearson Chi-square test.

Table 3 . Before and after threatment SOFA scores of the patients

	Favipiravir late group (n=18)		Favipiravir early group (n=17)	
SOFA-1	6.00±2.97		5.00±2.29	
SOFA-2	6.50±2.76		4.00±2.81	
SOFA-3	7.50±3.50		7.00±3.50	
Paired comparisons for SOFA scores in Favipiravir groups*				
	Z	P	Z	P
SOFA-2 vs SOFA-1	-1.038	0.299	-0.408	0.684
SOFA-3 vs SOFA-1	-2.079	0.007	-1.451	0.147
SOFA-3 vs SOFA-2	-2.509	0.012	-1.720	0.085

*Test:Wilcoxon Test

DISCUSSION

In our study, we evaluated the patients who were given favipiravir in the early and late periods in accordance with the algorithms in the guide, and we observed that the patients who were given favipiravir in the late period were hospitalized in intensive care with higher APACHE-II scores. Although it was not statistically significant, the mortality rate was higher in patients using favipiravir in the late period. Our results also support the hypothesis that early use of favipiravir is associated with more positive results.

Lopinavir / ritonavir compared to favipiravir in studies; favipiravir was shown to significantly reduce the mean time to viral clearance (12). Cai et al. (13) compared favipiravir and lopinavir / ritonavir for COVID-19 treatment in their study. In this study in which 35 patients were treated with favipiravir and 45 patients with lopinovir / ritonavir, favipiravir was independently associated with faster viral clearance and higher recovery rates on chest imaging 14 days after treatment. They also stated that favipiravir causes very rare side effects and is well tolerated by patients.

Preliminary results of the favipiravir study conducted by Ivashchenko et al. (14) have been published and they reported that favipiravir is significantly effective in viral clearance and is safely tolerated. In this manner the result of studies showing the effectiveness of favipiravir, the coronavirus treatment algorithms in Turkey also updated.

Studies have shown that the most common side effect is hyperuricemia (15). It has been theorized that it may be due to the inhibition of channel proteins responsible for uric acid excretion in the kidney (16). Controlled use has been recommended especially in cases such as gout and acute renal failure. In our study, hyperuricemia was observed in 48.5% of the patients .

Similar to our study, Doi et al. (17) evaluated the effects of early and late use of favipiravir in a study. The difference of the study was that they tried this in the newly diagnosed mild or asymptomatic patient groups. Almost no fever was reported in the group using early. Although not statistically significant, there was a numerical decrease in viral clearance. progression to severe pneumonia and exitus were not observed in any of the patients. Fujii et al. (18), similarly, showed that starting the drug in the earliest possible period after their study had a positive effect on the results.

The APACHE-II scoring system, which is the most widely used scoring system accepted in intensive care, is the most important predictive marker in determining the severity of the disease and mortality. In addition to the chronic diseases of the patients, APACHE-II calculates the hemogram, blood gas values, vital signs and electrolytes and estimated severity of the disease during admission (19). In our study, we examined patients with severe pneumonia requiring intensive care follow-up and we found that the group using favipiravir late comes with statistically significant higher APACHE-II scores. Although the mortality rate was not statistically significant, it was numerically higher in the group that used favipiravir in the late period.

To list the limitations of our study, the number of our patients was very low.Since we looked at it retrospectively, we only recorded the existing data. we only examined the

data of patients who needed intensive care follow-up. We do not have any data on how much favipiravir used in the early period protects patients from intensive care admission.

CONCLUSION

Patients using favipiravir in the late period came to us more severely and had a higher mortality rate. Favipiravir has an obvious effect even in studies with few patients, and larger studies are needed in this area.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Eskişehir Osmangazi University Medical Faculty Ethics Committee (Date: 14.07.2020, Decision No: 26).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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Evaluation of the etiological factors of thyroid gland neoplasms: our clinical experience

Tiroid bezi neoplazmalarının etiyolojik faktörlerinin değerlendirilmesi: klinik deneyimimiz

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ABSTRACT

Objective: Thyroid cancer (TC), the most common endocrine malignancy worldwide, has a 10-year survival rate of more than 90% and a better prognosis than other malignancies. However, there are still conflicting data on the stimulators of cancer development, and benign thyroid diseases, such as goiter, benign thyroid nodules, Graves' disease, chronic thyroiditis, breast cancer and various factors including age, gender, consumption of vegetables, fiber food, hypercaloric diet, and tobacco and alcohol use are considered to be responsible. In this study, we aimed to evaluate patients with thyroid neoplasms who underwent surgical treatment in terms of etiological factors discussed in light of the literature.

Material and Method: In our study, patients who underwent surgery with the diagnosis of thyroid gland neoplasms between 2010 and 2020 were evaluated. A total of 371 patients were included in the study. Statistical analyses were performed using IBM SPSS Statistics v. 22.

Results: Of the 371 cases included in the study, 78.16% were female and 21.83% were male. The histopathological distribution of diagnoses was as follows: 76.28% papillary thyroid carcinoma (PTC), 4.31% follicular thyroid carcinoma (FTC), 14.29% follicular adenoma (FA), 0.54% Hurthle cell carcinoma (HCC), 3.77% Hurthle cell adenoma (HCA), and 8.08% medullary thyroid carcinoma (MTC). A total of 567 etiological factors were detected in 371 cases, and the highest factors ratio (1.94) being detected in the FTC group and the lowest (1.49) in the FA group. The most common of these factors was chronic lymphocytic thyroiditis (CLT) (35.31%). While the most common etiological factor in the PTC diagnosis group was thyroid and other non-breast cancers and the history of radiotherapy resulting from their treatment, it was a family history of thyroid cancer in the HCA group. Other systematic organ diseases, CLT, and breast cancer were the most common factors. The body mass index was the highest in the MTC group and the lowest in the PTC group.

Conclusion: Increased human development index, technological developments, greater accessibility of ultrasonography, and better diagnostic sensitivity have led to an increase in the detection of TC. Knowledge of the underlying etiological factors is important for the development of preventive measures and achieving more successful results in terms of diagnosis and treatment.

Keywords: Thyroid cancer, thyroid gland neoplasms, etiological factors

ÖZ

Amaç: Dünya genelinde en sık karşılaşılan endokrin malignite olan tiroid kanserinde (TK) 10 yıllık sağ kalım oranı %90'dan fazla olup diğer malignitelere göre daha iyi bir prognoza sahiptir. Literatürde TK gelişiminde yaş, cinsiyet, sebze ve lifli besin tüketimi, hiperkalorik diyet,tütün ve alkol kullanımı gibi faktörlerin yanında, kanser gelişimi öncesi guatr, iyi huylu tiroid nodülleri, Graves hastalığı, kronik tiroidit gibi benign tiroid hastalıkları ve meme kanseri birlikteliği konusunda tartışmalar devam etmektedir.Çalışmamızda kliniğimizde cerrahi tedavi uyguladığımız tiroid neoplazmlarını literatür eşliğinde etiyolojik faktörler açısından değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmamızda 2010-2020 yılları arasında tiroid bezi neoplazmı tanısıyla cerrahi tedavi uyguladığımız hastalar değerlendirildi. Çalışmaya 371 hasta dahil edildi. İstatistikler IBM SPSS Statistics 22 kullanılarak yapıldı.

Bulgular: Çalışmaya dahil edilen 371 olgunun %78,16'sı kadın, %21,83'ü erkek cinsiyette olup, tanıların histopatolojik olarak dağılımı %76,28'i papiller tiroid karsinomu (PTK), %4,31'i foliküler tiroid karsinomu (FTK), %14,29'u foliküler adenom (FA), %0,54'ü Hurthle hücreli karsinom (HHK), %3,77'si Hurthle hücreli adenom (HHA) ve %8,08'i medüller tiroid karsinomu (MTK) şeklindeydi. Toplamda 371 olguda 567 etiyolojik faktör tespit edilmiş olup,olgu başına düşen etiyolojik faktör oranı en yüksek (1,94) FTK, en düşük (1,49)FA tanı grubundaydı. Bu faktörler arasında en sık görüleni %35,31 ile kronik lenfositik tiroidit (KLT) idi. PTK tanı grubunda en sık görülen etiyolojik faktör tiroid ve meme dışı diğer kanserler ve bunların tedavisinden kaynaklanan radyoterapi öyküsü iken; HHA'da ailede tiroid kanseri öyküsü olmasıydı. Sistematik diğer organ hastalıkları, KLT ve meme kanseri en sık görülen faktörlerdi. Vücut kitle indeksi (VKİ) değeri ise en yüksek MTK, en düşük PTK tanı grubunda gözlendi.

Sonuç: İnsani gelişmişlik indeksinin yükselmesi, teknolojik gelişmeler, ultrasonografinin erişilebilirliği ve tanı duyarlılığındaki yükselme, TK insidansında artışa neden olmaktadır. Bu artışın zemininde yer alan etiyolojik faktörlerin iyi bilinmesi; koruyucu önlemlerin geliştirilmesi, tanı ve tedavi açısından daha başarılı sonuçlar alınması için önemlidir.

Anahtar Kelimeler: Tiroid kanseri, tiroid bezi neoplazmaları, etiyolojik faktörler

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INTRODUCTION

Thyroid cancer (TC) is the most common endocrine malignancy (1), with an increasing incidence worldwide since the first use of neck ultrasonography for its diagnosis in the 1980s. The 10-year survival rate of TC is more than 90%, and it has a favorable prognosis compared to other malignancies (2). Although the incidence of TC is approximately the same in pre-pubertal males and females, it is seen predominantly in the female gender starting with adolescence. It is two to four times more frequent in women than in men, regardless of age (3, 4). It has a poor prognosis in the elderly and an excellent prognosis in children. Age has a critical effect on tumor development and prognosis (5-7).

Environmental factors and genetic background significantly affect the biological and clinical features of TC (8). The incidence of TC is higher in regions with iodine deficiency, and the risk of developing cancer is inversely proportional to vegetable and fiber consumption, and directly proportional to hypercaloric diet (9). It is considered that ethanol, caffeine and other endogenous factors may be effective in the development of TC (10). Tobacco and alcohol use increases the incidence of TC (11). Genetic inheritance is also thought to play an important role in familial non-medullary cancers, which constitute 5-10% of TC cases (12).

Benign thyroid diseases, such as goiter, benign thyroid nodules, Graves' disease and chronic lymphocytic thyroiditis (CLT) may be seen in the patient before TC occurs (13). Breast cancer and TC are the two most common malignancies in women and may occur metachronously. Women with TC are at high risk for developing breast cancer later (14).

In this study, we evaluated patients with benign and malignant thyroid neoplasms who underwent surgical treatment in our clinic in terms of etiological factors discussed in light of the literature.

MATERIAL AND METHOD

Our study was carried out after obtaining approval from the Clinical Researches Ethics Committee of Gülhane Training and Research Hospital (Date 15.12.2021, Decision No: 2021/90). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. In our study, the surgical treatment decision was made at the endocrinology council of our hospital in patients presenting with thyroid gland neoplasms between 2010 and 2020, and the data of those who underwent surgery in our clinic were evaluated using their files. This retrospective study included 371 cases whose files contained complete information concerning the etiological factors that were the subject of the study and whose surgery and pathology reports could be accessed. Cases with missing data were excluded from the study. The statistical analyses of the data were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Of the 371 cases included in the study, 290 (78.16%) were female and 81 (21.83%) were male. The distribution of histopathological diagnoses was as follows: 283 papillary thyroid carcinomas (PTCs), 16 follicular thyroid carcinomas (FTCs), 53 follicular adenomas (FAs), two Hurthle cell carcinoma (HCCs), 14 Hurthle cell adenomas (HCAs), and three medullary thyroid carcinomas (MTCs). The female gender (78.17%) was predominant in all pathological diagnoses. The most dominant group of female gender was found to be FTC at a rate of 81.25%, while the HCA group had the lowest rate of female patients at 64.28%. The male gender was most dominant in the HCA (35.7%) group, and there was no male patient in the HCC group (**Table 1**). During the study period, bilateral total thyroidectomy was the most frequently performed operation, accounting for 270 (78.49%) of all operations. There was no significant difference between the surgical procedures performed according to the tumor types in the distinction made according to the histopathological diagnoses. Lymph node dissection (LND) was performed in a total of 147 cases, among which central + cervical LND was the most common (n=67, 45.58%).

Table 1. Mean age and gender of the cases according to pathological diagnoses

Diagnosis/Gender-Age	PTC n (%)	FTC n %)	FA n (%)	HCC n (%)	HCA n (%)	MTC n (%)	Total n (%)
Female n (%)	221 (59.57)	13 (3.50)	43 (11.59)	2 (0.54)	9 (2.43)	2 (0.54)	290(78.17)
Male n (%)	62 (16.71)	3 (0.81)	10 (2.70)	0	5 (1.35)	1 (0.27)	81 (21.83)
Mean age, SD	43.99	47.80	44.15	54.00	46.20	41.5	44.29±12.31
Female	42.24	48.25	44.19	54.40	46.29	52.00	46.07± 13.1
Male	50.21	46.00	44.00	0	46.00	31.00	48.79±11.2
Total	283 (76.28)	16 (4.31)	53 (14.29)	2 (0.54)	14 (3.77)	3 (0.81)	371 (100)

PTC: Papillary Thyroid Carcinoma, FTC: Follicular Thyroid Carcinoma, FA: Follicular Adenoma, HCC: Hurthle Cell Carcinoma, HCA: Hurthle Cell Adenoma, MTC: Medullary Thyroid Carcinoma, SD: Standard Deviation

The mean age was 44.29±12.31 years for the whole sample, 46.07±13.1 years for the female patients, and 48.79±11.2 years for the male patients, with no statistically significant difference according to gender (p=0.234). Since the number of cases in the MTC and HCC groups was not sufficient for a reliable evaluation, the age differences according to the male and female genders were evaluated in the remaining diagnosis groups, and a statistically significant difference was found only for the PTC diagnosis (female: 42.24 years; male: 50.21 years) (p=0.071).

Considering the age distribution of the patients, more than half of the patients were in the 20-45 years group (n=187, 50.40%). There were only six cases of PTC in the 0-20 years group, and there was no patient with another diagnosis in this age group. PTC was the diagnostic group with the highest proportion of cases in the age range of 20-45 years (55.12%). FTC was the diagnosis with the highest proportion of cases in the 45-60 years group (81.25%). There were 49 (13.21%) cases aged ≥60 years, and this group most commonly presented with HCA (21.43%) among all the diagnoses (**Table 2**).

Among the 371 cases evaluated in our study, a total of 567 etiological factors were identified, including 196 secondary or multifactorial factors, and a secondary etiological factor was found in 52.83% of the cases. Since the number of cases with MTC and HCC was very small, these two groups were excluded from the evaluation. The ratio of etiological factors per case was 1.53 in all cases, with the highest ratio being observed in the FTC group (1.94) and the lowest ratio in the FA group at 1.49. The most common etiological factor was CLT (35.31%) and the least common was radiotherapy (RT) (2.16%). CLT association was most frequently observed in patients with FTC (43.75%). The history of RT was present in only eight (2.83%) cases with PTC. Although a family history of thyroid cancer was seen at a frequency of 3.50% in all cases, the highest rate was observed in the HCA group (7.14%). The most common etiological factors accompanying PTC were thyroid and other non-breast cancers (6.71%) and the presence of a history of RT (2.83%) due to their treatment. Breast cancer (6.25%), CLT (43.75%), and other systematic organ diseases (68.75%) were more common in the FTC group. A family history (35.71%), diabetes mellitus (DM) (21.42%), immune system-related diseases (14.29%), hyperlipidemia (21.42%), and hypertension (28.57%) were more common in the HCA group. The mean body mass index (BMI) was 26.05 (18.5-24.9), with the lowest value obtained from the PTC group (25.8) and the highest in the MTC group (28.4) (**Table 3**).

When all the cases were evaluated, the mean thyroid-stimulating hormone (TSH) was 3.35 mIU/mL, with the highest value being observed in the HCA group (6.12 mIU/mL) and the lowest (1.56 mIU/mL) in the MTC group. When graded according to the TSH serum concentrations

Table 2. Age range distribution according to pathological diagnoses

Diagnosis/Age Distribution	PTC	FTC	FA	HCC	HCA	MTC	Total
0-20 years n (%)	6 (2.12)	0	0	0	0	0	6 (1.60)
20-45 years n (%)	156 (55.12)	3 (18.75)	21 (39.62)	1 (50.00)	5 (35.71)	1 (33.33)	187 (50.40)
45-60 years n (%)	86 (30.39)	13 (81.25)	24 (45.28)	1 (50.00)	6 (42.86)	2 (66.67)	132 (35.58)
≥60 years n (%)	38 (13.43)	0	8 (15.09)	0	3 (21.43)	0	49 (13.21)
Total, n	283	16	53	2	14	3	371

PTC: Papillary Thyroid Carcinoma , FTC: Follicular Thyroid Carcinoma, FA: Follicular Adenoma, HCC: Hurthle Cell Carcinoma, HCA: Hurthle Cell Adenoma, MTC: Medullary Thyroid Carcinoma

Table 3. Distribution of accompanying diseases according to pathological diagnoses

	PTC n (%)	FTC n (%)	FA n (%)	HCC n (%)	HCA n (%)	MTC n (%)	Total n (%)
Familial history of thyroid cancer, n (%)	9 (3.18)	1 (6.25)	2 (3.77)	0	1 (7.14)	0	13 (3.50)
Diabetes mellitus, n (%)	31 (10.95)	1 (6.25)	6 (11.32)	0	3 (21.43)	0	41 (11.05)
Breast cancer, n (%)	14 (4.95)	1 (6.25)	0	0	0	0	15 (4.04)
*Immunological diseases, n (%)	31 (10.95)	1 (6.25)	3 (5.66)	1 (50.00)	2 (14.29)	0	38 (10.24)
Chronic lymphocytic thyroiditis, n (%)	98 (34.63)	7 (43.75)	21 (39.62)	1 (50.00)	3 (21.43)	1 (33.33)	131 (35.31)
Hyperlipidemia, n (%)	46 (16.25)	3 (18.75)	11 (20.75)	0	3 (21.43)	0	63 (16.98)
Hypertension, n (%)	61 (21.55)	4 (25.00)	15 (28.30)	1 (50.00)	4 (28.57)	0	85 (22.91)
Radiotherapy history, n (%)	8 (2.83)	0	0	0	0	0	8 (2.16)
**Other cancer history, n (%)	19 (6.71)	0	0	0	0	0	19 (5.12)
***Others, n (%)	71 (20.09)	11 (68.75)	14 (26.42)	1 (50.00)	2 (14.29)	0	99 (26.68)
Total	430 (75.84%)	31 (5.47%)	79 (13.93%)	4 (0.7%)	22 (3.88%)	1 (0.18%)	567 (100%)
Factor ratio per case	1.52	1.94	1.49	2.0	1.57	0.33	1.53
BMI	25.8	26.2	26.9	27.2	27.1	28.4	26.05
Total	283	16	53	2	14	3	371

PTC: Papillary Thyroid Carcinoma, FTC: Follicular Thyroid Carcinoma, FA: Follicular Adenoma, HCC: Hurthle Cell Carcinoma HCA: Hurthle Cell Adenoma, MTC: Medullary Thyroid Carcinoma *Immunological: Autoimmune, Rheumatological or Allergic Disease, **Other Cancer: Thyroid and History of Non-Mammary Cancer, **Others: Cardiac, Neurological, Lung, Kidney, Coagulopathy; Cases with Vasculitis, Smoking and Graves' Disease. BMI: Body Mass Index

as undertaken by Lun et al. (15), it was seen that only one case with HCA had a TSH value of ≥4.95 Since TSH was ≥10 mIU/mL in this case, the mean value of this group was higher compared to the remaining diagnoses. When the TSH range of 0-0.35 was evaluated, 14.82% of all cases were found to have a value within this range, and the FTC group had the highest proportion (18.75%) among all the diagnosis groups. The TSH range of 0.36-1.35 was detected in 21.02% of all cases, with the FA group having the highest rate (28.30%). The TSH range of 1.36-1.90 was observed in 19.95% of all cases and had the highest rate in the FTC group (31.25%). The TSH range of 1.91-4.94 had the highest number of cases (n=133 cases, 35.84%), and most (43.75%) were in the FTC group. Lastly, 8.36% of all cases and 9.54% of the PTCs had a TSH value of ≥4.95, (**Table 4**).

DISCUSSION

The incidence of TC is higher in countries with a high human development index compared to those with a low human development index (16). In a study by Lee et al. (17), 75.5% of the patients with PTCs were women. In our study, a similar rate of women was observed both for all cases and for those with a PTC diagnosis. Considering all the cases in the current study, the female patients were younger than the male patients, but the age difference according to gender was not statistically significant (p=0.071); however, proportionally the most significant difference was observed in cases with PTC. It has been suggested that age-related genetic background of thyroid tissue has a significant effect on tumor development and critical impact on prognosis (5). TC has a high recurrence rate in patients older than 45 years even if their tumor size is small. Mazzaferri et al. (18) found that the recurrence rate was the highest at the most extreme ages (<20 years and >59 years), and <15 years and >45 years constituted a high risk for TC recurrence and death from cancer. Sharon et al. (19) found that 53.8% of patients with well-differentiated thyroid carcinomas (WDTCs) were in the 20-45 age range. In our study, although there was no statistically significant difference between the diagnosis groups in terms of the mean age (p=0.234), the highest proportion of cases were in the 20-45 years group. It was noteworthy that proportionally, the highest rate of PTC cases was in the 20-45 years group, and the cases of FTC were in the 45-60 years group. While 13.21% of all cases were found in the age group of ≥60 years, the diagnosis with the highest rate of cases in this age group was HCA. In a study by Won Gu Kim et al. (20), patients with HCC were found to be significantly older and have more lymphovascular invasion compared to the FTC group. In our study, although only two cases were diagnosed with HCC, the highest mean age among all cases was 54.40 years in this diagnosis group. While the mean age of the patients with FTC was 43±14 years in the previous study, we found it to be 47.80 years in our group.

In our study, it was observed that more than one etiological factor coexisted in 52.83% of the cases, and the factor ratio per case was 1.53 at the mean age of all cases (44.29±12.3 years). It was also determined that PTC was the most similar diagnosis group in terms of the mean age and factor ratio. Although patients with PTC constituting 76.28% of all cases included in our study was considered to be effective in this similarity, a factor of 1.94 was observed in the FTC group with a higher mean age and a lower factor (1.49) in the FA group with a lower mean age. When all the cases and diagnoses were evaluated, it was determined that there might be a correlation between the mean age and factor ratio.

TC is among the cancers with the highest hereditary predisposition (21), but more than 90% of cases are sporadic due to somatic genetic changes (22). Apart from familial medullary cancer with a high hereditary transmission rate, approximately 3-9% of TCs are familial non-medullary thyroid carcinomas. In our study, a family history was present in 3.50% of all cases and most frequently observed in the HCA group, which is consistent with the literature.

In the literature, it has been shown that high TSH levels stimulate follicular proliferation and support the development of PTC, and the risk of malignancy is associated with abnormally increased serum TSH concentrations (23). In a previous study, it was stated that the risk of PTC increased by 53% in patients with a TSH of ≥2.00 uIU/ml compared to those with a TSH of <2.00 uIU/ml (24). It is considered that long-term TSH stimulation and BRAF mutations in PTC may play a role in this mechanism (25). Although serum TSH levels have been shown to be correlated with the rates of PTC, it has been hypothesized that TSH facilitates breast carcinogenesis both independently and in combination with estrogen (26, 27). When we evaluated the TSH concentration in our study by dividing it into levels as described by Lun et al. (15), although 85.2% of the cases had a TSH value within the normal range, the TSH range with the highest number of cases was 1.91-4.94. FTC was the diagnosis group with the highest rate of patients with a TSH value in this range. A TSH value of ≥4.95, which is also the limit of hypothyroidism, was both numerically and proportionally the highest in the PTC group. Although the cases in the PTC group had normal TSH values, most being in the range of 1.91-4.94 may explain why the association of breast cancer is mostly seen in cases with PTC. In our study, we observed that the cases of carcinoma predominantly had TSH values in the range of 1.91-4.94, while patients with benign neoplasms had a more homogeneous distribution in terms of TSH.

In this study, the most common etiological factor was CLT (35.31%) and the least common was a history of RT (2.16%). The formation of TC can also be induced by the production of proinflammatory cytokines and oxidative stress in autoimmune thyroiditis (25). Lun et al. (15) observed a significant difference in TSH concentrations between patients with PTC and Hashimoto's thyroiditis and those without thyroiditis, and they reported that elevated TSH concentrations associated with Hashimoto's thyroiditis might increase the risk of PTC. In a study conducted by Uhlirova et al. (28), Hashimoto's thyroiditis was detected in 15% of the cases. In contrast, although CLT was observed in 35.3% of all our cases and 34.63% of the PTC cases, the highest rate of CLT was observed in the FTC group at a rate of 43.75%. We also determined that 35.1% of the cases had CLT coexistence and this coexistence was seen at a higher rate in follicular origin cancer and benign neoplasms than in Hurthle cell neoplasms.

Breast cancer and TC are the two most common malignancies in women and often occur metachronously. Women with TC are at increased risk for breast cancer. Similarly, women with breast cancer have an increased incidence of subsequent TC development. In the literature, it is reported that while women with breast cancer are twice more likely to develop TC in future, women with TC have a 67% higher risk of developing breast cancer compared to the general population (14). Chung et al. (29) reported that the rate of TC detection was 2.6% when patients were screened simultaneously for breast cancer with ultrasound and fine-needle aspiration biopsy. Studies have shown that aggressive FTC is detected more frequently than PTC in patients with a history of breast cancer (30). The co-occurrence of these two diseases is even more common in men, with those having a history of TC being 29 times more likely to develop breast cancer. Metachronous thyroid cancer is also more common when the first breast tumor is HER2-positive (31). Studies have stated that familial characteristics are important in the association of these cancers, and they suggested that mutations in PTEN (32) and germline mutations in PARP4 (33) may be effective. In our study, breast cancer was seen only in WDTC cases, mostly PTC. In addition to this, it was seen in 4.04% of all cases. Breast cancer was not observed in other diagnostic groups.

Numerous studies have associated endocrine disrupting chemicals (EDCs) with obesity, developmental disorders, and hormone-dependent cancers (34). EDCs can stimulate the development of TC and breast cancer through estrogenic signaling. Behaviorally driven environmental factors including obesity, sedentary lifestyle, alcohol consumption, and tobacco use have been shown to increase the risk of cancer (35). A pooled analysis of five prospective studies also reported a higher risk of TC in obese subjects (36). Insulin regulates thyroid gene expression and stimulates thyrocyte proliferation, differentiation and transformation. In a previous study, insulin resistance was present in 50% of patients with PTC and 10% of matched controls (37). In another study, BMI at the time of diagnosis was found to be directly related to the risk of TC in women (38). Insulin-like growth factor1 (IGF-1), which has structural homology to insulin, binds to the IGF-1 receptor and acts as a potent growth factor stimulating malignant transformation, tumor progression, and metastasis (39). Zhao et al. (24) found the BMI of WDTCs as 25.18 and Cortney et al. (16) reported the BMI of PTCs as 29.4 (±5.3). In our study, the mean BMI was 26.05 (range, 18.5-24.9) for all cases, and the lowest BMI value was observed in the PTC group (25.8) and the highest in the MTC group (28.4). Therefore, the BMI of our cases was in a similar range to the values given in the literature. The cases with PTC with the lowest mean age had the lowest BMI, while those with other diagnoses presenting with a higher mean age had higher BMI values.

In the literature, physical inactivity and diabetes have been closely associated with obesity, which is also related to the risk of TC (40, 41). It has been shown that there is a significant positive association between diabetes and TC risk. Diabetes affects carcinogenesis in numerous biological ways, including hyperglycemia, hyperinsulinemia, and chronic inflammation (42). In our study, the frequency of DM was 11.05% for all cases, and the highest rate was seen in cases with HCA.

There are studies suggesting that a low-calorie diet is a preventive factor for TC (43). It is considered that hyperlipidemia may play a role in the increase in the incidence of TC (44). In a recent study conducted in the People's Republic of China, it was found that people with hypercholesterolemia had a 1.33 times higher risk of TC than those without this condition (24). In the current study, hyperlipidemia was present in 16.98% of all our cases, and the highest rate was observed among those with HCA.

Although radiotherapy is a good option for the treatment of many cancers, especially breast cancer, it is also a risk factor for the development of cancer, especially TC (45, 46). Many recent clinical studies have shown that the thyroid's ability to produce hormones changes following radiotherapy (47, 48). Most cases of TC that occur with irradiation are PTCs (49). When the patients who had received radiotherapy treatment for various diseases were evaluated in our study, it was observed that only the PTC group had a history of RT. In addition, all cases with a history of "breast cancer" or "thyroid and

other non-breast cancer", except for one patient, had PTC. Similarly, we observed that all the cases that had previously undergone radiotherapy presented with PTC. In light of the literature, we considered that radiotherapy, which may be used in the treatment of diseases that occur in other areas of the body, may also contribute to the development of PTC, although the neck is not directly irradiated.

CONCLUSION

The frequency of the diagnosis of micropapillary cancer is increasing as a result of conditions such as improvement in the socioeconomic situation worldwide, continuing increase in the human development index, increased diagnostic sensitivity of ultrasound with technological developments, widespread use of neck ultrasound (even for screening purposes in some countries), and increased use of iodine in the diet. This situation leads to the continuation of the increasing trend in the incidence of thyroid carcinoma. Knowing epidemiological factors underlying this increased incidence of TC is important for the development of preventive measures and achieving more successful results in terms of diagnosis and treatment.

ETHICAL DECLARATIONS

Ethical Committee Approval: Our study was carried out after obtaining approval from the Clinical Researches Ethics Committee of Gülhane Training and Research Hospital (Date 15.12.2021, Decision No: 2021/90).

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

Referee Evaluation Process: Externally peer-reviewed.

Conflict of interest: There is no conflict of interest among the authors of the article.

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Determination of nursing practices regarding port catheter care

Port kateter bakımına ilişkin hemşirelik uygulamalarının belirlenmesi

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ABSTRACT

Aim: The objective of this study is to determine the applications of nurses for port catheter care.

Material and Method: The research was conducted as a descriptive study. The study sample consisted of 196 nurses who worked in an Education and Research Hospital and agreed to participate in the study. In this study, data were collected using a data collection form created by researchers. Statistical data were expressed as mean±standard deviation (X±SS) and percentage (%).

Results: According to the results of this study, 90.8% of nurses were women, 65.8% were married, 69.4% had a bachelor's degree, and the average age was 38.08±8.76. 77.04% of nurses (n=151) are concerned about using a port catheter as a venous access point in a patient with a port catheter. 15.81% of the nurses (n=31) stated that they use port catheter right after controlling its location through radiography, 17.34% of the nurses (n=34) stated that pulling back blood on the syringe to confirm the location of the port catheter by observing the fluid flow, 20.4% of the nurses (n=40) state that they used a specific catheter needle to intervene the port catheter, 39.28% of the nurses (n=77) stated that they flushed the port catheter with saline and heparin saline to avoid clogging of the catheter. They flushed the catheter port once in 1-2 months with heparin saline when the catheter port cannot be used for a long time. 21.93% (n=43) of nurses stated that they dressed the area with antiseptic solution before application to prevent port catheter infection, and 17.34% (n=34) of them stated that they checked the location of the catheter by withdrawing blood before application to prevent extravasation.

Conclusion: The applications used by the nurses for port catheter care are compatible with the literature; however, these are limited.

Keywords: Port catheter, nursing, care

ÖZ

Amaç: Bu çalışmanın amacı hemşirelerin port kateter bakımına ilişkin uygulamalarını belirlemektir.

Gereç ve Yöntem: Araştırma tanımlayıcı bir çalışma olarak yürütülmüştür. Araştırmanın örneklemini bir eğitim ve araştırma hastanesinde çalışan ve araştırmaya katılmayı kabul eden 196 hemşire oluşturmuştur. Çalışmanın verileri araştırmacılar tarafından oluşturulmuş veri toplama formu ile toplanmıştır. Çalışma kapsamında toplanılan verilerin analizinde, Statistical Package for Social Sciences (SPSS) 21.0 bilgisayar paket programı kullanılmıştır. İstatistiksel veriler ortalama±standart sapma (X±SS) ve yüzde (%) olarak ifade edilmiştir.

Bulgular: Bu çalışmanın sonuçlarına göre, hemşirelerin %90.8'i kadın, %65.8'i evli, %69.4'ü lisans mezunu, yaş ortalaması ise 38.08±8.76'dır. Hemşirelerin %77.04'ü (n=151) port kateteri olan hastada venöz ulaşım yolu olarak port kateteri kullanmak konusunda endişe yaşamaktadırlar. Hemşirelerin %15.81'i (n=31) port kateteri radyografi ile yerinin kontrolünden hemen sonra kullandıklarını, hemşirelerin %25.51'i (n=50) port kateter alanında hematom gelişimini önlemek için soğuk uygulama yaptıklarını, %17.34'ü (n=34) port kateterin yerini doğrulamak için enjektörü yerleştirdikten sonra kanı geri çekerek mayinin gidişini kontrol ettklerini, %20.4'ü (n=40) port kateterden girişim yapmak için özel port kateter iğnesini kullandıklarını, %39.28'i (n=77) port kateterin tıkanmaması için serum fizyolojik ve heparinli serum fizyolojik ile yıkama yaptıklarını, port kateter uzun süre kullanılmayacağı durumlarda ise 1-2 ayda bir heparinli serum fizyolojikle yıkama yaptıklarını ifade etmiştir. Port kateter enfeksiyonunu önlemek için hemşirelerin %21,93'ü (n=43) uygulama öncesinde antiseptik solüsyonla pansuman yaptıklarını, %17.34'ü (n=34) ekstravazasyonu önlemek için uygulama yapmadan önce kanı geri çekerek kateterin yerini kontrol ettiklerini ifade etmiştir.

Sonuç: Port kateter bakımına ilişkin hemşirelerin yaptıkları uygulamalar literatürle uyumlu ancak sınırlıdır.

Anahtar Kelimeler: Port kateter, hemşirelik, bakım

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INTRODUCTION

Central venous catheters are commonly used to treat patients and are examined in three groups: external central venous catheters, peripherally placed central venous catheters, and subcutaneous central venous port catheters (1-3). The use of central venous catheters provides convenience in many procedures required by the treatment process, such as chemotherapy application, bone marrow transplantation, parenteral nutrition, monitoring of the patient in the perioperative process, administration of intravenous fluid and drugs, and taking blood samples and transfusion of blood products (1,4,5).

Port catheters are more preferred in cancer patients than other central venous catheters because of the long periods required to treat patients diagnosed with cancer, and their treatment can continue at home depending on the patient's health status, not to limit the patient's daily activities. Since their placement is under the skin, the risk of complications is less than other central venous catheters (occlusion, infection, dislocation, thrombosis, extravasation, phlebitis, bleeding, etc.), and no dressing is required (after healing of the wound) (1,6,7). Port catheter is a closed system consisting of a catheter extending into the central vein, a subdermal reservoir connected to the catheter, and a special needle inserted into the reservoir through the dermis (8,9). Port catheters are placed in the upper thoracic region (chest port), usually above the upper pectoral muscle. More rarely, it can also be placed in the upper arm region and femoral region (inguinal port) as alternatives (9,10). Although the cost of port catheters is high, there are significant advantages, such as patients experience less pain and anxiety due to a small number of needle interventions, a lower risk of infection, and do not interfere with the activities of patients due to their complete placement under the skin (bathing, swimming, etc.). It is not disturbing the cosmetic appearance (7,8,11,12). Early complications associated with catheter port are as follows; cardiac arrhythmias, pneumothorax, hemothorax, vascular injury, air embolism and while late-term complications can be listed as follows; functional disorders of the catheter, venous thrombosis, displacement of the catheter or port reservoir, occlusion, infection, and extravasation (2,5,8,11,13-16). Within the scope of this information, the knowledge and experience of nurses about port catheter care seems very important. Nurses who have a vital role in providing health services have critical roles in the care of patients with a port catheter related to safely performing interventions, preventing the development of complications, early detection of complications, and training the patient and their family about port catheter care (8,17,18). It was considered essential to identify nursing practices that could significantly affect the quality of patient care about the port catheter. We assume that the results of this study will also guide the training that will be planned in the field of nursing related to port catheter care.

MATERIAL AND METHOD

This research was planned as a descriptive study to determine the practices of the nurses in port catheter care. The research was conducted between May 2020 - December 2020 in an Education and Research Hospital in Izmir. 889 nurses constituted the population of the study. It is planned to include 208 people in the study when the sample size is calculated according to the confidence level of 90%, where the population size is 889, and the acceptable error rate is 5%. However, the research was completed with 196 nurses who agreed to participate in the study. In the study, 22.4% of the population was reached. Participation criteria in the study were determined as working as a nurse, and the exclusion criteria were determined as not agreeing to participate in the study. The approval of the İzmir Katip Çelebi University Ethics Committee (Decision No:687, Date: 12.05.2020) and the institution were obtained for the research. After being informed about the subject of the research, nurses were invited to participate in the research. Oral and written consent of the nurses who agreed to participate in the study was obtained.

The data collection form was prepared by researchers after a literature review on port catheter care (1,2,5,8,10,17,19,20). The prepared data collection form was submitted for the opinions of ten experts, including five doctors and five academic nurses, and it was edited according to the results of their feedback. The preliminary practice was conducted with 10 clinician nurses to test the intelligibility of the questions. Minor corrections were made in the form by evaluating the feedback. Data about the preliminary practice of the nurses were not included in the study. Nurses were asked to respond to the data collection form by using the face-to-face interview technique. The data collection form consisted of a total of 16 questions aimed at determining the demographic data of the nurses (age, gender, marital status, educational status, service period, and the unit they work in) and determining the nursing initiatives applied for the care of patients with a port catheter.

The computer package program called Statistical Package for Social Sciences (SPSS), version 21.0 for Windows, was used to analyze the obtained data. Identifying statistics as mean±standard deviation (X±SS), median, or percentage (%) was used to analyze the study data. Answers to open-ended questions were written using the scoreboard technique. The researchers read the answers given, and phrases pointing to the same topic were combined and

categorized. By interviewing clinician nurses again, it was evaluated whether the categorized statements matched the answers given.

RESULTS

Participants' sociodemographic characteristics are given in **Table 1**. 90.8% of the nurses involved in the study were female, 65.8% were married, 69.4% had a bachelor's degree, and the average age was 38.08±8.76. 77.04% of nurses (n=151) are concerned about using a port catheter as a venous access route when the patient they care for has a port catheter (**Table 2**). The reasons nurses are concerned about port catheter care are given in Table 2. 28.57% of nurses (n=56) are concerned about developing complications when they intervene through a port catheter.

In response to the question "when they first performed an application after the placement of a port catheter," 15.81% of nurses (n=31) answered that they "immediately after checking the location with radiography upon placement of the port catheter", 8.16% (n=16) stated "1-2 days after placing the port catheter", 2.55% (n=5) stated "one week after placing the port catheter", 2.55% (n=5) stated "after removing the stitches in the area where the port catheter was placed", and 70.91% (n=139) stated as "I have no idea".

In response to the question "Which practices they apply to prevent the development of hematoma when a port catheter is placed recently," 23.46% of nurses (n=46) answered as "frequent monitoring of the area where the port is inserted in terms of hematoma" and 25.51% (n=50) of the nurses answered as "they perform cold application".

The practices of nurses to verify the location of the port catheter were stated as follows: "pulling back blood on the syringe to confirm the location of the port catheter by observing the fluid flow" (17.34%, n=34), "manually palpate the port area" (13.26%, n=26), "Controlling the sound of contact of the port's needle to the reservoir" (1.53%, n=3).

In response to the question "What do nurses pay attention during intervention through port catheter" 20.4% (n=40) of nurses stated that they used a special port catheter needle, and 7.65% (n=15) said they paid attention to the thickness of the Huber needle according to the density of the drug or solution to be infused.

Referring to the practices used by nurses to prevent obstruction of the port catheter, 39.28% of nurses (n=77) stated that they "flush with saline and heparin saline" and "in cases where it is not possible to use the port catheter for a long time they use "flush with heparin saline every 1-2 months".

Table 1. Demographic characteristics of nurses

Features	n	%
Gender		
Woman	178	90.8
Man	18	9.2
Marital Status		
Married	129	65.8
Single	67	34.2
Education status		
High school	12	6.1
Associate Degree	27	13.8
Bachelor's Degree	136	69.4
Master Degree	20	10.2
Doctor's Degree	1	0.5
Working times		
0-1	17	8.7
2-5	12	6.1
6-10	29	14.8
11-20	80	40.8
21 years and over	58	29.6
Unit		
Brain Surgery	7	3.5
Nephrology	11	5.5
Ear-Nose-Throat	17	8.5
Bloodletting	3	1.5
Operating room	28	14.0
Urgent	5	2.5
Obstetrics	7	3.5
Cardiovascular	3	1.5
Nuclear medicine	3	1.5
Radiologist	9	4.5
Urology	2	1.0
Gastroenterology	15	7.5
General Surgery	26	13.0
COVID Units	6	3.0
Oncology	7	3.5
Thoracic surgery	2	1.0
Hematology	8	4.0
Internal	20	10.0
Cardiology	21	10.5
* Average age. 38.08±8.76	Total=196	Total=100

* Average Age

Table 2. Reasons for nurses ' concern over port catheter care

Causes of concern	n	%
Lack of information on Port catheter use	45	22.95
Lack of experience with Port catheter use	35	17.85
Damage to the port catheter reservoir	15	7.65
Risk of developing complications (hematoma, extravasation, embolism, thrombophlebitis, infection, blockage of the catheter)	56	28.57
Total	151	77.04

In response to the question of what their practices were to prevent port catheter infection; 21.93% of nurses (n=43) stated as "dressing with antiseptic solution before application", 37.5% (n=36) of the nurses stated that 'they follow-up the patient in terms of local and systemic signs of infection".

Referring to the practices to prevent the development of extravasation in the port catheter area, 17.34% of nurses (n=34) stated as "they check by withdrawing blood before any application", 18.87% (n=37) stated that "they monitor the area where the port is located in terms of the signs of extravasation", 6.12% (n=12) stated that "they inform patients and their relatives about the symptoms of extravasation. The topics on which nurses train patients on port catheter care are given in **Table 3**.

Table 3. Training topics given by nurses to patients about port catheter care

Topics	n	%
Signs and symptoms of local and systemic infection	21	10.71
Hygiene rules	6	3.06
Flushing the port catheter with heparin saline for 1-2 months	77	39.28
Dressing	43	21.93
Extravasation findings	12	6.12
Protection of the area where the port is located from trauma	23	11.73
Undesirable situations (displacement of the reservoir, fire, etc.) if it is necessary to contact the health care provider immediately	5	2.55

* More than one answer has been given.

DISCUSSION

Central venous catheters are devices that have to be used often in the treatment processes of patients. Especially central venous port catheters, which have a closed system, are suitable for long-term intravenous access in cancer patients compared to other external central venous catheters because these are safer, more comfortable, and less intrusive in terms of appearance and used very often for this purpose (8,11,12). Nurses can meet patients with port catheters in almost every clinic while providing patient care. For this reason, nurses must have sufficient knowledge and experience in port catheter care. Otherwise, although the patient has a port catheter, peripheral intravenous vascular access can be established again, creating a risk of infection with an extra intervention and causing the patient to experience pain and suffering (3). In this study, the practices of nurses on port catheter care were determined. When we consider the results, we observed that a considerable proportion of nurses had no idea about the questions asked about port catheter care and experienced anxiety when caring for a patient with a port catheter. When we consider why nurses are concerned about port catheter care, it is also seen that lack of knowledge and experience occupies a vital place. In studies, it was concluded that nurses' knowledge of port catheter care was low (8,17). The results reveal parallelism for the nurses with a lack of knowledge and experience in port catheter care. It is assessed that establishing training programs for nurses that include evidence-based practices related to port catheter care will positively impact both the level of knowledge and concern of nurses about this issue (21).

Referring to their initial application after the port catheter placement, the nurses stated that they intervened through the port catheter after different periods, but mainly "immediately after checking to utilize the radiography" and "after the day after the stitches were removed". After checking the location of the catheter when the port catheter is inserted, intervention can be made through the catheter (22). Different applications about the initial application time can reveal results ranging from establishing a second peripheral vascular access point although a port catheter exists to late initiation of treatment. For this reason, adding time information about the first use of the catheter will help eliminate the dilemmas in this regard when developing protocols for the use of a port catheter.

The following practices of the nurses seem consistent with the literature; palpate the port reservoir to confirm the location of the catheter before performing any intervention, pay attention to the sound of contact of the needle to the reservoir when inserting the needle, and check the fluid flow by withdrawing the blood after inserting the needle (8,22). These applications can prevent the development of extravasation. Extravasation begins with symptoms such as pain, erythema, burning, itching, edema, and continues with induration, desquamation, and bulla formation and may progress to the formation of necrotic plaques (23). In this study, nurses stated that they checked the location of the catheter by withdrawing blood to the injector before any intervention, monitored the area where the port was located for signs of extravasation and informed the patient and his relatives about the signs of extravasation to prevent the extravasation development, albeit at a low level. In addition to these practices, it is estimated that good fixing of the port catheter needle, the use of transparent cover in the port catheter area, and the creation of protocols to prevent extravasation by increasing nurses' awareness on this issue can reduce the incidence of extravasation (23,24).

The nurses stated that they used a special port catheter needle to perform the application from the port catheter and paid attention to the thickness of the Huber needle according to the density of the drug or solution to be infused. Huber needles used in Port catheter access are specially designed. When Huber needles are placed in the port septum, they prevent fragments from the tissue. In this way, it makes the texture durable up to about 2000 insertions. Otherwise, the patient's tissues are damaged by the septum of the port catheter, and the catheter life is shortened (24,25). Considering the importance of port catheters in the treatment of the patients and their cost, the attentive behavior of

nurses in this regard, will be positively reflected in the patient's output. Another critical issue regarding the use of Huber needles is the stabilization of the needle. It is also stated that recommended usage of the transparent cover to observe any symptoms of hematomas, infection, and extravasation are not sufficient and additional use of sterile strips or sterile tapes may contribute to the safety of Huber needles by preventing irritation, needle displacement, and infection (19).

In order to prevent the development of hematomas when the port catheter was first inserted, nurses stated that they performed cold application and monitored the area for the development of hematomas. Careful monitoring of the interference zone will allow you to notice complications early and start treatment immediately. The cold application will reduce the development of pain, edema, and hematoma in the area by reducing blood flow to the area where the port catheter is placed and causing vasoconstriction (24,26).

In this study, nurses stated that they flush with saline and heparin saline not to block the port catheter. In cases where the port catheter will not be used for a long time, they stated that they flush with heparin saline. These practices are consistent with the literature, although the rate of expression by nurses is not at the desired level. In order to prevent drug and blood accumulation in the catheter lumen, it is recommended to flush with 10 to 20 ml of saline before and after each application and to use heparin saline prepared with 10 to 100 units of heparin per milliliter in lock washing using positive pressure to prevent reflux back to the catheter after the patient's treatment is over (2,19). Here, another important issue is monitoring patients for complications such as bleeding caused by heparin, the risk, and the presence of heparin-related thrombocytopenia. Monitoring tissue plasminogen activator (tPA) value and taking measures such as extending flush intervals when this value runs up may benefit in the management of complications (19).

Port catheter-related infection rates are reported to be 0.018 to 0.35 per 1000 catheter days (10). Referring to port catheter-related infections, external-lumen infections are due to the lack of proper antiseptic application on the skin before the placement of Huber needles, and internal-lumen infections are due to infusion of the diluted solution into the catheter and thereby migration of organisms from the center of the catheter to the catheter lumen. Infection, which can also occur for reasons such as contamination caused by another source, provide a suitable environment for fungal or bacterial colonization at the fibrin sheath caused by the body's normal response to the catheter, is the most common complication associated with the port catheter (2,10,22). Port catheter infection causes the patient to undergo diagnostic procedures, undergo many antibiotic treatments, and even remove the port and install a new one, prolonging the patient's hospital stay, deteriorating comfort, and increasing health care costs (4,11,14,24). For all these reasons, the practices applied by nurses to prevent port catheter infection are of great importance. In this study, nurses stated that they dress the area with antiseptic solution before application to prevent port catheter infection and followed the patient in signs of local and systemic infection. In addition to these applications, some others are indicated in the literature as follows; to ensure hand hygiene infection prevention, not applying any dressing until the wound recovers after initial insertion of the port catheter, complying with port aseptic catheter techniques during the application, cleaning the skin before every intervention with 2% alcoholic chlorhexidine solution (for patients with allergy to alcoholic chlorhexidine, use povidone-iodine), providing a safe way of stabilization of the Huber needle, replacement of Huber needle every 7 days, and changing this infusion sets in every 24 hours (2,10,19). All these applications must exist in nursing practices to prevent catheter-related infections.

CONCLUSION

According to the results of this study, which evaluated nursing practices related to Port catheter care, the practices performed by nurses are compatible with the literature but limited. It is believed that conducting in-depth training programs, including evidence-based practices related to this issue, will improve the quality of patient care offered by nurses and positively contribute to patient outcomes.

Limitations of the study: The single-center execution of this study can be considered the research's limitations.

ETHICAL DECLARATIONS

Ethics Committee Approval: The approval of the İzmir Katip Çelebi University Ethics Committee (Decision No:687, Date: 12.05.2020)

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

Referee Evaluation Process: Externally peer-reviewed.

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

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Sağlık bakımı ilişkili enfeksiyonlarda *Staphylococcus aureus* dağılımının irdelenmesi: 6 yıllık deneyim

Examination of *Staphylococcus aureus* distribution in healthcare associated infections: 6 years of experience

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ÖZ

Amaç: *Staphylococcus aureus* (*S. aureus*) morbidite ve mortalitesi yüksek toplum kaynaklı ve sağlık bakım ilişkili enfeksiyonlara neden olmaktadır. En sık izole edildiği enfeksiyonlar; yara yeri enfeksiyonları, üriner sistem enfeksiyonları, pnömoni, septik artrit, osteomyelit ve sepsistir. Metisiline dirençli *S. aureus* (MRSA) ilk olarak 1960'larda tanımlanmış olup ve 1980'lerde hastanelerde önemli bir etken haline gelmiştir. Özellikle hastanede yatan hastalarda, sağlık hizmeti kaynaklı enfeksiyonlarda metisiline dirençli *S. aureus* önemli bir etkendir. Bu çalışmada, sağlık bakım ilişkili *S. aureus* enfeksiyonlarının ve MRSA izolatlarının altı yıllık dönemde, yıllara göre dağılımı irdelenmiştir. Bu veriler ışığında enfeksiyon kontrol önlemlerine ve akılcı antibiyotik kullanımına uyumun değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Ocak 2016-Aralık 2021 tarihleri arasında bir üçüncü basamak hastanede yatırılarak izlenen, sağlık bakım ilişkili enfeksiyon tanısı konulan hastalardan izole edilen *S. aureus* suşlarına ilişkin verilere Enfeksiyon Kontrol Komitesi kayıtlarından ulaşıldı. Altı yıllık dönemde 201 adet *S. aureus* suşlarının neden olduğu sağlık bakımı ile ilişkili enfeksiyon tanısı konuldu. Sağlık bakımı ile ilişkili *S. aureus* enfeksiyonlarının tutulum yaptığı organ ve sistemlere göre dağılımları, görüldüğü kliniklere (yoğun bakım ünitesi–servis) ve yıllara göre dağılımları değerlendirildi.

Bulgular: Sağlık bakımı ilişkili genel enfeksiyon etkenlerinin yıllara göre dağılımı incelendiğinde; 2016 yılında %1,29 olan oranının yıllar içinde artarak %6,41'e çıktığı saptandı. Servislerde yatırılarak izlenen hastalarda 2020 yılına kadar kümülatif bir artış olduğu izlendi, oranlar yıllara göre sırasıyla; %5, %3,8, %20,3, %25,3, %34,69 ve %17,1 şeklinde saptandı. Yoğun bakım ünitelerindeki (YBÜ) dağılım ise yıllara göre sırasıyla; %3,9, %10,3, %11,9, %19,4, %20 ve %23,5 olarak saptandı. YBÜ'de izlenen sağlık bakım ilişkili *S. aureus* enfeksiyonlarının yıllar içindeki artışı, servislerde izlenen artışa göre istatistiksel olarak anlamlı saptandı ($p<0,05$). Hastaların izlendikleri kliniklere göre MRSA dağılımları incelendiğinde, yıllar içinde değişkenlik göstermekle birlikte servis ve YBÜ MRSA oranlarının ortalamasının istatistiksel olarak farklılık göstermediği saptandı (%33,8-%31,3) ($p>0,05$).

Sonuç: Toplam 6 yıllık dönemde *S. aureus*'un etken olduğu sağlık bakımı ilişkili enfeksiyon oranlarında yaklaşık beş kat artış saptanmıştır. Ancak, bu artışın MRSA oranlarındaki artış ile korelasyon göstermediği belirlendi. El hijyeni eğitimleri, standart enfeksiyon kontrol önlemlerine uyumun artırılması ve akılcı antibiyotik kullanımda iyileştirme sağlanarak bu artışın önüne geçilebileceğini düşünmekteyiz.

Anahtar kelimeler: *Staphylococcus aureus*, MRSA, yoğun bakım ünitesi, sağlık bakımı ilişkili enfeksiyon

ABSTRACT

Aim: *Staphylococcus aureus* causes community-acquired and health care-related infections with high morbidity and mortality. The most common infections in which it is isolated are wound infections, urinary tract infections, pneumonia, septic arthritis, osteomyelitis and sepsis. Methicillin-resistant *S. aureus* was first identified in the 1960s and became an important factor in hospitals in the 1980s. Methicillin-resistant *S. aureus*, in healthcare-related infections, especially in hospitalized patients, is an important factor. In this study, the distribution of health care related *S. aureus* infections and MRSA isolates over a six-year period, by year, was examined. In the light of these data, it is aimed to evaluate compliance with infection control measures and rational antibiotic use.

Material and Method: The data of *S. aureus* bacteria isolated from patients diagnosed with healthcare-associated infections and followed up in a tertiary hospital between January 2016 and December 2021 were obtained from the Infection Control Committee records. A total of 201 diagnosis of healthcare-associated infections caused by *S. aureus* bacteria was detected in a six-year period. *S. aureus* infections; Health care associated infection diagnoses were evaluated by considering the years, the diagnoses made by infectious diseases, and the clinics (Intensive Care Unit-Service) where the patients were followed.

Results: According to the distribution of general healthcare-associated infectious agents in 2016, it was found that the rate, which was 1.29%, increased to 6.41% over the years. It was observed that there was a cumulative increase in the patients hospitalized and followed up in the wards until 2020, the rates were determined as 5%, 3.8%, 20.3%, 25.3%, 34.69% and 17.1%, respectively, over the years. The distribution in intensive care units (ICU) was determined as 3.9%, 10.3%, 11.9%, 19.4%, 20% and 23.5%, respectively. Health care-related *S. aureus* infections over the years were statistically significant compared to the increase observed in wards ($p<0.05$). When the MRSA distributions of the patients were examined according to the clinics they were followed, it was found that the average of MRSA rates in the service and ICU did not differ statistically (33.8%-31.3%) although it varied over the years ($p>0.05$).

Conclusion: In the 6-year period, the rates of healthcare-associated infections caused by *S. aureus* increased approximately 5 times. However, it does not correlate with the increase in MRSA rates. We think that this increase can be prevented by providing hand hygiene trainings, increasing compliance with standard infection control measures and improving the rational use of antibiotics.

Keywords: *Staphylococcus aureus*, MRSA, intensive care unit, healthcare associated infection

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GİRİŞ

Staphylococcus aureus morbidite ve mortalitesi yüksek toplum kaynaklı ve sağlık bakım ilişkili enfeksiyonlara neden olmaktadır. En sık izole edildiği enfeksiyonlar; yara yeri enfeksiyonları, üriner sistem enfeksiyonları, pnömoni, septik artrit, osteomyelit ve sepsistir (1). *S. aureus*'taki metisilin direnci, minimum inhibitör konsantrasyonu (MIC) oksasilin ≥4 mcg/mL. olarak tanımlar. Metisiline dirençli *Staphylococcus aureus* (MRSA), 5. kuşak sefalosporinler dışındaki tüm beta-laktam grubu antibiyotiklere dirençlidir. Metisiline dirençli *S. aureus* ilk olarak 1960'larda tanımlanmış olup ve 1980'lerde hastanelerde önemli bir etken haline gelmiştir (2). Özellikle hastanede yatan hastalarda, sağlık hizmeti kaynaklı enfeksiyonlarda metisiline dirençli *S. aureus* önemli bir faktördür.

Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) alışmasının verilerine göre *S. aureus* ülkemizde invaziv örneklerden en sık izole edilen mikroorganizmalar arasında 3. sırada yer almaktadır (3).

MRSA enfeksiyonları için tanımlanmış başlıca risk faktörleri; ameliyat, diyalize girme, hastaneye yatış; santral venöz kateterler veya besleme gibi kalıcı perkütan cihazlar tüpler veya hastanın daha önce kültürle kanıtlanmış MRSA enfeksiyonu varlığıdır. Sağlık hizmetleri ile ilişkili MRSA enfeksiyonu, yatıştan 48 saat sonra gelişen MRSA enfeksiyonu olarak tanımlanmaktadır (4).

Bu çalışmada sağlık bakım ilişkili *S. aureus* enfeksiyonlarının ve MRSA izolatlarının altı yıllık dönemde, yıllara ve kliniklere göre dağılımı irdelenmiştir. Bu veriler ışığında enfeksiyon kontrol önlemlerine ve akılcı antibiyotik kullanımına uyumun değerlendirilmesi amaçlanmıştır.

GEREÇ VE YÖNTEM

Ocak 2016-Aralık 2021 tarihleri arasında bir üçüncü basamak hastanede yatırılarak izlenen, sağlık bakım ilişkili enfeksiyon tanısı konulan hastalardan izole edilen *S. aureus* izolatlarına ilişkin verilere Ankara Eğitim ve Araştırma Hastanesi Enfeksiyon Kontrol Komitesi kayıtlarından ulaşıldı. Altı yıllık dönemde 201 adet *S. aureus* bakterisinin neden olduğu sağlık bakımı ile ilişkili enfeksiyon tanısı konuldu. Sağlık bakım ilişkili enfeksiyon tanısı, Ulusal Sağlık Hizmeti İlişkili Enfeksiyonlar Sürveyans Rehberi kriterlerine göre tanımlandı (5). Yatan hastalardan izole edilen *S. aureus* izolatlarının tanımlanması ve metisilin duyarlılığının belirlenmesi Ankara Eğitim ve Araştırma Hastanesi, Mikrobiyoloji Laboratuvarı'nda VITEK-2 (Biomerueux, USA) otomatize tanımlama ve antibiyotik duyarlılık sistemi kullanılarak gerçekleştirildi. İzole edilen bakterilerde metisilin ve diğer antibiyoıtik duyarlılıkları European Committee on Antimicrobial Susceptibility Testing (EUCAST) önerileri doğrultusunda değerlendirildi (6-8).

S. aureus enfeksiyonlarının; enfeksiyonların tutulum bölgesi, yıllara göre görülme sıklıkları ve saptandığı kliniklere göre (yoğun bakım ünitesi veya yoğun bakım dışındaki servisler) dağılımları tablo ve şekillerle gösterildi.

Araştırma verisi SPSS (Statistical Package For Social Sciences for Windows v.22,0, SPSS Inc. Chicago, IL) aracılığıyla bilgisayar ortamında değerlendirildi. Tanımlayıcı istatistikler ortalama (±) standart sapma, ortanca (min-maks), frekans dağılımı ve yüzde olarak sunuldu. Tanımlayıcı istatistiklerin yanı sıra Ki-Kare Testi ve Fisher'in Kesin Testi uygulandı. İstatistiksel anlamlılık düzeyi p<;0,05 olarak kabul edildi.

Bu çalışma için Ankara Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır (Tarih: 12.01.2022, Karar No: 863). Tüm işlemler Helsinki Deklarasyonu'nun etik kurul ve ilkelerine göre gerçekleştirilmiştir.

BULGULAR

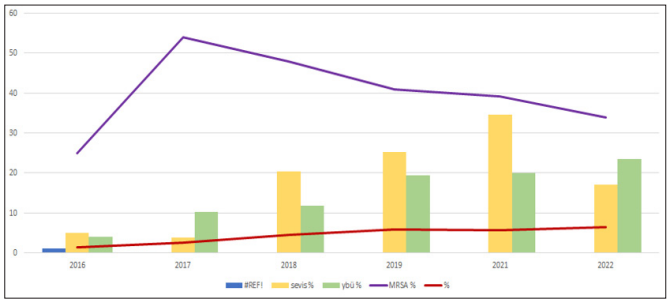
Ocak 2016-Aralık 2021 yılları arasında, Ulusal Sağlık Hizmeti İlişkili Enfeksiyonlar Sürveyans Rehberi kriterlerine göre 201 adet, *S. aureus* bakterisinin neden olduğu, sağlık bakımı ile ilişkili enfeksiyon saptandı. İzole edilen *S. aureus* izolatlarının % 48,5'i MRSA, %51,5'i ise metisiline duyarlı *S. aureus* (MSSA) idi. Bu enfeksiyonlar yıllara göre görülme oranı, hastaların izlendiği kliniklere göre dağılımı ve izole edilen bakterinin metisilin dirençli veya duyarlı olmasına göre göre irdelendi.

Yıllara göre sağlık bakım ilişkili *S. aureus* enfeksiyonlarının dağılımı incelendiğinde; 2016 yılında sağlık bakımı ilişkili genel enfeksiyon etkenleri dağılımına göre %1,29 olan oranın yıllar içinde artarak %6,41'e çıktığı saptandı. Servislerde yatırılarak izlenen hastalarda 2020 yılına kadar kümülatif bir artış olduğu izlendi, oranlar yıllara göre sırasıyla; %5, %3,8, %20,3, %25,3, %34,69 ve %17,1 şeklinde saptandı. Yoğun bakım ünitelerindeki (YBÜ) dağılım ise yıllara göre sırasıyla %3,9, %10,3, %11,9, %19,4, %20 ve %23,5 olarak belirlendi. YBÜ'de izlenen sağlık bakım ilişkili *S. aureus* enfeksiyonlarının yıllar içindeki artışı, servislerde izlenen artışa göre istatistiksel olarak anlamlı saptandı (p<0,05).

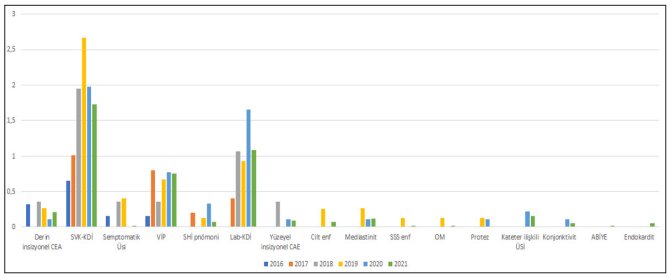
Sağlık bakım ilişkili enfeksiyonların yıllara-kliniklere göre dağılım ve MRSA oranları **Şekil 1**'de özetlenmiştir.

Ulusal Sağlık Hizmeti İlişkili Enfeksiyonlar Sürveyans Rehberi kriterlerine göre *S. aureus*'un neden olduğu sağlık bakım ilişkili enfeksiyon tanıları irdelendi. Tüm

yıllar değerlendirildiğinde en sık saptanan tanının santral venöz kateter ilişkili kan dolaşım enfeksiyonu olduğu belirlendi. Bunu laboratuvara dayalı kan dolaşım enfeksiyonu izlemekte idi. Enfeksiyon tanılarına göre dağılım **Şekil 2**'de gösterildi.



Şekil 1. Sağlık bakım ilişkili *S. aureus* enfeksiyonlarının yıllara, kliniklere göre dağılım ve MRSA oranları



CEA: Cerrahi alan enfeksiyonu SVK-KDİ: Santral venöz kateter ilişkili kan dolaşımı enfeksiyonu VİP: Ventilatör ilişkili pnömoni Lab-KDİ: Laboratuvar tarafından doğrulanmış kan dolaşımı enfeksiyonu OM: Osteomiyelit ÜSİ: Üriner sistem enfeksiyonu ABİYE: asemptomatik bakteriyemik üriner sistem enfeksiyonu
Şekil 2. Yıllara göre sağlık bakım ilişkili *S. aureus* enfeksiyonlarının dağılımı

Hastaların izlendikleri kliniklere göre MRSA dağılımları incelendiğinde, yıllar içinde değişkenlik göstermekle birlikte servis ve YBÜ MRSA oranlarının ortalamasının istatistiksel olarak farklılık göstermediği saptandı (%33,8-%31,3) (p>0,05). MSSA dağılımı açısından da YBÜ ve servisler arasında farklılık değerlendirildiğinde sırasıyla; %56,5, %43,5 olarak belirlendi. MSSA açısından klinik ve YBÜ değerlendirildiğinde; MSSA oranlarının ortalamasının istatistiksel olarak farklılık göstermediği saptandı (p>0,05). MRSA oranlarının yıllara göre dağılımı **Tablo 1**'de gösterilmiştir (**Tablo 1**).

Tablo 2. MRSA oranlarının yıllara göre dağılımı

Yıl	Servis %	YBÜ %
2016	0	25
2017	33,3	20
2018	33,3	40
2019	36,8	42,8
2020	61,9	29,6
2021	23,07	40,4

YBÜ*: Yoğun bakım ünitesi

TARTIŞMA

S. aureus tüm dünyada sağlık bakım ilişkili enfeksiyonların önemli bir nedenidir. MRSA insidansı tüm dünyada değişkenlik göstermektedir. EARS-Net 2015 verilerinde; Avrupa ülkelerinde MRSA oranının %0 ile %57,2 arasında değiştiği, Avrupa genelinde bu oranın ortalama %16,8 olarak saptandığı, 2018 ve 2019 yılı raporlarında bu oranın kısmi olarak düştüğü belirtilmiştir (9-11).

Sunduğumuz çalışmada, MRSA oranlarının 2016 yılından 2021 yılına servislerde %0'dan %23,07'ye YBÜ'de ise %25'ten %40,4'e arttığı saptanmıştır. 2016-2021 yılları arasında *S. aureus* un etken olduğu sağlık bakım ilişkili enfeksiyonların oranları ise sırasıyla %1,29- %6,41 olarak belirlenmiştir. Servis ve YBÜ ayrımı yapılmaksızın MRSA oranları değerlendirildiğinde ise oranlardaki artış %25, %53,85, %48, %40,9, %39,22 ve %33,9 bulunmuştur. Avrupa geneli ortalaması ile karşılaştırıldığı bu oranların yüksek olduğu görülmektedir. Çalışmanın yapıldığı dönemlerde hastanemizde *S. aureus* a bağlı herhangi bir salgın tespit edilmemiştir. MRSA oranlarının merkezlere ve coğrafi bölgelere değişiklik gösterdiği hatırlanmalıdır. Çalışmalarda bu oranlar yıllara ve merkezlere göre değişiklik göstererek %35-%75 aralığında saptanmıştır (12,13).

Zencir ve ark.'nın (14) hastanede yatan hastalarda yaptığı bir çalışmada kan kültüründe MRSA üreyen hastaların %84,6'sının yoğun bakım ünitelerinden, %14,4'ünün ise diğer kliniklerden gelen örneklerden elde edildiği bildirilmiştir. Yüksekkaya ve ark (15) ise kan kültüründe MRSA saptanan olguların %48'inin yoğun bakım ünitelerinden, %47'sinin dahili kliniklerden, %5'inin ise cerrahi kliniklerden izole edildiğini rapor etmiştir. Özkaya ve ark.'nın (16) çalışmasında kan kültüründe üreme saptanan hastalar değerlendirilmiş ve kan kültüründe *S. aureus* üremesi saptanan olgular tüm olguların %5,5'i iken, sadece *S. aureus* üremesi saptanan olguların %69'unu yoğun bakım ünitelerinden elde edilen örneklerden oluştuğu tespit edilmiştir. Çalışmamızda literatürle benzer şekilde YBÜ'lerinde *S. aureus*'a bağlı gelişen enfeksiyon oranlarının daha fazla olduğunu belirledik. Ayrıca, 2020 yılı verilerini incelediğimizde; servis hastalarında görülen MRSA'ya bağlı enfeksiyon oranlarının YBÜ'ye kıyasla artmış olduğunu olduğunu saptadık. Bu artışın nedenlerini irdelediğimizde; COVID-19 tanılı hastalar, immünosupresif hastalar ve steroid tedavisi alan hastaların bu artışa neden olduğunu belirledik. Ancak, çalışma tasarımı gereği *S. aureus* enfeksiyonlarına yönelik risk faktörlerini incelemedik.

Çalışmamızda *S. aureus* enfeksiyonlarını enfeksiyon tanılarına göre de değerlendirdik. Tüm yıllarda *S. aureus* a bağlı en sık kan dolaşım enfeksiyonları ve ikinci olarak ventilatörle ilişkili pnömoni (VIP) geliştiğini

saptadık. *S. aureus* a bağlı gelişen kan dolaşımı enfeksiyonlarında yüksek mortalite (%20-%40) görülebilmektedir (17,18). Mortalite oranlarınıdaki yüksekliğin yanı sıra hastanede yatış süreleri ve maliyet artışına da neden olmaktadırlar (19).

Bonnal ve ark.'nın (20) 10 yıllık bir dönemi inceledikleri çalışmalarında, nozokomiyal kan dolaşımı enfeksiyonlarının %18'inde *S. aureus*'un etken olduğu bildirilmiştir. Bu vakaların %38,2'sinde kateter ilişkili kan dolaşımı enfeksiyonu saptanmıştır. Çalışmalarında sonuç olarak, *S. aureus*'un etken olduğu sağlık bakım ilişkili kan dolaşımı enfeksiyonlarının kateter ilişkili kan dolaşımı enfeksiyonlarında basit ve kullanışlı bir indikatör olduğu yorumunu yapmışlardır. MRSA izolatlarının el hijyenine dikkat edilmediğinde hastane ortamında hastalar arasında kolaylıkla yayılabileceğini gösteren çalışmalar mevcuttur (21,22). Dolayısıyla *S. aureus*'un ve MRSA'nın etken olduğu sağlık bakım ilişkili kan dolaşımı enfeksiyonlarının, genel el hijyeni uygulamaları ve enfeksiyon kontrol önlemlerine uyum konusunda hastaneler özelinde belirteç olarak kullanılabileceği düşüncesindeyiz.

Sunduğumuz çalışmada 2016 yılından 2021 yılına *S. aureus* un etken olduğu sağlık bakımı ilişkili enfeksiyon oranlarında yaklaşık beş kat artış gözlemlendi. Ancak, MRSA'nın etken olduğu sağlık bakımı ilişkili enfeksiyon oranlarında bu artış yaklaşık 1,3 olarak saptandı, bu oran istatistiksel olarak anlamlı değildi. *S. aureus* oranlarındaki anlamlı artışın MRSA'daki artışa karşılık gelmediğini tespit ettik. Bu durumun yıllar içinde el hijyeni eğitim ve uygulamalarında etkinlik sağlanması, akılcı antibiyotik kullanımın önemi ve enfeksiyon kontrol önlemlerine uyumun sağlanması ile gerçekleşebildiğini düşünüyoruz.

Çalışmanın Kısıtlılıkları

Sunduğumuz çalışmada, *S. aureus* suşlarının sadece metisilin direnç durumları değerlendirilmiştir. Diğer antimikrobiyallere duyarlılık durumları ve bunun yıllar içindeki değişimi incelenmemiştir. MRSA veya *S. aureus* enfeksiyonları için risk analizi yapılmamıştır. Bunlar, çalışmamızın kısıtlılıklarıdır.

SONUÇ

Sonuç olarak, çalışmamızda yıllar içinde *S. aureus*'un etken olduğu sağlık bakımı ilişkili enfeksiyon oranlarında artmış saptarken, MRSA enfeksiyonlarının oranında artış saptamadık Hastanemizde el hijyeni eğitimleri, standart enfeksiyon kontrol önlemlerine uyumun artırılması ve akılcı antibiyotik kullanımda iyileştirme sağlanarak bu artışın önüne geçilebileceğini düşünmekteyiz.

ETİK BEYANLAR

Etik Kurul Onayı: Bu çalışma için Ankara Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır (Tarih: 12.01.2022, Karar No: 863).

Aydınlatılmış Onam: Çalışma retrospektif olarak tasarlandığı için hastalardan aydınlatılmış onam alınmamıştır.

Hakem Değerlendirme Süreci: Harici çift kör hakem değerlendirmesi.

Çıkar Çatışması Durumu: Yazarlar bu çalışmada herhangi bir çıkara dayalı ilişki olmadığını beyan etmişlerdir.

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MEDICINE PALLIATIVE CARE

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Pain score and other factors affecting the postoperative discharge time of patients who underwent lung resection: a retrospective study

Akciğer rezeksiyonu yapılan hastaların postoperatif taburculuk süresini etkileyen ağrı skoru ve diğer faktörler: retrospektif çalışma

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ABSTRACT

Aim: Many factors affect the hospitalization period of patients after surgery. One of the most important of them is postoperative pain. Our study aims to investigate the relationship between the postoperative discharge time and the postoperative 24-hour visual analog scale (VAS) pain scores of patients who underwent thoracotomy and lung resection. Additionally, we also want to identify the parameters that affect the day of discharge, VAS scores, and chest tube removal time of these patients.

Material and Method: Data of patients who underwent elective thoracic surgery between February 2021 and August 2021 in a tertiary chest disease and thoracic surgery center were analyzed patients aged between 18 and 75 years, in the ASA I-II-III risk group, with a body mass index (BMI) in the range of 18.5-35 kg/m², who underwent thoracotomy and resection due to lung malignancy. Following data were extracted co-morbidities, diagnoses, performed surgery, type of surgery, duration of surgery, intraoperative complications, intraoperative blood product transfusion history, postoperative advanced complications, postoperative 24-hour VAS, length of stay, and length of chest tube stay.

Results: A total of 104 patients who underwent elective thoracotomy and lung resection under general anesthesia between February 2021 and August 2021 were included in the study. There was a positive and highly statistically significant correlation between discharge time and chest tube removal time ($p < 0.001$). There was no statistically significant correlation between discharge times and VAS scores ($p=0.553$). Additionally, there was no statistically significant correlation between VAS scores and chest tube removal time. Discharge time had a low positive and statistically significant correlation with age ($p=0.027$), and with the duration of the operation ($p < 0.001$). There was a low degree of negative statistically significant correlation between discharge day and BMI ($p=0.017$).

Conclusion: While the prolonged chest tube withdrawal time was directly related to the longer discharge time, the VAS scores have no significant correlation with the discharge time and the chest tube removal time. Additionally, age and operation time were also found to be associated with prolonged discharge time. Prospective comprehensive studies on this subject will be useful in clarifying the factors affecting the discharge time after thoracic surgery.

Keywords: lung resection, pain, postoperative discharge time, thoracotomy, visual analog scale

ÖZ

Amaç: Birçok faktör hastaların cerrahi sonrası hastane yatış sürelerini etkilemekle birlikte bunlardan en önemlisi postoperatif ağrıdır. Bu çalışmamızdaki birincil amacımız torakotomi ile akciğer rezeksiyonu yapılan hastaların postoperatif taburculuk süresi ile postoperatif ilk 24 saatlik vizuel analog skala (VAS) ağrı skorları arasındaki ilişkiyi araştırmaktır. İkincil olarak bu hastalarda taburculuk gününü, VAS skorları ve göğüs tüpü çekilme zamanını etkileyen parametreleri tespit etmektir.

Gereç ve Yöntem: Çalışmamız, üçüncü basamak göğüs hastalıkları ve göğüs cerrahisi merkezi olan hastanemizde Şubat 2021 ve Ağustos 2021 tarihleri arasında elektif olarak göğüs cerrahisi ameliyatı olan hastalar postoperatif olarak incelenmiştir. 18-75 yaş arası, ASA I-II-III risk grubunda olan, vücut kitle indeksi (VKİ) 18,5-35 kg/m² aralığında olan, torakotomi ile akciğer malignitesi sebebiyle rezeksiyon uygulanmış hastalar çalışmamıza dâhil edilmiştir. Hastaların anestezi kayıtlarından ve dosyalarından yandaş hastalıklar, tanılar, yapılan ameliyat, ameliyat tipi, ameliyat süresi, intraoperatif komplikasyonlar, intraoperatif kan ürünü transfüzyonu öyküsü, postoperatif gelişmiş komplikasyonlar, postoperatif 24 saatlik VAS skorları, yatış süreleri, ve göğüs tüpü kalış süreleri gibi veriler kaydedilmiştir.

Bulgular: Şubat 2021-Ağustos 2021 tarihleri arasında genel anestezi altında elektif torakotomi ve akciğer rezeksiyonu yapılan toplam 104 hasta çalışmaya dahil edildi. Taburcu olma süresi ile göğüs tüpü çekilme süresi arasında pozitif ve istatistiksel olarak anlamlı bir ilişki bulundu ($p < 0,001$). Taburculuk süreleri ile VAS skorları arasında istatistiksel olarak anlamlı bir ilişki bulunamadı ($p=0,553$). VAS skorları ile göğüs tüpü çekilme zamanı arasında istatistiksel olarak anlamlı bir ilişki de bulunamadı. Taburculuk günü ile yaş ($p=0,027$) ve taburculuk günü ile operasyon süresi ($p < 0,001$) arasında düşük derecede pozitif yönlü istatistiksel olarak anlamlı korelasyon bulundu. Taburculuk günü ile VKİ arasında düşük derecede negatif yönlü istatistiksel olarak anlamlı bir korelasyon bulundu ($p=0,017$).

Sonuç: Göğüs tüpü çekilme zamanının uzaması taburculuk süresinin uzaması ile doğrudan ilişkili iken, VAS skorları ile taburculuk süresi ve göğüs tüpü çekilme zamanı arasında anlamlı bir korelasyon gözlenmemiştir. Ayrıca, yaş ve operasyon süresi de taburculuk süresinin uzaması ile ilişkili bulunmuştur. Bu konuda yapılacak prospektif kapsamlı çalışmalar göğüs cerrahisi sonrası taburculuk süresini etkileyen faktörlerin açığa kavuşturulmasında faydalı olacaktır.

Anahtar kelimeler: Akciğer rezeksiyonu, ağrı, postoperatif taburculuk süresi, torakotomi, vizuel analog skala

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INTRODUCTION

Many factors affect the hospitalization period of patients after surgery. One of the most important of them is postoperative pain (1). Thoracic surgery, particularly thoracotomy, is one of the most painful surgical procedures known (2). Thoracic epidural analgesia (TEA) is a gold standard in pain management after thoracic surgery. However, side effects, such as sympathetic blockade, respiratory depression, urinary retention, and serious conditions such as epidural hematoma and abscess may also be encountered (3).

Thoracic paravertebral block (TPVB) offers similar analgesia to TEA but causes fewer postoperative complications (4). Therefore, the usage of TPVB and other regional nerve block applications after thoracic surgery has increased in recent years (3,5-7). In addition to regional block applications; intravenous analgesia treatments, such as opioids, paracetamol, non-steroidal anti-inflammatory drugs, are also applied as a component of multimodal analgesia (8,9).

With the development of the thoracoscopy technique, the smaller incisions in video-assisted thoracic surgery (VATS) help to reduce the postoperative pain, however, acute severe pain that develops after thoracotomy is still a difficult situation to control (3). After these types of surgery, the most common source of the pain can be listed as surgical incision, rib injury, and chest tubes (2). Additionally, postoperative pulmonary complications, such as pain-related atelectasis and pneumonia, may develop and pain may result in longer hospital stays (2, 3). It is also known that acute pain increases postoperative morbidity and prolongs hospital stay (10, 11). Due to poor postoperative pain control, prolonged hospitalization, decreased patient satisfaction, and prolonged immobilization have been reported in studies (12, 13).

Many factors affect postoperative pain, such as obesity, young age, preoperative preparation of the patient, postoperative analgesia methods, type of the surgery, duration of the operation, perioperative complications, number of chest tubes, and length of stay (14). Although all these parameters are associated with pain, they also affect the postoperative discharge times of the patients.

Our study aims to investigate the relationship between the postoperative discharge time and the postoperative 24-hour visual analog scale (VAS) pain scores of patients who underwent thoracotomy and lung resection. Additionally, we also want to identify the parameters that affect the discharge time, VAS scores, and chest tube removal time of these patients.

MATERIAL AND METHOD

The study was initiated with the approval of the Ankara Training and Research Hospital Ethics Committee (Date: 11.01.2022, Decision No: 2012-KEAK-15/2448), data of patients who underwent elective thoracic surgery between February 2021 and August 2021 in a tertiary chest disease and thoracic surgery center were analyzed. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Following patients were included in the study: Patients aged between 18 and 75 years, in the American Society of Anesthesiologists (ASA) I-II-III risk group, with a body mass index (BMI) in the range of 18.5-35 kg/m², who underwent thoracotomy and resection due to lung malignancy. Following patients were excluded from the study: Patients under the age of 18 and over the age of 75, BMI below 18.5 kg/m² and above 35 kg/m², with advanced co-morbidity, with ASA score greater than III, operated under emergency conditions, and did not undergo thoracotomy. Additionally, patients with previous lung surgery, previous COVID-19 pneumonia, and diagnosis of pleural effusion and hemoptysis were not included in the study.

The medical records of patients were analyzed and the following data were extracted: age, height, body weight, BMI, gender, ASA score, co-morbidities, diagnoses, performed surgery, type of surgery, duration of surgery, intraoperative complications, intraoperative blood product transfusion history, postoperative advanced complications, postoperative 24-hour VAS, length of stay, and length of chest tube stay. Pulmonary infection, atelectasis, cardiopulmonary edema, pleural effusion, pneumothorax, pulmonary embolism, empyema, and hemoptysis were recorded as postoperative pulmonary complications during the patients' hospitalization period. Additionally, complications such as other cardiac, neurological and nephrological were recorded as extrapulmonary complications.

Analgesia Protocol

Before the end of the surgical procedure, TPVB was performed, the insertion site was identified at 2.5 cm lateral of the spinous process at the level of T5-T6. After the transverse process was felt with the needle, the needle was pulled back and directed 1 cm toward the upper side of the transverse process. Then, 20 mL of 0.5% bupivacaine was injected through the needle. 10 mg IV metoclopramide was administered to prevent nausea and vomiting and 100 mg IV tramadol with 50 mg IV dexketoprofen was administered for analgesia at the end of the surgery. Intravenous morphine was administered via patient-controlled analgesia (PCA) pump for 24 hours in the postoperative surgical intensive care unit. The PCA pump's dose delivery was limited to administering a bolus dose of 1 mg morphine and delivering a maximum dose

of 12 mg morphine in total within four hours with lockout intervals of 15 minutes. Paracetamol 1 g every 8 hours and dexketoprofen 50 mg twice daily were administered intravenously for multimodal analgesia. As a rescue analgesic agent, 0.5 mg/kg tramadol was given to patients intravenously when a score of VAS at rest is greater or equal to 4. The side effects such as allergic reactions, hypotension, nausea-vomiting, and itching were recorded.

Statistical Analyses

Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined by the Kolmogorov Smirnov test. Levene's test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean±standard deviation for normal distributions, and median (interquartile range) for skewed distributions. Categorical data were described as the number of cases (%). Statistical analysis differences between two independent groups, not normally distributed variables, were compared by the Mann-Whitney U test. Categorical variables were compared using Pearson's Chi-Square test or Fisher's exact test. Univariate and multivariate linear regression analyses were performed to find risk factors and assess the association between discharge times, VAS scores, and chest tube removal times. The degrees of the relationship between variables were evaluated with Spearman correlation analysis. p-value < 0.05 was accepted as statistically significant on all analyses.

RESULTS

A total of 104 patients who underwent elective thoracotomy and lung resection under general anesthesia between February 2021 and August 2021 were included in the study (**Figure 1**). Demographic data and surgical characteristics of the patients are given (**Table 1**).

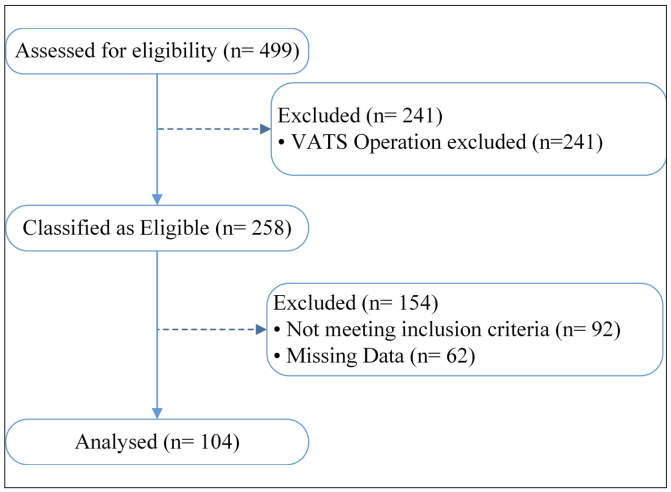

Figure 1. Flow chart of the patients

Table 1. Demographic characteristics of patients, operational characteristics, discharge Day, VAS scores and time of chest tube removal

	Patients (n:104)
Gender	
Women	30 (28.8%)
Men	74 (71.2%)
Age (year)	60.00 (3.0)
BMI kg/m²	27.72 (7.09)
Co-morbidity	
Hypertension	36 (40%)
Diabetes Mellitus	21 (23.3%)
Coronary Artery Disease	12 (13.3%)
Chronic Obstructive Lung Disease –Asthma	9 (10%)
Extra Pulmonary Malignancy	3 (3.3%)
Goiter	5 (5.5%)
Other	4 (4.4%)
ASA	
ASA II	34 (32.7%)
ASA III	70 (67.3%)
Operation Side	
Left	50(48.1%)
Right	54(51.9%)
Operation Duration (minute)	240.73±83.30
Additional Analgesic	7(6.7%)
PPCs	30(28.8%)
Extra Pulmonary Complications	3(2.9%)
Discharge Time (Day)	7.00 (3.00)
VAS Score (average of 24 hours postoperatively)	3.20 (1.60)
Chest tube removal time (Day)	5.00 (3.00)

Continuous variables are expressed as either mean±standard deviation (SD) or median (interquartile range). Categorical variables are expressed as either frequency or percentage. ASA: American Society of Anesthesiologists; BMI: Body Mass Index; PPCs: Postoperative Pulmonary Complication; VAS: Visual Analog Scale

The correlation analysis between discharge time, VAS scores, and chest tube removal time was analyzed. There was a positive and highly statistically significant correlation between discharge time and chest tube removal time (p < 0.001). There was no statistically significant correlation between discharge times and VAS scores (p=0.553). Additionally, there was no statistically significant correlation between VAS scores and chest tube removal time (p=0.690) (**Table 2**).

Table 2. The correlation between patients' discharge time, visual analogue scale (VAS) pain score, and chest tube removal time

		Discharge time (day)	VAS score	Chest tube removal time (day)
Discharge time (day)	r	1.000		
	p	.		
VAS score (average of the first 24 hours)	r	-0.059	1.000	
	p	0.553	.	
Chest tube removal time (day)	r	0.736	0.040	1.000
	p	<0.001	0.690	.

r: correlation coefficient, Spearman Correlation, VAS: Visual Analog Scale

The correlation analysis between discharge time, VAS scores, chest tube removal time and age, BMI, and operation time of the patients were performed. Discharge time had a low positive and statistically significant correlation with age (p=0.027), and with the duration of the operation (p < 0.001). There was a low degree of negative statistically significant correlation between discharge day and BMI (p=0.017). The VAS score had a low degree of positive statistically significant correlation with BMI (p=0.018) and operation time (p=0.001). The time of chest tube removal also had a low degree of positive statistically significant correlation with age (p=0.017) and with operation time (p < 0.001) (**Table 3**).

Table 3. The correlation between patients' discharge time, visual analogue scale (VAS) pain score, chest tube removal time, age, body mass index, and operation duration

		Discharge time (day)	VAS score	Chest tube removal time (Day)
Age (year)	r	0.217	-0.148	0.235
	p	0.027	0.133	0.017
BMI (kg/m²)	r	-0.234	0.231	-0.182
	p	0.017	0.018	0.067
Operation Duration (minute)	r	0.356	0.332	0.376
	p	<0.001	0.001	<0.001

r: correlation coefficient, Spearman Correlation, BMI: Body Mass Index

Discharge time and chest tube removal time in patients with PPC were statistically significantly higher than in patients without PPC (p < 0.05). The presence of extrapulmonary complications had no statistically significant relationship with discharge time, chest tube removal time, and VAS score (p > 0.05) (**Table 4**).

Table 4. The relationship between discharge day, VAS scores and chest tube removal time in patients with postoperative pulmonary complications and extra pulmonary complications

		Discharge time (day) med (IQR)	VAS score med (IQR)	Chest tube removal time (day) Med (IQR)
PPCs	Yes	6 (3)	3.1 (1.6)	5 (3)
	No	9 (7)	3.4 (1.5)	8 (7)
	p	<0.001	0.722	<0.001
Extra Pulmonary Complications	Yes	7 (3)	3.3 (1.6)	5 (3)
	No	4 (12)	1.5 (2.9)	4 (12)
	p	0.592	0.055	0.970

Med: Median, IQR: Interquartile range, VAS: Visual Analog Scale, PPCs: postoperative pulmonary complications

Univariate and multivariate linear regression analyses were applied to determine the factors affecting the discharge time of the patients. The results revealed that PPCs formation and prolongation of chest tube withdrawal were associated with prolonged discharge time (**Table 5**).

Univariate and multivariate linear regression analyses were used to determine the factors affecting the VAS scores of the patients. According to the results of the multivariate linear regression analysis, the increase in the operation time and the occurrence of extrapulmonary complications were the factors that increase the VAS score (p < 0.05).

Univariate and multivariate linear regression analyses were performed to determine the factors affecting the chest tube removal time of the patients. According to the results, the prolonged operation time and the formation of PPCs are the factors that increase the time of chest tube withdrawal (p<0.05).

DISCUSSION

In our study, the factors affecting the discharge time of patients who underwent thoracotomy and lung resection were evaluated. The postoperative 24-hour VAS scores had no significant correlation with the discharge time and with chest tube withdrawal time. Chest tube withdrawal time, age, and operation time were associated with prolonged discharge time.

Outpatient surgery and methods that decrease the discharge time have become one of the main topics in all surgical branches. Enhanced recovery after surgery (ERAS) is an increasingly accepted practice and has gained popularity in thoracic surgery as well. ERAS protocols aim to ensure rapid discharge. For this, ERAS protocols try to reduce the complications that may develop in patients by applying less invasive surgical techniques and by providing effective analgesia (15-17). Similarly, chest tube management following thoracic surgery procedures has an important role in rapid discharge (18).

Table 5. The results of univariate and multivariate linear regression analysis applied to determine the factors affecting the discharge days of the patients

Dependent variable : discharge time (day)	Univariate linear regression analyze					Multivariate linear regression analyze				
	Beta	t	p	95,0% CI for B		Beta	t	p	95,0% CI for B	
				Lower	Upper				Lower	Upper
Age (year)	0.219	2.267	0.026	0.010	0.147	0.001	-0.009	0.993	-0.036	0.035
Gender (reference : Woen)	0.250	2.603	0.011	0.535	3.961	0.085	1.739	0.085	-0.105	1.579
BMI kg/m²	-0.165	-1.688	0.095	-0.294	0.024					
Operation Side	-0.172	-1.758	0.082	-2.981	0.179					
Operation Duration (minute)	0.303	3.212	0.002	0.006	0.024	0.058	1.218	0.226	-0.002	0.007
PPCs	0.603	7.643	<0.001	4.025	6.846	0.137	2.498	0.014	0.249	2.181
Extra Pulmonary Complications	0.024	0.242	0.809	-4.202	5.371					
VAS	-0.112	-1.141	0.257	-0.926	0.250					
Chest Tube Removal Time (Day)	0.884	18.946	<0.001	0.748	0.923	0.764	13.566	<0.001	0.617	0.828

β; Standardized Coefficients, R2:0,811, Anova p<0,001, BMI: Body Mass Index, PPCs: Postoperative Pulmonary Complications, VAS: Visual Analog Scale

In the literature, many studies focus on different aspects of postoperative chest tube management in thoracic surgery (18, 19). According to these studies, prolonged chest tube application can prolong the hospital stay and can increase complications. Furthermore, the optimal timing of chest tube withdrawal has been debated for a long time, and many medical centers rely on the volume output threshold to decide the appropriate time for chest tube removal (19). The appropriate thresholds for output volumes have also been analyzed. Some surgeons argue that higher daily volume outputs (450-500 cc) should be used as acceptable thresholds for chest tube removal (20).

After surgery, many patients can be discharged the same day after chest tube withdrawal, however, others may require a longer stay. Furthermore, some factors such as chronic comorbidities, obesity, and smoking history are also important in prolonging the duration of the chest tube. For shortening the chest tube withdrawal time, indirectly the discharge time; a center-based algorithm can be an appropriate approach (18). In this study; the prolonged operation time and the development of PPCs were evaluated as effective factors in the prolonged chest tube withdrawal time, and this was also evaluated as a factor affecting the discharge time.

Effective perioperative analgesia is one of the most important components of ERAS. This situation can be achieved with a comprehensive multimodal perioperative analgesia management in which regional techniques are also applied (14, 15, 17). In our study, there was no correlation between VAS scores and discharge times. Low VAS scores observed in patients in the postoperative period indicate that effective analgesia is achieved for these patients. Since effective analgesia was provided in almost all of the patients, complications that may occur due to pain were not observed. We think that this is the reason why there was no relationship between VAS scores and discharge times in our study.

The duration of the operation, age, and BMI are among the factors that affect the discharge time (18). Studies have shown that the longer the BMI, the longer the discharge time. This can be explained by the increase in PPCs in obese patients. Unlike these results, in our study, no relationship was found between the increase in BMI and the duration of discharge. The absence of morbidly obese patients in the study may explain why BMI was not an effective factor in prolonged discharge time.

The increase in operation time with age may be related to PPCs that may develop (21, 22). Comorbid conditions may also increase with increasing age. Additionally, the prolonged operation time may cause problems in both anesthesia and surgery therefore it may affect the duration of hospitalization. In our study, age and duration of operation prolonged the duration of chest tube withdrawal and therefore the duration of discharge from the hospital. Prolonged time can be limited by preoperative comprehensive evaluation of age-related comorbid conditions and keeping the operation time as short as possible.

There are some limitations to this study. First of all, the study is a single-center and retrospective study. Additionally, long-term complications of the patients after surgery could not be evaluated.

CONCLUSION

While the prolonged chest tube withdrawal time was directly related to the longer discharge time, the VAS scores have no significant correlation with the discharge time and the chest tube removal time. Additionally, age and operation time were also found to be associated with prolonged discharge time. Prospective comprehensive studies on this subject will be useful in clarifying the factors affecting the discharge time after thoracic surgery.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Ankara Training and Research Hospital Ethics Committee (Date: 11.01.2022, Decision No: 2012-KEAK-15/2448).

Informed Consent: All patients were informed about the application and their informed consent was obtained.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article / Özgün Makale

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Büyük veya komplike abdominal hernilerin tedavisinde anterior kompenent seperasyon tekniği etkili mi?

Is the anterior component separation technique effective in the treatment of large or complicated abdominal hernias?

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ÖZ

Amaç: Büyük veya komplike abdominal herniler, popülasyonun yaklaşık %0,5 ila 1'inde görülür. Bu fıtıklar anterior kompenent seperasyon tekniği ile insizyonel fıtıklar dahil olmak üzere komplike abdominal hernilerin onarımı için yaygın olarak kullanılan teknikdir. Bu çalışmanın amacı geniş defektli büyük komplike hernilerin onarımında onlay polipropilen meshli anterior komponent seperasyon tekniğini değerlendirmektir.

Gereç ve Yöntem: Nisan 2018- Nisan 2021 tarihleri arasında Hitit Üniversitesi Genel Cerrahi polikliniğine başvuran komplike abdominal herni tanısı konulup anterior komponent seperasyon tekniğini ile opere edilen hastalar geriye yönelik olarak hastane sisteminden tarandı. 29 hastanın bilgilerine ulaşıldı. Hastalar yaş, cinsiyet, ASA skoru, ek hastalık sayısı, yoğun bakım ihtiyacı, preoperatif ve intraoperatif defekt çapı, postoperatif komplikasyon varlığı, cerrahi alan enfeksiyonu, seroma, cilt nekrozu, yapılan ameliyat, önceki operasyon sayısı ve etiyolojisi, mortalite, hastanede kalış süresi, takip süresi ve nüks açısından değerlendirildi.

Bulgular: Çalışmaya dahil edilen 29 kişinin 13'nün erkek (%44,8), yaş ortalamaları 60,9±12,23 yıl olduğu görüldü. Hastaların 18,1 (%62,1)'i ASA 2 idi. Komplike abdominal herni tanısının en sık nedeni jinekolojik operasyonlar 10 (%34,5) idi. Hastaların biri hariç hepsine anterior komponent seperasyon tekniğini ile opere edildi. Hastaların 4 (%13,8)'ünde yoğun bakım ihtayacı ve 1 (%3,4)'inde mortalite gelişmiştir. Ortalama takip süresi 18,79±7,63 (18) ay idi. Hastanede kalış süresi ortalama 6,76±5,04 gün idi. Postoperatif komplikasyonlardan en sık 3 (%10,3) hastada seroma görüldü. Cerrahi alan enfeksiyonu ise sadece 3 (%10,3) hastada görüldü. Tüm hastaların 25 (%86,2)'ine ölü boşlukları azaltmak için subkutan dokuları mesh üzerine tespit işlemi yapıldı. Hastaların takiplerinde sadece 2 (%6,9) hastada nüks görüldü.

Sonuç: Anterior komponent seperasyon tekniği, büyük insizyonel fıtıkları olan hastalar için güvenli, kolay ve hızlı bir seçenektir. Hastaların ihtiyaçlarına göre kişiselleştirilerek ve bu işlemle ilgili deneyim arttıkça komplikasyon oranı en aza indirilebilir.

Anahtar Kelimeler: Komplike büyük herni, anterior kompenent seperasyon tekniği, nüks, komplikasyon

ABSTRACT

Aim: Large or complicated abdominal hernias occur in approximately 0.5 to 1% of the population. These hernias are commonly used for repair of complicated abdominal hernias , including incisional hernias, with the anterior component separation technique. The aim of this study is to evaluate the anterior component separation technique with onlay polypropylene mesh in the repair of large complicated hernias with large defects.

Material and Method: Patients who were admitted to the General Surgery Outpatient Clinic of Hitit University between April 2018 and April 2021 and were diagnosed with complicated abdominal hernia and operated on with anterior component separation technique were retrospectively scanned from the hospital system. Data of 29 patients were obtained. The patients were age, gender, ASA score, number of additional diseases, need for intensive care, preoperative and intraoperative defect size, presence of postoperative complications, surgical site infection, seroma, skin necrosis, surgery performed, number of previous operations and etiology, mortality, hospitalization. Length of stay, follow-up and recurrence were evaluated.

Results: Thirteen (44.8%) of the 29 people included in the study were male, with a mean age of 60.9±12.23 years. Eighteen (62.1%) of the patients were ASA 2. The most common reason for the diagnosis of complicated abdominal hernia was gynecological operations 10 (34.5%). All but one of the patients were operated with anterior component separation technique. 4 (13.8%) patients required intensive care and 1 (3.4%) mortality developed. The mean follow-up period was 18.79±7.63 (18) months. The mean hospital stay was 6.76±5.04 days. Seroma was the most common postoperative complication in 3 (10.3%) patients. surgical site infection was seen in only 3 (10.3%) patients. In 25 (86.2%) of all patients, subcutaneous tissues were fixed on the mesh to reduce dead spaces. Recurrence was observed in only 2 (6.9%) patients during the follow-up of the patients.

Conclusion: Anterior component separation technique is a safe, easy and fast option for patients with large incisional hernias. Complication rates can be minimized by customizing patients' needs and increasing experience with this procedure.

Keywords: Complicated large hernia, Anterior component separation technique, Recurrence, Complication

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GİRİŞ

Büyük veya komplike abdominal herniler (KAH), popülasyonun yaklaşık %0,5 ila 1'inde görülür. Primer veya daha önce geçirilmiş karın ameliyatlarına (kesi yeri fıtığı) ikincil olabilir. Laparatomi yaralarının %2 ila 11'i insizyonel herniye dönüşür (1). KAH artan bir şekilde hastalarda görülmektedir. Bu tür defektler, çoklu karın operasyonları, karın duvarının cerrahi rezeksiyonu, nekrotizan karın duvarı enfeksiyonları veya terapötik açık karın ile ilişkili insizyon fıtığı nedeniyle ortaya çıkabilir. Büyük veya komplike fıtıklar, kronik sırt ağrısı, solunum yetmezliği ve değişen vücut görüntüsü gibi sorunlarla ilişkili olabilir. Bu defektler veya insizyonel herni ile ilgili semptomları olan hastalar cerrahi onarım yapılmalıdır (2).

KAH, defektin üzerine (onlay) veya defektin altına ve peritonun üstüne (sublay) yerleştirilebilen mesh ile takviye ile birlikte defektin gerilimsiz olarak kapatılmasıyla onarılır. KAH'ler için, primer sütür onarımı genellikle gerilimsiz kapatmaya izin vermek için yeterli değildir. Karın duvarı ilerlemesini sağlamak için bir tekniğin kullanılması, hala fıtık onarımının altın standardı olarak kabul edilmiş olup, karın duvarının bu gerilimsiz mesh takviyeli rekonstrüksiyonuna izin vermek için büyük defektlerde sıklıkla gereklidir (3-5).

Rives-Stoppa tekniği ve anterior kompenent seperasyon tekniği (AKST) (her ikisi de retromusküler mesh yerleştirme ile), insizyonel fıtıklar dahil olmak üzere karmaşık ve büyük ventral fıtıkların onarımı için yaygın olarak kullanılan tekniklerdir. (6-8).

Komponent seperasyon tekniği, kasların innervasyonlarını ve kan akımını kesmeden kas tabakalarının translasyonu ile karın duvarı yüzeyinin genişletilmesine dayalı olarak ortaya çıkmıştır. Bu, posterior rektus kılıfının rektus abdominis kasından ayrılması ve daha sonra rektus abdominis kası ile posterior rektus kılıfı arasındaki ağ ile büyütülmesiyle daha da geliştirildi (9-11). Bu teknikle 25-30 cm'ye kadar defektler belinde köprülenebilir. Bununla birlikte, yara komplikasyonları sıktır. Hematom, seroma ve enfeksiyonların hastaların yarısına kadar olduğu bildirilmektedir (12).

Bu çalışmanın amacı geniş defektli büyük komplike hernilerin onarımında onlay polipropilen meshli anterior komponent seperasyon tekniğini değerlendirmektir.

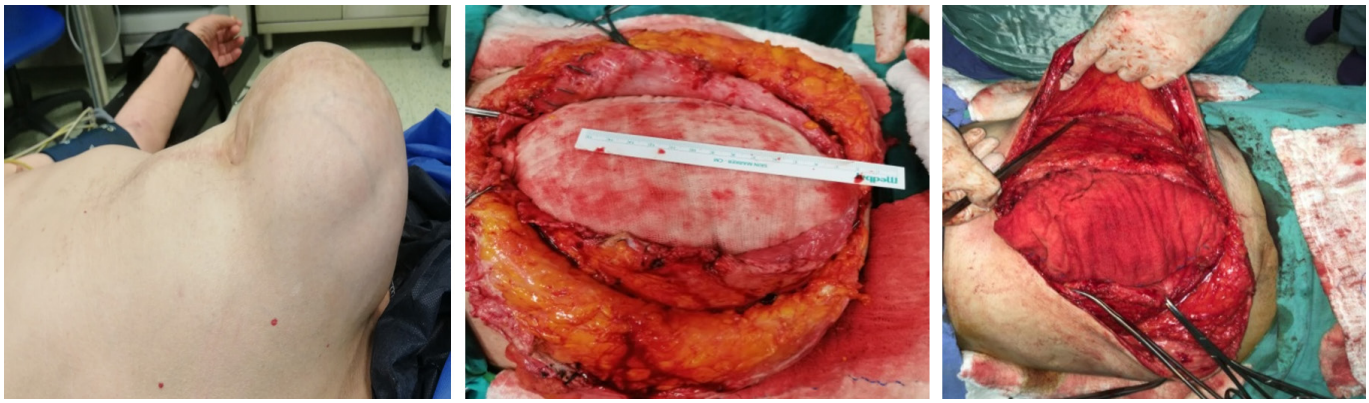
GEREÇ VE YÖNTEM

Bu çalışma için Hitit Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır (Tarih: 30.04.2021, Karar No: 2021-66). Ardından Nisan 2018-Nisan 2021 tarihleri arasında KAH tanısıyla opere edilen hastalar geriye dönük olarak araştırıldı. Tüm işlemler Helsinki Deklarasyonu'nun etik kurul ve ilkelerine göre gerçekleştirilmiştir.

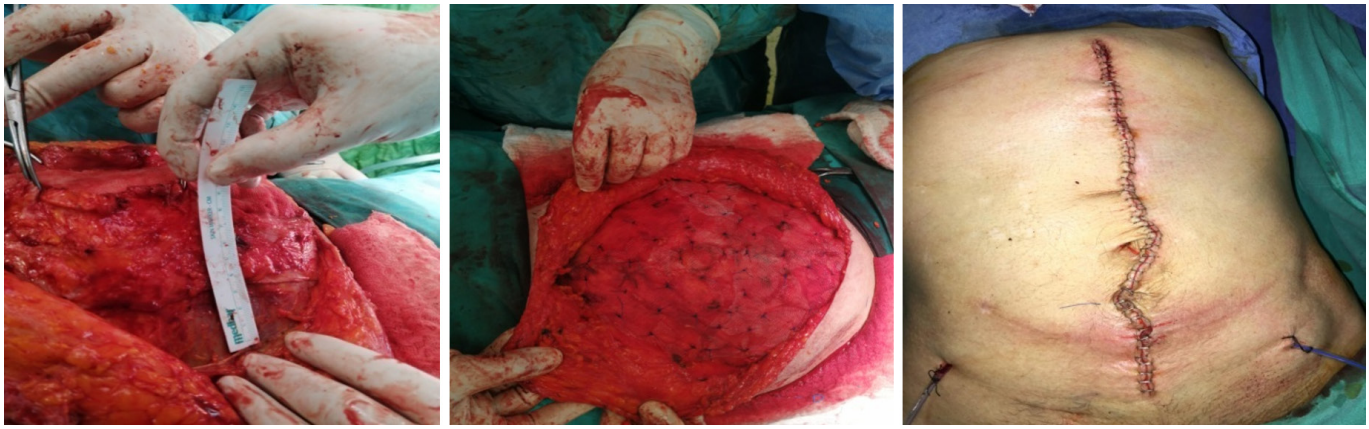
Belirlenen tarihler arasında Hitit Üniversitesi Genel Cerrahi polikliniğine başvuran KAH tanısı konulup AKST ile opere edilen hastalar geriye yönelik olarak hastane sisteminden tarandı. 29 hastanın bilgilerine ulaşıldı. Hastalar yaş, cinsiyet, ASA skoru, ek hastalık sayısı, yoğun bakım ihtiyacı, preoperatif ve intraoperatif defekt çapı, postoperatif komplikasyon varlığı, cerrahi alan enfeksiyonu(CAE), seroma, cilt nekrozu, yapılan ameliyat, önceki operasyon sayısı ve etiyolojisi, mortalite, hastanede kalış süresi, takip süresi ve nüks açısından değerlendirildi. Tüm hastalar aynı genel cerrahi uzmanı tarafından ameliyat edilmiş olup takipleri yine aynı cerrah tarafından yapıldı.

Anterior Kompenent Seperasyon Tekniği

Tüm operasyonlar genel anestezi altında yapıldı. İnsizyon, fıtık yerine, önceki cerrahi skarların varlığına ve apronektomi planlanıp planlanmadığına göre planlandı. Fıtık kesesi diseksiyonu yapıldıktan sonra içeriği azaltılarak açıldı. Defektin genişliği ölçüldü. Daha sonra her iki tarafta linea semilunaris'in ~2-5 cm lateralinde, üstte kosta kenarlarının ve altta simfizis pubisin ~2-5 cm lateraline kadar diseksiyona devam edildi. Ön komponent ayrımı, linea semilunaris'e paralel 1 cm lateralden vertikal bir kesi ile kostal marjdan inguinal bölgeye kadar bir veya her iki tarafta ihtiyaç duyulduğunda uzanan kesiler yapıldı (**Şekil 1-2-3**).



Resim 1-2-3: Anterior Kompenent seperasyon tekniğini (AKST) gerçekleştirmek için ilk cerrahi adım, deriyi ve deri altı dokularını alttaki fasyadan dekole edilmesi. Diseksiyon, kostal kenardan kaudalde pubise ve lateral olarak ön aksiller hatta iliak kreste uzanır (2).



Resim 4-5-6: External oblik kas, altta yatan internal oblik kastan künt olarak diseke edilmesi ve orta hattın kapatılması, Fasya üzerine mesh yerleştirilmesi,apronektomi ve tespit,ciltaltı ve cilt kapatılması (2).

Linea alba'nın sürekli kapatılması, bir veya her iki tarafta dış oblik aponevroz insizyonunda boşluk oluşmasına neden olacak ve gerilimsiz orta hat kapatması sağlayacak olan prolen 1 kullanılarak gerçekleştirildi. Daha sonra, üstteki kostal marjlardan aşağıdaki simfizis pubise uzanan ve gelişen boşlukları ve orta hat fasya kapanmasını kaplayan dış oblik aponevrozun lateral kenarının en az yaklaşık 5 cm ötesine uzanan geniş bir polipropilen ağ onlay yerleştirildi (**Şekil 4-5**). Apronektomi yapılması ve flep mobilizasyonunu en aza indirmek için, meş ile subkutan doku arasında ölü boşlukları azaltmak için önce apronektomi yapıldı sonra 2/0 vicrille tespit suturu yapıldı. Cilt kapatıldı ve her iki taraftan tüp drenler yerleştirildi (**Şekil 6**).

İstatistik Analizi

Sayısal değişkenler olan yaş, preoperatif ve intraoperatif defekt çapı,takip ve yatış süresi ortalama±standart sapma ve parantez içerisinde medyan kullanılarak raporlandı. Sayısal ölçümler arasındaki ilişkiler veri dağılımına uygun olarak Pearson veya Spearman korelasyon katsayısı ile araştırıldı. Kategorik değişkenler olan cinsiyet, ek hastalık sayısı, önceki ameliyat sayısı ve etiyolojisi,yapılan ameliyat, ASA skoru, mortalite ,postoperatif morbidite ve lokal komplikasyon varlığı sayı ve parantez içerisinde yüzde olarak raporlandı. Tüm istatistik analizleri IBM SPSS Statistics for Windows yazılımı kullanılarak yapıldı (versiyon 26; IBM Corp., Armonk, N.Y., USA).

BULGULAR

Çalışmaya dahil edilen 29 kişinin 13'nün erkek (%44,8), yaş ortalamaları 60,9±12,23 yıl olduğu görüldü. Ortanca yaş 62 yıldı. Hastalarda hiç hastalığı olmayan 8 (%27,5) hasta vardı, hastaların 18 (%62,1)'i ASA 2 idi, 1 (%3,4)'i ise ASA 4 idi.

Hastalarda 2 ve daha fazla ameliyat olanların sayısı 17 (58,6) ve KAH tanısının en sık nedeni jinekolojik operasyonlar 10 (%34,5) idi. Preoperatif batın tomografisine göre defekt çapı 11,28±2,58 (11) cm ve intraoperatif defekt çapı 14,06±2,60 (15) cm idi. Hastaların hepsi Anterior Kompenent Seperasyon tekniği (AKST) ile opere edildi. Bu hastalardan sadece 1 (%3,4)'ine kolon rezeksiyonu ve ince barsak rezeksiyonu yapıldığından meshsiz AKST yapıldı (**Tablo 1**).

Tablo 1: Hastaların Demografik bilgileri

Cinsiyet	
Erkek	13 (%44,8)
Kadın	16 (%55,2)
Yaş	60,9±12,23 (62)
ASA	
I	1 (%3,4)
II	18 (%62,1)
III	9 (%31)
IV	1 (%3,4)
Ek hastalık sayısı	
yok	8 (%27,5)
1	11 (%37,9)
2 ve daha fazla	10 (%34,4)
Yoğun bakım ihyiyacı	4 (%13,8)
Preoperatif defekt çapı(cm)	11,28±2,58 (11)
İntraoperatif defekt çapı(cm)	14,06±2,60 (15)
Nüks	2 (%6,9)
Takip (Ay)	18,79±7,63 (18)
Hastanede kalış(gün)	6,76±5,04 (5)
Mortalite	1 (%3,4)
Önceki operasyonlar	
Jinekolojik onkolojik operasyon	10 (%34,5)
Mezenter iskemi	2 (%6,9)
İnsizyonel herni	5 (%17,2)
Kolon kanserine bağlı operasyon	6 (%20,7)
Akut batın operasyonu	2 (%6,9)
Delici kesici alet yaralanmasına bağlı operasyon	3 (%10,3)
Trafik kazası+TRAM flep	1 (%3,4)
Operasyon sayısı	
1 defa operasyon olan	12 (%41,4)
2 ve daha fazla operasyon olanlar	17 (%58,6)
Komplikasyon	
Seroma	3 (%10,3)
Cerrahi alan enfeksiyonu	3 (%10,3)
Hematom	2 (%6,9)
Cillt nekrozu	Yok
Yapılan ameliyat	
AKST meshsiz+ileum+kolon rezeksiyonu	1 (%3,4)
AKST meshli	22 (%75,8)
AKST meshli + ileum rezeksiyonu	4 (%13,8)
AKST meshli+ Kolesistektomi	4 (%13,8)
AKST meshli+ petit herni onarımı	1 (%3,4)
Tespit sutur	25 (%86,2)

Hastaların 4 (%13,8)'ünde yoğun bakım ihtayacı ve 1 (%3,4)'inde mortalite gelişmiştir. Ortalama takip süresi 18,79±7,63 (18) ay idi. Hastanede kalış süresi ortalama 6,76±5,04 gün idi. Postoperatif komplikasyonlardan en sık 3 (%10,3) hastada seroma görüldü. CAE ise sadece 3 (%10,3) hastada görüldü. Tüm hastaların 25 (%86,2)'ine ölü boşlukları azaltmak için subkutan dokuları mesh üzerine tespit işlemi yapıldı. Hastaların takiplerinde sadece 2 (%6,9) hastada nüks görüldü (**Tablo 1**).

TARTIŞMA

Karın duvarı fıtığı onarımı en yaygın cerrahi prosedürlerden biridir. Karmaşık bir karın fıtığının nasıl tamir edileceğine karar vermek zor bir karardır ve ameliyat öncesi karar vermeyi ve risk danışmanlığını yönlendiren kanıta dayalı birkaç kılavuz vardır. Büyük veya komplike fıtıklar, kronik sırt ağrısı, solunum yetmezliği ve değişen vücut görüntüsü gibi sorunlarla ilişkili olabilir. KAH ile ilgili semptomları olan hastalar cerrahi onarım yapılmalıdır. KAH'in nonoperatif tedavisi ile ilgili birkaç küçük randomize olmayan çalışmada, yıllık ortalama acil başvuru insidansı %2,6 (%0-20)'dır (12). Bununla birlikte, nonoperatif tedavi seçen hastalar, yaşam boyu acil duruma girme riskinin yüksek olabileceği konusunda bilgilendirilmelidir. Kompenent seperasyon tekniği, büyük fıtıkların orta hat onarımında gelişmiş miyofasyal mobilizasyona izin veren önemli bir teknik gelişmedir. Bu teknik en sık olarak dış oblik aponevrozun transeksiyonu ile karın ön duvarı diseksiyonunu içerir. İlk olarak Ramirez tarafından 1990 yılında tarif edilen kompenent seperasyon tekniği, büyük veya komplike orta hat karın duvarı defektlerini kapatmada etkili yöntem olduğu görülmüştür (9). Ayrıca bu teknik, komplike insizyonel hernileri yönetmek için kullanılan bir cerrahi teknik olup, mesh kullanılarak veya kullanılmadan karın duvarının şekillendirilebilirliğini artırdığı görülmüştür (13). Bu çalışmada bir hastaya meshsiz AKST uygulanmış ve diğer hastaların hepsine meshli AKŞT uygulanmıştır.

Kesi fıtıkları genişlemeye eğilimlidir (14,15). Büyüdükçe şikayetler ve fiziksel yetersizlikler artar, onarımları zorlaşır ve ameliyat sonrası morbidite ve mortalite riskleri artar. Fıtık defekti boyutunun postoperatif komplikasyon risklerini öngörmede büyük önem taşıdığı gösterilmiştir (16). Büyük ve dev kesi fıtığı olan hastalar genellikle obezite, diabetes mellitus ve kardiyorespiratuvar problemler gibi eşlik eden komorbiditeler gösterirler. Bu çalışmada ek hastalık sayısı 11 (%37,9) hastada bir hastalık 10 hastada 10 (%34,4) hastalık olup ağırlıklı olarak hipertansiyon, DM ve KOAH mevcuttu. Postoperatif yoğun bakım ihtiyacı 4 (%13,8) hastada olmuştur, mortalite ise sadece 1 (%3,4) hastada gelişti. Preoperatif ASA 4 olan hasta postoperatif 5. günde pulmoner emboli tanısıyla eksitus oldu. Bu hastanın ameliyata bağlı komplikasyonlardan ziyade mevcut ko-morbiditeye bağlı eksitus olduğunu düşünmekteyiz. Fıtık defektleri ve hacimleri uç noktalarda olmasına rağmen hastalarımızda herhangi bir solunum yetmezliği veya abdominal kompartman sendromu yaşanmadı. Kesicioğlu ve ark. (17) yaptığı çalışmada mortalite %2,5 olarak bulmuşlar. Başka bir çalışmada ise mortalite %1,2 olarak bulmuşlar (18). Çalışmamız literatürle uyumlu olup mortalitenin hafif yüksek olması vaka sayısının az olmasına bağlamaktayız.

Bu çalışmada obstetrik cerrahi 10 (%34,5) ve kolon kanseri için laparotomi 6 (%20,7) herniasyonun yaygın nedenleriydi. Trehan ve ark. (13) yaptığı çalışmada benzer sonuçlar bulunmuştur. Samir ve ark. (19) tarafından yapılan çalışmada, muhtemelen tamamen farklı popülasyon nedeniyle, tekrarlayan ventral herni karın duvarı onarımı için en yaygın (%45) endikasyondu.

Yara komplikasyonları, AKST'de fıtık onarımının yüzde 0 ila 50 arasında değişen en yaygın komplikasyonudur. Obez hastalarda daha yüksek enfeksiyon oranları görülmektedir (20,21). Bir çalışmanın geniş serilerinde AKST' den sonra %42,9' luk bir yara komplikasyonu bildirmişlerdir (22). Van Geffen ve ark. (11) 95 hastanın 23 (%24)'ünde hematom/seroma oluşumunu bildirirken, Samir ve ark. (19) hematom insidansını %6,3 ve seroma insidansını %37,5 olarak bulmuşlardır. Bu çalışmada yara komplikasyonları toplam 8 (%27,5) idi. Bunlardan 3 (%10,3)'ünde CAE, 3 (%10,3)'ünde seroma ve 2 (%6,9)'sinde hematom görüldü. Cilt nekrozu hiç gelişmedi. Seromanın ve enfeksiyonun literatüre göre az olmasını aprenektomiye ve ölü boşluk oluşturan alanlara mesh ile subkutan arasına tespit suturu konmasına bağlamaktayız. Ama yine bunu geniş serili randomize prospektif çalışmalarla da desteklenmesi gerektiğini düşünmekteyiz.

AKST sonrası nüks oranlarının %7'den %32'ye kadar geniş bir aralıkta olduğu bildirilmektedir (20,21,23,24). Bu çalışmada ortalama takip süresi 18,79±7,63 ay idi. Sadece 2 (%6,9) hastada nüks görüldü. Bunlardan biri meshsiz yapılan AKST hastasıydı. Hastaya mesh konulmamasının nedeni hem ince barsak rezeksiyonu hem de kolostomi acılması idi. Van Geffen ve ark. (11) hastalarının 15 (%15,7)'inde nüks görmüşlerdir. Sailes ve ark. (25) 10 yıllık bir süre içinde %18,5'lik bir nüks oranı bildirmişler, Hultman ve ark. (26) ortalama 4,4 yıllık bir takipte %19,8'lik bir oran bildirmişlerdir. Başka bir çalışmada ise Ortalama 50 aylık takip süresinde 5 (%5,5) hastada fıtık nüksü gözlenmiştir (27). Çalışmamızda nüks oranları literatüre göre düşük olduğu görülmüştür. Bunu mesh kullanılmasına ve takip sürelerinin kısa olmasına bağlamaktayız.Tekrarlama oranlarını azalttığı gösterildiğinden operasyonların biri haricinde hepsine meshli AKST uygulandı (28,29).

Bu çalışmanın sınırlamaları; bizim görüşümüze göre, bu çalışma AKST kullanılarak KAH onarımı yapılan hastaların retrospektif ve kapsamlı bir incelemesini sağlar ve tüm hastaların tedavi ve takibi ileriye dönük olarak gerçekleştirilmiştir ve hastanemiz veri tabanına kaydedilmiştir. Hasta sayısının az olması, takip süresinin uzun olmaması ve kompenent seperasyon tekniği uygulanmayan diğer yöntemler kullanılarak büyük fıtıklarla karşılaştırmalı çalışma olmaması çalışmamızı kısıtlamıştır.

SONUÇ

AKST, büyük insizyonel fıtıkları olan hastalar için güvenli, kolay ve hızlı bir seçenektir. Hastaların ihtiyaçlarına göre kişiselleştirilerek ve bu işlemle ilgili deneyim arttıkça komplikasyon oranı en aza indirilebilir. Ayrıca büyük boyutlu fıtıkları yönetmek için kullanılan bu yöntemin, mesh kullanılarak karın duvarının şekillendirilebilirliğini arttırdığı ve kozmetik olarak iyi sonuçlar vermenin yanı sıra karın içi basıncını koruyabildiğini düşünmekteyiz.

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Comparison of lung involvement related to COVID-19 infection in patients using sulfasalazine and biological agents diagnosed with ankylosing spondylitis

Ankilozan spondilit tanılı sulfasalazin ve biyolojik ajan kullanan hastaların COVID-19 enfeksiyonuna bağlı akciğer tutulumlarının karşılaştırılması

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ABSTRACT

Objectives: The aim of this study is to examine the lung involvement caused by the SARS CoV-2 factor in patients diagnosed with ankylosing spondylitis using sulfasalazine and biological drugs.

Material and Method: File systems of patients with RT-PCR positive AS diagnosis who have undergone COVID-19 were retrospectively reviewed. Patients with a diagnosis of AS were divided into two groups as those using sulfasalazine and biological agents. Thoracic computed tomography (CT) results of the patients were divided into mild, moderate, severe, bilateral or unilateral. The data were also compared between the patient and control groups.

Results: Of the 58 patients included in the study, 26 were receiving biological agent and 32 were receiving sulfsalazine. Of the patients using DMARD, 17 were receiving adalimumab, 4 etanercept, 2 golimumab, 2 certolizumab, and 1 patient infliximab. Thirteen patients in the AS group had lung involvement due to SARS CoV-2 on thorax computed tomography. It was seen that patients, 9 men and 4 women, were hospitalized due to COVID-19. In 10 patients, involvement due to COVID-19 was found in both lungs.

Conclusion: It is not yet known whether immunomodulatory treatments used in autoimmune and inflammatory rheumatic diseases will affect the course of COVID-19 positively or negatively. In this study, COVID-19 progressed with mild symptoms in patients diagnosed with AS using sulfasalazine and biological agents.

Keywords: Ankylosing spondylitis, COVID-19, sulfasalazine, DMARDs

ÖZ

Amaç: Bu çalışmanın amacı, ankilozan spondilit tanılı sülfasalazin ve biyolojik ilaç kullanan hastalarda SARS CoV-2 faktörünün neden olduğu akciğer tutulumunu incelemek.

Gereç ve Yöntem: COVID-19 geçirmiş RT-PCR pozitif AS tanısı olan ve en az bir yıldır hastanemizde takibi olan hastaların dosya sistemleri retrospektif olarak gözden geçirildi. AS tanısı alan hastalar sülfasalazin ve biyolojik ajan kullananlar olarak iki gruba ayrıldı. Hastaların toraks bilgisayarlı tomografi (BT) sonuçları hafif, orta, şiddetli, iki taraflı ve tek taraflı olarak ayrıldı. Veriler ayrıca hasta ve kontrol grupları arasında karşılaştırıldı.

Bulgular: Çalışmaya alınan 58 hastanın 26'sı biyolojik ajan, 32'si sülfasalazin alıyordu. DMARD kullanan hastalardan 17'si adalimumab, 4'ü etanercept, 2'si golimumab, 2'si sertolizumab ve 1'i infliximab kullanıyordu. AS grubundaki 13 hastada toraks bilgisayarlı tomografisinde SARS CoV-2 nedeniyle akciğer tutulumu vardı. 9'u erkek, 4'ü kadın olan hastaların COVID-19 nedeniyle hastaneye yatırıldığı görüldü. 10 hastada her iki akciğerde de COVID-19'a bağlı tutulum saptandı.

Sonuç: otoimmün ve inflamatuar romatizmal hastalıklarda kullanılan immünomodülatör tedavilerin COVID-19 seyrini olumlu ya da olumsuz etkileyeceği henüz bilinmemektedir. Bizim çalışmamızda sulfasalazin ve biyolojik ajan kullanan AS tanılı hastalarda COVID-19 hafif semptomlarla seyretmiştir.

Anahtar Kelimeler: Ankilozan spondilit, COVID-19, sulfasalazin, DMARDs

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INTRODUCTION

In the epidemic that occurred in Wuhan, China in December 2019, pneumonia developed due to the newly defined SARS CoV-2 factor was defined as Coronavirus disease 2019 (COVID-19) (1). The World Health Organization, the disease in many countries to spread, and many due to lead to the death of people on March 11, 2020 COVIDien-19 has been declared a pandemic on the same date in Turkey have also been reported by the health ministry first COVIDien-19 cases (2,3). The disease-causing SARS CoV-2 is an enveloped RNA virus from the corona virus family. Although it has been shown that the infection is mainly transmitted by droplets and by touching the mucous membranes of the mouth, nose or eyes of the sick people who have touched the floors contaminated with the droplets they emit, the virus has also been found in whole blood, serum, urine and fecal samples (1). The incubation time for virus after exposure is thought to be 2-14 days, and most cases have been found to be symptomatic about 4 to 5 days after exposure. SARS CoV-2 attaches to angiotensin converting enzyme II (ACE2) via the receptor-binding region (RBB) of spike proteins and initiates membrane fusion and thus reaches host cells in humans (4). Clinical findings mostly include gastrointestinal symptoms such as fatigue, fever, cough, myalgia, shortness of breath, nasal congestion, headache, runny nose, sore throat, vomiting and diarrhea (5). The gold standard in the diagnosis of SARS CoV-2 is to show the presence of viral RNA in appropriate clinical samples by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) (6). The World Health Organization (WHO) recommends taking nasopharyngeal and oropharyngeal swab or washing samples together in possible cases, since the virus has more replication in the upper respiratory tract. Identification of COVID-19 infected people who do not have a definitive treatment and vaccine, laboratory diagnosis, treatment, isolation and patient management, including contact surveillance, slowing the spread of the virus, determining infection control strategies and slowing down the pandemic are of great importance (7). Among the causes that negatively affect the course of COVID-19, advanced age, male gender, diabetes mellitus, hypertension and coronary artery disease are among the most common causes (8). Although it is known that inflammatory rheumatic diseases with a rate of 2-3.5% increase the risk of infection, especially in the respiratory system, due to both the relationship with the immune system and the drugs used in their treatment, the course of COVID-19 in individuals with rheumatological diseases has not been clearly determined (9,10). The existence of publications and suggestions supporting the use of some immunomodulators and biological treatments used in the treatment of rheumatological patients in COVID-19 indicates that more studies should be done on these patients (11).

In this study, we aimed to compare the pulmonary involvement of patients with ankylosing spondylitis (AS) diagnosed with sulfasalazine and biological drugs from the inflammatory type rheumatic disease group with COVID-19 individuals who do not have any additional disease.

MATERIAL AND METHOD

This study was approved by Hitit University Clinical Research Ethics Committee (Date: 10.03.2021, Decision No:422). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The file systems of patients who applied to our hospital between March 2020 and December 2020 and had a diagnosis of RT-PCR positive AS with COVID-19 and had been followed up in our hospital for at least one year were retrospectively reviewed. Permission was obtained from the chief physician of our hospital to enter the hospital automation system. Patients' age, gender, height, weight, additional disease history, medication used for AS, medications used for COVID-19, hospitalization history, thorax tomography results taken in COVID-19 and medical treatments were recorded. In addition, all patients were called by phone and questioned whether they continued their AS treatment before COVID-19 and whether there was postCOVID-19 AS disease activation. Patients with a diagnosis of AS were divided into two groups as those using sulfasalazine and biological agents. Thoracic computed tomography (CT) results of the patients were divided into mild, moderate, severe, bilateral or unilateral. Patients without thoracic CT were not included in the study. The data obtained were compared between both groups. In addition, a control group consisting of 27 age- and gender-matched persons who applied to our hospital on the same date using the hospital automation system, had no chronic disease, had undergone COVID-19, had RT-PCR positive and thorax CT was formed by random assignment method. The data were also compared between the patient and control groups.

Statistical Analysis

Statistical analyzes were made using a package program called SPSS (IBM SPSS Statistics 24). Frequency tables and descriptive statistics were used in the interpretation of the findings. Nonparametric methods were used for measurement values that are not suitable for normal distribution. In accordance with non-parametric methods, the "Kruskal-Wallis H" test (χ2-table value) method was used to compare the measurement values of three or more independent groups. The expected Pearson-χ2 cross tables were used to examine the relationships between two qualitative variables. Binary Logistic Regression: Backward LR model was used to determine risk factors.

RESULTS

Among the patients who had COVID-19, who applied to our hospital between March 2020 and December 2020, 109 patients with a diagnosis of AS were reached. 39 patients were excluded from the study because they did not use any medication for AS and they did not have thorax CT, and 12 patients only used nonsteroidal anti-inflammatory drugs.

Of the 58 patients included in the study, 26 were receiving biological agent and 32 were receiving sulfsalazine. In the group receiving sulfasalazine, 5 patients were taking acemetacin, 2 patients indomethacin, and 3 patients diclofenac sodium, in addition to the treatment. Seventeen patients using DMARD were receiving adalimumab, 4 etanercept, 2 golimumab, 2 certolizumab, and 1 patient infliximab.

It was determined that the mean age of the sulfasalazine group was 44.25±11.21 (years) and the mean BMI was 24.36±3.02 (kg / m²). It was determined that the mean age of the biological agent group was 43.69±11.68 (year) and the mean BMI was 25.00±3.61 (kg / m²).

In terms of comorbidity, the group receiving sulfasalazine included 3 patients with hypertension (HT), 2 patients with diabetes mellitus (DM), 3 patients with familial Mediterranean fever (FMF), 1 patient with Behçet's disease, 2 patients with hypothyroidism, 1 patient with asthma and 1 patient with thyroid papillary cancer.

It was observed that 2 of the 58 patients in the AS group died. One of these patients was in the group receiving sulfasalazine and the other was in the group using biological agents (adalimumab). Both patients were male and the patient who used sulfasalazine had a diagnosis of HT and DM as an additional disease, and the patient who used adalimumab had a diagnosis of DM (**Table 1**).

Thirteen patients in the AS group had lung involvement due to SARS CoV-2 on chest CT. It was seen that patients, 9 men and 4 women, were hospitalized due to COVID-19. Involvement due to COVID-19 was found in both lungs in 10 patients (**Table 2**). Tomography involvements of the patients are shown in **Table 2**.

There was no statistically significant difference between the groups in terms of age, gender, BMI classes, lung involvement and treatment type (p> 0.05). The groups were determined to be homogeneous and independent from each other in terms of the specified characteristics (**Table 3**).

The optimal model is given in **Table 4** as a result of the Backward LR logistic regression analysis made on the basis of the involvement risk using predictive parameters that may have all effects. In the current model; Age (years) was found to be a significant factor affecting the risk of involvement (p <0.05). When age (year) increases by 1 unit, the risk of involvement will increase by 9.1%.

Table 1: Demographic data of patients diagnosed with ankylosing spondylitis with COVID-19 infection

	AS group using sulfasalazine (n=32)	AS group using biological agents (n=26)
Age (years)	44.25±11.21	43.69±11.68
BMI		
Normal	21 (65.6%)	16 (61.5%)
Overweight	10 (31.3%)	7 (26.9%)
Obese	1 (3.1%)	3 (11.6%)
Treatments taken with sulfasalazine		
Acemetacine	5	-
Indomethacin	2	-
Diclofenac sodium	3	-
Biological agent		
Adalimumab		17
Etanercept		4
Golimumab		2
Infliximab		1
Certolizumab		2
Comorbidity		
HT	3	3
DM	2	3
FMF	3	2
Behçet Disease	2	-
Thyroid papillary cancer	1	-
Hypothyroidism	2	2
Asthma	1	
Number of patients who died	1 (Male patient)	1 (Male patient)
Those who stopped AS treatment before COVID-19	-	1 (adalimumab)
PostCOVID AS activation	-	1

HT: Hypertension DM: Diabetes mellitus FMF: Familial Mediterranean Fever

Table 2: History of pulmonary involvement and hospitalization of Ankylosing Spondylitis patients

	n	%
Lung Involvement		
No	45	77.6
Unilateral mild involvement	3	5.2
Bilateral mild involvement	2	3.4
Bilateral middle involvement	4	6.9
Double sided heavy involvement	4	6.9
	Female (n=24)	**Male (n=34)**
No	n.%	n.%
Unilateral mild involvement	20 (83.4%)	25 (73.5%)
Bilateral mild involvement	-	2 (5.9%)
Bilateral middle involvement	2 (8.3%)	1 (2.9%)
Double sided heavy involvement	2 (8.3%)	2 (5.9%)
	-	4 (11.8%)
Home isolation	45	77.6

Hospitalization	13	22.4	

Table 3: Examining the relationships between groups and parameters

	AS group using sulfasalazine (n=32)	AS group using biological agents (n=26)	Control group (n=27)	Statistical analysis* Possibility
Age (years)				
≤40	14 (43.8%)	11 (42.3%)	11 (40.7%)	χ^2=2.553
>40	18 (56.2%)	15 (57.7%)	16 (59.3%)	p=0.862
Sex				
Female	17 (53.1%)	7 (26.9%)	11 (40.7%)	χ^2=4.069
Male	15 (46.9%)	19 (73.1%)	16 (59.3%)	p=0.131
BMI (kg/m²)				
Normal	21 (65.6%)	16 (61.5%)	10 (37.0%)	χ2=6.316
Overweight	10 (31.3%)	7 (26.9%)	15 (55.6%)	p=0.120
Obese	1 (3.1%)	3 (11.6%)	2 (7.4%)	
Thoracic Involvement				
Yes	27 (84.4%)	18 (69.2%)	18 (66.7%)	χ^2=2.860
No	5 (15.6%)	8 (30.8%)	9 (33.3%)	p=0.239
Treatment				
Home isolation	25 (78.1%)	20 (76.9%)	20 (74.1%)	χ^2=0.138
Hospitalization	7 (21.9%)	6 (23.1%)	7 (25.9%)	p=0.933
Hospital stay (days)	11.6	12.8	13.7	χ2=0.168 p=0.853

*χ^2cross tables were used to examine the relationship between two qualitative variables.

Table 4: Logistic Regression model established on the basis of lung involvement risk status

Variable	B	S.H.	Wald	sd	p	OR	95% Confidence Interval (OR)	
Group-Control*			1.849	2	0.397			
Sulfasalazine	-0.982	0.857	1.313	1	0.252	0.375	0.070	2.009
Biological agents	0.057	0.799	0.005	1	0.943	1.059	0.221	5.065
Age	0.087	0.031	7.869	1	0.005	1.091	1.026	1.159
Sex A	-0.352	0.738	0.228	1	0.633	0.703	0.166	2.985
BMI (kg/m²)	0.125	0.098	1.644	1	0.200	1.133	0.936	1.372
Constant	-8.779	3.079	8.132	1	0.004	0.000		

* Reference category + A: Male, B: No, CCR=83,5%χ2 (8)=10,427; p=0,166

DISCUSSION

AS is an inflammatory rheumatic disease and is included in the spondyloarthropathy (SpA) group with similar clinical, radiological, epidemiological and genetic characteristics. While inflammatory back pain, axial skeleton, enthesal and peripheral joint involvement is predominant, lung involvement is rare and apical fibrosis is the most common pulmonary finding (12,13).

Sulfasalazine and anti TNF-α inhibitors (infliximab, etanercept, adalimumab, certolizumab, golimumab) used in the treatment of ankylosing spondylitis are disease modifying drugs (DMARDs), and anti TNF-α inhibitors are the most commonly used biological agents (14,15).

SARS-CoV-2, the agent of COVID-19, first appeared in Wuhan, China and caused pneumonia epidemic worldwide.1 Since inflammatory rheumatic diseases are at high risk for many infectious diseases, including viral infections, SARS-CoV-2 infection has become a concern for these diseases (16).

Due to the fact that SARS-CoV-2 is a new and recently identified virus, information about the risk and clinical course of individuals with inflammatory rheumatic diseases is still insufficient (8,17).

In COVID-19, male gender, diabetes mellitus, hypertension and coronary artery disease are among the most common causes that negatively affect the clinical course (18). In our study, 9 out of 13 patients with pulmonary involvement were men. While severe lung involvement was not detected in female patients, severe lung involvement was found in 4 male patients. In addition, the fact that 2 patients who lost their lives are men, and a history of hypertension and diabetes mellitus support the studies.

In the telephone questionnaire study conducted by Emmi et al. (19) on 458 patients with rheumatological disease, it was reported that 40 patients were diagnosed with spondyloarthropathy and 41% of the patients had a history of using biological drugs. In 7 of 13 patients with suspected COVID-19, the swab test was found to be positive. Symptoms requiring hospitalization were encountered in only one patient with a diagnosis of COVID-19. In general, the prevalence of SARS-CoV-2 infection among patients with systemic autoimmune diseases was reported to be 0.22%, and this rate was reported to be similar to the general population prevalence (0.20%) in the same region. In another study, it was reported that 43% of 320 chronic arthritis cases who received DMARD treatment had spondyloarthropathy, spondyloarthropathy was detected in only one of 4 patients diagnosed with COVID-19, and one was hospitalized. In addition, it was found that none of the 700 patients admitted to the hospital with a diagnosis of severe COVID-19 on the same date did not receive DMARDs (20). In another cohort study conducted by Favelli et al. (21), it was observed that 36.8% of 530 patients with a history of inflammatory disease followed up due to COVID-19 had spondyloarthropathy, and 2 patients, one using infliximab and the other using secukinumab, died with the diagnosis of COVID-19. In this study, it was reported that most individuals with inflammatory diseases had COVID-19 asymptomatic.

There are case reports in the literature reporting that patients who used etanercept and golimumab for the diagnosis of AS had a mild course of COVID-19 (22-24). In our study, there were 4 patients using etanercept and 2

golimumab. A patient using etanercept was hospitalized, but lung involvement was found to be mild.

Studies show that the course of COVID-19 in individuals with inflammatory diseases is similar to the general population. In our study, it was observed that most of the AS cases had a mild course of COVID-19 and were followed up on an outpatient basis. Approximately 22.4% of our patients needed hospitalization. The mortality rate in this patient group was 3.4%. Pulmonary involvement was not found to be more severe than the general patient population. The duration of treatment in the hospital was similar to the control group.

Another important issue in patients with inflammatory rheumatic disease is the decision of whether or not the biological therapy of the patients should be stopped. Considering the data to date, pre-discontinuation of biological therapy is not recommended in patients without signs of SARS-CoV-2 infection (25,26). In patients with a definite diagnosis or a history of SARS-CoV-2 contact, stopping immunosuppressant therapy should be considered (27,28). In our study, it was found that the treatment of a patient using adalimumab before COVID-19 was stopped by the doctor and the same patient had an exacerbation after COVID-19.

CONCLUSION

As a result, it is not yet known whether immunomodulatory treatments used in autoimmune and inflammatory rheumatic diseases will affect the course of COVID-19 positively or negatively. In our study, COVID-19 progressed with mild symptoms in patients diagnosed with AS using sulfasalazine and biological agents.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Hitit University Clinical Research Ethics Committee (Date:10.03.2021, Decision No:422).

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

Referee Evaluation Process: Externally peer-reviewed.

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Bir eğitim araştırma hastanesinde diyabetik ayak doku biyopsi enfeksiyonlarının dört yıllık değerlendirilmesi

Four-year evaluation of diabetic foot tissue biopsy infections in a training and research hospital

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ÖZ

Amaç: Bu çalışmada bölgemizde en sık görülen diyabetik ayak enfeksiyonu (DAE) etkenlerinin ve antibiyotik direnç oranlarının belirlenmesi, ayrıca DAE tedavi etkinliğinin artırılması hedeflenmiştir.

Gereç ve Yöntem: Retrospektif olarak yapılan çalışmada 2018-2021 tarihleri arasında Wagner sınıflamasına göre evre 2 ve üzeri, 240 diyabetik ayak enfeksiyonu tanılı hastanın diyabetik ayak biyopsi örneklerinden izole edilen 442 bakteri ve maya dâhil edildi. Örneklerin kültürü için %5 koyun kanlı agar, eosin methylen blue agar, çikolata agar ve saboraund dextroz agar besiyerleri kullanıldı. Etkenlerin konvansiyonel metotlar ve VITEK®-2 (BioMérieux, Fransa) otomatize identifikasyon cihazı kullanılarak identifikasyonları ve antibiyotik duyarlılık testleri yapıldı.

Bulgular: Hastalardan izole edilen 442 mikroorganizma değerlendirildi. Hasta başına ortalama 1,8 patojen düşmekteydi. İzole edilen mikroorganizmalar sırasıyla; 397 Gram-negatif bakteri, 38 izolat Gram-pozitif bakteri, 7 izolat ise maya idi. En sık izole edilen Gram-negatif bakteri; *Pseudomonas aeruginosa* (%39,6), en sık izole izole edilen Gram-pozitif bakteri ise; *Staphylococcus aureus* (%3,6) idi. En etkili antibiyotikler ve duyarlılıkları sırasıyla; fosfomisin (%96,2), tigesiklin (%92,3), eritromisin (%77,4), sefotaksim (%74,7), kolistin (%73,8), sefoksitin (%69,4) ve fusidik asit (%68,8) olarak tespit edilmiştir.

Sonuç: Çalışmamız sonucunda DAE'ndan en sık izole edilen *P. aeruginosa* ve diğer Gram-negatif bakterilerin saptanmış olması ampirik tedavinin belirlenmesine katkı sağlanacaktır. Ülkemizin DAE patojen dağılımlarının ve antibiyotik dirençlerinin belirlenmesine de katkısı olacaktır. Ayrıca kültür ve antibiyogram sonuçları rehberliğinde tedavi protokollerinin daha etkili olması ve antibiyotik direnç gelişimi azaltılacaktır.

Anahtar Kelimeler: Diyabetik ayak enfeksiyonu, doku biyopsisi, antimikrobiyal duyarlılık

ABSTRACT

Aim: In this study, it was aimed to determine the most common diabetic foot infection (DFI) agents and antibiotic resistance rates in our geographical region, and to increase the effectiveness of DFI treatment.

Material and Method: In the retrospective study, 442 bacteria and yeasts isolated from diabetic foot biopsy specimens of 240 diabetic foot infection patients with stage 2 and above according to the Wagner classification between 2018-2021 were included. For the culture of the samples, 5% sheep blood agar, eosin methylene blue agar, chocolate agar and saborund dextrose agar media were used. Identification of the agents and antibiotic susceptibility tests were performed using conventional methods and VITEK®-2 (BioMérieux, France) automated identification device.

Results: 442 microorganisms isolated from the patients were evaluated. There was an average of 1.8 pathogens per patient. The isolated microorganisms are respectively; 397 Gram-negative bacteria, 38 Gram-positive bacteria and 7 isolates were yeast. The most frequently isolated Gram-negative bacteria; *Pseudomonas aeruginosa* (39.6%), the most frequently isolated Gram-positive bacteria; *Staphylococcus aureus* (3.6%). The most effective antibiotics and their susceptibilities are respectively; fosfomycin (96.2%), tigecycline (92.3%), erythromycin (77.4%), cefotaxime (74.7%), colistin (73.8%), cefoxitin (69.4%), and fusidic acid (68.8%) was determined.

Conclusion: As a result of our study, the detection of *P. aeruginosa* and other Gram-negative bacteria, which are the most frequently isolated from DFI, will contribute to the determination of empirical treatment. It will also contribute to the determination of pathogen distributions and antibiotic resistance in DFI in our country. In addition, under the guidance of culture and antibiogram results, more effective treatment protocols and antibiotic resistance development will be reduced.

Keywords: Diabetic foot infection, tissue biopsy, antimicrobial susceptibility

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GİRİŞ

Diyabet hastalarında mikrovasküler dolaşım bozukluğu, immün cevap yetersizliği, anatomik deformasyon ve nöropati gibi sebeplere bağlı diyabetik ayak enfeksiyonu gelişme riski, diyabetik olmayan insanlara kıyasla yüksek bir orana sahiptir. Diyabetik ayak ülseri (DAÜ) diabetes mellitusun ciddi komplikasyonlarından biridir ve hastaların %12-25'inde yaşamlarının herhangi bir döneminde gelişme riski vardır. Yara formasyonu bakteri çoğalması için uygun bir alandır ve enfeksiyon yaranın iyileşmesini olumsuz etkiler. Bu yüzden, yara enfeksiyonu nedenlerini tanımlamak, yaranın tedavi yönetiminde önemlidir (1,2). DAÜ'lerinin %15-20'inde ampütasyon yapılmakta ve ampütasyonların yarısından fazlasının enfeksiyon sonucu olduğu bildirilmektedir.

Diyabetik ayak enfeksiyonlarının (DAE) seyrini belirleyen majör faktörlerden birisi de, çoklu ilaç dirençli (ÇİD) etkenlerinin varlığıdır (3). DAÜ'nin yüzeyel ve hafif enfeksiyonlarında çoğunlukla Gram-pozitif bakteriler etkenken, ileri evre enfeksiyonlarda Gram-negatif bakteriler daha sık görülmektedir. Ek olarak kangren görülen enfeksiyonlarda anaerop bakteriler düşünülmelidir. İlerlemiş enfeksiyonlarda Gram-pozitif, Gram-negatif ve anaerop bakterilerin birlikte olduğu polimikrobiyal etkenler görülebilir (4,5).

Avrupa ve Asya'nın kavşağında bulunan Türkiye, büyük ve artan bir nüfusa sahiptir; 2010 yılı tahminlerine göre diyabetli yaklaşık 3,6 milyon hastanın olduğu ve bu sayının 2030 yılına kadar iki katına çıkacağı bildirilmektedir (4). Yeni yapılan araştırmalarda, DAE'de üretilen patojenlerin coğrafi bölgelere göre değişiklik gösterdiği bildirilmektedir. Ülkemizin de içinde bulunduğu ılıman iklime sahip coğrafyalarda Gram-negatif bakterilerin özellikle *Pseudomonas aeruginosa*'nın sık izole edildiği, Avrupa ve Kuzey Amerika'da ise Gram-pozitif bakteriler, özellikle metisiline dirençli *Staphylococcus aureus* dikkat çekmektedir (6,7). Mikrobiyal patojenlerdeki bu farklılıkların tanımlanması ve DAE üzerindeki etkilerinin anlaşılması, etkin bir tedavi uygulama imkanı vermiştir. Sonuç olarak çalışmalar, kültür rehberliğinde parenteral ve oral antibiyotik tedavinin, DAÜ veya şüpheli osteomiyelit ile başvuran diyabetli hastaların büyük bir kısmında ampütasyonları başarılı bir şekilde önlediğini göstermiştir (8). Bu çalışmada coğrafi bölgemizde en sık görülen diyabetik ayak enfeksiyonu etkenlerinin ve antibiyotik direnç oranlarının belirlenmesi, ayrıca DAE tedavi etkinliğinin artırılması hedeflenmiştir.

GEREÇ VE YÖNTEM

Bu çalışma için Hitit Üniversitesi Girişimsel Olmayan Araştırmalar Etik Kurulu'ndan onay alınarak (Tarih: 02.12.2021, Karar No: 2021-306), Helsinki Bildirgesine uygun olarak yapılmıştır. Çalışmamıza 2018-2021 tarihleri arasında Wagner sınıflamasına göre evre 2 ve üzeri, 240 diyabetik ayak enfeksiyonu tanılı hastanın tıbbi mikrobiyoloji laboratuvarına gönderilen diyabetik ayak biyopsi örneklerinden izole edilen 442 bakteri ve maya suşları dâhil edildi. Tüm veriler hastane otomasyon sisteminden alınarak retrospektif olarak değerlendirildi. Laboratuvarımızda anaerop kültür yapılmadığı için anaerop bakteriler çalışmaya dahil edilmedi. Biyopsi örnekleri, mikroorganizmaları ortaya çıkarmak ve homojenizasyonu sağlamak amacıyla bisturi ile kesilerek steril şartlarda ezildi ve kültür için işlenmiş doku haline getirildi. Daha sonra %5 koyun kanlı agar, eosin methylen blue agar, çikolata agar ve saboraund dextroz agar besiyerlerine ekildi. 37°C'de 18-24 saat inkübasyon sonunda etkenlerin identifikasyonu amacıyla konvansiyonel metodlar (Gram boya, katalaz, oksidaz, koagülaz, IMVIC, PYR, Strep grup testleri) ve VITEK®-2 (BioMérieux, Fransa) otomatize identifikasyon cihazı ile tür tanımlamaları yapıldı. Antibiyotik duyarlılık testleri otomatize olarak VITEK®-2 (BioMérieux, Fransa) identifikasyon cihazında yapıldı. Direnç oranları ve MIK (Minimal inhibitör konsantrasyonu) değerleri CLSI (Clinical and Laboratory Standards Instuitute) ve EUCAST (The European Committee on Antimicrobial Susceptibility Testing) standartlarına göre belirlendi. Kullanılan antibiyotiklere orta düzeyde duyarlı suşlar dirençli kabul edildi. Çalışmamıza 30 antibiyotik dahil edilerek direnç ve duyarlılıkları değerlendirildi. Bu çalışmada istatistiksel analizler SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA; lisans, Hitit Üniversitesi) paket programı kullanılarak yapıldı. Normallik dağılımı Kolmogorov-Smirnov ve Shapiro-Wilk testi ile incelendi.

BULGULAR

Çalışmaya 240 hasta dahil edildi. Bu hastaların 165'i erkek, 75'i kadındı. Hastalardan izole edilen 442 mikroorganizma retrospektif olarak değerlendirildi. Hasta başına ortalama 1,8 patojen düşmekteydi. 397 izolat Gram-negatif bakteri, 38 izolat Gram-pozitif bakteri, 7 izolat ise maya idi. En sık izole edilen Gram-negatif bakteriler; *P. aeruginosa* (%39,6), *Escherichia coli* (%12,4), *Morganella morganii* (%8,6), *Acinetobacter baumannii* (%7,2) ve *Klebsiella pneumoniae* (%4,5) idi. En sık izole izole edilen Gram pozitif bakteriler ise; *Staphylococcus aureus* (%3,6), *Enterococcus faecalis* (%2,5) ve *Streptococcus agalactiae* (%1,6) idi (**Tablo 1, Tablo 2**). İzole edilen mayaların sayısı oldukça azdı. Sadece *Candida parapsilosis* ve *Candida albicans* saptandı (**Tablo 3**). İzole edilen bakterilerin antibiyotik duyarlılıkları **Tablo 4**'de gösterilmiştir.

Tablo 1. Diyabetik ayak biyopsi örneklerinden izole edilen gram negatif bakteriler

No		İzolat Sayısı (n/%)
1	*Pseudomonas aeruginosa*	175 (39,6)
2	*Escherichia coli*	55 (12,4)
3	*Morganella morganii*	38 (8,6)
4	*Acinetobacter baumannii*	32 (7,2)
5	*Klebsiella pneumoniae*	20 (4,5)
6	*Proteus mirabilis*	17 (3,8)
7	*Serrratia marcescens*	10 (2,3)
8	*Citrobacter freundii*	8 (1,8)
9	*Enterobacter cloacae* complex	8 (1,8)
10	*Stenotrophomonas maltophilia*	6 (1,4)
11	*Proteus hauseri*	5 (1,1)
12	*Proteus vulgaris*	5 (1,1)
13	*Providencia rettgeri*	5 (1,1)
14	*Achromobacter xylosoxidans*	4 (0,9)
15	*Burkholderia cepacia*	3 (0,6)
16	*Proteus penneri*	2 (0,4)
17	*Klebsiella oxytoca*	1 (0,2)
18	*Providencia stuartii*	1 (0,2)
19	*Pseudomonas fluorescens*	1 (0,2)
20	*Pseudomonas oleovorans*	1 (0,2)
	Toplam	397 (89,8)

%; İzole edilen mikroorganizmanın tüm izolatlara (442) oranıdır.

Tablo 2. Diyabetik ayak biyopsi örneklerinden izole edilen gram-pozitif bakteriler

No		İzolat Sayısı (n/%)
1	*Staphylococcus aureus*	16 (3,6)
2	*Enterococcus faecalis*	11 (2,5)
3	*Streptococcus agalactiae*	7 (1,6)
4	*Enterococcus* spp	1 (0,2)
5	*Enterococcus faecium*	2 (0,2)
6	*Enterococcus avium*	1 (0,2)
	Toplam	38 (8,6)

%; İzole edilen mikroorganizmanın tüm izolatlara (442) oranıdır.

Tablo 3. Diyabetik ayak biyopsi örneklerinden izole edilen mayalar

No		İzolat Sayısı (n/%)
1	*Candida parapsilosis*	4 (0,9)
2	*Candida albicans*	3 (0,6)
	Toplam	7 (1,6)

%; İzole edilen mikroorganizmanın tüm izolatlara (442) oranıdır.

Tablo 4. İzole edilen bakteri ve mayaların antibiyogram ve antifungal duyarlılıkları

No	Antibiyotikler	Duyarlılık (S/N)	Duyarlılık %
1	Fosfomisin	25/26	96,2
2	Tigesiklin	26/28	92,3
3	Eritromisin	24/31	77,4
4	Sefotaksim	292/391	74,7
5	Kolistin	271/367	73,8
6	Sefoksitin	84/121	69,4
7	Fusidik asit	86/125	68,8
8	Ertapenem	71/104	68,3
9	Moksifloksasin	114/202	56,4
10	Meropenem	109/199	54,8
11	Nitrofurantoin	72/133	54,1
12	Aztreonam	188/386	48,7
13	Amikasin	182/376	48,4
14	Seftriakson	59/127	46,5
15	Sefepim	123/299	41,1
16	İmipenem	60/169	35,5
17	Seftazidim	121/343	35,3
18	Trimetoprim sülfametoksazol	6/17	35,3
19	Gentamisin	119/344	34,6
20	Daptomisin	52/151	34,4
21	Sefiksim	85/315	27,0
22	Sefıroksim aksetil	39/146	26,7
23	Sefuroksim	28/106	26,4
24	Kloramfenikol	45/173	26,0
25	Amoksisilin klavulanik asit	39/158	24,7
26	Klindamisin	104/427	24,4
27	Siproflokasin	86/370	23,2
28	Levofloksasin	32/141	22,7
29	Sefazolin	29/142	20,4
30	Ampisilin	24/129	18,6

%; İzole edilen mikroorganizmanın tüm izolatlara (442) oranıdır.

TARTIŞMA

Diyabetik ayak enfeksiyonlarından izole edilen patojen mikroorganizmaların bölgelere göre farklılıklar gösterdiğini bildiren çalışmalar yapılmıştır (9). Sıcak iklime sahip Asya ülkelerinde yapılan çalışmalarda *P. aeroginosa* başta olmak üzere Gram-negatif bakterilerin Gram-pozitif bakterilere göre DAÜ'de daha yaygın olduğu bildirilmiştir (10,11). DAÜ'nde *Enterobacteriaceae* grubuna dahil türlerin baskın olduğu birçok çalışmada raporlanmıştır (12-14).

Çalışmamızda diyabetik ayak enfeksiyonu olarak tanımlanmış erkek hasta oranı (%69) kadınlardan belirgin olarak fazla bulunmuştur. Diğer ülkelerde de benzer eğilimler gözlenmiş ve yazarlar, erkeklerin açık havada çalışmasının daha olası olduğunu ve bunun da sonuçta ayak travması ve yaralanma riskini artırdığını öne sürmüşlerdir (15). Diyabetik ayak enfeksiyonlarında; uygun olmayan ayakkabı kullanımı ve çorapsız ayakkabı giyilmesine bağlı travma, ayakların yıkandıktan sonra kurulanmaması sonucunda nemli ve ıslak ortamda mikroorganizmaların çoğalması, ayak hijyeninin yetersiz olması ve diyabet hastalarının bu konuda bilinçsiz olması risk nedenleri arasında olabileceği düşüncesindeyiz.

Al Benwan ve ark. Kuveyt'te yaptıkları bir çalışmada en sık izole edilen etkenin %17 oranı ile *P. aeruginosa* olduğunu ve Gram-negatif/Gram-pozitif oranını %51/%32 olarak bildirmişlerdir (16). Shankar ve ark. en fazla *P. aeruginosa* ve ikinci sırada *S. aureus* saptarken, Ako-Nai ve ark. ise en fazla *E. coli* ve ikinci sırada *S. aureus* saptamışlardır (17,18). İtalya'da yapılan bir araştırmada Gram-pozitif bakterilerin tüm etkenlerin %52'sini, Gram-negatif bakterilerin %40'ını kapsadığı bildirilmiştir (19). Ilıman iklimin özelliklerini yansıtan bölgelerden olan Hindistan'da 17 yılı kapsayan olgu sayısı oldukça fazla olan bir çalışmada kültürlerden izole edilen en yaygın mikro-

organizmalar sırasıyla *P. aeruginosa* (20,1%), *S. aureus* (17,2%) ve *E. coli* (16,3%) olmuştur. Aynı çalışmada Gram-negatif bakterilerin oranı %57, Gram-pozitif bakterilerin oranı %40 olarak bildirilmiştir (10).

Türkiye'de 2000-2014 yılları arasında yapılan 28 çalışmanın sonuçlarının ve DAE'ndan izole edilen etkenlerin 5 yıllık periyotlarda dağılımlarının değerlendirildiği bir derlemenin verilerinde; Gram-negatif bakteriler %53,7 oranında, Gram-pozitif bakterilerin ise %45,8 oranında olduğu, ayrıca beşer yıllık periyotlar karşılaştırıldığında Gram-pozitif bakterilerin yıllar ilerledikçe artış gösterdiği, Gram-negatiflerin ise azaldığı bildirilmiştir (20). Utlu ve arkadaşları Gram-negatif etkenlerin %63,6 pay ile Gram-pozitif bakterilerden daha yüksek bir oranda olduğu bildirilmiştir (3). Hatipoğlu ve ark. 1989–2011 yılları arasında 20 yıllık süreçte 31 çalışmayı değerlendirdikleri derlemenin sonuçlarında Gram-negatif ve Gram-pozitif bakterilerin DAE'de birbirine yakın oranda izole edildiğini bildirmişlerdir (32). Aynı yazarların daha yeni olan 35 merkezi dâhil ettikleri çalışmalarında, tüm izolatların %60'ını Gram-negatif bakterilerin, %36'sını Gram-pozitif bakterilerin oluşturduğunu ve Gram-pozitifler arasında en yaygın olarak *S. aureus* (%11)'un olduğu gösterilmiştir (21,22).

Bizim çalışmamızda Gram-negatif bakteriler tüm izolatların %89,2 gibi oldukça yüksek bir oranı ile baskın bir durum sergilemektedir. *P. aeroginosa* %39,6 ile en sık izole edilen bakteri olmuştur. Gram-negatif bakterilerin bu yüksek izolasyon oranı diyabetik ayak biyopsisi alınan hastaların Wagner sınıflamasına göre evre 2 ve üzeri olmasından ve ciddi enfeksiyonlarda Gram-negatif bakterilerin artmasından kaynaklanmış olabileceği düşüncesindeyiz.

Ülkemizde 2018 yılında yapılan bir çalışmada mayalar tüm izolatların %2,6'sını oluşturuyordu (1). Bizim çalışmamızda mayaların tüm izolatlara oranı (%0,16) oldukça düşük bulunmuştur. Ertuğrul ve ark. (20)'nın 2017 yılında yaptıkları bir çalışmada 5 yıllık dönemlerde *S. aureus* izolasyon oranı %29'dan %18'e gerilemiştir. Son yıllarda DAÜ'den *S. aureus* izolasyon oranını %10 ve daha altında bildiren çalışmalar yapılmıştır. (2,23-26). Bizim çalışmamızda *S. aureus* en sık izole edilen Gram-pozitif bakteri olmasına rağmen, tüm izolatların sadece %3,6'sını oluşturuyordu. Acinetobacter türleri yara ve cerrahi alan enfeksiyonlarını da kapsayan, nozokomiyal enfeksiyonlara neden olan dirençli etkenler olarak bilinmektedir. Diyabetik ayak enfeksiyonlarından Acinetobacter türlerinin izolasyon oranları; Hindistan'da yapılan çalışmalarda Ramakant ve ark. (10) %3,7, Gadepalli ve ark. (27) %9,3, Bangladeş'te Karmaker ve ark. (28) %10, Türkiye'de Hatipoğlu ve ark. (22) %2,84, Öztürk ve ark (2) %12,3 olarak bildirmişlerdir. Bizim çalışmamızda da bildirilen verilere benzer oranda *A. baumannii* oranı %7,2 olarak bulunmuştur.

Diyabetik ayak enfeksiyonlarına neden olan etkenlerin antibiyotik direnci giderek artmakta olduğu günümüzde, bu enfeksiyonların tedavi süreçlerinin yönetilmesi konusu önemini artırmaktadır (29). Hindistan'da yapılan bir çalışmada diyabetik ayak enfeksiyonlarında *E. coli*, Enterobacter spp., *Klebsiella pneumoniae* gibi enterik Gram-negatif bakterilerde çoklu ilaç direnci (ÇİD) oranlarının %60-70 seviyelerinde olduğu, direncin *P. aeruginosa*'da %50'ye yaklaştığı bildirilmiştir (30). Çalışmamızda 30 antibiyotiğin duyarlılıkları değerlendirilmiştir. En etkili antibiyotikler ve duyarlılıkları sırasıyla; fosfomisin (%96,2), tigesiklin (%92,3), eritromisin (%77,4), sefotaksim (%74,7), kolistin (%73,8), sefoksitin (%69,4) ve fusidik asit (%68,8) iken, en az etkili antibiyotikler ve duyarlılıkları sırasıyla; ampisilin (18,6), sefazolin (20,4), levofloksasin (%22,7), siproflokasin (%23,2), klindamisin (%24,4), amoksisilin klavulanik asit (%24,7) ve kloramfenikol (%26,0) olarak tespit edilmiştir.

Anaerop bakteriler diyabetik ayak enfeksiyonlarında çok az da olsa etken olabilmektedir. Birçok merkezde anaerop bakterilerin identifikasyonu için uygun şartların sağlanamaması gibi nedenlerden dolayı ülkemizde yeterli veri saptanamamıştır. Çalışmamızın önemli bir limitasyonu laboratuvarımızda anaerop bakterilerin kültürünün yapılamamasından dolayı anaerop bakterilerin çalışmaya dâhil edilememesidir.

SONUÇ

Çalışmamız sonucunda; hastanemiz ve bölgemiz özelinde DAE'nda başta nozokomiyal enfeksiyon etkeni olan *P. aeruginosa* ve Gram-negatif bakterilerin baskın olduğu göz önüne alınarak ampirik tedavinin belirlenmesine katkı sağlanacaktır. Gram-pozitif bakterilerde ise *S. aureus* unutulmamalıdır. Bölgesel veriler ülkemizin DAE patojen dağılımlarının ve antibiyotik dirençlerinin belirlenmesine katkı sağlayacaktır. İlk olarak ampirik tedavi uygulanmasına rağmen, kültür ve antibiyogram sonuçları rehberliğinde tedavi protokolleri daha etkili olacak ve dirençli bakterilerin gelişimi azaltılabilecektir.

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The effect of manual lymphatic drainage on the postoperative recovery process following total knee arthroplasty

Manual lenfatik drenajın total diz artroplastisini takip eden toparlanma süreci üzerindeki etkisi

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ABSTRACT

Background: Knee joint has great importance on daily living activities thus gonarthrosis does affect quality of life of patients very dramatically. Total knee arthroplasty (TKA) is accepted as gold standard in order to cope with pain, deformity and instability especially in patients with gonarthrosis who are in terminal stage. Physical therapy and rehabilitation programs are known to increase the success of this surgical procedure. As edema around knee joint is one of the major postoperative complications, which prolong recovery process, it is important to use therapeutic modalities against this problem.

Objective: In this study it was aimed to evaluate the effectiveness of manual lymphatic drainage (MLD) following TKA on edema, range of motion, pain, independence of daily living activities, gait distance and knee functionality.

Material and Method: 16 patients with TKA were divided into two groups while one of them is applied standard postoperative rehabilitation procedure (exercise therapy, cryotherapy and positioning) and the other group had MLD therapy on the second and fourth days of the postoperative process for thirty minutes and in one session during the day in addition to standard protocol. On post-op 2nd, 4th, and 6th days, the volumetric changes were calculated based on a formula of Sitzia et al. for each 4 cm segment of the lower extremity, active ROM and knee posture at rest were measured by a universal goniometer, pain by using visual analog scale (VAS), walking distance by calculating total walking distance in a day, independence level in daily living activities by using Functional independence measurement (FIM) scale. In addition, Lysholm knee score was calculated on postoperative 15th day in order to evaluate functionality of knee joint.

Results: At postoperative 2nd day, 4th day and 6th day, the mean of FIM (p=0.972, p=0.575, p=0.398, respectively), active ROM (p=0.288, p=0.522, p=0.622, respectively), knee posture (p=0.870, p=0.521, p=0.445, respectively), gait distance (p=1.000, p=0.258, p=0.113, respectively), volume of the operated lower extremity (p=0.451, p=0.384, p=0.268, respectively), VAS for pain daytime (p=0.192, p=0.488, p=0.506, respectively) and night (p=0.137, p=0.562, p=0.748, respectively) were similar in both MLD and non-MLD groups. The mean of Lysholm score was 46.25±24.50 in MLD group and 61.12±17.70 in non-MLD group (p=0.186).

Conclusion: Although there is no significant difference between groups, the effectiveness of MLD can be showed in studies which will be performed with a larger sample size.

Keywords: Manual lymphatic drainage, total knee arthroplasty, physical therapy

ÖZ

Giriş: Diz ekleminin günlük yaşam aktivitelerinde büyük önemi vardır, bu nedenle gonartroz hastaların yaşam kalitesini çok dramatik bir şekilde etkiler. Total diz artroplastisi (TDA), özellikle terminal dönemdeki gonartrozlu hastalarda ağrı, deformite ve instabilite ile baş edebilmek için altın standart olarak kabul edilmektedir. Fizik tedavi ve rehabilitasyon programlarının bu cerrahi işlemin başarısını arttırdığı bilinmektedir. Diz eklemi çevresindeki ödem, iyileşme sürecini uzatan majör postoperatif komplikasyonlardan biri olduğundan, bu soruna karşı tedavi yöntemlerinin kullanılması önemlidir.

Amaç: Bu çalışmada TDA sonrası manuel lenfatik drenajın (MLD) ödem, hareket açıklığı, ağrı, günlük yaşam aktivitelerinin bağımsızlığı, yürüme mesafesi ve diz fonksiyonelliği üzerine etkinliğinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Total diz artroplastisi geçiren 16 hasta iki gruba ayrılarak bunlardan birine standart postoperatif rehabilitasyon prosedürü (egzersiz terapisi, cryoterapi ve pozisyonlama) uygulanırken diğer gruba standart protokole ek olarak, postoperatif sürecin 2. ve 4. günlerde günde bir kez 30 dakikalık MLD terapisi uygulandı. Ameliyat sonrası 2., 4. ve 6. günlerde hacimsel değişiklikler alt ekstremitenin her bir 4 cm'lik segmenti için Sitzia ve ark.'nın formülüne dayanarak hesaplandı; aktif EHA ve istirahatte diz postürü universal gonyometre ile ölçüldü; ağrı görsel analog skala (GAS) ile; yürüme mesafesi, bir gün içindeki toplam yürüme mesafesi hesaplanarak; günlük yaşam aktivitelerindeki bağımsızlık seviyesi Fonksiyonel bağımsızlık ölçeği ile değerlendirildi. Ayrıca diz ekleminin işlevselliğini değerlendirmek için postoperatif 15. günde Lysholm diz skoru hesaplandı.

Bulgular: Postoperatif 2. gün, 4. gün ve 6. gün FİM ortalaması (sırasıyla p=0.972, p=0.575, p=0.398), aktif EHA (sırasıyla p=0.288, p=0.522, p=0.622), diz postürü (sırasıyla p=0.870, p=0.521, p=0.445), yürüme mesafesi (sırasıyla p=1.000, p=0.258, p=0.113), ameliyat edilen alt ekstremite hacmi (sırasıyla p=0.451, p= 0.384, p=0.268), gün içindeki ağrıya yönelik GAS (sırasıyla p=0.192, p=0.488, p=0.506) ve gece ağrısına yönelik GAS (sırasıyla p=0.137, p=0.562, p=0.748) manuel lenfatik drenaj yapılan ve yapılmayan gruplarda benzerdi Lysholm skorunun ortalaması manuel lenfatik drenaj grubunda 46.25±24.50 ve manual lenfatik drenaj yapılmayan grupta 61.12±17.70 idi (p=0.186).

Sonuç: Gruplar arasında anlamlı bir fark olmamasına rağmen MLD'nin etkinliği daha büyük örneklemle yapılacak çalışmalarda gösterilebilir.

Anahtar Kelimeler: Manuel lenfatik drenaj, total diz artroplastisi, fizik tedavi

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INTRODUCTION

Total knee arthroplasty (TKA) is a traumatic event leading to a significant inflammatory process that persistently occurs after the surgical procedure for over six weeks (1). Post-surgical joint swelling and edema are intrinsically related to the inflammation mechanisms as natural consequences of arthroplasty surgeries (2). Post-TKA joint swelling causes pain, a decrease in range of motion (ROM), and a delay in functional recovery (3,4). Standard joint rehabilitation programs after TKA have often focused on mostly ROM, the strength of quadriceps, gait, and functional activities (5). However, a therapy targeting swelling after TKA could improve post-surgical recovery. Yet, it was previously reported that some treatment modalities, such as cryotherapy (6), compression (7), pulsed electromagnetic field (8), demonstrated no effect on knee swelling.

On the other hand, manual lymphatic drainage (MLD) was documented to lead to blood circulation and movement of lymphatic and other soft tissue fluids, thus contributing to softening of tissues (9). It can minimize edema as it increases lymphatic motility and stimulates lymphatic vessels' collateral activity and anastomosis (10-12). It is also believed that MLD favors inflammation-related mediators and interstitial fluid reabsorption (2,13). Therefore, it might be an effective rehabilitation method to reduce post-TKA swelling.The literature hosts some randomized control studies of MLD that demonstrated substantial effectiveness on swelling after distal radius fracture (14,15), hindfoot surgery (16), and TKA (17). Ultimately, we hypothesized that MLD could decrease swelling after TKA and improve knee functionality and recovery. Therefore, we carried out this study to explore the effects of MLD on swelling in the early postoperative period after TKA and its consequences on pain, ROM, and knee functions.

MATERIAL AND METHOD

The Clinical Research Ethics Committee of Kırıkkale University granted ethical approval to our study (Date: 27.11.2018, Decision No: 20/01), and we performed all procedures in accordance with the ethical rules and the principles of the Declaration of Helsinki. This was a randomized study that included 16 patients with TKA who were recruited to a postoperative physical therapy with MLD or without MLD between January and December 2019. On post-op 2nd, 4th, and 6th days, we calculated the volumetric changes through the formula of Sitzia et al. (18) for each 4 cm segment of the lower extremity while measuring active ROM and knee posture at rest using a universal goniometer (19) Moreover, we determined pain on thevisual analog scale (VAS), and walking distance was accepted as the total walking distance in a day. The Functional Independence Measure (FIM) was utilized to discover the patients' independence in activities of daily living (20). Since body mass index (BMI) may affect the outcomes of the study, we also evaluated the BMI of the patients. Finally, we calculated Lysholm knee score (LKS) on the postoperative 15th day to evaluate the functionality of patients' knee joints (21).

We carried out the study with patients undergoing posterior-stabilized TKA. All patients underwent TKA by a single experienced orthopedic surgeon specializing in arthroplasty surgery. Patients were positioned supine on the surgery table with the bilateral arm in an arm sling for the operation. Padded cushions were placed under bony prominences to avoid excessive pressure. Cemented femoral and tibial components of TKA in pre-determined sizes (with the aid of radiographic templates) and an intraoperatively-decided, proper insert (Stryker®, Triathlon®, Total Knee System, USA) were applied through an anterior medial parapatellar approach.

Knee-based exercises were performed in the supine (active-assisted knee flexion, quadriceps strengthening exercises, gluteal settings,and straight-leg raise), seated (active-assisted and active knee flexion, and quadriceps strengthening exercises), and standing (hip and knee flexion, mini squats, active hamstring curls,and hamstring stretch) positions.Between postoperative day-1 to day-7, a physiotherapist moderated these exercises progressively in 15 repetitions three times a day until hospital discharge.

The prosthetic extremity was elevated during MLD treatment. The sessions were launched by stimulating the relevant lymphatic nodes. The decongestion of the collected lymphatic fluid was provided manually through these nodes. Appropriate axillar and inguinal anastomoses were built for therapeutic purposes. Besides, diaphragmatic breathing, having been practicedby the patients before, was performed during the sessions to get better results. Both lymphatic node stimulation and decongestion of the edematous areas were done from proximal to distal.

On the postoperative second day (day-2), we randomly divided the patients into the MLD group and the non-MLD group. MLD group underwent MLD therapy (22) for 30 minutes on the TKA limb by an experienced therapist. After the MLD therapy, we evaluated all patients regarding knee pain, ROM, volumetric changes, independence in activities of daily living, knee posture, and functionality. The treatment process was repeated on postoperative day-4, while the assessment process was repeated both on postoperative day-4 and day-6.

Statistical Analyses

We presented the data as percentages, means, standard deviations, and medians (minimum-maximum). The normality of distribution was checked using a Kolmogorov–Smirnov test. Accordingly, we compared the data showing normal distribution between and within the groups with independent and paired t-tests, respectively, while using Mann-Whitney U and Friedman tests to analyze the data with a non-normal distribution.We performed all statistical analyses on SPSS 22.0 (SPSS Inc., Chicago, Illinois) and accepted a p-value <0.05 statistically significant at the 95% confidenceinterval.

RESULTS

The findings revealed the mean age to be 60.75±7.40 (51-70 years) in the MLD group and 66.25±10.57 (51-86 years) in the non-MLD group. While 14 patients were females, only 2 were males. Moreover, we calculated the mean BMI to be 29.71±11.56 in the MLD group and 35.25±10.39 in the non-MLD group. Although 8 patients were recruited to physical and MLD therapies, the remaining received only physical therapy. **Table 1** presents the demographic characteristics of the patients.

The findings revealed that, on postoperative 2nd day, 4th day and 6th day, mean FIM scores (p=0.972, p=0.575, p=0.398, respectively), active ROM (p=0.288, p=0.522, p=0.622, respectively), knee posture (p=0.870, p=0.521, p=0.445, respectively), walking distance (p=1.000, p=0.258, p=0.113, respectively), volume of the operated lower extremity (p=0.451, p=0.384, p=0.268, respectively), VAS for daytime pain (p=0.192, p=0.488, p=0.506, respectively) and night pain (p=0.137, p=0.562, p=0.748, respectively) were similar in both MLD and non-MLD groups. Moreover, the mean of LKS was found to be 46.25±24.50 in the MLD group and 61.12±17.70 in the non-MLD group (p=0.186). **Table 1** summarizes all the measurements.

Table 1. Details of parameters on follow-up days

	MLD	Non-MLD		
	Mean±SD (min-max)/ Median (min-max)/ N (%)	Mean±SD(min-max)/ Median (min-max)/ N (%)	t /Z /X2	p
Age	60.75±7.40 (51-70)	66.25±10.57 (51-86)	-1.206*	0.248
Sex				
Women	8 (50.0%)	6 (37.5%)	2.286‡	0.131
Men	0 (0.0%)	2 (12.5%)		
BMI	29.71±11.56	35.25±10.39	-1.007*	0.331
Side of TKA				
Right	6 (37.5%)	3 (18.8%)	2.286‡	0.131
Left	2 (12.5%)	5 (31.2%)		
FIM, post-op 2nd day	69.13±15.91	69.38±12.27	-0.035*	0.972
FIM, post-op 4th day	79.87±7.72	77.25±10.39	0.574*	0.575
FIM, post-op 6th day	83.63±5.90	80.50±8.25	0.872*	0.398
Active ROM, post-op 2nd day	62.63±14.14	53.00±20.19	1.104*	0.288
Active ROM, post-op 4th day	77.13±12.71	73.38±9.94	0.657*	0.522
Active ROM, post-op 6th day	83.00±9.84	81.25±4.30	0.461*	0.652
Knee posture, post-op 2nd day	26.50±3.89	26.00±7.50	0.167*	0.870
Knee posture, post-op 4th day	21.25±4.33	20.00±3.16	0.659*	0.521
Knee posture, post-op 6th day	19.63±3.66	18.38±2.62	0.786*	0.445
Gait distance, post-op 2nd day	5.88±3.40	5.88±1.13	0.000*	1.000
Gait distance, post-op 4th day	7.63±3.82	5.75±2.38	1.180*	0.258
Gait distance, post-op 6th day	9.13±4.67	6.00±2.33	1.693*	0.113
Lysholm score	46.25±24.50	61.12±17.70	-1.392*	0.186
Volume, post-op 2nd day	7540.00±707.13	8264.38±2543.78	-0.776*	0.451
Volume, post-op 4th day	7549.50±868.46	8361.63±2403.48	-0.899*	0.384
Volume, post-op 6th day	7341.38±947.11	8445.25±2538.31	-1.152*	0.268
VASforpain, daytime,post-op 2nd day	5.25±2.77	7.25±3.06	-1.372*	0.192
VAS forpain,daytime, post-op 4th day	3.63±1.69	4.38±2.45	-0.714*	0.488
VAS for pain, daytime, post-op 6th day	2.00±1.31	2.75±2.82	-0.683*	0.506
VAS for pain, night, post-op 2nd day	5.37±2.45	7.50±2.93	-1.576*	0.137
VAS for pain, night, post-op 4th day	4.25±2.05	5.00±2.93	-0.593*	0.562
VAS for pain, night, post-op 6th day	4.38±2.83	3.88±3.27	0.327*	0.748

(*) t value, Independentsamples t-test; (†) Z value, Mann Whitney U test; (‡) X2 value, Pearson ki-square test; FIM, Functional independent measurement; ROM, Range of motion; VAS, Visual analog scale;

In general, we concluded that swelling showed significant reduction on the postoperative 6th day compared to the previous follow-up day (p=0.021). However, active ROM significantly increasedon the postoperative 6th day compared to the previous follow-up day in both groups (p=0.027, p=0.025, respectively).The comparison of the parameters by follow-up days is given in **Table 2**.

DISCUSSION

Management of TKA patients with postoperative edema has always been a significant health issue owing to increased pain, decreased active knee ROM, and other associated functional consequences. The swelling, the primary target of the study, was measured for each 4 cm segment of the lower extremity. Despite insignificant compared to the previous postoperative follow-up days, we found the mean volume to decrease in the MLD group on the postoperative 6th day, whereas it increased in the control group.

The lymphatic drainage treatment was shown to improve blood circulation and stimulate lymphatic fluid movement in TKA patients (23). In the current study, knee swelling increased postoperatively until the 4th day in both groups. MLD particularly made a difference on the postoperative 6th day; thus, we found the volume to decrease significantly on that day compared to the post-op 4th day. On the other hand, knee swelling decreased only in the MLD group onthe postoperative 6th day, while knee ROM increased significantly in both groups on all follow-up days despite no significant difference between groups. One possible explanation for our findings may be related to the small number of patients in the study. In addition, the regular physical rehabilitation program of TKA patients may have affected the swelling. Similarly, Fujiura et al. (24) also reported that MLD interventions after surgery accompanied by standard physical therapy did not reduce pain intensity in the patients. Moreover, there was no significant difference between the groups regarding ROM, muscle strength, circumference, walking speed, and walking rate. Conversely, Pichonnaz et al. (2) reported that MLD treatment had no effect on swelling in the early postoperative period in TKA patients; however, it provided a reduction in postoperative knee flexion contractures. Besides, Rigoni et al. (23) demonstrated that lymphatic drainage treatment has a positive effect on rehabilitation outcomes, and Ebert et al. (17) revealed that MLD therapy is highly beneficial for knee ROM in the early postoperative period.

A wide array of factors that may affect knee ROM postoperatively may have also existed in this study. First of all, the rehabilitation program may have affected the study outcomes but is not likely to have affected the differences between groups. The relevant exercise program may have decreased swelling or increased inflammatory response in both groups. Secondly, the living environments of patients and their activity habits, which are not controllable parameters, may have influenced outcomes of MLD on extremities. Finally,

Table 2. Details of swelling and its' consequences on knee parameters.

	MLD		Non-MLD	
	t / Z	p	t / Z	p
FIM, post-op 2nd dayvs post-op 4th day	-3.042*	0.019	-2.943*	0.022
FIM, post-op 2nd dayvs post-op 6th day	-3.679*	0.008	-3.580*	0.009
FIM, post-op 4th dayvs post-op 6th day	-3.319*	0.013	-3.389*	0.012
Active ROM, post-op 2nd dayvs post-op 4th day	-3.885*	0.006	-2.963*	0.021
Active ROM, post-op 2nd dayvs post-op 6th day	-5.351*	0.001	-4.596*	0.002
Active ROM, post-op 4th dayvs post-op 6th day	-2.798*	0.027	-2.852*	0.025
Knee posture, post-op 2nd dayvs post-op 4th day	4.200*	0.004	2.487*	0.042
Knee posture, post-op 2nd dayvs post-op 6th day	6.488*	0.000	3.221*	0.015
Knee posture, post-op 4th dayvs post-op 6th day	2.154*	0.068	2.728*	0.029
Gait distance, post-op 2nd dayvs post-op 4th day	-1.549*	0.165	0.168*	0.871
Gait distance, post-op 2nd dayvs post-op 6th day	-3.265*	0.014	-0.215*	0.836
Gait distance, post-op 4th dayvs post-op 6th day	-1.426*	0.197	-0.607*	0.563
Volume, post-op 2nd dayvs post-op 4th day	-0.052*	0.960	-1.117*	0.301
Volume, post-op 2nd dayvs post-op 6th day	0.922*	0.387	-2.129*	0.071
Volume, post-op 4th dayvs post-op 6th day	2.980*	0.021	-1.196*	0.271
VAS for pain, daytime, post-op 2nd dayvs post-op 4th day	1.879*	0.102	6.524*	<0.001
VAS for pain, daytime, post-op 2nd dayvs post-op 6th day	4.333*	0.003	7.180*	<0.001
VAS for pain, daytime, post-op 4th dayvs post-op 6th day	3.870*	0.006	5.017*	0.002
VAS for pain, night, post-op 2nd dayvs post-op 4th day	1.567*	0.161	5.000*	0.002
VAS for pain, night, post-op 2nd dayvs post-op 6th day	0.748*	0.479	6.085*	<0.001
VAS for pain, night, post-op 4th dayvs post-op 6th day	-0.122*	0.906	3.813*	0.007

(*) t value, PairedSamples t-test; (†) Z value, WilcoxonSignedRanks test; p<0.05; FIM, Functional independent measurement; ROM, Range of motion; VAS, Visual analog scale.

the statistical power of the study was limited because of the sample size. Further, more extensive research is needed to reveal the effects of MLD in TKA patients.

In the current study, MLD demonstrated no significant effect on knee swelling and consequences of swelling such as ROM, pain, FIM, knee posture, and gait. MLD treatment may contribute to improving knee ROM, particularly in the early postoperative period. However, the clinical significance of its effect is still unclear.

ETHICAL DECLARATIONS

Ethics Committee Approval: We carried out the research following ethical approval by the Clinical Research Ethics Committee of Kırıkkale University (Date: 27.11.2018, Decision No: 20/01)

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Case Report / Olgu Sunumu

MEDICINE PALLIATIVE CARE

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Görme kaybı ve serebral apse ile seyreden geç tanı konan bir rinoorbitoserebral mukormikozis olgusu

A case of late diagnosed rhinoorbitocerebral Mucormycosis with visual loss and cerebral abscess

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ÖZ

Rino-orbito-serebral mukormikozis, *Zygomycetes* türü küf mantarlarının neden olduğu, mortalitesi ve morbidite oranı yüksek fırsatçı bir mantar enfeksiyonudur. Mukormikozis için en önemli risk faktörü kontrolsüz diyabet ve diyabetik ketoasidozdur. Bunun dışında; desferoksamin tedavisi, demir yüksekliği, immünosüpresif ilaçlar, kortikosteroid kullanımı diğer risk faktörleridir. Bu yazıda, geç tanı konulan rinoorbitoserebral mukormikozise bağlı olarak görme kaybı ve serebral apse gelişen 62 yaşında diyabetik bir erkek sunuldu. Hastaya cerrahi debridman ile birlikte lipozomal amfoterisin-B tedavisi uygulandı.

Anahtar Kelimeler: Rino-orbito-serebral mukormikozis, komplikasyon, görme kaybı, serebral apse

ABSTRACT

Rhino-orbito-cerebral Mucormycosis is an opportunistic fungal infection caused by *Zygomycetes* species mold fungi with a high mortality and morbidity rate. The most important risk factor for Mucormycosis is uncontrolled diabetes and diabetic ketoacidosis. Except this; desferoxamine treatment, high iron, immunosuppressive drugs, corticosteroid use are other risk factors. In this article, a 62-year-old diabetic man who developed vision loss and cerebral abscess due to late diagnosed rhinocerebral Mucormycosis was presented. The patient was treated with liposomal amphotericin-B with surgical debridement.

Keywords: Rhino-orbito-cerebral Mucormycosis, complication, vision loss, cerebral abcess

GİRİŞ

Mukormikozis (Zigomikozis), *Zygomycetes* sınıfında yer alan küf mantarlarının neden olduğu, farklı klinik tablolara neden olabilen mortalitesi yüksek fırsatçı bir mantar enfeksiyonudur. Mukormikozis, sıklıkla altta yatan diyabetik ketoasidoz, hematolojik malignite, uzun süreli kortikosteroid kullan hastalarda görülür, nadiren sağlıklı bireylerde de görülebilir (1,2). Mukormikozisin en sık görülen formu rinoserebral mukormikozistir. Rino-orbitoserebral mukormikozis formu daha nadir görülen bir formudur. Bu formda bulgular; orbital ağrı, oftalmopleji ve körlüğe kadar değişebilir (3). Bu yazıda, sağ gözde görme kaybı ve serebral apseyle seyreden geç tanı konulmuş rino-orbito-serebral mukormikozis olgusu sunularak literatür gözden geçirildi.

OLGU

Altmış iki yaşında erkek hasta baş ağrısı, sağ gözde görme kaybı, sağ yüzde uyuşma şikayetleriyle ve Tolosa-Hunt sendromu ön tanısıyla dış merkezden nöroloji polikliniğine başvurdu. Anamnezinden diyabetes mellitus ve astım bronşiyale tanılarının olduğu ve 6 ay önce COVID-19 enfeksiyonu nedeniyle favipiravir ve 10 gün süreyle kortikosteroid tedavisi aldığı öğrenildi. Nöroloji servisinde preseptal selülit ön tanısıyla seftriakson tedavisi alırken, mukormikozis ön tanısıyla enfeksiyon hastalıklarına konsülte edildi. Hastanın göz çevresindeki preseptal selülit lezyonunun ilerlemesi üzerine hastaya ampirik olarak preseptal selülit için meropenem 3x1 gr intravenöz (IV) ve rinoserebral mukormikozis ön tanısı içinse lipozomal amfoterisin-B 3-5 mg/kg/gün başlandı,

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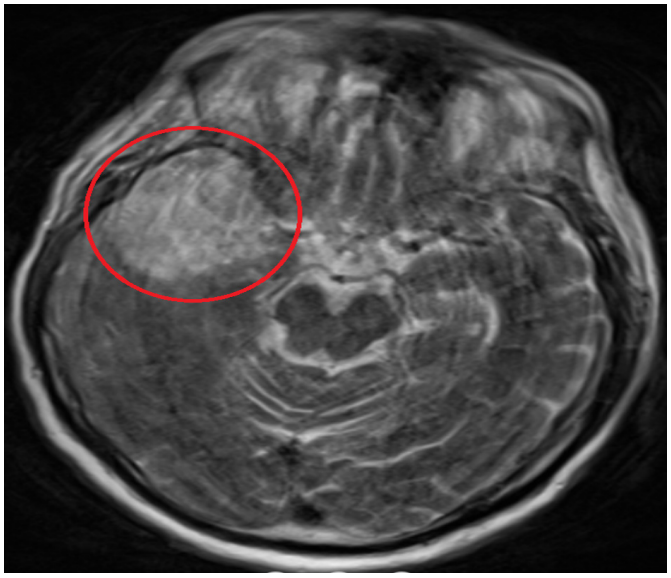
kesin tanı için sinüs biyopsisi önerildi. Kraniyal manyetik rezonans görüntüleme (MRG)'de "Sağ temporal lob anteriorunda 45x37x36 mm boyutlarında lobule konturlu, santrali difüzyon kısıtlayan, çevresel kontrastlanan, bir dizi fokal kan yıkım ürünlerine sekonder parlama artefaktının izlendiği, geç serebrit-apse formasyonu izlenmiştir. Tanımlı lezyon komşuluğunda pakimeningeal kalınlaşma ve kontrastlanma kaydedilmiştir. Sağ maksiller ve etmoidal sinuslerde yaygın sekresyona ve inflamasyona sekonder sinyal değişiklikleri mevcuttur. Sağ etmoidal sinus komşuluğunda,sağ orbita medial ve inferior rektus kas ve çevresinde izlenen orbital apekse ilerleyip sağ kavernöz sinus ve sağ sfenopariyetal sinus trasesini tutan, kontrastlanan enfeksiyoz/inflamatuvar olduğu düşünülen sinyal değişiklikleri izlenmiştir. Sağ optik sinirde ödematöz sinyal değişikliği ve difüzyon kısıtlaması izlenmiştir. Beyin sapı ve serebelluma ait intensite homojendir" şeklinde raporlandı (**Resim**).



Resim. Kraniyal MRG'de Sağ temporal lob anteriorunda beyin apsesi

Hastaya fonksiyonel endoskopik sinüs cerrahisi uygulandı.Maksiler sinüs, etmoid sinüs ve sfenoid sinüslerdeki pürülan maeryal ve nekrotik alanlar temizlendı, sfenoplalatin bölgeden biyopsi için örnek alındı. Patoloji sonucu olarak , "Yaklaşık 4 cc hacminde krem kahve renkli yer yer nekrotik görünümde dokularda PAS ve Giemsa boyamasında mukormikozisle uyumlu spor ve hifa yapıları ile aktif süpüratif inflamasyon bulguları" olarak rapor edildi. Hastanın mukormikozis için lipozomal amfoterisin-B, serebriti için ise meropenem tedavisine devam edildi. Hastanın lipozomal amfoterin-B'ye bağlı olarak geliştiği düşünülen hiponatremisi sodyum replasmanı ile düzeltildi ve kan şekeri regülasyonu sağlandı. Hasta tedavisinin 37.gününde tedavisi devam etmek üzere kendi isteği ile başka bir merkeze sevk edildi.

TARTIŞMA

Mukormikozis (zigomikoz), *Zygomycetes* sınıfında yer alan küf mantarlarının neden olduğu fırsatçı bir mikozdur. *Zygomycetes* sınıfında yer alan başlıca küf mantarları; *Rhizopus*, *Lichtheimia* (önceki adı *Absidia*), *Mucor*, *Rhizomucor*, *Cunninghamella* cinsi mantarlar enfeksiyondan sorumludur. Mucurmikozise neden olan mantarların dağılımı coğrafi bölgelere göre farklılık gösterebilir (4). En sık enfeksiyona neden olan *Rhizopus* cinsi mantarlardır. Bu mantarlar toprakta, organik materyal ve çürümüş bitkilerde doğada yaygın olarak bulunur. Etken solunum, sindirim ve deri yoluyla bulaşabilir (4,5).

Özellikle diyabet ve diyabetik ketoasidoz, maligniteler, solid organ veya kemik iliği transplantasyonu, demir yüklenmesi, diğer immünosupresif ilaçlar, desferoksamin tedavisi, geniş spektrumlu antibiyotik kullanımı mukormikozis için önemli risk faktörleridir (2,5).

Hastalık farklı klinik tablolar şeklinde görülebilir. Bunlar içerisinde; rinoserebral mukormikozis, rinoorbitoserebral sendrom, pulmoner mukormikozis, kutanöz mukormikozis, gastrointestinal mukormikozis, dissemine mukormikozis, izole apseler veya enfeksiyonlar yer almaktadır. En sık görülen formu rinoserabral mukormikozistir. Bunu pulmoner, kutanöz ve serebral formlar izler. *Zygomyetes* türü küf mantarlar damar invazyonu sonucunda trombüslere ve buna bağlı olarak nekroz ve infarkta neden olur. Komşuluk yolu, hematojen yol ve sinirler aracılığı ile santral sinir sistemine ulaşır. Cerrahi ve antifungal tedaviye rağmen mortalite oranları %40-70 arasında bildirilmektedir (2,4,5).

Sunduğumuz olguda rinoorbitoserebral mukormikozis klinik tablosu mevcuttu. Hastada mukormikozis için risk faktörü olarak diyabetes mellitus mevcuttu. Hastada orbita tutulumuna bağlı görme kaybı ve serebral apse gelişmesi nedeniyle gecikmiş bir olgu olarak değerlendirildi.

Sunduğumuz olguda başlangıçta Tolosa-Hunt sendromu (THS) sendromu tanısı mevcuttu. THS ağrılı oftalmopleji ile prezente olan kavernöz sinüs veya süperior orbital fissürün idyopatik granülamatöz hastalığıdır. Bu sendrom, tek yanlı (peri) orbital ağrı, ipsilateral oftalmopleji ve kortikosteroidlere iyi yanıt ile karakterize olan nadir bir ağrılı oftalmopleji tablosudur. THS kavernöz sinüs veya superior orbital fissürün bilinmeyen bir enflamasyonu sonucunda gelişir. Glukokortikoid tedavisi hem tanı hem de tedavi amaçlı olarak kullanılmaktadır. Tanıda uluslararası baş ağrısı derneği tanı kriterlerini güncellemiş granülomun MRG veya biyopsi ile gösterilmesi olarak belirlemiştir (6).

Mukormikozis, *Aspergillus* ve *Candida* enfeksiyonlarından sonra üçüncü en sık görülen fırsatçı mikoz etkenidir. İlk klinik semptomlar genellikle nonspefik olup, bu durum tanıda ve tedavide gecikmeye ve buna bağlı olarak komplikasyon gelişimine neden olabilir (7).

Rinoserebral mukormikoziste klinik bulgular sinüzitle başlar, hızlıca orbita, göz, optik sinir ve beyin dokusu gibi komşu dokulara yayılabilir. Fasiyal ödem, ağrı, nekroz, görme kaybı, siyah renkte akıntı,nazal kavite ve göz köşesi boyunca propitozis yaygın özelliklerdir. Mukormikoziste anjiyoinvazyon oldukça sıktır. Sfenopalatin ve santral retinal arterin tıkanıklığı sıklıkla körlükle sonuçlanır (2).

Literatürde rinoorbitoserebral mukormikozis olgularında görülen komplikasyonlar; bulanık görme, tam görme kaybı, bilinç değişikliği, kraniyal nöropati veya serebral apse olarak bildirilmiştir.Bu komplikasyonlar gözden hastalığın santral sinir sistemine yayılımı sonucunda gelişir (4). Sunduğumuz olguda da görme kaybı ile birlikte sağ temporal lobda apse mevcuttu.

Sinüsler veya orbita tutulumu olmaksızın izole beyin tutulumu da görülebilir. İzole beyin tutulumunda klinik bulgular ; inme benzeri sendrom, menenjit, intrakraniyal yer kaplayan kitle olabilir (2). Roden ve ark. (8) 928 mukormikozisli olguyu değerlendirdikleri çalışmasında; en sık görülen mukormikozis tutulumunu sinüsler (%39), akciğerler (524), ve cilt tutulumu (%19) olarak bildirmişlerdir. Mukormikozise bağlı olarak yayılım olguların %23'ünde saptanmıştır. Akciğer tutulumu olan hastaların büyük kısmında altta yatan hastalık olarak malignite saptanırken, sinüs tutulumu olanlarda en sık saptanan altta yatan hastalık diyabet olarak bildirilmiştir. Çok değişkenli analizde *Cunninghamella* türlerinin nende olduğu enfeksiyon ve dissemine hastalık artmış mortalite ile ilişkili saptanmıştır.

Sundaram ve ark. (2) 56 serebral mukormikozisli olguyu araştırdıkları çalışmalarında, 44 olguda rinoserebral mukormikozis, 20 olguda ise izole santral sinir sistemi mukormikozisi bildirmişlerdir. Kırk dört olgunun 31'inde diyabet predispozan faktör olarak belirlenmiştir. Toplam 44 hastanın 12'sinden doku kültürü alınmış, 8'inde *Rhizopus oryzae*, 2'sinde *Mucor* izole edilirken, bir olguda *Rhizopus* türü (spp.) ile birlikte *Candida* spp. saptanırken, 2 olguda kültürde üreme saptanmamıştır. Sunduğumuz olguda tanı sinüslerden alınan materyalin patolojik incelemesi ile konuldu, mantar kültürü yapılmadı. İnvaziv mukormikoziste altta yatan hastalıklar klinik bulgular ve klinik sonuçları etkileyebilir (9).

Guerreiro ve ark. (10) 15 yaşında diyabetik ketoasidozu olan bir erkek hastada orbito-rinoserebral mukormikozis bildirmişlerdir. Tedaviyle hasta iyileşmesine rağmen, rezidüel oftalmopileji ve sağ gözde körlük geliştiği rapor edilmiştir. Sunduğumuz olguda da tanıda olası gecikme nedeniyle sağ gözde görme kaybı mevcuttu.

Türkiye'den Kara ve ark. (1) diyabetik ketoasidozu olan iki hastada rino-orbitoserebral mukormikozis bildirmişlerdir. Olgular cerrahi debritman ve amfoterisin B ile tedavi edilmiştir. Tatar ve ark. (3) 72 yaşında kontrolsüz tip 2 diyabetes mellitusu olan bir kadın hastada orbital apseyle seyreden rino-orbital mukormikozis bildirmişlerdir. Olgu sol gözde ekzoftalmus, diplopi ve baş ağrısı yakınmaları ile müracaat etmiş, bilgisayarlı tomografide sol orbitada apse saptanmıştır. Endoskopik sinüs cerrahisi uygulanan hastada biyopsi materyalinin histopatolojik incelemesi sonucunda invaziv mukormikozis tanısı konmuştur. Sunduğumuz olguda da tanı endoskopik sinüs cerrahisi ile alınan materyalin patolojik incelemesi ile konmuştur.

Sonuç olarak, sunduğumuz olguda olduğu gibi altta yatan diyabet gibi predispozan faktörleri olan hastalarda mukormikozis akılda tutulmalı, erken tanı ve tedavi gecikme olmaksızın uygulanmalıdır.

ETİK BEYANLAR

Aydınlatılmış Onam: Bu çalışmaya katılan hastalardandan yazılı onam alınmıştır.

Hakem Değerlendirme Süreci: Harici çift kör hakem değerlendirmesi.

Çıkar Çatışması Durumu: Yazarlar bu çalışmada herhangi bir çıkara dayalı ilişki olmadığını beyan etmişlerdir.

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Yazar Katkıları: Yazarların tümü; makalenin tasarımına, yürütülmesine, analizine katıldığını ve son sürümünü onayladıklarını beyan etmişlerdir.

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Letter to the Editor / Editöre Mektup

MEDICINE PALLIATIVE CARE

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Synovial antibody index as a marker of synovitis in knee osteoarthritis

Diz osteoartritinde sinovit belirteci olarak sinoviyal antikor indeksi

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Dear editor,

I was very delighted to read your latest issue with various articles about the different aspects of medicine. I was also pleased that among the authors were many faculties from multiple disciplines. I read, with interest, the study by Yılmaz et al. (vol.2, number 4, 2021) analyzing the antibody response of various viruses in patients with synovitis. I had several concerns about the article that I wanted to emphasize. First, the term "synovitis" has an extremely wide use among physicians with a very wide range of etiologies. The article pointed out that only advanced patients with knee osteoarthritis (Kelgreen stage 3-4) were included in the study group. Nevertheless, the type of osteoarthritis (primary or secondary) and the stage of synovitis (acute vs chronic or early vs late) and if the patients have any history of inflammatory diseases are not clear enough in the article (1,2). Second, the synovial antibody index, which was mentioned in the materials and methods section, had no reference. The authors used this index to get a definitive conclusion for the source of the viral antibodies in the synovial fluid. So it is the most important parameter in the study. I did a search in English literature and could not find any article defining an index like that. If this was a first description by the authors, then I recommend doing a validation analysis in a different study. Finally, the literature contains numerous studies analyzing the inflammatory reaction of the synovium against various viruses (3,4). In these studies, for the detection of the viral load, an immunohistochemical analysis of the synovial tissue was also frequently performed (5). In short, although well-designed, I believe that, it would have been much better if the study and control groups were meticulously composed with well-defined inclusion and exclusion criteria. Moreover, the synovial antibody index has to be clarified, it would be more helpful if a contribution from the literature was added to the manuscript and an immunohistochemical analysis was added to the final conclusion.

Keywords: Synovitis, osteoarthritis, antibody

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Case Report: These are rare or different articles in diagnosis and treatment. It should be supported with sufficient number of photographs and diagrams. Abstract (about 250 words; no section; Turkish and English), Introduction, case report, discussion, conclusion.

Letter to the Editor: The articles that are published in the journal within the last year include a maximum of 500 words containing various opinions, experiences and questions of the readers. There are no Title and Abstract sections. The number of references is limited to 5 (max. 10). It should be indicated which article (number, date) is dedicated and at the end there should be the name, institution and address of the author. The answer to the letter is given by the editor or the author (s) of the article and published in the journal.

Education: Scientific articles supported by the latest clinical and laboratory applications that send messages to readers on current issues within the scope of the journal. Abstract (about 250 words; no section; Turkish and English), related titles, references.

Book Evaluations: Evaluations of national or internationally accepted books of current value within the scope of the journal.

WHAT SHOULD BE INDICATED BEFORE THE RESOURCES

ETHICAL DECLERATIONS

Ethics Committee Approval: The study was carried out with the permission of ..... Ethics Committee (Date:....., Decision No. .....).

Informed Consent: Written informed consent was obtained from all participants who participated in this ....study (If study retrospective: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Acknowledgements: If any, it should be written before references.

References: References should be written according to the order of arrival. If the number of authors in the source is 6 or less, all authors (surname and first name should be the first letter, the names of the authors should be separated by commas) should be specified; ("et al "), the name of the article (only the first letter of the sentence and the first letter of the special names will be capitalized), short journal name, year, volume, short page number (15-8, not 15-18) and a space between the punctuation marks. The format used for the manuscript submission should be as specified in Index Medicus (www.icmje.org). The list of references should only include studies that have been published or accepted for publication or have a Doi number. Journal abbreviations should follow the style used in **Cumulated Index Medicus** (http://www2.bg.am.poznan.pl/czasopisma/medicus.php?lang=eng.). The number of references should be limited to 40 in research articles, 60 in reviews, 20 in case reports and 5 (max. 10) in letter to the editor. References should be given in parentheses at the end of the sentence just before the period. For example (4,5). The author (s) is responsible for the accuracy of the references. Importance should be given to the synthesis of domestic and foreign sources.

4. Figures and Table Titles

Titles should be written after the references. Each must be submitted as a separate image file (at least 300 dpi resolution, jpg).

After the article is accepted for publication, the first copy of the string will be sent to the responsible author by e-mail. In this text, only the spelling errors will be corrected and no additions or substitutions will be made. The responsible author will notify the editorial center by e-mail of the corrections within 2 days.

SOURCE WRITING EXAMPLES

Excerpt from journals;

Cesur S, Aslan T, Hoca NT, Cimen F, Tarhan G, Cifci A. Clinical importance of serum neopterin level in patients with pulmonary tuberculosis. Int J Mycobacteriol 2014; 3: 15-8 (not 15-18).

Excerpt from the book;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Excerpt from the book, which is the only author and editor;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams & Wilkins; 1996: 46-60.

Excerpt from the book with multiple authors and editors;

Schulz JE, Parran T Jr.: Principles of identification and intervention. In: Principles of Addicton Medicine, Graem AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams & Wilkins; 1998: 1-10.

If the editor is also the author of the chapter in the book;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag; 1988: 45-67.

Excerpt from PhD/Undergraduate Thesis;

Kilic C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Excerpt from an internet site;

Site name, URL address, author names, access date should be given in detail.

Giving a Doi number;

Joos S, Musselmann B, Szecsenyi J. Integration of complementary and alternative medicine into the family market in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi: 10.1093/ecam/nep019).

For other reference styles, see "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References".

Eder I hereby declare that all or part of the material in this study has not previously been published in any place and is not currently being evaluated elsewhere for publication. electronic submissions and all kinds of pre-declarations.

Sponsorship Statement

Authors should declare, if any, the roles of sponsors of the study:

1. Design of the study 2. Data collection, analysis and interpretation of the results 3. Writing the report

CHECKLIST/CONTROL LIST

The checklist must be complete.

What should be in the article;

—Editor to Presentation Page

—Title Page

- Ethical Status,
- "Conflict of Interest"
- Orcid numbers and author information should be on this page.

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1. **Presentation page to the Editor:** It should be written by the responsible author addressed to the editor. Phone and E-mail must be added. The title, short name of the submitted article, mamış Unpublished previously, has not been sent to any journal for review and is the original work of the authors "should include a Conflict of Interest Statement".
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7. **M**aterial and Method section should indicate the approval of the **Ethics Committee** (it is recommended to include the place, date, ethics committee number). In articles that do not require Ethics Committee Approval, it should be stated that the Approval/Permission of the Institution has been obtained (in order to avoid Conflict of Interest). Related documents should be sent on request. It should be noted that the author (s) is responsible for ethical problems.
8. **S**tatistical terms (such as p, r, α) should **not** be used in the discussion.
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12. **Copyright Transfer Form:** Must be filled in the original language of the manuscript. It must be signed by all authors. In the absence of the signature of all authors, the **Corresponding Author** may take responsibility and sign on behalf of all authors.

YAYIN KURALLARI, YAYIN POLİTİKASI, GENEL İLKELER VE GÖNDERME KURALLARI

YAZARLARA BİLGİ

Journal of Medicine and Palliative Care (JOMPAC) hakemli, açık erişimli, periyodik olarak çıkan bir dergidir. Dergi yazım kurallarına göre düzenlenmiş makaleler **DergiPark** sistemi üzerinden kabul edilmektedir. https://dergipark.org.tr/tr/pub/jompac/archive web adresinden ve **Dergipark** web sayfasından tüm sayılara ücretsiz olarak erişilebilmektedir. Amacımız uluslararası bir tabanda hastalıkların teşhis ve tedavisinde yenilikler içeren yüksek kalitede bilimsel makaleler yayımlamak ve bilime katkı sağlamaktır. Yılda dört kez (**Mart, Haziran, Eylül, Aralık**) yayımlanmaktadır. Hakemli bir dergi olarak gelen yazılar biyomedikal makalelere ait **Uluslararası Tıp Dergileri Editörleri Komitesi** (www.icmje.org) tarafından tanımlanan standart gereksinimler ile ilgili ortak kurallara uygunluğu açısından değerlendirilmektedir. Dergimizde yayımlanmış makalelerin tamamına elektronik ortamdan ulaşabilir, **DergiPark** web sitemizden (https://dergipark.org.tr/en/pub/jompac) okuyabilir, indirebilirsiniz. Amacımız siz meslektaşlarımızın göndermiş olduğu yayınların karar ve yayımlanma sürecini en kısa sürede sonuca ulaştırmaktır. Dergimizin kalitesini yükseltmek için her zaman önerilere ve yapıcı eleştirilere açık olduğumuzu ve bu konudaki bildirimlere gereken hassasiyeti göstereceğimizi belirtmek isteriz. Makale işletim sisteminde ve atıflarda derginin İngilizce adı kullanılacaktır.

Journal of Medicine and Palliative Care (JOMPAC) kapsam olarak tıbbın ve tıpla ilgili sağlık bilimlerinin her branşı ile ilgili retrospektif/prospektif klinik ve laboratuvar çalışmaları, ilginç olgu sunumları, davet üzerine yazılan derlemeler, editöre mektuplar, orijinal görüntüler, kısa raporlar ve teknik yazıları yayımlayan bilimsel, hakemli bir dergidir. Derginin dili **İngilizce** ve **Türkçe**'dir. Makaleler hem Türkçe hem de İngilizce olarak kabul edilmektedir. Türkçe gönderilen makalelerde ayrıca İngilizce Başlık, Abstract, Keywords olmalı, İngilizce olarak gönderilen makalelerde de ayrıca Türkçe Başlık, Öz, Anahtar Kelimeler olmalıdır. Başka bir dergide yayımlanmış veya değerlendirilmek üzere gönderilmiş yazılar veya dergi kurallarına göre hazırlanmamış yazılar değerlendirme için kabul edilmez. Editör, yardımcı editör ve yayıncı dergide yayımlanan yazılar için herhangi bir sorumluluk kabul etmez. Dergimizde yayımlanmış makalelerin tamamına elektronik ortamdan ulaşabilir, https://dergipark.org.tr/tr/pub/jompac web sitemizden okuyabilir, indirebilirsiniz. Yazıların tüm bilimsel sorumluluğu yazar(lar)a aittir.

DERGİ ADI

Journal of Medicine and Palliative Care

DERGİ ADININ KISALTMASI

J Med Palliat Care/JOMPAC/jompac

YAZIŞMA ADRESİ

Yazılar e-posta yoluyla sorumlu yazar tarafından, **DergiPark**'a kayıt olunduktan sonra **DergiPark** üzerinden https://dergipark.org.tr/tr/journal/3258/submission/step/manuscript/new linkine girilerek gönderilmelidir.

MAKALE GENEL YAZIM KURALLARI

Yazıların tüm bilimsel sorumluluğu yazar(lar)a aittir. Editör, yardımcı editör ve yayıncı dergide yayımlanan yazılar için herhangi bir sorumluluk kabul etmez.

EDİTÖRİYEL ÖN KONTROL DEĞERLENDİRMESİ

Journal of Medicine and Palliative Care (JOMPAC)'e gönderilen yazılar format ve intihal 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 yayıma kabul edilmesi sonrası isim sırası değiştirilemez, yazar ismi eklenip çıkartılamaz.

BİLİMSEL VE ETİK SORUMLULUK

Journal of Medicine and Palliative Care (JOMPAC)'in yayın ve yayın süreçleri, Dünya Tıbbi Editörler Derneği (World Association of Medical Editors (**WAME**)), Yayın Etiği Komitesi (Committee on Publication Ethics (**COPE**)), Uluslararası Tıbbi Dergi Editörleri Konseyi (International Council of Medical Journal Editors (**ICMJE**)), Bilim Editörleri Konseyi (Council of Science Editors (**CSE**)), Avrupa Bilim Editörleri Birliği (**EASE**) ve Ulusal Bilgi Standartları Organizasyonu (National Information Standards Organization (NISO)) kurallarına uygun olarak şekillendirilmiştir. Dergi, Bilimsel Yayıncılıkta Şeffaflık ve En İyi Uygulama İlkeleri'ne (Principles of Transparency and Best Practice in Scholarly Publishing (**doaj.org/bestpractice**)) uygundur.

Klinik araştırma makalelerinin protokolü Etik Komitesi tarafından onaylanmış olmalıdır. İnsanlar üzerinde yapılan tüm çalışmalarda "**Gereç ve Yöntem**" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın **Helsinki İlkeler Deklarasyonu**'na (**https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/**) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır. Çalışmaya dahil edilen tüm kişilerin **Bilgilendirilmiş Onam Formu'**nu imzaladığı metin içinde belirtilmelidir. **Journal of Medicine and Palliative Care (JOMPAC)'**e gönderilen makalelerdeki çalışmaların **Helsinki İlkeler Deklarasyonu'**na uygun olarak yapıldığı, kurumsal etik ve yasal izinlerin alındığı varsayılacak ve bu konuda sorumluluk kabul edilmeyecektir. Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntem bölümünde hayvan haklarını **Guide for the Care and Use of Laboratory Animals** (**https://www.nap.edu/catalog/5140/guide-for-the-care-and-use-of-laboratory-animals**) prensipleri doğrultusunda koruduklarını, çalışmalarında ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır. Olgu sunumlarında hastanın kimliğinin ortaya çıkmasına bakılmaksızın hastalardan "Bilgilendirilmiş rıza" alınmalıdır. Makalede Etik Kurul Onayı alınması gerekli ise; alınan belge makale ile birlikte gönderilmelidir. Makale yazarlar tarafından **akademik intihal önleme programı**ndan geçirilmelidir. Makalenin etik kurallara uygunluğu yazarların sorumluluğundadır.

Tüm makale başvuruları intihal araştırılması için taranmalı ve sonrasında dergi sistemine yüklenmelidir. İntihal, atıf manipülasyonu ve gerçek olmayan verilerden şüphelenilmesi veya araştırmaların kötüye kullanılması durumunda, yayın kurulu **COPE** yönergelerine uygun olarak hareket eder. Bakınız: **Guidance from the Committee on Publication Ethics** (**COPE**).

Yazar olarak listelenen her bireyin **Uluslararası Tıp Dergisi Editörleri Komitesi** (**ICMJE - www.icmje.org**) tarafından önerilen yazarlık kriterlerini karşılaması gerekir. **ICMJE** yazarlığın aşağıdaki 4 kritere dayanmasını önerir: (1) Çalışmanın tasarımı, verilerin elde edilmesi, analizi veya yorumlanması (2) Dergiye gönderilecek kopyanın hazırlanması veya bu kopyanın içeriğini bilimsel olarak etkileyecek ve ileriye götürecek şekilde katkı sağlanması (3) Yayımlanacak kopyanın son onayı (4) Çalışmanın tüm bölümleri hakkında bilgi sahibi olma ve tüm bölümleri hakkında sorumluluğu alma.

Bir yazar, yaptığı çalışmanın bölümlerinden sorumlu olmanın yanı sıra, çalışmanın diğer belirli bölümlerinden hangi ortak yazarların sorumlu olduğunu bilmeli ayrıca yazarlar, ortak yazarlarının katkılarının bütünlüğüne güvenmelidir. Yazar olarak atananların tümü yazarlık için dört kriteri de karşılamalı ve dört kriteri karşılayanlar yazar olarak tanımlanmalıdır. Dört kriterin tümünü karşılamayanlara makalenin başlık sayfasında teşekkür edilmelidir. Yayın kurulu yazarlık şartlarını karşılamayan bir kişinin yazar olarak eklendiğinden şüphe ederse yazı daha fazla incelenmeksizin reddedilecektir.

Journal of Medicine and Palliative Care (JOMPAC)'e gönderilen bir çalışma için bireylerden veya kurumlardan alınan mali hibeler veya diğer destekler Editör Kurulu'na bildirilmelidir. Potansiyel bir çıkar çatışmasını bildirmek için, **ICMJE Potansiyel Çıkar Çatışması Bildirim Formu**, katkıda bulunan tüm yazarlar tarafından imzalanmalı ve gönderilmelidir. Editörlerin, yazarların veya hakemlerin çıkar çatışması olasılığı, derginin Editör Kurulu tarafından **COPE** ve **ICMJE** yönergeleri kapsamında çözümlenecektir. Derginin Editör Kurulu, tüm itiraz durumlarını **COPE** kılavuzları kapsamında ele almaktadır. Bu gibi durumlarda, yazarların itirazları ile ilgili olarak yazı işleri bürosu ile doğrudan temasa geçmeleri gerekmektedir. Gerektiğinde, dergi içinde çözülemeyen olayları çözmek için bir kamu denetçisi atanabilir. Baş editör itiraz durumlarında karar alma sürecinde alınacak kararlarla ilgili nihai otoritedir. Yazarlar, dergiye bir makale gönderirken, yazıların telif haklarını **Journal of Medicine and Palliative Care (JOMPAC)**'e devretmiş olmayı kabul ederler. Yazı yayımlanmamak üzere reddedilirse veya herhangi bir sebepten geri çekilirse telif hakkı yazarlara geri verilir.Şekiller, tablolar veya diğer basılı materyaller de dahil olmak üzere basılı ve elektronik formatta daha önce yayımlanmış içerik kullanılıyorsa yazarlar telif hakları sahiplerinden gerekli izinleri almalıdır. Bu konudaki hukuki, finansal ve cezai yükümlülükler yazarlara aittir. **Journal of Medicine and Palliative Care'de (JOMPAC)** yayımlanan makalelerde belirtilen ifade veya görüşler, editörlerin, yayın kurulunun veya yayıncının görüşlerini yansıtmaz; editörler, yayın kurulu ve yayıncı bu tür materyaller için herhangi bir sorumluluk veya yükümlülük kabul etmez. Yayınlanan içerikle ilgili nihai sorumluluk yazarlara aittir.

MAKALE "BAŞKA BİR YERDE YAYIMLANMAMIŞTIR" İBARESİ

Her yazar makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, editöre sunum sayfasında belirtmelidirler. Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir. Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal, vb.) yazarlara aittir.

YAYIN HAKKI DEVİR FORMU

Telif Hakkı Devir Formu (https://dergipark.org.tr/tr/journal/3258/file/3177/show) linkinden temin edilebilir. Makalenin ana dilinde (makalenin dili İngilizce ise, İngilizce olmalıdır, makalenin dili Türkçe ise, Türkçe olmalıdır) doldurulmalı, makale (https://dergipark.org.tr/tr/journal/3258/submission/step/manuscript/new) adresi üzerinden yüklenirken on-line olarak gönderilmelidir 1976 Copyright Act'e göre, yayımlanmak üzere kabul edilen yazıların her türlü yayın hakkı yayıncıya aittir.

YAZIM DİLİ KONTROLÜ

Derginin yayın dili **Türkçe** ve **İngilizce**'dir, makaleler hem Türkçe hem de İngilizce olarak kabul edilmektedir. Türkçe yazılan yazılarda düzgün bir Türkçe kullanımı önemlidir. Bu nedenle Türk Dil Kurumu'nun Türkçe sözlüğü veya www.tdk.org.tr adresi ayrıca Türk tıbbi derneklerinin kendi branşlarına ait terimler sözlüğü esas alınmalıdır. İngilizce makaleler ve İngilizce Abstract gönderilmeden önce profesyonel bir dil uzmanı tarafından kontrol edilmelidir. Yazıdaki yazım ve gramer hataları içerik değişmeyecek şekilde İngilizce dil danışmanımız ve redaksiyon komitemiz tarafından düzeltilmektedir.

İSTATİSTİK DEĞERLENDİRMESİ

Tüm prospektif, deneysel ve retrospektif araştırma makaleleri istatistik yönünden (gerekirse istatistik uzmanı tarafından) değerlendirilmeli ve uygun plan, analiz ve raporlama ile belirtilmelidir.

YAYIMA KABUL EDİLMESİ

Editör ve hakemlerin uygunluk vermesi sonrası makalenin gönderim tarihi esas alınarak yayım sırasına alınır. Her yazı için bir **Doi** numarası alınır.

MAKALE YAZIM KURALLARI

Yazılar Microsoft Word programı ile çift satır aralıklı ve başlık yazıları (Makale Adı, Öz, Abstract, Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Kaynaklar vs.) 12 punto olarak, makalenin diğer kısımları 11 punto olacak şekilde, her sayfanın iki yanında ve alt ve üst kısmında 2,5 cm boşluk bırakılarak yazılmalıdır. Yazı stili Times New Roman olmalıdır. "System International" (SI) unitler kullanılmalıdır. Şekil, tablo ve grafikler metin içinde refere edilmelidir. Kısaltmalar, kelimenin ilk geçtiği yerde parantez içinde verilmelidir. Türkçe makalelerde %50 bitişik yazılmalı, aynı şekilde İngilizcelerde de 50% bitişik olmalıdır. Türkçe'de ondalık sayılarda virgül kullanılmalı (55,78) İngilizce yazılarda nokta (55.78) kullanılmalıdır. Araştırma makalesi ve derleme 4000, olgu sunumu 2500, editöre mektup 500 kelimeyi (ABSTRACT/ÖZ ve REFERENCES/KAYNAKLAR hariç olmak üzere) geçmemelidir. Öz sayfasından itibaren sayfalar numaralandırılmalıdır.

Yazının Bölümleri

1. Editöre Sunum Sayfası

Journal of Medicine and Palliative Care (Tıp ve Palyatif Bakım Dergisi)'de yayımlanmak üzere değerlendirilmesi isteğinin belirtildiği, makalenin sorumlu yazarı tarafından dergi editörüne hitaben gönderdiği yazıdır. Bu kısımda makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığı ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığı, "**Maddi Destek ve Çıkar İlişkisi**" durumu, dil ve istatistik kontrolünün yapıldığı belirtilmelidir.

2. Başlık Sayfası

Sayfa başında gönderilen makalenin kategorisi belirtilmedir (klinik analiz, araştırma makalesi, deneysel çalışma, olgu sunumu, derleme vs). Tüm yazarların ad ve soyadları yazıldıktan sonra üst simge ile 1'den itibaren numaralandırılıp, çalıştıkları kurum, klinik, şehir ve ülke yazar isimleri altına eklenmelidir. Başlık sayfasında her yazarın **Orcid no** bilgisi, **e-posta** adresi olmalıdır. Bu sayfada Sorumlu Yazar belirtilmeli isim, açık adres, telefon ve e-posta bilgileri eklenmelidir (Dergimizin formatı gereği adres bilgileri, kurumları makale dili Türkçe ise Türkçe olarak, İngilizce ise İngilizce olarak belirtilmelidir). Kongrelerde sunulan Sözlü veya Poster bildiriler başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmelidir.

3. Makale Dosyası

Yazar ve kurum isimleri bulunmamalıdır, bu bilgiler sadece başlık sayfasında olmalıdır.

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemeli, Türkçe ve İngilizce olarak yazılmalıdır. Öz: Türkçe ve İngilizce (Abstract) yazılmalıdır. Araştırma makalelerinde Öz; Amaç, Gereç, Yöntem, Bulgular ve Sonuç bölümlerine ayrılmalı ve 400 kelimeyi geçmemelidir. Derleme, olgu sunumları ve benzerlerinde Öz; kısa ve tek paragraflık olmalı, derlemelerde 300, olgu sunumlarında 250 kelimeyi geçmemelidir.

Anahtar Kelimeler: Türkçe Öz'ün ve İngilizce Abstract'ın sonlarında bulunmalıdır. En az 3 en fazla 6 adet yazılmalıdır. Kelimeler birbirlerinden noktalı virgül ile ayrılmalıdır. İngilizce Anahtar Kelimeler (Keywords) "**Medical Subject Headings (MESH)**"e uygun (www.nlm.nih.gov/mesh/MBrowser.html) olarak verilmelidir. Türkçe Anahtar Kelimeler "Türkiye Bilim Terimleri' ne uygun olarak verilmelidir (www.bilimterimleri.com). Bulunamaması durumunda bire bir Türkçe tercümesi verilmelidir.

Şekil, Fotoğraf, Tablo ve Grafikler: Metin içinde geçtiği yerlerde ilgili cümlenin sonunda belirtilmeli, metin içine yerleştirilmemeli, kaynaklardan sonra metin sonuna eklenmelidir. Kullanılan kısaltmalar altındaki açıklamada belirtilmelidir. Daha önce basılmış şekil, resim, tablo ve grafik kullanılmış ise yazılı izin alınmalıdır ve bu izin açıklama olarak şekil, resim, tablo ve grafik açıklamasında belirtilmelidir. Makale yazarlar tarafından akademik intihal önleme programından geçirilmelidir. Resim/fotoğraf jpeg ve en az 300 dpi çözünürlükte olmalıdır.

Metin Bölümleri: Yayımlanmak üzere gönderilecek yazı örnekleri şu şekildedir.

Editöriyel Yorum/Tartışma: Yayınlanan orijinal araştırma makaleleri ile ilgili, araştırmanın yazarları dışındaki, o konunun uzmanı tarafından değerlendirilmesidir. Dergide makalelerden önce yayımlanır.

Araştırma Makalesi: Prospektif-retrospektif ve her türlü deneysel çalışmalar yayımlanabilmektedir. Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Sonuç olarak düzenlenmelidir. Öz (yaklaşık 400 kelime; amaç, gereç ve yöntem, bulgular ve sonuç bölümlerinden oluşan Türkçe ve İngilizce), Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Sonuç, Kaynaklar.

Derleme: Davet edilen yazarlar tarafından veya doğrudan hazırlanabilir. Tıbbi özellik gösteren her türlü konu için son tıp literatürünü de içine alacak şekilde hazırlanabilir. Öz (yaklaşık 300 kelime, bölümsüz, Türkçe ve İngilizce), konu ile ilgili Başlıklar, Kaynaklar.

Olgu Sunumu: Tanı ve tedavide farklılık gösteren veya nadir görülen makalelerdir. Yeterli sayıda fotoğraflarla ve şemalarla desteklenmiş olmalıdır. Öz (yaklaşık 250 kelime; bölümsüz; Türkçe ve İngilizce), Giriş, Olgu sunumu, Tartışma, Sonuç olarak düzenlenmelidir.

Editöre Mektup: Dergide son bir yıl içinde yayımlanan makaleler ile ilgili okuyucuların değişik görüş, tecrübe ve sorularını içeren en fazla 500 kelimelik yazılardır. Başlık ve Öz bölümleri yoktur. Kaynak sayısı 5 (en fazla 10) ile sınırlıdır. Hangi makaleye (sayı, tarih verilerek) ithaf olunduğu belirtilmeli ve sonunda yazarın ismi, kurumu, adresi bulunmalıdır. Mektuba cevap, editör veya makalenin yazar(lar)ı tarafından, yine dergide yayımlanarak verilir.

Eğitim: Derginin kapsamı içinde güncel konularda okuyucuya mesaj veren son klinik ve laboratuvar uygulamaların da desteklediği bilimsel makalelerdir. Öz (yaklaşık 250 kelime; bölümsüz; Türkçe ve İngilizce), konu ile ilgili Başlıklar, Kaynaklar.

Kitap Değerlendirmeleri: Derginin kapsamı içinde güncel değeri olan ulusal veya uluslararası kabul görmüş kitapların değerlendirmeleridir.

KAYNAKLARDAN HEMEN ÖNCE BELİRTİLMESİ GEREKENLER

ETİK BEYANLAR

Etik Kurul Onayı (Eğer gerekiyorsa): "Çalışma için …….. Etik Kurulu'ndan .....tarih ve ..... sayı /karar no ile etik kurul onayı alınmıştır." ifadesiyle yazarlar tarafından belirtilmelidir.

Aydınlatılmış Onam: Bu çalışmaya katılan hasta(lar)dan yazılı onam alınmıştır (Olgu sunumlarında ve kişilerle yapılan prospektif çalışmalarda mutlaka olmalıdır. Eğer çalışma retrospektif ise: "Aydınlatılmış Onam: Çalışma retrospektif olarak dizayn edildiği için hastalardan aydınlatılmış onam alınmamıştır." ifadesiyle yazarlar tarafından belirtilmelidir.

Hakem Değerlendirme Süreci: "Harici çift kör hakem değerlendirmesi" ifadesiyle yazarlar tarafından belirtilmelidir.

Çıkar Çatışması: "Yazarlar bu çalışmada herhangi bir çıkara dayalı ilişki olmadığını beyan etmişlerdir." ifadesiyle yazarlar tarafından belirtilmelidir.

Finansal Destek: "Yazarlar bu çalışmada finansal destek almadıklarını beyan etmişlerdir" ifadesiyle yazarlar tarafından belirtilmelidir.

Yazar Katkıları: "Yazarların tümü; makalenin tasarımına, yürütülmesine, analizine katıldığını ve son sürümünü onayladıklarını beyan etmişlerdir." ifadesiyle yazarlar tarafından belirtilmelidir.

Teşekkür Yazısı: Varsa kaynaklardan önce yazılmalıdır.

Kaynaklar: Kaynaklar makalede geliş sırasına göre yazılmalıdır. Kaynaktaki yazar sayısı 6 veya daha az ise tüm yazarlar (soyadı ve adının ilk harfi olacak şekilde olmalı, yazar isimleri birbirinden virgül ile ayırılmalı) belirtilmeli, 7 veya daha fazla ise ilk 3 isim yazılıp ve ark. ("et al") eklenmeli, makale ismi (Tümce şeklinde sadece cümlenin ilk harfi ve özel isimlerin ilk harfi büyük olacak), kısa dergi adı, yıl, cilt, kısa sayfa no (15-8. şeklinde olacak, 15-18 olmayacak) eklenmeli ve noktalama işaretleri arasında birer boşluk bırakılmalıdır. Kaynak yazımı için kullanılan format Index Medicus'ta belirtilen şekilde olmalıdır (www. icmje.org). Kaynak listesinde yalnızca yayınlanmış ya da yayınlanması kabul edilmiş veya Doi numarası almış çalışmalar yer almalıdır. Dergi kısaltmaları **Cumulated Index Medicus**'ta kullanılan stile uymalıdır (http://www2.bg.am.poznan.pl/czasopisma/ medicus.php?lang=eng.). Kaynak sayısının araştırma makalelerinde 40, derlemelerde 60, olgu sunumlarında 20, editöre mektupta 5 (en fazla 10) ile sınırlandırılmasına özen gösterilmelidir. Kaynaklar metinde cümle sonunda nokta işaretinden hemen önce parantez kullanılarak belirtilmelidir. Örneğin (4,5). Kaynakların doğruluğundan yazar(lar) sorumludur. Yerli ve yabancı kaynakların sentezine önem verilmelidir.

4. Şekil, Grafik, Resim ve Tablo Başlıkları

Başlıklar kaynaklardan sonra yazılmalıdır. Her biri ayrı bir görüntü dosyası (en az 300 dpi çözünürlükte, jpg) olarak gönderilmelidir.

Makalenin basıma kabulünden sonra Dizginin ilk düzeltme nüshası sorumlu yazara e-posta yoluyla gönderilecektir. Bu metinde sadece yazım hataları düzeltilecek, ekleme çıkartma yapılmayacaktır. Sorumlu yazar düzeltmeleri 2 gün içinde bir dosya halinde e-posta ile yayın idare merkezine bildirecektir.

Kaynak Yazım Örnekleri

Dergilerden yapılan alıntı;

Cesur S, Aslan T, Hoca NT, Çimen F, Tarhan G, Çifci A. Clinical importance of serum neopterin level in patients with pulmonary tuberculosis. Int J Mycobacteriol 2014; 3: 15-8 (15-18 değil).

Kitaptan yapılan alıntı;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Tek yazar ve editörü olan kitaptan alıntı;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams&Wilkins; 1996: 46-60.

Çoklu yazar ve editörü olan kitaptan alıntı;

Schulz JE, Parran T Jr: Principles of identification and intervention. In:Principles of Addicton Medicine, Graham AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams&Wilkins; 1998: 1-10.

Eğer editör aynı zamanda kitap içinde bölüm yazarı ise;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag; 1988: 45-67.

Doktora/lisans tezinden alıntı;

Kılıç C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Bir internet sitesinden alıntı;

Sitenin adı, URL adresi, yazar adları, erişim tarihi detaylı olarak verilmelidir.

Doi numarası vermek;

Joos S, Musselmann B, Szecsenyi J. Integration of complementary and alternative medicine into family prac- tice in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi:10.1093/ecam/nep019).

Diğer referans stilleri için "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References" sayfasını ziyaret ediniz.

"Bu çalışmanın içindeki materyalin tamamı ya da bir kısmının daha önce herhangi bir yerde yayımlanmadığını ve halihazırda da yayın için başka bir yerde değerlendirilmede olmadığını beyan ederim." Bu 400 kelimeye kadar olan özler hariç, sempozyumlar, bilgi aktarımları, kitaplar, davet üzerine yazılan makaleler, elektronik formatta gönderimler ve her türden ön bildirileri içerir.

Sponsorluk Beyanı

Yazarlar aşağıda belirtilen alanlarda, varsa çalışmaya sponsorluk edenlerin rollerini beyan etmelidirler:

1. Çalışmanın dizaynı 2. Veri toplanması, analizi ve sonuçların yorumlanması 3. Raporun yazılması

KONTROL LİSTESİ

Kontrol listesindekiler eksiksiz yapılmalıdır.

Makalede mutlaka olması gerekenler;

—Editöre Sunum Sayfası

—Başlık Sayfası

- Etik Durum,
- "Çıkar Çatışması Durumu" belirtir cümle,
- Orcid numaraları ve yazar bilgileri bu sayfada olmalıdır.

—Ana Metin

—Telif Hakkı Devri Formu

1. **Editöre Sunum Sayfası:** Sorumlu Yazar tarafından editöre hitaben yazılmış olmalıdır. Telefon ve E-posta eklenmelidir. Gönderilen makalenin adı, kısa adı, "Daha önceden yayımlanmamış, şu an herhangi bir dergiye değerlendirilmek üzere gönderilmemiştir ve yazarların kendi orijinal çalışmasıdır" ibaresi, "Çıkar Çatışması Beyanı" içermelidir.
2. **Başlık sayfası:** Türkçe ve İngilizce Makale başlıkları/Kısa başlıklar, Yazarlar ve Kurumları, Sorumlu Yazar posta adresi ve telefon, tüm yazarların **Orcid no** (2019 yılından itibaren zorunludur) ve **E-posta** adresleri. **Başlıkta özel isimler ve ilk harf dışında küçük harf kullanılmalıdır**.
3. **Makalenin Ana Metin sayfaları:** Türkçe ve İngilizce Makale Başlıkları/Kısa Başlıklar, Türkçe ve İngilizce Öz/Abstract ve Anahtar Kelimeler/Keywords, Makale Metni, Kaynaklar, Tablo ve Şekil Başlıkları, Tablolar. **Bu sayfada yazar isimleri, kurum bilgileri olmayacaktır.**
4. **Yazı tipi:** Başlıklarda "Times New Roman" ve 12 punto olmalı, makalenin diğer kısımlarında 11 punto, çift boşluklu satır arası ve tüm alanlarda 2,5 cm girinti ayarıyla yazılmalıdır.
5. **Öz/Abstract:** Türkçe özet **ÖZ** ile başlamalı; "**Giriş/Amaç, Gereç ve Yöntem, Bulgular ve Sonuç**" kısımlarını içermelidir. İngilizce özet **ABSTRACT** başlığıyla başlamalı "**Introduction/Aim, Material and Method, Findings/Results, Conclusion**" kısımlarını içermelidir.
6. **Anahtar Kelimeler/Keywords:** Türkçe Öz kısmının altına "**Anahtar Kelimeler**", İngilizce "Abstract" kısmının altında "**Keywords**" (birleşik) halde eklenmelidir. Anahtar kelimeler en az 3, en çok 6 kelime/sözcük olmalı, birbirlerinden virgülle ayırılmalı ve MeSH'e uygun olmalıdır.
7. **G**ereç ve Yöntem kısmında **Etik Kurul Onayı** alındığı (Alındığı yer, tarih, etik kurul no olacak şekilde yazılması önerilir) belirtilmelidir. Etik Kurul Onayı gerektirmeyen makalelerde Kurum Onayı/İzni alındığı (Çıkar Çatışması olmaması için) belirtilmelidir. İlgili belgeler talep edildiğinde gönderilmelidir. Etik problemlerde sorumluluğun yazar(lar)da olduğu unutulmamalıdır.
8. **T**artışmada istatistiksel terimler (p, r, α gibi) **kullanılmamalıdır.**
9. **"Maddi Destek/Çıkar Çatışması Durumu"** kaynakçadan önce belirtilmeli, "***Teşekkür Yazısı***" varsa kaynakçadan önce yazılmalıdır.
10. **Kaynak Gösterimi;** yazım kurallarında detaylı anlatıldığı gibi olmalıdır. Derginin sayı numarası "(2)" parantez içinde olacak şekilde bizim kaynakça gösterimimizde **bulunmamaktadır.** Altı yazara kadar yazarı olan makalelerde bütün yazarların adı yazılmalı (Soyadı ve Adının ilk harfi olacak şekilde), yedi ve daha üstü yazarlı makalelerde ilk üç yazar, et al. (ve ark.) şeklinde kaynak gösterilmelidir. Makalenin adı Tümce kullanımı şeklinde (**özel isimler ve ilk harf dışında küçük harf kullanılmalıdır**) olmalıdır. **Derginin kısa adı verilmelidir.** Dergi adından sonraki noktalama işaretleri arasında birer boşluk bırakılmalıdır.
11. **T**ablo, Şekil ve Resimler ayrı bir başlık altında kaynakçadan sonra yerleştirilmelidir. **Şekil/Resim** (En az 300 dpi çözünürlükte, **jpeg** dosyası olmalıdır) ve **Tablo**lar ayrı bir veya daha fazla dosya halinde gönderilmelidir.
12. **Telif Hakkı Devri Formu:** Makalenin asıl dilinde doldurulmalıdır. Tüm yazarlar tarafından imzalanmalıdır. Tüm yazarların imzasının olmadığı durumlarda **Sorumlu Yazar** tüm yazarlar adına sorumluluğu alarak imzalayabilir.