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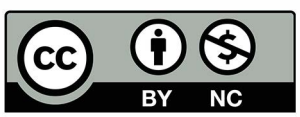

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Research Article / Araştırma Makalesi

A Cross Sectional Analysis of Etiology of Anemia Among Elderly Patients

Yaşlı Hastalarda Anemi Etiyolojisinin Kesitsel Analizi

[1]Büşra Tuğce Akman, [1]Deniz Arica, [2]Mesut Buğra Hatipoğlu, [2]Enes Arslanoğlu, [1]Ebru Koca, [1]Sema Karakuş, [1]Şahika Zeynep Aki,

[1]Ankara Baskent University Medical Faculty, Department of Hematology, Ankara, Türkiye
[2]Ankara Baskent University Medical Faculty, Department of Internal Medicine, Ankara, Türkiye

Abstract: The aim of this study is to evaluate the etiology and features of anemia in elderly patients from the perspective of hematology and to determine the rate of unexplained anemia. The medical records of elderly patients over the age of 65 who applied to the Hematology Department of Ankara Baskent University Hospital between January 2015 and January 2020 were retrospectively analyzed. According to WHO criteria, the threshold value accepted for anemia was Hb <12 g/dL for women and <13 g/dL for men. The prevalence of anemia was 18% among 3330 elderly patients. The ratio of women to men diagnosed with anemia was 1.5:1, and the mean age was 77.34±8.32. The mean Hb value was 9.79±1.75 g/dl and decreased significantly with advancing age (p<0.001). Polypharmacy was present in 68.3% of the patients. The etiological distribution of anemia was nutritional anemia in 339 (56.5%), hematologic malignancy in 127 (21.1%), anemia of chronic disease in 125 (20.8%), and unexplained anemia in 58 (9.7%) patients. 72% of the patients with indications for bone marrow biopsy had the procedure. Anemia in the elderly is a challenging issue due to comorbidity, polypharmacy, and problems in further examination. Hematological evaluation of anemia in elderly patients will reduce the rate of unexplained anemia. Patient selection for invasive procedures should be based on a risk-benefit ratio in frail elderly patients.
Keywords: Aged, Anemia, Etiology, Frail Elderly, Polypharmacy

Özet: Bu çalışmanın amacı yaşlı hastalarda aneminin etiyolojisini ve özelliklerini hematoloji bakış açısıyla değerlendirmek ve açıklanamayan anemi oranını belirlemektir. Ocak 2015-Ocak 2020 tarihleri arasında Ankara Başkent Üniversitesi Hastanesi Hematoloji Kliniğine başvuran 65 yaş üstü yaşlı hastaların tıbbi kayıtları retrospektif olarak incelendi. WHO kriterlerine göre anemi için kabul edilen eşik değer, kadınlarda Hb <12 g/dL, erkeklerde <13 g/dL idi. 3330 yaşlı hastada anemi prevalansı %18 idi. Kadınların anemi tanısı alan erkeklere oranı 1,5:1, yaş ortalaması 77,34±8,32 idi. Ortalama Hb değeri 9,79±1,75 g/dl idi ve yaş ilerledikçe anlamlı olarak azaldı (p<0,001). Hastaların %68,3'ünde polifarmasi mevcuttu. Aneminin etiyolojik dağılımı; 339 (%56,5) hastada beslenme anemisi, 127 (%21,1) hastada hematolojik malignite, 125 (%20,8) hastada kronik hastalık anemisi ve 58 (%9,7) hastada açıklanamayan anemi idi. Kemik iliği biyopsisi endikasyonu olan hastaların %72'sine prosedür uygulandı. Yaşlılarda anemi komorbidite, polifarmasi ve ileri tetkiklerdeki sorunlar nedeniyle zorlu bir konudur. Yaşlı hastalarda aneminin hematolojik olarak değerlendirilmesi açıklanamayan anemi oranını azaltacaktır. İnvaziv prosedürler için hasta seçimi, kırılgan yaşlı hastalarda bir risk-fayda oranına dayanmalıdır.
Anahtar Kelimeler: Anemi, Etiyoloji, Kırılgan Yaşlılar, Polifarmasi, Yaşlı

ORCID ID of the authors:BTA. 0000-0002-5821-9473, DA. 0000-0001-8076-1704, MBH. 0000-0002-0168-2993, EA. 0000-0002-1696-0124, EK. 0000-0002-7566-4456, SK. 0000-0001-7615-4581, ŞZA. 0000-0002-3068-5085

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Correspondence: Büşra Tuğçe AKMAN- Ankara Baskent University Medical Faculty, Department of Hematology, Ankara, Türkiye
e-mail: akmantugce@hotmail.com

1. Introduction

Anemia is a common health problem in elderly patients and is associated with decreased quality of life and increased morbidity and mortality. Although the prevalence of anaemia is highly variable according to the population studied, anaemia is observed in approximately 10% of the elderly in the community (1). Many comorbid conditions, including chronic diseases, nutritional deficiencies and inflammation may cause anemia (2). Hematological and solid organ malignancies are also important causes of anemia in the elderly population (1). After the exclusion of these causes, the diagnosis of unexplained anemia (UEA) is mentioned (3). Low serum erythropoietin (EPO) level, decreased testosterone level, occult inflammation and clonal changes in hemopoiesis have been blamed as the etiology (1, 4). In clinical practice, it is essential to determine the cause of anemia for the most appropriate treatment. However, comorbidities and multiple drug use make the diagnosis difficult in elderly patients (5, 6). In addition, it is not easy to perform an etiological evaluation with invasive procedures, including endoscopic examination and bone marrow biopsy, in elderly and frail patients. UEA has been reported with variable rates in studies. While this rate was reported between 25% and 44% in population-based studies (7, 8), rates varying according to the depth of the study are available in clinical studies. However, bone marrow biopsy was performed at a very low rate or was not performed in most studies (9–14). These differences have led to different prevalence rates of UEA in the literature. Understanding the etiology of anemia is still a challenging problem in the elderly patient population. In this study, we aimed to determine the prevalence of UEA in hematology outpatient clinics by examining the characteristics and underlying etiology of anemia in elderly patients in detail.

2. Materials and Methods

In this single center retrospective study, medical records of anemic patients over the age of 65 who were referred to the Ankara Baskent University Hematology Department between January 2015 and January 2020 were analyzed. According to WHO criteria; threshold value for anemia was accepted as Hb < 12 g/dL for women and < 13 g/dL for men. Morphologically, mean erythrocyte volume (MCV) < 80 fL was defined as microcytic, 80–100 fL normocytic, and > 100 fL macrocytic anemia (15). Patients with ferritin < 30 µg/L and/or transferrin saturation (TS) < 20% and C-reactive protein (CRP) < 3 mg/L was diagnosed with iron deficiency anemia (IDA) (16), while patients with a vitamin B12 level < 200 ng/L was diagnosed with vitamin B12 deficiency (17), and folic acid level <3.5 µg/L with folic acid deficiency (18). Anemia of chronic disease (ACD) was diagnosed with serum ferritin level > 100 µg/L and TS of < 20% in patients with chronic illness (chronic kidney disease, liver disease, congestive heart failure, chronic infection etc.) with positive acute phase reactants. In patients with advanced heart failure or chronic kidney failure undergoing dialysis; iron deficiency anemia accompanying anemia of chronic disease was diagnosed in patients with TS <20% and/or ferritin 100-500 µg/L (19). Bone marrow aspiration and biopsy (BMBX) were planned in patients without nutritional or hemolytic anemia, with unexplained cytopenia accompanying anemia, suspected hematological malignancy and/or UEA. Study approval was obtained from the Institutional Ethics Committee of Baskent University.

Statistical Analysis

Summary statistics (mean and standard deviation, median and range) were used to define continuous variables. For categorical variables, the number and percentage of participants in each category were reported. In order to compare the triple group in terms of continuous variables, ANOVA was used for the normally distributed variables, while the Kruskal Wallis test was used for the non-normally distributed variables. All statistical tests were performed at a significance level of 0.05. Statistical analyses were performed using the IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA) package program.

3. Results

In this retrospective study, the medical records of 3330 elderly patients who were referred to the hematology department between January 2015 and January 2020 were analyzed. Anemia was suspected in 968 individuals and diagnosed in 600 patients. The prevalence of anemia was 18% in patients aged 65 years and older. This rate was 18.6% for women and 17.2% for men. The ratio of anemia prevalence in women to men was 1.5:1, and the mean age was 77.34±8.32 (65-97), (77.71± 8.51 in women and 76.78±8.00 in men).

In the study population, cardiovascular disease (81.2%) was the most common comorbidity, followed by diabetes mellitus (34.7%) and chronic obstructive pulmonary disease (15.3%). Polypharmacy was present in 68.3% of the patients including anticoagulants in 24%, antiaggregants in 38.3%, proton pump inhibitors (PPI) in 36%, metformin in 19.2%, and non-steroidal anti-inflammatory drugs or steroids in 11%.

The most common complaints of the patients were fatigue (48.6%), shortness of breath (14.8%), weight loss (7.5%), and joint pain (7%). In 12.3% of the patients, the diagnosis of anemia was made during routine tests without any complaints. In symptomatic patients 14.5% of them had more than one complaint.

According to the morphological classification, normocytic anemia (66.4%) was the most common type, followed by microcytic anemia in 27.9% and macrocytic anemia in 5.7% (Table 1).

The patients were analyzed within 3 age groups; 65-75 years, 76-85 years and over 85 years old. Analysis of mean hemoglobin values between age groups showed a significant decrease with advancing age ($p<0.001$) (Table 2). There was no significant difference in MCV, leukocyte and creatinine values within age groups. Serum albumin levels were found to be significantly lower in the elderly patient groups compared to the age group of 65-75 years ($p=0.03$). The CRP level of the patients aged 76-85 years was significantly higher than that of the patients over the age of 85. There was no significant difference between the CRP levels of the other age groups ($p=0.024$) (Table 2).

Nutritional anemia was detected in 339 (56.5%) patients. Hematologic malignancy was present in 127 (21.1%) patients, and ACD in 125 (20.8%) patients. The multifactorial etiology of anemia was present in 87 (14.5%) patients, where the presence of ACD with IDA (6.3%) was the most common combination. Unexplained anemia was present in 58 (9.7%) patients (Table 3).

In 339 patients with nutritional anemia; esophagogastroduodenoscopy (EGD) was performed in 49.3% and colonoscopy in 44.8%. EGD and colonoscopy were performed together in 208 (34.6%) patients. The most common pathology detected in EGD was chronic nonatrophic gastritis (23%), followed by Hp (Helicobacter pylori) related gastritis (19%) and chronic atrophic gastritis (16%) (Fig. 1). Polyps (31%), internal hemorrhoids (31%), and colorectal tumors (17%) were the most common pathologies found during colonoscopic examination (Fig. 2).

72% of the patients with indications for BMBX had the procedure. There were 206 (34.3%) patients with an indication and 148 (24.7%) patients accepted the procedure. 50 (8.3%) of 58 patients with UEA did not accept further investigations. Although monoclonal gammopathy was detected in serum and/or urine tests in 6 (1%) of 58 patients, plasma cell dyscrasias could not be diagnosed due to the patient's unwillingness for BMBX. Despite the detailed examination of the patients, the etiology of anemia could not be diagnosed in 2 (0.3%) patients

.

Table 1. Characteristics of Patients

Characteristics	
Age mean±SD (min, max)	77.34±8.32 (65, 97)
Male	76.78±8 (65, 92)
Female	77.71±8.51(65, 97)
Female:male	1.5:1
Patients' Complaints % n:600	
Weakness	48.6%
Shortness of breath	14.8%
Asymptomatic	12.3%
Weight loss	7.5%
Joint pain	7%
Anorexia	4.8%
Fatigue	3.9%
Active bleeding	2.8%
Vertigo	2.8%
Palpitation	2.5%
Others	7.1%
Multiple complaints	14.5%
Morphological classification % n:600	
Normositer anemia	66.4%
Microcytic anemia	27.9%
Macrocytic anemia	5.7%
Co-morbidities % n:600	
Cardiovasculer disorder	81.2%
Diabetes mellitus	34.7%
Chronic obstructive pulmonary disease	15.3%
Renal failure	13.3%
Gastrointestinal disorder	12.2%
Neurological disorder	12.5%
Cancer	10.2%
Rheumatic disease	7.2%
Drugs % n:600	
Anticoagulants	24.2%
Antiaggregants	38.3%
Proton pump inibitor	36%
Non-steroidal anti-inflammatory/steroid	11%
Metformin	19.2%
Multiple drug use (more than 1 drug)	93.8%
Polypharmacy (5 or more drug use)	68.3%

Table 2. Comparison of Laboratory Values by Age Groups

Age group (100%)	**1.group** 65-75 (44.7%)	**2.group** 76-85 (36.2%)	**3.group** >85 (19.2%)	**P value**	**P value between age groups**
Hb (g/dL) (Mean±std.deviation)	10.10±1.67	9.72±1.70	9.20±1.87	**<0.001**	**1-2 **** **1-3 **** **2-3 ****
MCV (fL) Median (min-max)	86,15 (53.9-126.6)	85 (57-114)	85 (56-134)	0.574	
Leukocytes (µL) Median (min-max)	6745 (90-265000)	6910 (10-224000)	6180 (1000-57100)	0.402	
Thrombocyte (µL) Median (min-max)	231500 (3000-606000)	257500 (3600-933000)	234000 (17900- 567000)	**0.020**	**1-2 **** **1-3 *** **2-3 ***

Creatinine (mg/dl) Median (min-max)	0.96 (0.52- 8.75)	1.07 (0.12 -10)	1.08 (0.58- 5.02)	0.329	
Albumin (g/dl) Median (min-max)	4 (2- 5)	3.9 (2.2- 4.9)	3.8 (2.4- 4.7)	**0.030**	**1-2 ** 1-3 ** 2-3 ***
CRP (mg/l) Median (min-max)	6.84 (0.3- 417)	10.9 (0.3-256)	4.48 (0.4-167)	**0.024**	**1-2 * 1-3 * 2-3 ****

*** p value<0.05 * p value>0.05*

Table 3. Etiological Classification of Anemia

	Patient number(n:600) Percentage(%100)
Total Nutritional Deficiency Number	339 (56.5%)
Total Iron Deficiency	284
Total Folate Deficiency	57
Total Vitamin B12 Deficiency	31
Multiple Nutritional Deficiency #	33
Total Hematological Malignancy	127 (21.1%)
Myelodysplastic Syndrome	40
Multiple Miyeloma	28
Nonhodgkin Lymphoma	26
Acute Leukemia	10
Chronic Lymphoblastic Leukemia	9
Monoclonal Gammopathy of Undetermined Significance	9
Chronic Myeloproliferative Disease	5
Total Anemia of Chronic Disease(ACD)	125 (20.8%)
Chronic Kidney Disease	28
Solid organ malignancy	21
Chronic obstructive pulmonary disease	19
Congestive Heart Failure	17
Chronic liver disease	10
Rheumatological disease	10
Other *	20
Total Bone Marrow Failure**	21 (3.5%)
Total Hemolytic anemia	17 (2.9%)
Unexplained Anemia	58 (9.7%)
Unexplored,	56
Underexplored anemia	2
More than one cause #	87(14.5%)

**Other: Complicated Diabetes Mellitus, Inflammatory Bowel Diseases, Chronic Infections*
***Bone Marrow Failure: Hypoplastic anemia, aplastic anemia, hypothyroidism,acute hyperinflammation-associated anemia and drug-associated anemia*
 # The ratios given above are the total ratios of the causes seen in the etiology, more than one etiological cause is given as a separate ratio, and it is subtracted from the total ratio to avoid double addition.

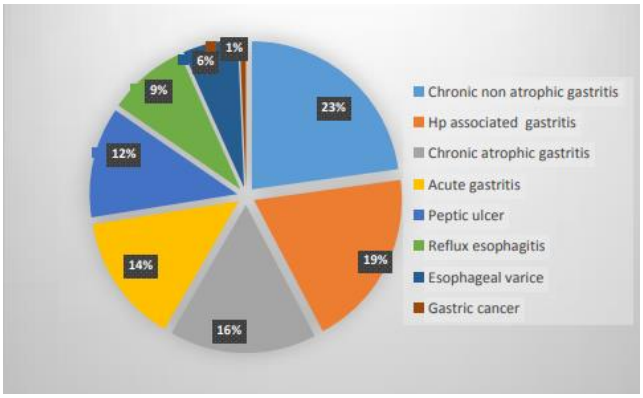

Figure 1. Esophagogastroduodenoscopy Results in Patients with Nutritional Anemia

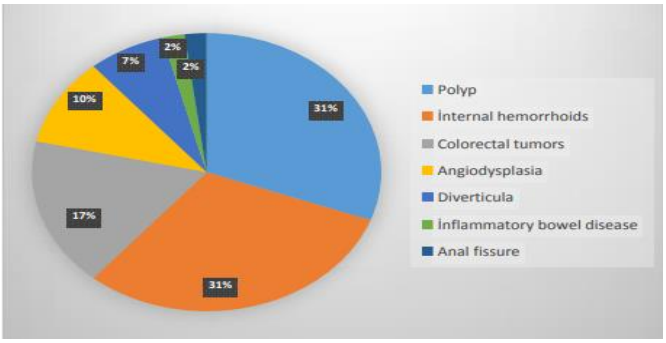

Figure 2. Colonoscopy Results in Patients with Nutritional Anemia

4. Discussion

This cross-sectional study analyzed the rate, characteristics and etiology of anemia in patients over the age of 65 at the hematology outpatient clinic. The prevalence of anemia was 18%, which was compatible with the range of 13.6-25% in other studies (9,19,20). The diagnosis of anemia was more common in women than in men with a ratio of 1.5:1. In the literature, anemia rates ranged from 9.9 to 11% in men and 10.2 to 14.2% in women (7,20). The differences in the rate of anemia between genders may be related to the number of people participating in the study, regional etiological differences and the place where the study was performed (hospital, home, etc.).

The most common symptoms in our study were fatigue (48.6%), shortness of breath (14.8%), weight loss (7.5%) and joint pain (7%); 12.3% of the patients were asymptomatic. Typical symptoms of anemia in elderly patients, such as fatigue, weakness and shortness of breath are not specific and might be multifactorial and often attributed to advancing age (21). Typical symptoms are usually less severe in older patients than expected in younger adults. When anemia first appears, most of the patients continue their usual daily activities (22). It should be noted that patients may have symptoms of anemia without active complaints or the symptoms may be similar to those of other diseases.

In our study, hemoglobin levels decreased significantly with increasing age (Table 2) and normocytic anemia (66.4%) was the most common form, similar to previous studies (11, 23). The prevalence of anemia increases after the age of 60 to 65 years and becomes more pronounced over the age of 80 (22). It has been shown that hemoglobin levels over the age of 65 decrease gradually, whether they are anemic or not (8).

Various studies have shown that there is a decrease in serum albumin concentration

between 0.08 and 0.17 g/L per year associated with aging (24, 25). Despite these age-related changes, albumin levels remain above 38 g/L in healthy elderly people until after 90 years of age, and there is no evidence of a pathological decrease in albumin levels with age. Therefore, in the case of clinical stability, albumin may be a good predictor of nutritional status in the elderly population (26). In our study, albumin levels were found to be significantly higher in patients aged 65 to 75 years compared to the 75 to 85 years and > 85 years age groups. Similar to the literature, the mean serum albumin levels decreased within normal ranges in elderly patients.

In the elderly patient population, nutritional deficiencies and chronic inflammatory disorders were the most common causes of anemia, respectively (6, 27). In our analysis, hemological malignancies were the second most prevalent condition after nutritional deficiencies. The rate of unexplained anemia (UAE) was quite low. In one of the population-based study, Guralnik et al. (7) examined the third National Health and Nutrition Examination Survey (NHANES) of 4199 community-dwelling men and women over the age of 65 years. The rate of UEA was found to be 33.6% among all anemic elderly. In another community-based study of 8744 people in Italy, the rate of UEA was 26.4% (8). In another study by Artz et al. (10), the rate of UEA was reported as 43.7% and BMBX is performed only %32 of patients. In a retrospective study conducted by Michalak et al.(9) the rate of UEA was 28.4% in 169 elderly anemic patients. Bone marrow biopsy or genetic studies could not be performed in 81.3% of these patients. Although the UEA rates were similarly high both in community and hospital-based studies, we think the low rate in our study is related to more comprehensive hematological examination of patients, including invasive procedures. BMBX rate is quite higher than other studies. This may explain why hematologic malignancies were the second most common cause of anemia in the elderly patient population in our study.

In elderly patients with IDA, blood loss from the gastrointestinal (GI) tract is mostly occult and may not be excluded by negative stool guaiac tests (28). The endoscopic examination in patients over the age of 50 years with IDA shows lesions in 33- 56% of the upper GI tract and 14-36% of the lower GI tract. In a summary of seven studies about the GI tract examination in patients with IDA over the age of 50, 721 patients were evaluated. The most common lesion in the upper GI tract was peptic ulcer (13.4%) and the rate of gastric cancer was 2%. The most common lesion in the lower GI tract was colorectal cancer (8.4%), followed by adenomatous polyps (5.5%) (29). In our study, the most common cause of upper GI pathology was chronic non-atrophic gastritis, while polyps and internal hemorrhoids were the most common causes of lower GI pathology.

The incidence of cancer increases with age and anemia is present in more than 60% of cancer patients with an increasing rate in advanced stages of cancer (30). In our study, endoscopic examinations detected gastric cancer in 1 patient and colon tumors in 17 patients. Solid organ malignancies were present in 21 patients with anemia from chronic disease. A total of 166 (27.6%) patients had hematological or solid organ malignancies. The increasing rates of malignancy with age underscore the importance of a detailed examination of the etiology of anemia in the elderly. However, in frail patients, the procedures should be done while considering the risk-benefit ratio. In addition, it is difficult to persuade patients to undergo invasive procedures such as endoscopic examinations and BMBX in this age group. In our study, endoscopic procedures could not be performed on more than half of the patients with nutritional anemia. The etiology of anemia could not be investigated in 8.3% of the patients due to their unwillingness for further invasive procedures. Despite all the analysis, the etiology of anemia could not be identified in 0.3% of our patients. In this group of patients, low serum EPO levels, decrease in testosterone level, occult inflammation, unidentified iron deficiency, clonal hematopoiesis; especially idiopathic cytopenia

of uncertain importance (ICUS) may be the cause of anemia. However, next generation sequencing (NGS) could not be used in our center at the time of this study.

As another cause of anemia in the elderly patient population Kara O et al.(31) reported the importance of polypharmacy. In a multicenter analysis of 579 geriatric patients who receive more than five drugs, Röhrig G et al.(32) reported an increased rate of anemia. In our study, 93.8% of the patients were using more than one drug, while 68.3% of the patients were using five or more drugs. The high rate of polypharmacy in the elderly anemic patient groups supports the relationship between polypharmacy and anemia.

The retrospective nature of this study and the unavailability of NGS technology for cytogenetic analysis were limitations of this study. The high rate of BMBX performed in necessary patients is the strength of the study in terms of contributing to a better understanding of the etiology of anemia in the elderly.

In conclusion, anemia in the elderly is a challenging issue due to comorbidity, polypharmacy, and problems in further examination. Since the success of the treatment is associated with the reduction of morbidity and mortality and the development of geriatric syndromes, the etiology of anemia should be investigated in detail to guide treatment. Hematological evaluation of anemia in the elderly patient population will reduce the rate of unexplained anemia. However, patient selection for invasive procedures should be based on a risk-benefit ratio in frail elderly patients.

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Ethics

Ethics Ethics Committee Approval: The study was approved by Baskent University Ethical Committee (Approval Date/ Number: 05.07.2022 / KA22/302).
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Research Article / Araştırma Makalesi

A Single-center Experience of Synchronous and Metachronous Hematologic and Oncologic Tumors

Senkron ve Metakron Hematolojik ve Onkolojik Tümörlerin Tek Merkez Deneyimi

[1]Filiz Yavaşoğlu, [2]Çiğdem Özdemir, [3]Yiğit Şenol, [4]Hacer Demir, [4]Meltem Baykara

[1]Eskisehir Osmangazi University Faculty of Medicine, Department of Hematology, Eskisehir, Türkiye
[2]Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Pathology, Afyonkarahisar, Türkiye
[3]Afyonkarahisar Provincial Health Directorate, Department of Public Health, Afyonkarahisar, Türkiye
[4]Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Oncology, Afyonkarahisar, Türkiye
[4]Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Oncology, Afyonkarahisar, Türkiye

Abstract: The incidence of cancer is increasing in the world. With the developments in cancer treatment, the life expectancy of patients is prolonged and the incidence of secondary malignancies is increasing. We retrospetively patients with syncronous / metachronous oncological malignancies accompanying hematological malignancies in a newly established hematology center. Data were obtained from the medical records. Demographic data, treatments and overall survival of the patients were evaluated. Twenty eight (6%) of 433 patients hematological malignancies were included in the study. 12 patients (42.9) were diagnosed with syncronous and 16 (57.1%) patients with metachronous hematologic-oncologic tumors. Sixteen of the patients were male,twelve were female. In syncronous tumors, the most common hematologic malignancy was Non-hodgkın lymphoma (NHL), while the most common oncologic malignancies were thyroid papillary cancer and colon cancer. In metachronous tumors, the most common malignancies were NHL and breast cancer. The median time between diagnosis of metachronous tumors was 49.5 months (8-192 months). The median survival of patients with syncronous malignancies was 19 months (SE=12.19) (95% CI 0-42.89), with metachronous malignancies was 22 months (SE=14.0) (95% CI 0-49.44). There was no statistically significant difference in the comparison of survival curves of patients with syncronous and metachronous malignancies (p=0.382). Oncological malignancies accompanying hematological malignancies are not uncommon. There is no standart treatment for syncronous / metachronous hematologic malignancies. In the presence of syncronous multipl malignancies should be evaluated individually.
Keywords: Multipl primary neoplasms, syncronous neoplasms, hematologic malignancies

Özet: Dünyada kanser görülme sıklığı giderek artmaktadır. Kanser tedavisindeki gelişmelerle birlikte hastaların ortalama yaşam süreleri uzamakta ve sekonder malignitelerin görülme sıklığı artmaktadır. Yeni kurulan bir hematoloji merkezinde hematolojik malignitelere eşlik eden senkron / metakron maligniteleri retrospektif olarak inceledik.Veriler tıbbi kayıtlardan elde edildi.Hastaların demografik verileri, tedavileri ve genel sağ kalımları değerlendirildi. Hematolojik maligniteli 433 hastanın 28'i (%6) çalışmaya devam edildi. 12 hasta (%42,9) senkron, 16 (%57,1) hasta ise metakron hematolojik-onkolojik tümör tanısı almıştır. Hastaların 16'sı erkek, 12'si kadındı. Senkron tümörlerde en sık görülen hematolojik malignite non-hodgkın lenfoma (NHL), en sık görülen onkolojik maligniteler ise tiroid papiller kanseri ve kolon kanseri idi. Metakron tümörlerde en sık görülen maligniteler NHL ve meme kanseri idi. Metakron tümörlerin tanısı arasındaki medyan süre 49,5 aydı (8-192 ay). Senkron malignitesi olan hastalrın medyan sağkalımı 19 aydı (SE=12,19))%95 CI 0-42,89), metakron maligniteleri olan hastaların medyan sağkalımı 22 aydı (SE=14,9= (%95 CI 0-49,44). Senkron ve metakron maligniteleri olan hastaların sağkalım eğrilerinin karşılaştırılmasında istatistiksel olarak anlanmlı fark saptanmadı (p=0,382). Hematolojik malignitelere eşlik eden onkolojik maligniteler nadir değildir. Senkron / metakron hematolojik maligniteler için standart bir tedavi yoktur. Senkron multipl malignite varlığında, malignitelerin her biri ayrı ayrı değerlendirilmelidir.
Anahtar Kelimeler: Multipl primer tümörler, senkronize tümörler, hematolojik maligniteler

ORCID ID of the authors: FY. 0000-0002-4017-4668, ÇÖ. 0000-0001-8500-0744, YŞ. 0000-0002-2220-4595, HD. 0000-0003-1235-9363, MB. 0000-0003-3291-8134

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Correspondence: Filiz YAVAŞOĞLU-- Eskisehir Osmangazi University Faculty of Medicine, Department of Hematology, Eskisehir, Türkiye
e-mail: filiz.yavasoglu@ogu.edu.tr

1. Introduction

The incidence of cancer is increasing in the world. According to the world cancer statistics for 2020, it is estimated that there are 18.1 million cancer patients (excluding non-melanoma skin cancers). 9.3 million of them are men and 8.8 million are women (1). Despite the increasing incidence of cancer; with advances in cancer treatment, the life expectancy of patients' is prolonged. With the prolongation of the patients' life spans, the long-term effects of chemotherapeutics and radiotherapy may occur. Genetic susceptibility and exposure to environmental factors continue(cümlesi çıkarıldı). The incidence of cancer increases with age. Secondary or even tertiary malignancies may occur in these patients. If the time between the diagnosis of multiple cancers is less than 6 months, they are called syncronous tumors. If the time longer than 6 months, they are called metachronous tumors (2). The incidence of syncronous /metachronous tumors was found to be 0.73-11.7% in studies. The prevelance was found to be higher in the elderly (3-4).

In our study, we aimed to evalute the demographic characteristics of patients with syncronous / metachronous hematologic and oncologic malignancies diagnosed in a newly established hematology center, the treatments they received, the duration of diagnosis in patients with diagnosis of metachronous and overall survive.

2. Materials and Methods

We included patients with a diagnosis of syncronous / metachronous oncologic malignancy accompanying hematologic malignancy between 01.01.2017 and 01.01.2022 in the Department of Hematology of Afyonkarahisar Health Sciences University. In our study, patients under the age of 18 and patients with synchronous / metachronous solid tumors were not included in the study. The data of the patients were obtained by retrospectively scanning the medical records. The ages, genders, treatments they received, diagnosis times in metachronous tumors, and overall survival times were evaluated.

Statistical Analysis

PASW Statistics 18.0 package program was used for statistical analysis. In descriptive statistics, categorical data were evaluated as percentage frequency, continuous data as mean and standard deviation (mean±sd). Chi-Square Test was used for statistical analysis of categorical data. Kaplan-Meier Method was used to determine survival rates. Log Rank Test was used to compare survival curves. $p<0.05$ was accepted as the cut-off value for statistical significance. Overall survival (OS) was defined as the time from the date of diagnosis of the solid tumors or hematological malignancy, whichever was diagnosed first, and the last follow-up or death from any cause. All P values were two-sided, and P = 0.05 or less was considered to indicate statistical significance.

3. Results

Four houndred thirty three patients with hematological malignancies were evaluated. Twenty-eight patients with both hematologic and oncologic malignancies were included in the study. Sixteen (57.1%) patients were male and twelve (42.9%) were female. The mean age of hematological malignancy diagnosis was 66.5±11.5 (40-85). The mean age of oncological malignancy was 65.3±11.2 (37-84).

Metachronous malignancy diagnosis was made in 57.1% of the patients included in the study, and synchronous in 42.9%. Seventy five percent of patients with a diagnosis of metachronous were initially diagnosed with hematological malignancies. The median time between synchronous diagnoses was 2 months (1-6 months). The median time between metachronous diagnoses was 49.5 months, maximum 16 years and minimum 8 months. Eight (66.7%) of the synchronous patients and twelve (75.0%) of the metachronous patients were 65 years or older. There was no statistical difference between the synchronous and metachronous groups in the distribution of patients over 65 years of age (p=0.691) (Table 1). Hematological diagnoses and oncological diagnoses of synchronous and

metachronous cases are shown in Tables 2 and 3.

The median follow-up period of patients after hematological malignancy was 19.5 months (1-91 months). The median survival time after hematologic malignancy was 20 months (SE=8.56) (95% CI 3.21-36.78). The cumulative survival rate at 1 year after hematologic malignancy was 60.0±9.2%, and the 5-year cumulative survival rate was 31.2%±9.6% (Figure 1).

The mean life expectancy of patients with malignancies under the age of 65 was 46.06 months (SE=13.83) (95% CI 19.83-72.29). In patients younger than 65 years, the cumulative survival rate at 1 year after hematological malignancy was 75.0±15.3%, and the 5-year cumulative survival rate was 56.3%±19.9%. The mean life expectancy of patients with malignancies aged 65 and over was 28.53 months (SE=7.97) (95% CI 12.91-44.14). In patients aged 65 and over with malignancy, the cumulative survival rate at 1 year after hematological malignancy was 55.0±11.1%, and the 5-year cumulative survival rate was 21±10.0%. There was no statistically significant difference in the comparison of the survival curves of patients aged below 65 years and over 65 years of age with a diagnosis of hematological malignancy (p=0.183) (Figure 2).

The median survival of patients with synchronous malignancies was 19 months (SE=12.19) (95% CI 0-42.89). In patients with synchronous malignancy, the cumulative survival rate at 1 year after hematological malignancy was 58.3%±14.2%, and the 5-year cumulative survival rate was 13.0±11.7%. The median survival of patients with metachronous malignancies was 22 months (SE=14.0) (95% CI 0-49.44). In patients with metachronous malignancy, the cumulative survival rate at 1 year after hematological malignancy was 62.5%±12.1%, and the 5-year cumulative survival rate was 32.8%±13.3%. There was no statistically significant difference in the comparison of the survival curves of patients with synchronous and metachronous malignancies (p=0.382) (Figure 3).

Table 1. Distribution of synchronous and metachronous tumors under 65 years old and over 65 years

	Age <65		Age≥65		Total		p
	n	%	n	%	n	%	
Metachronous	4	25.0	12	75.0	16	100.0	0.691
Synchronous	4	33.3	8	66.7	12	100.0	
	8	28.6	20	71.4	28	100.0	

Table 2. Clinical characteristics of syncronous hematologic and oncologic tumors

	Sex	Age	Hematological malignancy	Treatment	Oncological malignancy	Treatment	OS	Cause of death
1	M	50	Small lymphocyctic lymphoma	Follow-up without treatment	Nasopharyngeal cancer	Radiotherapy	3 months	Oncological malignancy
2	F	67	Diffuse large B cell lymphoma	Chemotherapy (Rituximab, cyclophosphamide, doxorubucine, vincristine)	Thyroid papillary carcinoma	Surgical treatment	37 months	Cardiac event
3	F	53	Multiple myeloma	Chemotherapy Bortezomib, cyclophosphamide, dexametazone, lenalidomide AutoSCT	Thyroid papillary carcinoma	Surgical treatment	21 months	Alive
4	F	66	Multiple myeloma	Follow-up without treatment	Renal clear cell carcinoma,colon cancer	Surgical treatment -chemotherapy (oxaliplatin,flurourasil)	20 months	Oncological malignancy
5	F	66	Multiple myeloma	Follow-up without treatment	Uterin cancer	Surgical treatment -chemotherapy	19 months	Oncological

						(carboplatin paclitaxel)		malignancy
6	M	45	Castleman diasease	Surgical treatment	Squamosis cell carcinoma (Vocal cord)	Surgical treatment	13 months	Alive
7	M	72	Multiple myeloma	Chemotherapy (Bortezomib,dexametazone)	Lung cancer	Surgical treatment	2 months	Oncological malignancy
8	M	64	Hairy cell leukemia	Chemotherapy (Cladribine)	Colon cancer	Surgical treatment -chemotherapy (kapesitabin)	65 months	Alive
9	M	82	Acute myeloid leukemia	Chemotherapy (Azacytidine)	Prostate cancer	Surgical treatment	2 months	Hematological malignancy
10	M	84	Non- hodgkın lymphoma (Marginal zone lymphoma)	Follow-up without treatment	Skin squamosis cell carcinoma	Surgical treatment	4 months	Cardiac event
11	M	83	Non- hodgkın lymphoma (T cell, thyroid)	Chemotherapy (cyclophosphamide,vincristine, prednisolone)	Skin squamosis cell carcinoma	Surgical treatment	29 months	Cardiac event
12	F	73	Chronic lymphocytic leukemia	Follow-up without treatment	Rectal cancer	Surgical treatment	1 months	Oncological malignancy

Table 3. Clinical characteristics of Metachronous Hematologic and Oncologic Tumors

	Sex	Age	Primary malignancy	Treatment	Time interval	Secondary malignancy	Age	Treatment	OS after hematological malignancy	Cause of detah
1	F	63	Breast cancer	Operation, radiotherapy, hormone therapy(anastrazol)	54 months	NHL (Chronic lymphocyctic leukemia)	67	Follow up- without treatment	14 months	Alive
2	F	61	Endometrium cancer	Operation, Chemotherapy (paclitaxel,carboplatin)	66 months	T cell acute lymphoblastic leukemia	66	Chemotherapy (vincristine, dexametazone, doxorubicine)	1 months	Hematological malignancy
3	F	51	Breast cancer	Operation, radiotherapy	192 months	Chronic myeloproliferat ive disease	67	acetylsalicylic acid	28 months	Alive
4	F	55	Breast cancer	Operation, hormone therapy (anastrazol)	124 months	Multipl myeloma	65	Chemotherapy (bortezomibe, dexametazone)	1 months	Hematological malignancy
5	M	60	Renal cell carcinoma	Operation	120 months	NHL (Burkitt lymphoma)	70	Chemotherapy (rituximab, bendamustine)	1 months	Hematological malignancy
6	M	70	Renal cell carcinoma	Operation	12 months	NHL (Hepatic marginal zone lymphoma)	71	Operation	14 months	Alive
7	F	37	Cervix cancer	Operation, Radiotherapy, chemotherapy (cisplatin)	45 months	Aplastic anemia	40	Supportive treatment	1 months	Aplastic anemi
8	F	74	Breast cancer	Operation, Radiotherapy, hormone therapy (letrozol, anastrozol,eksemestan) Chemotherapy (gemcitabine, carboplatine, paxlitaxele)	42 months	NHL (Mantle cell lymphoma)	78	Chemotherapy (rituximab, bendamustine)	8 months	Hematological malignancy
9	M	67	Prostate cancer	Operation, hormone therapy (bikatulamide,loprolide)	9 months	Chronic myeloproliferat ive disease	68	Acetylsalicylic acid	61 months	Alive
10	M	82	Skin squamous cell carcinoma	Operation	37 months	Acute myeloid leukemia	85	Chemotherapy (azasitidine)	13 months	Hematological malignancy
11	M	74	Skin squamous cell carcinoma	Operation	8 months	Multipl myeloma	75	Chemotherapy bortezomibe, cyclophosphamide, dexametazone, lenalidomide)	22 months	Hematological malignancy
12	F	62	Breast cancer	Operation, Radiotherapy, hormone therapy(letrozole)	120 months	NHL (Diffuse large b cell lymphoma)	72	Chemotherapy(rituximab, cyclophosphamide, vincristine, doxorubicine,prednison)	1 months	Hematological malignancy
13	M	58	Multipl myeloma	Chemotherapy (bortezomibe, cyclophosphamide, dexametazone, lenalidomide, pomalidomide)	60 months	Hepatocelluer carsinoma	63	Operation	72 months	Oncological malignancy
14	F	53	NHL (Follicular lymphoma)	Chemotherapy (rituximab, doxorubicine, vincristine, cyclophosphamide,prednisolon)	30 months	Breast cancer	55	Operation, radiotherapy, hormone therapy (anastrazole) Chemotherapy (paklitaxel)	66 months	Alive
15	M	53	NHL (Mantle cell lymphoma)	Chemotherapy (rituximab, bendamustin, ibrutinib)	19 months	Lung cancer	55	Operation	27 months	Oncological malignancy
16	M	66	Chronic myeloproliferativ e disease	acetylsalicylic acid	63 moths	Skin squamous cell carcinoma	71	Operation	91 months	Alive

NHL: Non-Hodgkın Lymphoma
M: male
F: female
OS: Overall survival

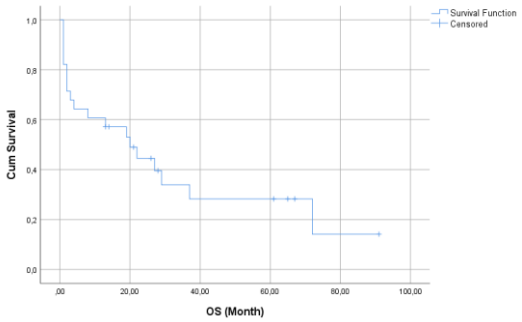

Figure 1. The cumulative survival rate after hematologic malignancy

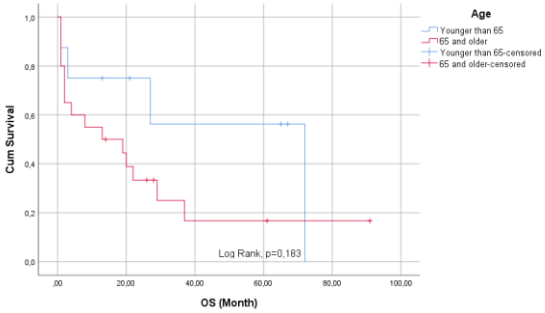

Figure 2. Graph of overall survival of patients under 65 and over 65 years of age

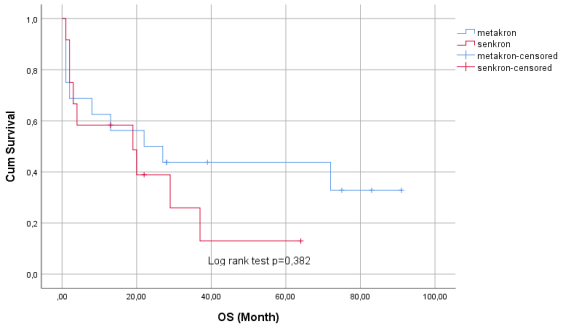

Figure 3. OS graph of patients with metachronous and syncronous tumors

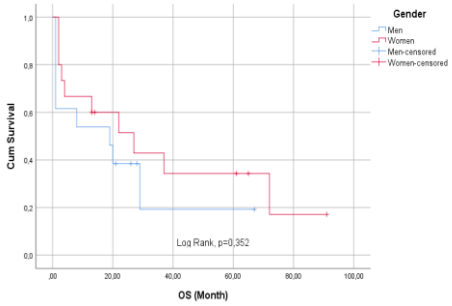

Figure 4. Os graph by gender

4. Discussion

Incidence of cancer continues to increase. With advances in cancer treatment, the life expectancy of patients is increasing. Prolonged life expectancy also increases the risk of second cancer. (5-6). Secondary or even tertiary malignancies may occur in these patients. If secondary malignancies are diagnosed in the first 6 months after the diagnosis of the primary tumor, they are called synchronous tumors, and if diagnosed after the first 6 months, they are called metachronous tumors (2). Synchronous / metachronous tumor pathogenesis is not completely clear. Familial cancer syndromes and genetic predisposition are thought to be effective in etiology. In addition, smoking, alcohol consumption, environmental factors, previous chemotherapy due to tumor, radiotherapy are other factors in the etiology. Genetic instability may play an important role in the development of multiple primary cancers. Studies have shown that genetic defects in the mismatch repair system carry a high risk for multiple primary tumors (7). Epidemiology studies show that approximately 20% of newly diagnosed malignancies have a previous history of malignancy (8).

The incidence of synchronous and metachronous tumors is increasing day by day. The prevalence was found to be higher in the elderly (4). The incidence of synchronous / metachronous tumors was found to be 1.4% in a study conducted in Turkey. Hematologic malignancies comprised 11.9% of this population (9). In another study from Turkey, the incidence of synchronous / metachronous malignancy was found to be 3.9% in patients with hematological malignancies (10). Our study is a cross-sectional study aiming to provide descriptive data on synchronous and metachronous oncological malignancies accompanying hematological malignancies. Although it is a newly established hematology center, the incidence of synchronous / metachronous oncological malignancy was found to be 6% in patients with hematological malignancies. The difference in this incidence might be attributable to differences in geography, environment, race, or various diagnostic criteria or, more importantly, the experience of the clinicians or the examination methods between studies.

In a study evaluating 649 hematological malignancies, syncronous malignant tumors were found in 19 patients. In this study, the most common hematological malignancy was non-Hodgkin lymphoma (NHL) (11). In a study from Turkey, the most common hematological malignancy was NHL (12). In a study evaluating 32 synchronous hematological malignancies and solid tumors, NHL was the most common hematological malignancy. The most common solid tumors are stomach and thyroid cancer (13). NHL was the most common hematological malignancy in both groups in our study. In our study, thyroid cancer and skin squamous cell carcinoma were the most common solid tumors in synchronous malignancies, while breast cancer in metachronous tumors. In the study of Burak Deveci et al., NHL and lung cancer are the most common malignancies in both synchronous and metachronous groups (12). In our study, the most common oncological malignancy was breast cancer (25%). The most common malignancy in the world is breast cancer (14).

There are studies showing an increased risk of second primary malignancy in patients with mantle cell lymphoma in population-based studies (15). In our study, we had 2 patients who were diagnosed with mantle cell lymphoma after breast ca and lung cancer .

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults. In CLL, the incidence of secondary malignancy has increased due to immune dysregulation, the treatments they have received, and environmental exposures (16). In our study, there were 2 CLL and 1 small lymphocyctic lymphoma (SLL) patients. The patient with SLL was diagnosed with synchronous nasopharyngeal carcinoma, 1 patient with rectal carcinoma synchronous with CLL, and 1 patient with metachronous CLL after breast cancer. Two of the patients with synchronous diagnosis died due to oncological malignancy.

In our study, unlike studies evaluating other synchronous / metachronous malignancies, one of our patients was diagnosed with Castleman syndrome and synchronized skin squamous cell carcinoma. One of our patients was diagnosed with aplastic anemia after cervical cancer.

Castleman disease is a rare lymphoproliferative disease characterized by hyperinflammation. In a study of 66 Castleman patients, one of the two most common causes of death was malignant cancer (17). In our study, a patient with stage 1 Castleman disease was cured by surgical treatment, and vocal cord squamoze squamous cell carcinoma was diagnosed 2 months after the diagnosis of Castleman. The patient, who was cured after radiotherapy, continues to live in good health.

Aplastic anemia (AA) complicated by a solid tumor is often found in hereditary bone marrow failure syndromes such as Fanconi anemia (FA), which is characterized by congenital malformations, bone marrow failure, and predisposition to cancer. (18). It is known that chemotherapy and radiotherapy are involved in the etiology of acquired aplastic anemia. In a study evaluating 25 patients with secondary aplastic anemia, only 5 patients (20%) were diagnosed with aplastic anemia secondary to cervical cancer. Of these patients, 4 received only chemotherapy, and 1 received both chemotherapy and radiotherapy (19). Our patient received chemotherapy and radiotherapy for cervical cancer and was diagnosed with aplastic anemia 3 years after the diagnosis of cervical cancer. Fanconi aplastic anemia was ruled out in the patient. And died due to sepsis.

Mutiple myeloma is the second most common hematological malignancy in the world. It constitutes 1-2% of all malignancies and 2% of malignancy-related deaths (20). With the prolongation of the life expectancy of myeloma patients, the incidence of secondary malignancies also increases. The etiology is multifactorial and different antimyeloma drugs pose varying risks for the development of secondary malignancy. In a study evaluating the malignancies accompanying multiple myeloma, the risk of developing secondary malignancy was found to be 2.19 times higher in the multiple myeloma population (21). In our study, 4 out of 7 (25%) patients were diagnosed with multiple myeloma as synchronous and 3 as metachronous. Of 7 patients, 2 patients died due to multiple myeloma and 4 patients due to concomitant solid tumor. Concomitant solid malignancy of 1 patient was synchronous thyroid papillary carcinoma. The patient underwent autologous stem cell transplantation and continues to live. Although it is known that the incidence of secondary malignancy increases in patients with multiple myeloma, there are few recommendations and guidelines for screening. Therefore, age-appropriate oncological screening of patients is required (22).

Acute myeloid leukemia constitute the majority of secondary acute leukemias. Secondary acute lymphoblastic leukemias are rare and the prognosis is poor. In our study, synchronous / metachronous acute leukemia was detected in 3 patients. Two of them were acute myeloid leukemia and one was T-cell acute lymphoblastic leukemia (ALL). In our study, there were two patients, one diagnosed with metachronous and one diagnosed with synchronous acute myeloid leukemia (AML). The overall survival time of two patients was less than 12 months. In a study evaluating patients with secondary AML, OS was 12.5 (3.8-48.0) months (23). Due to the low incidence of secondary AML, there is no standard treatment protocol. Induction, consolidation chemotherapy, hematopoietic stem cell transplantation, hypomethylating agents and supportive treatments used in the treatment of AML are among the treatments that can be applied (24). Treatment-related ALL accounts for 3-9% of adult ALL patients. Poor cytogenetic features are observed more frequently in treatment-related ALL and the prognosis is worse. In a study in which 1022 ALL cases were evaluated, 9.1% of the patients consisted of treatment-related ALL patients. Only 9% of treatment-associated ALL cases were of the T cell phenotype (25). Our patient was also diagnosed with T-cell ALL after the diagnosis of endometrial

cancer. However, the patient died in the first month of the diagnosis. All 3 of our patients diagnosed with acute leukemia had acute leukemia diagnoses that determined the surveys.

Studies conducted in recent years have shown that the incidence of secondary cancer is increased in patients with myeloproliferative disease. The cumulative incidence can reach 5-10% after the first 5 years of diagnosis. In our study, 3 patients had solid malignancy accompanying chronic myeloproliferative disease. None of these patients had myelofibrosis. Studies have shown that the development time of secondary cancer in primary myelofibrosis is shorter than in polycythemia vera and essential thrombocytosis (26). In our study, solid tumors accompanying chronic myeloproliferative disease were diagnosed as metachronous. Solid tumors of the patients were breast cancer, prostate cancer and skin squamous cell carcinoma. Studies have shown that 75% of patients with solid malignancies accompanying chronic myeloproliferative disease are over 50 years of age. In our study, all 3 of our patients were over 50 years old (27-28).

Studies have shown that synchronous multiple primary malignancies are associated with a significant reduction in overall survival compared to metachronous malignant tumors (29). However, there are also studies showing that overall survival is not different in synchronous / metachronous tumors (17). In our study, no statistical difference was found in terms of overall survival, whether synchronous or metachronous.

Multiple primary cancer is difficult to diagnose. A biopsy must be performed to confirm the diagnosis. After diagnosis, which malignancy will be treated first will depend on the patient and the biology of the accompanying tumors. Multifactorial evaluation of the patient and multidisciplinary follow-up is required. There is no standard treatment for synchronous / metachronous hematological malignancies. It is common practice to treat synchronous multiple primary malignancies as stand-alone malignancies and to begin treatment of the most aggressive cancer rather than treating the tumor with the least malignant potential (30-31).

Limitations

Our study includes a population with a small number of patients with a short follow-up period in a newly established hematology center. Due to its retrospective nature and the small number of non-randomized patients, it did not give us much information in terms of etiology. We think that this incidence will increase as the follow-up period of the patients increases and the awareness of synchronous / metachronous tumors increases. There is a need for more comprehensive studies that will also explain the etiologies of synchronous / metachronous hematological and oncological malignancies.

5. Conclusions

All systems should be evaluated in the presence of symptoms, physical examination, and laboratory findings that do not match clinically in an individual with an oncological / hematological malignancy. It is necessary to be suspicious in terms of secondary malignancy that may accompany. The presence of a second malignancy must also be confirmed by biopsy. Although there is no standard treatment, the patient should be evaluated multidisciplinary according to the biology and course of the disease, and malignancy with an aggressive course should be treated primarily.

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Ethics

Ethics Ethics Committee Approval: The study was approved by Afyonkarahisar Health Scıences University Ethical Committee (Approval Date/ Number: 07.01.2022 / 2011-KAEK-2)
Informed Consent:
Author Contributions: Idea/concept: F.Y, M.B.., İ.G.K.Y., Design: F.Y., Data Collection: F.Y., H.D., M.B., Data Processing: F.Y., Analysis/Comment: F.Y., Y.Ş., Literature research/review: F.Y., Writing: F.Y., All authors discussed the results and contributed to the final manuscript.
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Research Article / Araştırma Makalesi

Ceza Sorumluluğu Değerlendirilen Olguların Sosyodemografik, Klinik Özellikleri ve Psikopati Düzeylerinin İncelenmesi

Investigation of Sociodemographic, Clinical Characteristics and Psychopathy Levels of the Patients who were Under Criminal Responsibility Evaluation

[1]Elif Baştürk-Karımmoajenı, [1]İmran Gökçen Yılmaz-Karaman, [2]Beycan Doğan, [1]Zeynep Betül Erzurum, [1]Furkan Demircan, [3]Muzaffer Bilgin

[1]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Psikiyatri Anabilim Dalı, Eskişehir, Türkiye.
[2]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Adli Tıp Anabilim Dalı, Eskişehir, Türkiye.
[3]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Biyoistatistik Anabilim Dalı, Eskişehir, Türkiye.

Özet: Çalışmamızda adli psikiyatri polikliniğinde ceza sorumluluğu açısından değerlendirilen olguların sosyodemografik, klinik özelliklerinin ve psikopati düzeylerinin incelenmesi amaçlanmıştır. Eskişehir Osmangazi Üniversitesi Sağlık Uygulama ve Araştırma Hastanesi Psikiyatri Anabilim Dalı Adli Psikiyatri polikliniğinde 16.03.2022 ve 02.12.2022 tarihleri arasında ceza sorumluluğu değerlendirilmek üzere yönlendirilen kişiler çalışmaya dâhil edilmiştir. Sosyodemografik ve klinik veri formu ile Revize Hare Psikopati Ölçeği uygulanmıştır. Ceza sorumluluğu tam olan 75 olgu, ceza sorumluluğu kısmen azalmış olan 6 olgu ve ceza sorumluluğu yok kararı verilen 20 olgu karşılaştırılmıştır. Ceza sorumluluğu tam olan grup en yüksek psikopati düzeyine sahiptir (14.00, χ^2=18.817 df=2 p<0.001). Tüm katılımcılar değerlendirildiğinde (n=111) psikopati skorlarının erkeklerde (p<0.001), sigara içenlerde (p=0.004), madde kullananlarda (p<0.001), self mutilasyon yapanlarda (p<0.001), özkıyım girişimi öyküsü olanlarda(p<0.001), suçu reddedenlerde (p=0.010) daha yüksek olduğu görülmüştür. Ceza sorumluluğu tam olan olgularda psikopati düzeyi diğer gruplardan daha yüksek saptanmıştır. Psikopati düzeyi olumsuz ruh sağlığı çıktıları ile ilişkilidir. Adli psikiyatrik değerlendirmeler zarar azaltma amaçlı koruyucu ruh sağlığı müdahaleleri açısından uygun bir fırsat olabilir.
Anahtar Kelimeler: Adli Psikiyatri, Ceza Sorumluluğu, Suç Davranışı, Psikopati

Abstract: Our study aimed to examine the sociodemographic, clinical characteristics and psychopathy levels of the cases evaluated regarding criminal responsibility in the forensic psychiatry outpatient clinic. Persons referred to the Eskisehir Osmangazi University Health Practice and Research Hospital, Department of Psychiatry, Forensic Psychiatry outpatient clinic between 16.03.2022 and 02.12.2022 to be evaluated for criminal responsibility were included in the study. Sociodemographic and clinical data form and Revised Hare Psychopathy Scale were applied. 75 cases with full criminal responsibility, 6 with partially reduced criminal responsibility, and 20 with no criminal responsibility were compared. The group with full criminal responsibility had the highest psychopathy level (mean=14.00, χ^2=18.817 df=2 p<0.001). When all participants were evaluated (n=111), psychopathy scores were found to be higher in males (p<0.001), smokers (p=0.004), substance users (p<0.001), self-mutilators (p<0.001), and those with a history of suicide attempt (p<0.001).), and in those who denied the crime (p=0.010). The psychopathy level was higher in cases with full criminal responsibility than in other groups. The level of psychopathy is associated with adverse mental health outcomes. Therefore, forensic psychiatric evaluations may be an appropriate opportunity for preventive mental health interventions to reduce harm.
Keywords: forensic psychiatry, insanity defense, criminal behavior, psychopathy, criminal responsibility

ORCID ID of the authors: EBK0000-0002-3829-1259, .İGYK. 0000-0003-2821-7749, BD. 0000-0001-7389-8323, ZBE. 0000-0003-3082-1566, FD. 0000-0002-7014-5120, MB. 0000-0002-6072-6466

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Correspondence: Elif BAŞTÜRK KARIMMOAJENI - Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Psikiyatri Anabilim Dalı, Eskişehir, Türkiye e-mail: basturk.elf@gmail.com

1. Giriş

Modern hukuka göre cezanın asıl amacı ıslah etmek, suçluya örnek olmak ve toplumu suçlulardan korumaktır (1). Ceza sorumluluğu ceza hukukunda suça elverişli ve yeterli olmak olarak tanımlanır (2). Evrensel hukuka göre bir kişinin eylem ya da eylemsizliği ile ilgili ceza sorumluluğunun olması için, kişinin işlediği suçun anlamı ve sonuçlarını algılayabilmesi, eyleminin neticesinde ceza alacağından bilgisinin olması, davranışlarını yönlendirme yeteneğinin olması ve dürtülerini kontrol edebilmesi gerekmektedir (3). Bu ruhsal yetilerden bir ya da birkaçı eksik olması toplumu koruma amacı dışında, kişinin bundan cezadan fayda sağlamayacağı anlamına gelir, bu nedenle, bu kişilere ceza vermek anlamsızdır (1,2,3). Ceza ehliyeti olmaması durumunda kişi suç işlemiş sayılmaz, suç olmadığında ise kişinin ceza almasını gerektiren eylemden bahsedilemez, bu durum kişinin ceza sorumluluğu açısından değerlendirilmesini gerektirir (2,3).

5237 sayılı yeni Türk Ceza Kanunu'nun 31, 32, 33 ve 34. Maddelerinde ceza sorumluluğu ile ilgili bilgiler bulunmaktadır (2,4). Bunlardan 32.madde özellikle yetişkinlerin akıl hastalıkları ve akıl zayıflıklarına odaklanır. TCK 32. madde 1. fıkrası "Akıl hastalığı nedeniyle, işlediği fiilin hukukî anlam ve sonuçlarını algılayamayan veya bu fiille ilgili olarak davranışlarını yönlendirme yeteneği önemli derecede azalmış olan kişiye ceza verilmez. Ancak bu kişiler hakkında güvenlik tedbirine hükmolunur." şeklinde akıl hastalığı veya zayıflığı bulunanlarda ceza sorumluluğunu belirtir (4). TCK 32. maddesinin 2. fıkrasında ise birinci fıkrada yazılı derecede olmamakla birlikte işlediği fiille ilgili olarak davranışlarını yönlendirme yeteneği azalmış olan kişiye ceza indirimi uygulanacağı kararı belirtilmiştir (4,5).

Psikopati duygusal, kişilerarası ilişkiler, yaşam biçimi alanlarında birtakım sorunlarla ve antisosyal özelliklerle karakterize olan ciddi bir kişilik sorunudur (6). Psikopati ilk olarak Fransız hekim Pinel tarafından hezeyansız delilik anlamına gelen "manie sans délire" ile dile getirilmiştir (6). Psikiyatri alanında psikopati terimini ilk kullanan kişi Alman psikiyatrist Julius Ludwig August Koch olup psikopati terimini güncel şekliyle tanımlayan Harvey Clekley'dir (6). Psikopatili bireyler duygusal olarak empatiden, suçluluktan, vicdan azabından yoksundurlar, yüzeysel ve yetersiz duygulanımları vardır, kişilerarası ilişkiler açısından incelendiğinde kibirli, aldatıcı ve manipülatiftirler, başkalarının duygularını ve düşüncelerini önemsemezler, istediklerini elde edene kadar bencilce davranabilir, bu durumdan suçluluk hissetmeyip, sosyal normları kendi keyifleri için yok sayabilirler (6,7). Herhangi bir psikiyatrik hastalığı bulunan kişilerin suça eğilim sıklığının genel popülasyona göre daha yüksek olduğunu gösteren çalışmalar her geçen gün artmaktadır (8). Araştırmalar en sık Antisosyal Kişilik Bozukluğu (ASKB) ve Psikopati tanıları olan kişilerin suç işlediklerini göstermektedir (9). Psikopatili bireylerin genel popülasyonda prevalansının yaklaşık olarak %1 olduğu düşünülmektedir (7). Cezaevlerinde psikopati yaygınlığının ise %16 ile %25 arasında değişmektedir ve genel nüfusa göre daha yüksektir (7). ASKB ile psikopati tanılarının her ikisinin de yaşam boyu süren bir antisosyal davranış modelini içermesi ve ASKB tanı kriterleri ile psikopati tanı ölçeği maddelerinin bir kısmının örtüşmesi nedeniyle sıklıkla aynı eş anlamlı oldukları düşünülmektedir (7). Ancak birbirlerinden ayrı kavramlar olmakla birlikte, ASKB için tanı koyulurken çoğunlukla ciddi ve kronik bir antisosyal ve suçlu davranış modeline odaklanılır, psikopatide ise duygusal bozukluklar, kişilerarası sorunlar, kişilik özellikleri dikkate alınır (7).

Çalışmamızda bir üniversite hastanesinin adli psikiyatri polikliniğinde ceza sorumluluğu açısından değerlendirilen olguların sosyodemografik, klinik özelliklerinin ve psikopati düzeylerinin incelenmesi amaçlanmıştır.

2. Gereç ve Yöntem

Eskişehir Osmangazi Üniversitesi Sağlık Uygulama ve Araştırma Hastanesi Psikiyatri Anabilim Dalı Adli Psikiyatri polikliniğinde 16.03.2022 ve 02.12.2022 tarihleri arasında ceza sorumluluğu değerlendirilmek üzere yönlendirilen kişiler çalışmaya dâhil

edilmiştir. Dışlama kriterleri çalışmaya katılmayı kabul etmeme, orta ve ağır dereceli mental retardasyon, organik mental bozukluklar, demans olarak belirlendi. Olgular psikiyatri uzmanlık öğrencisi ve psikiyatri uzmanı tarafından değerlendirilerek formları doldurduldu.

2.1. Kullanılan Ölçekler

Sosyodemografik ve klinik veri formu: Araştırmacılar tarafından oluşturulan bu form, yaş, cinsiyet, eğitim gibi sosyodemografik özellikleri; alkol ve madde kullanımı, psikiyatrik tedavi geçmişi gibi klinik özellikleri; ayrıca ceza sorumluluğu değerlendirmesindeki özellikleri kaydetmeyi amaçlar. Klinisyen tarafından uygulanmıştır.

Revize Hare psikopati ölçeği: Hare Psikopati Kontrol Listesi 1980 yılında Robert Hare ve meslektaşları tarafından suçlu popülasyonlarda klinik yapı psikopatisinin değerlendirilmesi için geliştirilmiş bir ölçektir (10,11). PCL 1991 ve 2003 yıllarında güncellenmiş ve PCL-R olarak revize edilmiştir (12,13). Türkçeye Recep Tütüncü ve meslektaşları tarafından 2015 yılında uyarlanmıştır (14). Ruh sağlığı alanında eğitim almış profesyonellerce uygulanabilmektedir (14). Revize Hare Psikopati Kontrol Listesi toplamda 20 maddeden oluşmaktadır. 0'dan 2'ye kadar derecelendirilen 20 madde vardır (0=yok, 1=belki var, 2=kesinlikle var). Bu ölçeğe göre katılımcıların alabileceği maksimum puan 40, minimum puan 0'dır. 0-8 puan arası çok düşük psikopati, 9-16 puan arası düşük psikopati, 17-24 puan arası orta psikopati, 25-32 puan arası yüksek psikopati, 33-40 puanlar arası çok yüksek psikopati olarak değerlendirilmektedir (14).

2.2. İstatistiksel Analiz

Verinin analizinde IBM SPSS 25.0 versiyonu kullanılmıştır. Sürekli veriden normal dağılıma uyanlar ortalama ve standart sapma şeklinde, normal dağılıma uymayanlar ortanca ve çeyreklikler şeklinde sunulmuştur. Kategorik veri frekans ve yüzde şeklinde gösterilmiştir. Sürekli verilerin ilişkisi Pearson korelasyon testi ile incelenmiştir. Psikopati düzeyleri açısından ikili grupların karşılaştırılması bağımsız gruplarda t testi ile yapılmıştır. Normal dağılmayan sürekli verilerin çoklu gruplarda karşılaştırılması Kruskal Wallis testi ile yapılmıştır. İstatistiksel olarak anlamlı p değeri 0.05 olarak kabul edilmiştir.

3. Bulgular

3.1. Sosyodemografik Özellikler

Belirtilen tarihler arasında çalışmaya katılan 111 olgunun verisi ile analizler yapıldı. Katılımcıların ortalama yaşı 36.63 ± 11.11, %85.6'sı (n=95) erkekti. Bekar olanlar örneklemin %70.3'ünü oluşturuyordu (n=78). Olguların %56,8'inin çocuğu yoktu (n=63). Eğitim durumları değerlendirildiğinde %26,1'inin ilkokul mezunu (n=29), %29.7'sinin ortaokul (n=33), %28.8'inin lise düzeyinde eğitim almış olduğu görüldü (n=32). Bulgular Tablo 1'de özetlenmiştir.

3.2. Klinik Özellikler

Olguların %61.3'ünde DSM-IV-TR Eksen 1 bozukluklar tespit edildi (n=68). Olguların %17.1'i psikotik bozukluklar (n=19), %13.5'ü alkol ve madde kullanım bozuklukları (n=15), %9'u anksiyete bozuklukları (n=10) tanıları ile izlenmekteydi. DSM-IV-TR Eksen 2 bozukluklar açısından ise %37.8'inde ASKB (n=42) bulunmaktaydı. Sigara kullanım miktarları açısından değerlendirildiğinde olguların %17.1'i günde 31 adet veya daha fazla (n=19), %32.4'ü günde 11-20 adet (n=36), % 19.8'i günde 10 veya daha fazla (n=22) sigara kullanıyor olduğu tespit edildi. Sigara kullanımı olmayanların oranı %38.7 olduğu görüldü n(=43). Olguların %68,5'inin alkol kullanmadığı (n=76), %20,7'sinin sosyal içici olduğu (n=23), %10.8'inin riskli alkol kullanımının olduğu görüldü(n=12). Örneklemin %23.4'ü madde kullanmaktaydı(n=26). Self mutilasyon öyküsü olanlar örneklemin %30.6'sını (n=34), daha önce özkıyım girişimi olanlar olguların %33.6'sını oluşturuyordu (n=37). Psikiyatrik ilaç kullanımı açısından değerlendirildiğinde %18,9'unun antidepresan (n=21), %34,2'sinin antipsikotik (n=38), %14.4'ünün duygudurum düzenleyici kullandığı tespit edildi(n=16). Ayrıntılar Tablo 2'de bulunmaktadır.

3.3. İsnat edilen suçlara dair özellikler ve ceza sorumluluğu değerlendirmeleri

İsnat edilen suç niteliklerine bakıldığında en sık görülenler %29.73 ile kasten yaralama (n=33), %26.13 ile hırsızlık (n=29), %22.52 ile hakaret (n=25), %18.2 ile tehdit (n=20) suçları olmuştur. Olguların suçla ilgili güncel yorumları incelendiğinde %52,3'ünün suçu kabul ediyor olduğu (n=58), %47.7'sinin reddediyor olduğu (n=53) görüldü. Akıl hastalığı nedeniyle, işlediği fiilin hukuki anlam ve sonuçlarını algılayıp algılayamadığı veya bu fiille ilgili olarak davranışlarını yönlendirme yeteneği azalmış olup olmadığı (TCK 32. Madde) açısından değerlendirildiğinde %67.6'sının ceza sorumluluğunun tam olduğu (n=75), %18'inin ceza sorumluluğu olmadığı, %5.4'ünün ceza sorumluluğunun kısmen azalmış olduğu (n=6) tıbbi kararına varıldı. TCK 57. Maddesinde uyarınca ayaktan zorunlu tedavi kararı verilenler örneklemin %7,2'sini (n=8), yatarak zorunlu tedavi kararı verilenler ise %3,6'sını (n=4) oluşturmaktaydı. Tablo 3'te bulgular özetlenmiştir.

3.4. Psikopati Düzeyleri ve İlişkili Faktörler

Olguların psikopati skorları sosyodemografik, klinik özelliklerine ve adli psikiyatrik değerlendirmelerine göre incelendi. Yaş ve psikopati skorları arasında negatif bir korelasyon saptandı (r=-0.314 p=0.001). Kadınlarda psikopati düzeyi erkeklerden düşüktü (p<0.001). Eğitim düzeyi, medeni durum, çocuk sahibi olup olmama psikopati düzeyi ile ilişkili bulunmadı (her biri p>0.05).

Klinik özelliklerden sigara kullanımı, madde kullanımı, self mutilasyon, özkıyım girişimi daha yüksek psikopati düzeyi ile ilişkili bulundu (sırasıyla p=0.004, p<0.001, p<0.001, p<0.001). Alkol kullanımı olanlar ile olmayanların psikopati düzeyleri arasında anlamlı farklılık saptanmadı (p=0.087).

İsnat edilen suçu kabul eden ve reddeden grupların psikopati düzeyleri arasında anlamlı bir farklılık izlendi (p=0.010). Suçu reddeden grupta psikopati düzeyi daha yüksekti. Belirlenen ceza sorumluluğuna göre psikopati düzeyleri ceza sorumluluğu olmayan, ceza sorumluluğu azalmış olan ve ceza sorumluluğu tam olan gruplar arasında karşılaştırıldığında gruplar arasında anlamlı fark olduğu görülmüştür (χ^2=18.817 df=2 p<0.001). Farkın hangi gruplardan kaynaklandığını anlayabilmek için ikili karşılaştırmalar ve Bonferroni düzeltmesi uygulanmıştır. Gruplar arasındaki farkın ceza sorumluluğu olmayan grup ile ceza sorumluluğu tam olan grup arasındaki farktan kaynaklandığı (p<0.001), diğer ikililer arasında psikopati düzeyleri açısından anlamlı farklılık olmadığı görülmüştür (her biri için p>0.05). Bulgular Tablo 4'te özetlenmiştir.

Tablo 1. Olguların sosyodemografik özellikleri (n=111)

Sosyodemografik özellikler		Sayı/ Ortalama	Yüzde/ Standart Sapma
Yaş		36.63	± 11.11
Cinsiyet	Kadın	16	%14.4
	Erkek	95	%85.6
Medeni durum	Bekar	78	%70.3
	Evli	33	%29.7
Çocuk sayısı	Yok	63	%56.8
	1	17	%15.3
	2	17	%15.3
	3	11	%9.9
	4 veya daha fazla	3	%2,7
Eğitim durumu	Okuma yazması yok	3	%2.7
	İlkokul	29	%26.1
	Ortaokul/ İlköğretim	33	%29.7
	Lise	32	%28.8
	Üniversite	14	%12.6

Tablo 2. Olguların klinik özellikleri (n=111)

Eksen 1 Bozukluklar	**Sayı**	**Yüzde**
Psikotik bozukluklar	19	17.1
Alkol ve madde kullanım bozuklukları	15	13.5
Anksiyete bozuklukları	10	9.0
Bipolar bozukluk	7	6.3
Hafif dereceli mental retardasyon	7	6.3
Depresyon	5	4.5
Sınırda mental kapasite	3	2.7
Dikkat eksikliği ve hiperaktivite bozukluğu	1	0.9
Travma sonrası stres bozukluğu	1	0,9
Yok	43	38.7
Eksen 2 Bozukluklar		
Antisosyal kişilik bozukluğu	42	37.8
Yok	69	62.2
Sigara kullanımı		
Günde 31 adet ve daha fazla	19	17.1
Günde 21-30 adet	3	2.7
Günde 11-20 adet	36	32.4
Günde 10 veya daha az	22	19.8
Yok	31	27.9
Alkol kullanımı		
Riskli alkol kullanımı	12	10.8
Sosyal içici	23	20.7
Yok	76	68.5
Madde kullanımı		
Var	26	23.4
Yok	85	76.6

Tablo 3. İsnat edilen suçlara dair özellikler ve ceza sorumluluğu değerlendirmeleri (n=111)

Suçun niteliği	**Sayı**	**Yüzde**
Kasten yaralama	33	29.73
Hırsızlık	29	26.13
Hakaret	25	22.52
Tehdit	20	18.02
Diğer	49	44.1
Olgunun suçla ilgili güncel yorumu		
Suçu kabul ediyor	58	52.3
Reddediyor	53	47.7
Değerlendirme sonucu		
Ceza sorumluluğu yok (TCK 32/1)	20	18.0
Ceza sorumluluğu kısmen azalmış (TCK 32/2)	6	5.4
Ceza sorumluluğu tam	75	67.6
Diğer	10	9.0
Zorunlu tedavi kararı		
Ayaktan zorunlu tedavi (TCK 57/3)	8	7.2
Yatarak zorunlu tedavi (TCK 57/1)	4	3.6

Tablo 4. Değişkenlere göre psikopati düzeyinin değerlendirilmesi

		Hare Psikopati Ölçeği		İstatistiksel değerlendirme
		Ortalama/ Ortanca	Standart sapma/Q1-Q3	
Cinsiyet	Kadın	3.00	0.00-8.50	**U=1215.00 p<0.001**
	Erkek	12.00	5.00-20.00	
Medeni durum	Bekar	12.83	8.54	t=1.307 p=0.194
	Evli	10.45	9.28	
Çocuk sahibi olma	Var	10.88	8.35	t=1.357 p=0.178
	Yok	13.14	9.08	
Eğitim düzeyi	Ortaokul ve altı	12.12	8.92	t=0.004 p=0.997
	Lise ve üstü	12.13	8.70	
Sigara kullanımı	Var	13.58	8.44	**t=2.906 p=0.004**
	Yok	8.35	8.68	
Alkol kullanımı	Var	14.22	8.73	t=1.724 p=0.087
	Yok	11.15	8.70	
Madde kullanımı	Var	19.00	7.46	**t=5.032 p<0.001**
	Yok	10.02	8.10	
Self mutilasyon	Var	18.58	8.01	**t=6.105 p<0.001**
	Yok	8.95	7.42	
Özkıyım girişimi	Var	16.16	9.16	**t=3.599 p<0.001**
	Yok	10.10	7.92	
Olgunun suçla ilgili güncel yorumu	Kabul etme	10.08	8.20	**t=2.624 p=0.010**
	Reddetme	14.35	8.95	
Belirlenen ceza sorumluluğu düzeyi*	Ceza sorumluluğu yok	3.50	0.50-6.75	**χ^2=18.817 df=2 p<0.001**
	Ceza sorumluluğu kısmen azalmış	7.50	4.50-12.25	
	Ceza sorumluluğu tam	14.00	7.00-21.00	

*(n=101)

4. Tartışma

Bu çalışmada bir üniversite hastanesinin adli psikiyatri polikliniğinde ceza sorumluluğu açısından değerlendirilen olguların sosyodemografik, klinik özellikleri ve psikopati düzeyleri incelenmiştir.

Yaş, cinsiyet, eğitim durumu ve medeni durum açısından literatürdeki diğer adli

psikiyatrik popülasyonlarla benzer olduğu görülmüştür (2,5,8,15-21). Olguların %56,8'inin çocuğunun olmaması, çocuk sahibi olmanın suç işleme davranışında koruyucu faktör olduğu görüşüyle tutarlı olduğu görülmüştür (15).

Çalışmamıza dahil edilen olguların adli psikiyatrik değerlendirmesi sonucunda %61.3'üne DSM-IV-TR Eksen 1 bozukluklar tanısı konulmuştur. En sık rastlanan tanılar sırasıyla psikotik bozukluklar (%17.1), alkol ve madde kullanım bozuklukları (%13.5), anksiyete bozuklukları (%9), bipolar bozukluktur (%6.3). Literatürdeki çalışmalar incelendiğinde ceza ehliyeti olmayan olguların çoğunluğunun duygudurum bozuklukları ve psikotik bozuklular tanılarının olduğu, ceza sorumluluğu tam olan grupta ise antisosyal kişilik bozulduğunun anlamlı ölçüde daha yüksek oranda bulunmuştur (20). İnsana yönelik ciddi suç işleyen adli psikiyatri olgularına yönelik bir çalışmada %42.5 ile şizofreni tanısının en yüksek oranda görüldüğü, sonrasında %19.4 ile duygudurum bozukluğu ve %13.1 ile atipik psikoz tanılarının takip ettiği bulunmuştur (8). 2011 yılında Kanada'da adli psikiyatri hastalarına yönelik yapılan bir çalışmada ise psikiyatri tanısı olan olgularda en sık şizofreni spektrum bozukluğu tanısının olduğu (%53.8), sırasıyla duygudurum bozuklukları (%15.6) ve madde kullanım bozukluğu (%9.9) tanılarının olduğu gösterilmiştir (22). Daha önceki yapılan çalışmalarda duygudurum bozukluğu, psikotik bozukluk, alkol madde kullanım bozuklukları gibi psikiyatrik tanısı olan hastaların suça karışma olasılıkları daha yüksek olduğu ortaya koyulmuştur (5,23,24). Benzer şekilde Sırlıer ve arkadaşlarının 2022 tarihindeki çalışmasında adli psikiyatri hastaları ruhsal hastalıklar açısından incelendiğinde hastaların %40.7'sinin şizofreni ve diğer psikotik bozukluklar tanısı olduğu gösterilmiştir (19).

Çalışmamızdaki adli psikiyatrik olgular DSM-IV-TR Eksen 2 bozukluklar açısından incelendiğinde en sık ASKB tanısına rastlanmıştır (%37.8). Türkiye'de yapılan adli psikiyatri çalışmalarında benzer oranlarda ASKB oranlarına rastlanmıştır (25,26).

Olgularımız sigara kullanımı açısından incelendiğinde sigara kullanımının belirgin olduğu (%72.1 n=80) görülmüştür. Bununla birlikte oransal olarak sigara kullanımının daha fazla olduğu bulunmuştur. Bu durum tek merkezde belirli zaman aralığında yapılan bir çalışma olması ve örnekleminin küçük olması ile ilişkili olabilir. Adli psikiyatri servisinde yapılmış bir çalışmada katılımcıların %59.2'sinin sigara kullanım öyküsünün olduğu, yine başka bir çalışmada adli psikiyatri olgularının %55.2'sinin sigara kullanımının olduğu görülmüştür (19,27). Türkiye'de bir çalışma sonucunda suç işlemeyle psikopati, sigara kullanımı arasında bağlantı saptanmıştır, sigara tüketiminin suça karışmış bireylerde daha sık olduğu görülmüştür (28). Adolesanlarda yapmış olduğu çalışmada psikopati puanlarının sigara kullanımını arasındaki ilişki saptanmıştır (29). Sigara, psikopati ve suç işleme davranışları arasındaki ilişki göz önüne alındığında cezaevlerinde yapılacak sigara bırakma müdahalelerinin önemli bir koruyucu sağlık uygulaması olabileceği görülmektedir. Suç işleyen ve sigara kullanan bireylere sigara kullanımının sağlığa zararları açıklanmalı ve sigara kullanım bozukluğuna yönelik danışmanlık, psikoterapi ve medikal tedaviler bireylere sunulmalıdır. Sigara kullanımına yönelik koruyucu sağlık uygulamalarının adli psikiyatri olgularında suç işleme oranlarının düşmesini sağlayabileceği düşünülmüştür.

Çalışmamızdaki olgular ise alkol tüketimi açısından incelendiğinde %31.5 oranında alkol tüketiminin olduğu, alkol tüketim miktarı açısından bakıldığında olguların %10.8'inin riskli alkol kullanımın olduğu, %20.7'sinin sosyal içici olduğu bulunmuştur. Öncü ve meslektaşlarının yapmış oldukları çalışmada adli psikiyatrik olguların %25'inde komorbid bir durum bildirilmiş ve bunların %75'inde kişilik bozukluğu ve/veya alkol madde kullanım bozukluğu olduğunu gösterilmiştir (25). 2014 yılında Adli Tıp Kurumuna ateşli silahla suç işleme iddiası ile yönlendirilen olguların %12'sinin alkol kullanımının olduğu saptanmıştır (27). Saldırı ve öldürmeye yönelik suçlarda %40-60 oranında, tecavüz suçlarında %30-70 oranında, aile içi şiddet suçlarında %40-80 oranında alkol kullanımı olduğu bildirilmiştir (30,31). Çalışmamıza dahil edilen olguların bir kısmının önceden alkol kullanımları olmasına rağmen çalışma esnasında

cezaevinde olmaları ve alkol temin edememeleri nedeniyle alkol tüketimlerinin olmaması alkol kullanım oranların daha düşük bulunmasına neden olmuş olabilir. Literatürdeki verilerin oranları birbirinden farklı olmakla birlikte alkol kullanımı ile suç işleme davranışı arasında ilişki olduğu düşünülmektedir. Alkol kullanım bozukluğu olanların diğer psikiyatrik bozuklukları olanlara göre daha fazla suç işlediğini gösteren çalışmalar mevcuttur (32-34).

Örneklemimizdeki kişilerin %23.4'ü madde kullanmaktadır. Adli psikiyatri olgularında yapılan bir çalışmada katılımcıların %37.6'sının madde bağımlısı olduğu, %23.9'unun madde kullandığı fakat bağımlı olmadığı, % 3.9'unun remisyonda olduğu saptanmıştır (5). Çalışmamızda alkol ve madde kullanımıyla ilgili elde edilen bulgular Emir ve meslektaşlarının yaptığı çalışma (alkol ve veya madde kötüye kullanım oranı %23) ve Kılıçaslan ve meslektaşlarının yapmış oldukları çalışma (alkol ve veya madde kötüye kullanım oranı %18) ile benzer niteliktedir (19,35). Madde kötüye kullanımı olan kişiler maddeyi temin edebilmek için dolaylı yoldan suça karışabilmektedirler. Diğer yandan benzer sosyal dezavantajlar hem madde kullanımını hem de suça karışmayı kolaylaştırabilir. Madde kullanımı ile tekrarlayan suçlar arasında anlamlı pozitif bir ilişkinin olduğu tespit edilmiştir (32). Madde kötüye kullanımının tekrarlayıcı suç işleme olasılığını 15.3 kat arttırdığı gösterilmiştir (32).

Katılımcıların %30.6'sında self mutilasyon öyküsü olduğu tespit edilmiştir. Gürkan ve meslektaşlarının suç işlemiş ve işlememiş şizofreni hastalarına yönelik çalışmasında suç işleyenlerde kendine zarar verme davranışının daha sık görüldüğü saptanmıştır (28). Ayrıca komorbid madde kullanımı kendine zarar verme ile ilişkili olabilir (32). Çalışmamızda olguların özkıyım öyküsü incelendiğinde literatürdeki diğer çalışmalarla benzer şekilde adli olgularda özkıyım girişimi oranlarının yüksek olduğunu göstermiştir (32,36).

Çalışmamızda olguların psikopati skorları bireylerin yaşlarının artmasıyla azalmaktadır. Tülü'nün 2013 yılındaki cinsel saldırı suçlularının psikopati düzeylerini incelediği çalışmasında cinsel suçlardan hüküm giyenlerin çoğunun genç erişkinlerden oluştuğu, 2012 yılında Meksika'da yapılan çalışmada erken yaşta cezaevine girmenin psikopati düzeyi ile ilintili olduğu, Birleşik Krallık'ta yapılan bir çalışmada genç yaş ile psikopati düzeyinin bağlantılı olduğu elde edilmiştir (37-39). Psikopati düzeyi ile yaş arasında ilişki olmadığı gösteren çalışmalar da mevcuttur (40). Çalışmalardan elde edilen veriler farklılıklar göstermektedir. Psikopatili bireylerde beyin görüntüleme yöntemleri kullanılarak psikopatinin prefrontal korteksin hacminde azalma ve hipokampus ve amigdalanın hacminde azalma ve anormal şekliyle ilişkili olduğu gösterilmiştir (7,41,42). Psikopatide görülen prefrontal korteks disfonksiyonunda suçluluk duyma, utanma ve empati yapabilme, sorumluluk alabilme, ceza ile öğrenebilme, organize olabilme, plan yapabilme yeteneğinin azaldığı, sinirlilik halinin arttığı saptanmıştır (41,43). Bu özelliklerin yaşla değişiklik gösterebileceği düşünülmüştür.

Araştırmalar erkeklerin psikopati düzeylerinin kadınlardan daha yüksek olduğunu göstermektedir (44,45). Önceki çalışmalarla uyumlu olarak çalışmamızda kadınlarda psikopati düzeyinin ortalaması erkeklerden düşük bulunmuştur. Bu durum toplumsal cinsiyet rolleri, kadının toplumsal alanda bulunurluğunun görece az olması ile ilgili olabileceğini düşündürmektedir.

Eğitim düzeyi, medeni durum, çocuk sahibi olup olmama ise psikopati düzeyi ile ilişkili bulunmamıştır (her biri $p>0.05$). Literatürde bu konuyla ilgili yeterli çalışma bulunmamakla birlikte 2013 yılında suçlularda psikopati düzeylerine yönelik yapılan bir çalışma düşük eğitim düzeyinin yüksek psikopati düzeyi ile ilintili olduğu saptanmıştır (46). Bu durum olasılıkla düşük sosyoekonomik düzey ile ilişkilidir.

Çalışmamızda klinik özelliklerden sigara kullanımı, madde kullanımı psikopati skorları arasında pozitif ve anlamlı bir korelasyon olduğu saptanmıştır. Önceki yapılan çalışmalarla uyumlu olarak sigara ve madde kullanımının psikopati düzeyleriyle ilişkili olduğu görülmüştür (28,29,47). Yüz doksan beş üniversite öğrencisi üzerinde yapılan bir

çalışmada madde kullanımı ile psikopati arasında güçlü bir ilişki olduğu bildirilmiştir (48). New Brunswick'te çeşitli suçlar nedeniyle hüküm giymiş kişilere yönelik bağımlılık psikopati ilişkisinin incelendiği çalışmada psikopati ile opioid, halüsinojen ve uyarıcı madde bağımlılığı arasında pozitif korelasyon olduğu gösterilmiştir (49).

Self mutilasyon, özkıyım girişimi daha yüksek psikopati düzeyi ile ilişkili bulunmuştur. Literatürdeki çalışmalarla benzerlik göstermektedir (50,51). Verona ve arkadaşlarının çalışmasında intihar öyküsü ile psikopati skorlarının ve ASKB tanısının ilişkili olduğu saptanmıştır (50).

Alkol kullanımı olanlar ile olmayanların psikopati düzeyleri arasında anlamlı farklılık saptanmamıştır. Alkol ile psikopati arasındaki ilişkinin araştırıldığı çalışmalarda literatürde farklı sonuçlar elde edildiği görülmüştür. Daha önce bahsedilmiş olan New Brunswick'te suçlulara yönelik çalışmada psikopati ile madde bağımlılığı arasında pozitif ilişki saptanmış olmasına rağmen psikopati ile alkol bağımlılığı arasında pozitif anlamlı korelasyon saptanmamıştır (49). Amerika'daki bir çalışmada ise farklı olarak psikopatinin alkol kötüye kullanımı ile anlamlı ve orta derecede ilişkili olduğu bulunmuştur (52).

Çalışmamızda ceza sorumluluğu tam olan grupta psikopati düzeyi en yüksek bulunmuştur. Suça karışan kişinin psikopati tanısının olması o kişiyi ceza sorumluluğundan muaf etmez (53-55). Bu bireyler genel olarak ahlaki ve yasal normlar bilgisine sahip olsalar da bu bilgiyi davranış kontrolüne dönüştüremeyebilirler (55). Çalışmamızda ceza sorumluluğu tam olduğuna karar verilen bireylerde psikopati düzeyinin yüksek olmasının nedeni ceza sorumluluğu olmayan ve azalmış olan grubun suç davranışlarının mevcut hastalıklarıyla ilişkili olması ve ceza sorumluluğu tam olan grubun suç işleme nedeninin psikopati düzeyleri ile ilişkili olması olabilir. Yüksel'in çalışmasında ceza sorumluluğu tam olan grupta en sık ASKB psikiyatri tanısının olduğu, ceza sorumluluğu olmayan grupta en sık psikotik bozukluk tanısı olduğu görülmüştür (9). ASKB ve psikopati tanılarının belirtilerinin örtüşmesi nedeniyle her iki tanı sıklıkla aynı eş anlamlı olarak görülmektedir (7). Bu açıdan bakıldığında çalışmamıza benzer olarak Yüksel'in çalışmasında da ceza sorumluluğu tam olduğuna karar verilen grupta en sık ASKB tanısının görülmesi şaşırtıcı değildir. Yapılan bir çalışmada psikopatik bireyler, yüksek güvenlikli cezaevlerinde tedavi gören bireylere göre genel suçlular arasında daha fazla görülmesi, ceza sorumluluğu tam olarak değerlendirilen bireylerde psikopati görülme sıklığının ceza sorumluluğu olmayan ve azalan bireylere nazaran daha fazla olması yönünde yorumlanabilir (56).

Britanya'da 638 kişiden oluşan genel popülasyon üzerinde yapılan çalışmada psikopatinin mahkumlar, evsizler ve psikiyatrik yatışlar arasında yaygın olmasına rağmen genel popülasyonun %0.6'sını etkilediği gösterilmiştir (57). Psikopati ilintili şiddet davranışı, toplumsal ceza ve sağlık sisteminde büyük yüke neden olur ve bu nedenle önemli bir halk sağlığı sorunudur (58). Bu kişiler hem suç işleyerek hem başkalarına zarar vermekte hem de sigara içerek, madde kullanarak, self mutilasyon yaparak ve intihar girişiminde bulunarak kendi sağlıklarına zarar vermektedirler. Finlandiya'da psikopatik bireylerin 20-30 yıl takip edildiği çalışmada, psikopatik bireylerin genel popülasyona göre yaşam sürelerinin daha kısa olduğu ve psikopati olmayan gruba göre şiddet nedeniyle ölümlerin daha sık görüldüğü bulunmuştur (59). Psikopatinin korkmayı gerektirecek ve potansiyel tehdit edici unsurların ipuçlarına karşı daha az duyarlı olması uzun ömürlülüğü azalttığını ve bu durumun amigdala disfonksiyonuyla ilişkili olduğunu savunan çalışmalar da mevcuttur (60).

Bu kişiler çalışarak topluma ve kendilerine fayda sağlayamamakta ve hatta kişilerarası ve toplumsal alanlarda belirgin işlev kaybına neden olmaktadır (61). Bu açıdan bakıldığında psikopati ve ASKB'nin önemli bir halk sağlığı sorunu olduğu söylenebilir. Diyabet, kalp hastalığı ve obezite gibi ciddi halk sağlığı sorunu olan hastalıklar açısından yüksek risk taşıyan kişileri hedef alan ve bu hastalıkların başlamasını önlemek veya geciktirmek, beslenme ve fiziksel aktiviteyi iyileştirmek

için tasarlanmış tarama, tedavi, yaşam tarzı müdahaleleri sunan bir takım önleyici sağlık hizmetleri bulunmaktadır (62-65). Buna benzer şekilde psikopati için de biyolojik ve çevresel risk faktörlerini hedef alan, erken teşhis edilmesine yardımcı olan ve şiddet içeren davranışın başlamasını önleyen veya kapsamını ve sonuçlarını azaltan müdahaleler geliştirmek gerekmekte ve önleyici sağlık politikalarını hayata geçirmek gerekmektedir.

Yetişkin popülasyonda tedavinin etkinliğini inceleyen daha fazla araştırmalara ihtiyaç duyulsa da literatür yetişkin psikopatlarda tedavinin zor olduğunu göstermektedir (58). Bunun yanı sıra Mendota Çocuk Tedavi Merkezinde en az 6 ay boyunca günde birkaç saat terapötik tedavi protokolü uygulanan düşük ila orta düzeyde psikopatik özelliklere sahip olan çocuklarda şiddet içeren yeniden suç işleme oranlarını yarı yarıya azaldığı gösterilmiştir (66). Bu bulgular, yaşamın erken bir aşamasında başlayan birincil koruma yaklaşımlarına duyulan ihtiyacın önemini vurgulamaktadır. Gerçekte çalışmalar psikopatiye ne kadar erken müdahale edilirse, müdahalenin etkinliğinin o kadar fazla olacağını göstermektedir (58,67,68). Elde edilen bulgularla bu bireylerin henüz suça yönelmeden ve suç nedeniyle adli psikiyatri polikliniğine başvurmadan önce yaşamın erken yıllarında koruyucu sağlık müdahaleleri yapılması gerekmektedir.

Psikopati ile ilgili çalışmalara daha fazla ilgi gösterilmesi, psikopatiye yönelik koruyucu faktörler, zemin hazırlayan gelişimsel yörüngeler ve müdahale için en uygun gelişim dönemleri konusunda bilgi sağlayacak ve yalnızca psikopati tanılı bireyler için değil, aynı zamanda bu bireylerin içinde yaşadıkları toplum için de maksimum fayda sağlayacaktır.

5. Sonuç

Çalışmamızda olguların psikopati skorları erkeklerde, gençlerde, sigara ve madde kullananlarda, self mutilasyon ve özkıyım öyküsü olanlarda daha yüksektir. Psikopati skorları incelendiğinde ceza sorumluluğu olmayan grup ile ceza sorumluluğu tam olan grubun psikopati düzeyleri arasında anlamlı bir farklılık izlenmiştir.

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Hakem Değerlendirmesi: Hakem değerlendirmesinden geçmiştir.

Yazar Katkı Oranları: Fikir/kavram: İGYK, EBK, BD Tasarım: İGYK, MB Veri Toplama: EBK, ZBE, FD, BD Veri İşleme: EBK, ZBE, FD, BD, MB Analiz/Yorum: İGYK, MB Literatür taraması: EBK, BD Yazma: EBK, İGYK

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Research Article / Araştırma Makalesi

Tıp Fakültesi Öğrencileri ve Sağlık Uygulama ve Araştırma Hastanesi Personellerinin Ruhsal Bozukluklar Açısından Değerlendirilmesi: Bir Üniversite Örneği

Evaluation of Medical Faculty Students and Health Practice and Research Hospital Staff in Terms of Mental Disorders: A University Example

[1]Mine Tepetaş, [2]Sevil Aydoğan Gedik, [3]Ayşegül Mutlu, [1]Sevda Sungur, [1]Tuğçe Arslan Torba, [1]Didem Arslantaş, [1]Alaattin Ünsal

[1]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Halk Sağlığı Anabilim Dalı, Eskişehir, Türkiye.
[2]Eskişehir Odunpazarı İlçe Sağlık Müdürlüğü, Eskişehir, Türkiye.
[3]Muş Bulanık İlçe Sağlık Müdürlüğü, Muş, Türkiye.

Özet: Ruhsal bozukluklar sık görülen, kronikleşebilen, yeti kaybıyla sonuçlanabilen, zor fark edilebilen ve bu nedenle tedavi edilemeyerek toplumsal maliyetlerini arttıran hastalıklar olması nedeniyle öncelikle değerlendirilmelidir. Bu sebeplerle ruhsal bozukluklar önemli bir halk sağlığı sorunudur. Çalışmada, ruhsal bozukluklar açısından riskli ve üretkenliğin yüksek olduğu bir grup olan Eskişehir Osmangazi Üniversitesi (ESOGÜ) Tıp Fakültesi öğrencileri ve Sağlık Uygulama ve Araştırma Hastanesi personellerinin herhangi bir ruhsal bozukluk yaşama şüphesi açısından değerlendirilmesi amaçlandı. Çalışma, Eylül 2021-Mart 2022 tarihlerinde 1425 kişi üzerinde yapılan kesitsel bir araştırmadır. Kullanılan anket formun birinci bölümü bazı sosyodemografik özellikleri ve ruhsal bozukluk yaşama şüphesiyle ilişkili bazı değişkenleri, ikinci bölümü Öz Bildirim Ölçeği (ÖBÖ-20) sorularını içermektedir. Katılımcıların yaşları ortalama 26,04 ± 8,04 olup %53,20'si kadın idi. Çalışmamızda herhangi bir ruhsal bozukluğa sahip olma şüphesi sıklığı %56,9 bulundu. ÖBÖ-20'den alınan puanlar ortalama 7,16 ± 5,11 idi. Regresyon analizinde herhangi bir ruhsal bozukluğa sahip olma riskinin aile gelir durumu orta ve kötü olanlarda, iyi olanlara kıyasla 1,65 ve 3,39; hayatını etkileyen büyük bir travma yaşayanlarda, yaşamayanlara göre 1,92; aldığı sosyal desteği yeterli bulmayanlarda, bulanlara göre 2,48 kat arttığı saptandı. Bu çalışma sonucunda katılımcıların herhangi bir ruhsal bozukluğa sahip olma şüphesi sıklığının orta düzeyde olduğu ve bu sıklığı etkileyen birçok faktör olduğu saptandı.
Anahtar Kelimeler: Ruhsal hastalık, Hastane personeli, Tıp öğrencisi, ÖBÖ-20

Abstract: Mental disorders are common, can become chronic or result in disability. In addition, they can increase their social costs by not being treated because they are difficult to notice. For these reasons, mental disorders are an important public health problem. In the study, it was aimed to evaluate the students of Eskişehir Osmangazi University (ESOGU) Faculty of Medicine and the staff of the University Hospital, who are at risk for mental disorders, in terms of the suspicion of having a mental disorder. The study is a cross-sectional study conducted on 1425 people between September 2021 - March 2022. The first part of the questionnaire includes sociodemographic characteristics and the variables related to the suspicion of having a mental disorder, the second part includes the Self-Report Scale (SRQ-20) questions. The mean age of the participants was 26.04 ± 8.04, and 53.2% of them were women. In our study, the suspicion of having a mental disorder was found to be 56.9%. The mean scores from the SRQ-20 were 7.16 ± 5.11. It was determined that the risk of having a mental disorder was 1.645 and 3.386 times higher in those with moderate and poor family income; 1,922 times more for those who have experienced a life-affirming trauma; 2,484 times more for those who did not find the social support they received sufficient. As a result of this study, it was determined that the frequency of suspicion of having a mental disorder was moderate and there were many factors affecting this.
Keywords: Mental disorder, Hospital staff, Medical student, SRQ-20

ORCID ID of the authors: MT. 0000-0003-4747-7220, SAG. 0000-0002-7314-5900, AM. 0000-0002-6929-6837, SS. 0000-0002-0186-0331, TAT.0000-0002-5844-7775, DA. 0000-0002-5263-3710, AÜ. 0000-0001-8353-1605

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Correspondence: Mine TEPETAŞ - Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Halk Sağlığı Anabilim Dalı, Eskişehir, Türkiye e-mail: minetepetas@gmail.com

1. Giriş

Dünya Sağlık Örgütü (DSÖ), sağlığı sadece hastalık ve sakatlığın olmayışı değil, fiziksel, ruhsal ve sosyal açıdan tam bir iyilik hali olarak tanımlamaktadır (1). Sağlığın belirleyicileri bedensel ve ruhsal sağlıktır. Birinde ortaya çıkan bir sorun diğerini de etkilemektedir. Bütün olarak sağlığı koruyabilmek adına bedensel sağlığa verilen önem kadar ruh sağlığına da önem verilmelidir (2). Bireyin biyolojik açıdan var olan sağlık durumunun tanımlanması ve var olan fiziksel problemlerin giderilmesi veya oluşmadan önlenmesi, fiziksel sağlığın korunması açısından önemlidir (3). Ruhsal sağlık için ise birey günlük yaşamında, yaşadığı zaman dilimi ve değişen mekanlarda kendisiyle, ailesiyle, yakın çevresiyle, toplumla ve çalıştığı işle olan ilişkilerinde süreci denge, uyum ve doyum içinde sürdürmelidir. Bu denge ve uyum bozulduğunda ise ruhsal bozukluklar ortaya çıkabilmektedir (4).

Ruhsal bozukluklar; sıkıntıya neden olan düşünce, duygu veya davranışsal bozukluklara yol açan, bireylerde uyum sorunlarına sebep olan ve farklı düzeylerde olmak üzere tutarsızlık, yetersizlik, aşırılık ya da uygunsuzlukla karakterize olan bozukluklar olarak tanımlanabilir (5). Dünyada ortalama ruhsal bozukluk görülme sıklığı DSÖ tarafından % 24,0 olarak bulunmuş ve her dört kişiden birinin hayatlarının bir döneminde ruhsal bozukluklardan etkilendiğini belirtmiştir (6). Ülkemizde Sağlık Bakanlığı tarafından yapılan Türkiye Hastalık Yükü Çalışması'nda ulusal hastalık yükü nedenlerinin temel hastalık gruplarına göre dağılımı yapıldığında, %13,3 ile ikinci sırada psikiyatrik hastalık grubunun yer aldığı bildirilmiştir (7). Bununla birlikte ruhsal bozuklukların %2 ila %10'unun tedavi gerektirecek düzeyde olduğu saptanmıştır (8).

Ruhsal bozukluklar sık görüldükleri, kronikleşebildikleri, yeti kaybı ile sonuçlanabildikleri, akademik başarıyı düşürebildikleri ve iş gücü-iş günü kayıplarına neden olabildikleri için öncelikle ele alınması gereken hastalıklardandır (9). Ayrıca ruhsal bozuklukların fark edilebilmesindeki zorluk nedeniyle yeterince tedavi edilememesi bu hastalıkların topluma maliyetinin yüksek olmasına sebep olmaktadır (10). Bu nedenlerden dolayı ruh sağlığı bozuklukları tüm dünyada etkili olan önemli bir halk sağlığı sorunudur.

Küresel hastalık yükünün önde gelen nedenlerinden olan ruhsal bozuklukların ortaya çıkışı genelde erken yaşlarda olmasına rağmen saptanması ancak yaşamın sonraki dönemlerinde sağlanabilmektedir (11). Bu çalışmada, ruhsal bozukluklar açısından riskli ve aynı zamanda üretkenliğin yüksek olduğu yaş grubunda bulunan bireylerin yer aldığı ESOGÜ Tıp Fakültesi öğrencileri ve Sağlık Uygulama ve Araştırma Hastanesi personellerinin herhangi bir ruhsal bozukluk yaşama şüphesi açısından değerlendirilmesi amaçlandı.

2. Gereç ve Yöntem

Çalışma, Eylül 2021-Mart 2022 tarihleri arasında Eskişehir Osmangazi Üniversitesi'nde (ESOGÜ) öğrenim görmekte olan Tıp Fakültesi öğrencileri ve Sağlık Uygulama ve Araştırma Hastanesi çalışanları üzerinde yapılan kesitsel tipte bir çalışmadır. Çalışmada ESOGÜ Tıp Fakültesinde öğrenim görmekte 1579 öğrenci ve Sağlık Uygulama ve Araştırma Hastanesi'nde çalışmakta olan 975 personelin tamamına ulaşılması hedeflenmiştir. Çalışmaya katılmayı kabul eden 645 (%66,2) personel ve 780 (%49,4) öğrenci (n=1425) çalışma grubunu oluşturdu.

Çalışmanın yapılabilmesi için Eskişehir Osmangazi Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan 28.09.2021 tarih ve 24 sayılı izin ile ESOGÜ Dekanlığı'ndan ve ESOGÜ Sağlık Uygulama Ve Araştırma Hastanesi Başhekimliği'nden gerekli olan idari izinler alındı. Çalışmanın yapılacağı bölümlere önceden belirlenen gün ve saatlerde gidilerek çalışmanın konusu ve amacı anlatıldıktan sonra, çalışmaya katılmayı kabul edenlerden sözlü onamları alındı. Önceden hazırlanmış olan anket formlar gözlem altında katılımcıların kendileri tarafından doldurduldu. Ulaşılamayan kişilere ise anket formların online olarak ulaştırılması

sağlandı. Anketin doldurulması işlemi yaklaşık 10-15 dakika sürdü.

Çalışmanın amacına uygun olarak literatürden de faydalanılarak bir anket formu hazırlandı (12–15). Anket formu iki bölümden oluşmaktadır. Formun birinci bölümü katılımcıların bazı sosyodemografik özellikleri (yaşı, cinsiyeti, mesleği, aile tipi, aile gelir durumu, kimlerle yaşadığı) ve ruhsal bozukluk yaşama şüphesi ile ilişkili olduğu düşünülen bazı değişkenleri (ruhsal hastalık öyküsü, çevreden alınan sosyal desteğin yeterli olup olmadığı, hekim tanılı kronik hastalık varlığı, hayatını etkileyen büyük bir travma yaşama durumu), ikinci bölümü ise Öz Bildirim Ölçeği (ÖBÖ-20) sorularını içermektedir.

Çalışmamızda personelin ve öğrencilerin ruhsal bozukluklar açısından değerlendirmesi amacıyla ÖBÖ-20 kullanıldı. Ölçek DSÖ tarafından, özellikle gelişmekte olan ülkelerde psikiyatrik rahatsızlığı taramak için Beusenberg ve arkadaşları tarafından geliştirilmiştir (15). Türkçe geçerlik ve güvenirlik çalışması 2020 yılında Torba ve arkadaşları tarafından yapılmış olup (11), 2023 yılında Aydoğan-Gedik ve arkadaşları tarafından kestirim puanı hesaplanmıştır. ÖBÖ-20, evet veya hayır olarak yanıtlanması gereken 20 sorudan oluşmaktadır. Evet yanıtı "1", hayır yanıtı "0" olarak puanlanmaktadır ve ölçekten alınabilecek en yüksek puan 20'dir. Kadınlarda 6,5, erkeklerde ve tüm örneklemde 4,5 puan ve üstü alanların herhangi bir ruhsal bozukluk şüphesi olduğu bildirilmiştir (16).

Elde edilen veriler bilgisayar ortamında SPSS (versiyon 15.0) istatistik paket programında değerlendirildi. Ölçülebilir verilerin normal dağılıma uygunluğu Shapiro-Wilk testi ile değerlendirildi. İstatiksel analizler için Kİ-Kare testi ve Lojistik Regresyon Analizi (Backwark:Wald) kullanıldı. İstatistiksel anlamlılık değeri olarak $p<0,05$ kabul edildi.

3. Bulgular

Çalışmaya 780 (%54,7) ESOGÜ Tıp Fakültesi öğrencisi ve 645 (%45,3) Sağlık Uygulama ve Araştırma Hastanesi personeli olmak üzere toplamda 1425 kişi katılmıştır. Katılımcıların yaşları 18-66 arasında değişmekte olup ortalama 26,04 ± 8,04 idi. Katılımcıların 758'i (%53,2) kadın ve 667'si (%46,8) erkek idi. Katılımcıların bazı sosyodemografik özellikleri Tablo 1'de verilmiştir.

Tablo 1. Çalışma grubunu oluşturanların bazı sosyodemografik özellikleri

Sosyodemografik Özellikler	Sayı (n)	Yüzde (%)
Yaş(Yıl)		
25 ve altı	929	65,2
26 ve üstü	496	34,8
Cinsiyet		
Kadın	758	53,2
Erkek	667	46,8
Meslek		
Hastane Çalışanı	645	45,3
Öğrenci	780	54,7
Aile Tipi		
Çekirdek	1104	77,5
Geniş	222	15,6
Parçalanmış	99	6,9
Aile Gelir Durumu		
İyi	287	20,1
Orta	1009	70,8
Kötü	129	9,1
Birlikte Yaşadığı Kişi		
Tek başına	600	42,1
Ailesiyle	565	39,7
Arkadaşlarıyla	260	18,2
Toplam	1425	100,0

Katılımcıların %9,1'inin (n=130) hekim tanılı ruhsal bir bozukluğu, %17,4'ünün (n=248) hekim tanılı kronik herhangi bir hastalığı var idi. Katılımcıların %29,3'ü (n=417) hayatını etkileyen büyük bir travma yaşadığını bildirdi. Ayrıca %33,8'i (n=432) çevresinden aldığı sosyal desteği yeterli bulmadığını beyan etti. Çalışmaya katılanların ruhsal bozukluklarla ilişkili olduğu düşünülen bazı özellikleri Tablo 2'de verilmiştir.

Tablo 2. Çalışma grubunu oluşturanların ruhsal bozukluğa sahip olma şüphesi ile ilişkili olduğu düşünülen bazı özellikleri

Ruhsal Bozukluğa Sahip Olma Şüphesi ile İlişkili Olduğu Düşünülen Özellikler	Sayı (n)	Yüzde (%)
Hekim Tanılı Herhangi Bir Ruhsal Bozukluk Hikayesi		
Yok	1295	90,9
Var	130	9,1
Daha Önce Hekim Tanılı Herhangi Bir Ruhsal Bozukluk Yaşama Hikayesi		
Yok	1168	82,0
Var	257	18,0
Ailesinde Doktor Tanılı Herhangi Bir Ruhsal Bozukluğu Olan Birey Varlığı		
Yok	1116	78,3
Var	309	21,7
Hekim Tanılı Kronik Herhangi Bir Hastalık Hikayesi		
Yok	1177	82,6
Var	248	17,4
Hayatını Etkileyen Büyük Bir Travma Yaşama Durumu		
Yok	1008	70,7
Var	417	29,3
Çevreden Aldığı Sosyal Desteği Yeterli Bulma Durumu		
Hayır	482	33,8
Evet	943	66,2
Toplam	1425	100,0

Çalışmamızda herhangi bir ruhsal bozukluğa sahip olma şüphesi sıklığı %56,9 (n=811) olarak bulunmuştur. Herhangi bir ruhsal bozukluğa sahip olma şüphesi ile ilişkili olduğu saptanan değişkenlerle (aile gelir durumu, kiminle yaşadığı, hekim tanılı herhangi bir ruhsal bozukluk hikayesi, daha önce hekim tanılı herhangi bir ruhsal bozukluk hikayesi, ailesinde hekim tanılı herhangi bir ruhsal bozukluk hikayesi, hekim tanılı kronik herhangi bir hastalık hikayesi, hayatını etkileyen büyük bir travma yaşama durumu, çevreden aldığı sosyal desteği yeterli bulma durumu) oluşturulan Lojistik Regresyon Analizi sonuçları Tablo 3'te verilmiştir.

Tablo 3. Herhangi bir ruhsal bozukluğa sahip olma şüphesi ile ilişkili olduğu saptanan değişkenlerle oluşturulan Lojistik Regresyon Analizi sonuçları (step final)

Değişkenler	p	OR	GA
Aile gelir durumu (Referans: İyi)			
Orta	**0,001**	1,645	1,236-2,189
Kötü	**<0,001**	3,386	2,002-5,726
Kiminle Yaşadığı (Referans: Arkadaşlarıyla)			
Tek Başına	**0,002**	1,647	1,192-2,276
Ailesiyle	0,769	1,049	0,761-1,448
Hekim Tanılı Herhangi Bir Ruhsal Bozukluk Hikayesi (Referans: Yok)			
Var	**0,001**	2,836	1,606-5,007
Daha Önce Hekim Tanılı Herhangi Bir Ruhsal Bozukluk Yaşama Hikayesi (Referans: Yok)			
Var	**0,043**	1,444	1,012-2,060
Ailesinde Hekim Tanılı Herhangi Bir Ruhsal Bozukluğu Olan Birey Varlığı (Referans: Yok)			
Var	**0,022**	1,434	1,053-1,953
Hekim Tanılı Kronik Herhangi Bir Hastalık Hikayesi (Referans: Yok)			
Var	**<0,001**	1,859	1,340-2,579
Hayatını Etkileyen Büyük Bir Travma Yaşama Durumu (Referans:Yok)			
Var	**<0,001**	1,922	1,470-2,514
Çevreden Aldığı Sosyal Desteği Yeterli Bulma Durumu (Referans: Evet)			
Hayır	**<0,001**	2,484	1,931-3,195
Sabit (Constant)	<0,001	0,312	

Katılımcıların Öz Bildirim Ölçeği'nden aldıkları puanların ortancası 7 (0-20), ortalaması 7,16 ± 5,11 idi. Çalışma grubunda gerçekleştirilen çok değişkenli lojistik regresyon analizinde herhangi bir ruhsal bozukluğa sahip olma riski aile gelir durumu orta ve kötü olanlarda, iyi olanlara kıyasla 1,645 (%95 GA 1,236-2,189) ve 3,386 (%95 GA 2,002-5,726) kat; hayatını etkileyen büyük bir travma yaşayanlarda, yaşamayanlara göre 1,922 (%95 GA 1,470-2,514) kat; çevreden aldığı sosyal desteği yeterli bulmayanlarda, yeterli bulanlara göre 2,484 (%95 GA 1,931-3,195) kat arttığı saptanmıştır.

4. Tartışma

Toplumun sağlık ihtiyaçlarının karşılanması ve sürdürülebilmesinde sağlık çalışanları ve sağlık alanında öğrenim görmekte olan öğrenciler en önemli role sahip olan gruptur. Bu sebeple sağlık alanında çalışanların ve öğrenim görmekte olanların iyi duygu durumlarının ve psikolojik iyilik durumlarının sağlanması ve sürdürülmesi, bununla birlikte olası psikolojik sorunların erken tespit edilerek giderilmesi için gerekli çabanın gösterilmesinin oldukça önemli olduğu söylenebilir.

Gelir durumu kötü olan bireylerin kendilerinin ve ailelerinin ihtiyaçlarını karşılamakta zorluk yaşaması beklenen bir durumdur. Yaşanan bu zorluğun aynı zamanda kişileri psikolojik olarak da olumsuz etkilemesi beklenir. Bu çalışmada, aile gelir düzeyi azaldıkça hastane personeli ve öğrencilerin ruhsal bozukluğa sahip olma riskinin arttığı saptandı. Literatürde yer alan çalışmalarda da aile gelir düzeyi azaldıkça bireylerde ruhsal bozukluk görülme ihtimalinin yükseldiği rapor edilmiştir (17,18).

Aynı evin içinde bir yaşamı duygusal, sosyal, fiziksel ve finansal olarak paylaşabilecek bir kişinin olmaması, kişinin fiziki ve maddi yükünü arttırmasının yanı sıra ruhsal ve duygusal açıdan da yalnız hissetmesine neden olabilir. Bu olumsuz şartlara maruz kalan kişilerin ruhsal bozukluğa yatkınlığının daha yüksek olması beklenen bir durumdur. Çalışma grubunda yalnız yaşadığını belirtenlerin ruhsal bozukluğa sahip olma ihtimalinin daha yüksek olduğu tespit edildi. Gyasi ve arkadaşları ile Tlili ve arkadaşları tarafından farklı yaş gruplarında yapılan çalışmalarda da yalnız yaşayanlarda ruhsal bozukluğa sahip olma ihtimalinin daha yüksek olduğu bildirilmiştir (19,20).

Hayatlarının herhangi bir döneminde herhangi bir ruhsal bozukluk yaşamış olanların profesyonel destek ihtiyacı duymaları ve psikiyatrik risk etmenlerine karşı daha duyarlı olmaları beklenen bir durumdur Literatürde yer alan pek çok çalışmada da geçmiş ya da şuan ki ruhsal bozuklukların kişinin ruhsal bozukluğa sahip olma ihtimalini arttırdığı raporlanmıştır (21–23). Çalışmamızda da şuan ya da daha önce hekim tanılı herhangi bir ruhsal bozukluk yaşama hikayesi olanların ruhsal bozukluğa sahip olma ihtimalinin daha yüksek olduğu bulundu.

Ailesinde ruhsal bozukluk öyküsü bulunan bireylerin genetik yatkınlığa sahip olabilmelerinin yanı sıra ruhsal bozukluğa sahip olan aile bireyleriyle iletişimde maruz kalabilecekleri sorunlar, bu durumun neden olabileceği stres, kaygı ve sorumlulukla baş etme gerekliliği bu kişilerin de ruhsal bozukluk yaşama olasılığını artırdığı söylenebilir. Yaptığımız çalışmada da ailesinde ruhsal bozukluğu olanların ruhsal bozukluk yaşama olasılığının yüksek olduğu tespit edildi. İngiltere ve Finlandiya'da yapılan çalışmalarda da ailesinde ruhsal bozukluk öyküsü bulunan kişilerin ruhsal bozukluk yaşama olasılığının yüksek olduğu raporlanmıştır (24,25).

Sağlık; fiziksel, sosyal ve ruhsal bir bütün olarak değerlendirilen bir kavramdır. Kişinin fiziksel herhangi bir hastalığının olmasının sağlık durumunu direk etkileyerek ruhsal durumu üzerinde de olumsuz etki oluşturacağı söylenebilir. Bu çalışmada hekim tanılı kronik herhangi bir hastalık hikayesi olanların ruhsal bozukluk yaşama olasılığı yüksek bulundu. Butler ve arkadaşlarının yaptığı bir çalışmada da kronik hastalığı olan bireylerin ruhsal bozukluk yaşama olasılığının yüksek olduğu rapor edilmiştir (26). Pesen ve Mayda'nın yaptığı bir çalışmada ise kronik hastalığı olanlar ve olmayanlar arasında ruhsal

bozukluk yaşama olasılığı açısından bir fark tespit edilemediği bildirilmiştir (27). Çalışmalarda bildirilen farklı sonuçların nedenlerinden biri çalışmaların yapıldığı toplumların farklı sosyokültürel ve sosyoekonomik özelliklere sahip olması ve kişilerin ruhsal durumlarının bundan direk olarak etkilenmesi olabilir.

Bireylerin hayatlarını etkileyecek büyüklükte bir travmaya maruz kalmaları onların aşırı korku, dehşet, çaresizlik, yetersizlik, savunmasızlık, suçluluk, pişmanlık gibi pek çok olumsuz duygu yaşamalarına neden olabilir. Bu olumsuz duygularla yeterli düzeyde baş edemeyen kişilerde ruhsal bozukluk görülmesi beklenen bir durumdur. Çalışmamızda hayatını etkileyen büyük bir travma yaşadığını belirtenlerde ruhsal bozukluk yaşama olasılığı yüksek saptandı. Literatürde yer alan farklı çalışmalarda da hayatını etkileyen önemli bir travma yaşayanlarda ruhsal bozukluk görülme olasılığının yüksek olduğu bildirilmiştir (28,29).

Sosyal destek sayesinde bireylerin karşılıklı sorunlarını dile getirme, bilgi alışverişi yapma, duygularını paylaşma, kendileriyle ilgili geri bildirim alabilme gibi imkanları olabilmektedir. Böylece bireyde çevresi tarafından sevildiği, anlaşıldığı, önemsendiği ve yalnız olmadığı hissinin oluşması sağlanarak bireylerin ruhsal bozukluk yaşama oranının azaldığı, yaşayanların ise topluma yeniden kazandırıldığı söylenebilir. Bu çalışmada çevreden aldığı sosyal desteği yeterli bulmayanlarda ruhsal bozukluk görülme olasılığının yüksek olduğu bulundu. Meltzer ve arkadaşları ile Symth ve arkadaşlarının yaptıkları çalışmalarda da benzer sonuç rapor edilmiştir (30,31).

5. Sonuç

Bu çalışma ruhsal bozukluklar açısından tarama amaçlı kullanılabilecek geçerli ve güvenilir bir ölçek olan Öz Bildirim Ölçeği kullanılarak Türkiye'de yapılmış ilk çalışma olması açısından önem arz etmektedir. Elde edilen sonuçlar Öz Bildirim Ölçeği kullanılarak farklı ülkelerde yapılmış olan çalışmalarda elde edilen sonuçlarla da yakın benzerlik göstermektedir.

Yapılan bu çalışma sonucunda ESOGÜ Tıp Fakültesi öğrencileri ve Sağlık Uygulama ve Araştırma Hastanesi personellerinde herhangi bir ruhsal bozukluğa sahip olma şüphesi sıklığı orta düzeyde bulundu. Çalışma grubunu oluşturanların herhangi bir ruhsal bozukluğa sahip olma şüphesi sıklığını etkileyen birçok faktör olduğu saptandı.

Çalışmanın sonuçları değerlendirildiğinde çalışanların ve öğrencilerin ruhsal bozukluğa sahip olma şüphesi sıklığını azaltabilmek adına yapılacak eğitimler yararlı olabilir. Bireylere sosyal destek sağlanması, sorunlarla baş etme yöntemlerinin öğretilmesi, psikolojik sağlamlıklarının arttırılmasının sağlanması gibi önlemler sonucunda bir ruhsal bozukluğa sahip olma şüphesi sıklıklarının azalması beklenir. Toplumda herhangi bir ruhsal bozukluğa sahip olma şüphesi sıklığını belirleyebilmek için farklı sosyodemografik özelliklere sahip gruplarda da benzer çalışmaların planlanması önerilmektedir.

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Research Article / Araştırma Makalesi

Anemik Preterm Bebeklerde Copeptin, Mid-Regional Proadrenomedullin ve N-Terminal Pro-Beyin Natriüretik Peptit Düzeylerinin Değerlendirilmesi: Prospektif Klinik Çalışma

Evaluation of Copeptin, Mid-Regional Proadrenomedullin and N-Terminal Pro-Brain Natriuretıc Peptit Levels in Anemic Preterm Babies: A Prospective Clinical Study

Tuğba Barsan Kaya, Özge Aydemir, Özge Sürmeli Onay, Ayşe Neslihan Tekin

Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Neonatoloji Bilim Dalı, Eskişehir, Türkiye

Özet: Yoğun bakım ihtiyacı olan prematüre yenidoğanlar en sık transfüzyon yapılan hasta grupları arasındadır. Literatürde transfüzyon kararını vermekte kullanılan kriterler ve bu kriterlerin sonuçlarını inceleyen çalışmalar olsa da transfüzyon endikasyonları konusunda net bir fikir birliği yoktur. Bu çalışmanın amacı anemik bebeklerde transfüzyon ihtiyacını belirlemede kalp debisindeki değişikliklere duyarlı olan NT-proBNP, copeptin ve MR-proADM düzeylerinin kullanılabilirliğini değerlendirmektir. Yenidoğan yoğun bakım ünitesinde izlenmekte olan ve eritrosit transfüzyonu ihtiyacı olan 24 preterm bebek Transfüzyon grubu ve yenidoğan yoğun bakım ünitesinde izlenen, hematokrit (Hct)>%25 olan ve transfüzyon endikasyonu olabilecek klinik bulgusu olmayan 23 preterm bebek Kontrol Grubuna olarak çalışmaya dahil edildi. Transfüzyon grubunda transfüzyon öncesi ve sonrası copeptin, NT-ProBNP ve MR-proADM düzeyleri arasında fark saptanmadı (p değeri sırasıyla 0,44, 0,64, 0,41). Transfüzyon grubunun transfüzyon öncesi copeptin, NT-proBNP, ve MR-proADM düzeyleri kontrol grubunun düzeyleri ile kıyaslandığında anlamlı fark saptanmadı (sırasıyla p=0,85, 0,75, 0,88). Hemoglobin düzeyi 8 mg/dl altında olan hastalarda copeptin, NT-ProBNP ve MR-proADM düzeyleri Hb düzeyi >8mg/dl iken transfüzyon yapılanlar ve kontrol grubuna göre sayısal olarak yaklaşık 2 kat yüksek bulunmasına rağmen gruplar arasındaki fark istatistiksel olarak anlamlı değildi (p değeri sırasıyla 0,15, 0,47, 0,57). Çalışma grubunun semptomatik, asemptomatik alt gruplarının kontrol grubu ile birlikte olan analizinde copeptin, NT-ProBNP ve MR-proADM düzeyleri açısından fark saptanmadı (p değeri sırasıyla 0,81, 0,99, 0,93). Serolojik belirteçler pek çok durumda yol göstericidir ancak çalışmamızda yer alan Copeptin, NT-proBNP ve MD-proADM'in anemide, transfüzyon kararı vermede kullanışlı olmadığı kanaatine varılmıştır.
Anahtar Kelimeler: Anemi, yenidoğan, eritrosit transfüzyonu, biyobelirteç

Abstract: Premature newborns in need of intensive care are among the most frequently transfused patient groups. Although there are studies in the literature examining the criteria used to make transfusion decision and the results of these criteria, there is no clear consensus on the indications for transfusion. The aim of this study was to evaluate the usefulness of NT-proBNP, copeptin and MR-proADM levels, which are sensitive to changes in cardiac output, in determining the need for transfusion in anemic infants. Twenty-four preterm infants who were being followed up in the neonatal intensive care unit and needed erythrocyte transfusion were included in the study as the Transfusion group and 23 preterm infants who had haematocrit >25 and no clinical findings indicating transfusion were included in the study as the Control group. No difference was found between pre- and post-transfusion copeptin, NT-ProBNP and MR-proADM levels in the transfusion group (p value 0.44, 0.64, 0.41, respectively). No significant difference was found between the pre-transfusion copeptin, NT-proBNP, and MR-proADM levels of the Transfusion group and the Control group (p=0.85, 0.75, 0.88, respectively). Although copeptin, NT-ProBNP and MR-proADM levels in patients with haemoglobin level below 8 mg/dl were found to be approximately 2-fold higher than those transfused with Hb level >8 mg/dl and the Control group, the difference between the groups was not statistically significant (p value 0.15, 0.47, 0.57, respectively). In the analysis of symptomatic and asymptomatic subgroups of the study group together with the Control group, no difference was found in copeptin, NT-ProBNP and MR-proADM levels (p value 0.81, 0.99, 0.93, respectively). Serological markers are guiding in many cases, but copeptin, NT-proBNP and MD-proADM in our study were not found to be useful in making transfusion decision in anaemia.
Keywords: Anemia,neonatorum, red blood cell transfusion,biomarker

ORCID ID of the authors: TBK. 0000-0003-0698-1850, ÖA. 0000-0002-4106-0873, ÖSO. 0000-0002-7658-3594
ANT. 0000-0002-2993-5737

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Correspondence: Tuğba BARSAN KAYA – Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Neonatoloji Bilim Dalı, Eskişehir, Türkiye
e-mail : tugbarsan@hotmail.com

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1. Giriş

Anemi, yenidoğan yoğun bakım ünitelerinde (YYBÜ) sık kan alma, yetersiz eritropoez, hızlı büyüme gibi nedenlerle sık görülen bir problemdir. Literatürde transfüzyon kararını vermekte kullanılan kriterler ve bu kriterlerin sonuçlarını inceleyen çalışmalar olsa da(1-3) transfüzyon endikasyonları konusunda net bir fikir birliği yoktur.(4-5) Aneminin en büyük klinik yansıması doku oksijenasyonunun yetersiz kalmasıdır ancak doku oksijenasyonunun doğrudan ölçümü mümkün değildir.

Sistemik oksijen sunumu kalp debisi ve arteriyal oksijen içeriğine bağlıdır. Anemik bebeklerde anemiye bağlı gelişen hipoksi hiperkinetik bir dolaşım yanıtına ve kalp debisinde artışa neden olur.(6-7) Anemi arttıkça kalbe daha fazla yük biner ve sol ventrikül disfonksiyonu gelişir.

Beyin natriüretik peptit (BNP) ventrikül duvarının hacim ve/veya basınç yüklenmesine bağlı mekanik gerilmesine yanıt olarak kalpten salgılanan bir nöro-hormondur.(8) Kardiyomiyozitlerden proBNP olarak salgılanır ve proteolitiklerce biyolojik aktif formu BNP ve inaktif formu N-terminal BNP'ye parçalanır. Kalp yetmezliğinde biyobelirteç olarak klinik pratikte kullanılmaktadır.

Böbreklerden serbest su emilimini düzenleyen arjninin vazopressin (AVP) sıvı dengesi, kan volümü, vazokonstriksiyon ve miyokardiyal kasılma fonksiyonları üzerindeki etkileri nedeniyle kalp yetmezliğindeki önemli nörohumoral medyatörler arasında yer almaktadır. Copeptin, AVP öncül proteini pre-proAVP'nin C-terminal segmentidir. Arjinin vazopressin ile aynı miktarda sentezlenir ve plazmada daha uzun süre saptanabilir seviyede kalır.(9)

Adrenomedüllin (ADM) kalp yetmezliğinde yükselen diğer bir nörohumoral medyatördür. Plazmada komplemana bağlandığı ve dolaşımdan hızla temizlendiği için ADM ölçümü güçtür. Mid-regional proAdrenomedullin (MR-proADM), ADM ile aynı miktarda salgılandığı ve plazmada daha stabil olduğu için ADM'nin indirekt ölçümünde kullanılmaktadır.(10)

Bu çalışmanın amacı anemik bebeklerde transfüzyon ihtiyacını belirlemede kalp debisindeki değişikliklere duyarlı olan NT-proBNP, copeptin ve MR-proADM düzeylerinin kullanılabilirliğini değerlendirmektir.

2. Gereç ve Yöntem

Bu prospektif vaka kontrol çalışması Ekim 2021-Haziran 2022 tarihleri arasında Eskişehir Osmangazi Üniversitesi Tıp Fakültesi 3. düzey Yenidoğan Yoğun Bakım Ünitesinde etik kurul onayı alınarak yapıldı (28.09.2021 kayıt no:11). Ünitemizde kord klemplenmesi canlandırma gereksinimi olmayan tüm term ve preterm bebeklerde 30-60 sn geciktirilmektedir. Ailelerden çalışma ile ilgili bilgilendirilmiş onam alındı.

Hasta Seçimi

Yenidoğan Yoğun Bakım Ünitesi'nde izlenen ve eritrosit süspansiyonu transfüzyonu yapılan prematüre bebekler çalışma grubuna (Transfüzyon grubu) dahil edildi. Transfüzyon kararında, Türk Neonatoloji Derneğinin Transfüzyon Rehberi referans alınmakla birlikte hemoglobin değeri rehberde belirtilen sınırlarının üzerinde olup aneminin klinik belirtileri (taşikardi (24 saatten uzun süren kalp hızı>180/dk), taşipne (24 saatten uzun süren solunum sayısı>80/dk), oksijen ihtiyacında artış, yetersiz kilo alımı (son 4 gündür 100 Kcal/kg/gün kalori alımı ile <10 g/gün kilo artışı)(11) olan hastalarda klinisyen kararı ile transfüzyon yapılmıştır.(12) Eritrosit süspansiyonu transfüzyonu 20 ml/kg'dan 4 saatte uygulandı.

Anemiyi değerlendirmek veya kan grubu tiplendirmesi ve uygunluğu için kan örneği alınması esnasında ve transfüzyondan 3-5 gün sonra hemoglobin (Hb) düzeyi kontrolü amacıyla kan örneği alınırken serum NT-proBNP, copeptin ve MR-proADM düzeyleri için fazladan 1 ml kan örneği alındı. Yenidoğan yoğun bakım ünitesinde izlenen, hematokrit (Hct) >%25 olan ve transfüzyon

endikasyonu olabilecek klinik bulgusu olmayan yenidoğanlar Kontrol Grubuna dahil edildi ve rutin kan tetkikleri sırasında bu bebeklerden de 1 ml kan serum NT-proBNP, copeptin ve MR-proADM düzeyleri için ayrıldı. Transfüzyon grubu ve Kontrol grubunun kan örnekleri aynı dönemde toplandı ve 3600 devirde 10 dakika santrifüj edildikten sonra, süpernatant kısmı ayrılıp alınarak eppendorf tüplerinde, çalışma anına kadar -80 C°'de saklandı. Transfüzyon öncesi ve sonrası Hb, Hct, laktat, kan basıncı, perfüzyon indeksi kaydedildi. Kontrol grubunun ise kan örnekleri alındığı sıradaki değerleri kaydedildi. Tüm hastaların klinik ve demografik verileri dosyalarından veri toplama formuna kaydedildi. Majör konjenital veya kromozomal anomali, perinatal asfiksi, patent duktus arteriozus, siyanotik konjenital kalp hastalığı, kalp yetmezliği ve sepsis tanısı olan, inotropik tedavi almakta olan ve kan değişimi yapılan bebekler çalışmaya dahil edilmedi. Transfüzyon grubunun transfüzyon öncesi ve sonrasına ait klinik, hematolojik ve serolojik parametreleri hem kendi içinde hem de Kontrol grubunun verileriyle karşılaştırıldı. Transfüzyon grubu içinde Hb<8 olan ve olmayanlar ile semptomatik ve asemptomatik alt grup karşılaştırması yapıldı.

İstatistiksel analiz

İstatistiksel analizler için Statistical Package for the Social Sciences (SPSS) (Release 20.0; SPSS Inc. Chicago, Illinois, USA) programı kullanıldı. Verilerin normal dağılıma uygunluk durumları Shapiro-Wilk testiyle değerlendirilmiştir. Tanımlayıcı istatistikler normal dağılan veriler için ortalama±standart sapma (SD), normal dağılmayan veriler için ortanca ve 25-75 persentil değerleri (Q1-Q3) ile verilmiştir. Kategorik değişkenler ise olgu sayısı (n) ve yüzdesi (%) ile gösterilmiştir. Bağımsız kategorik değişkenlerin karşılaştırılmasında Pearson ki-kare ve Fisher'in exact testleri, sürekli değişkenlerin karşılaştırılmasında normal dağılım varsa Student's t-testi ve tek yönlü varyans analizi (ANOVA), normal dağılım yoksa Mann Whitney-U testi ve Kruskal Wallis testi kullanılmıştır. Bağımlı değişkenlerin analizinde Wilcoxon Signed Rank testi kullanılmıştır. Gestasyon haftası ile biyobelirteçler arasındaki ilişkiyi belirlemek için Pearson korelasyon analizi kullanılmıştır. Tüm hipotez testlerinde $p<0.05$ istatistiksel olarak anlamlı kabul edilmiştir.

3. Bulgular

Çalışmaya eritrosit transfüzyonu alan 24 bebek (Transfüzyon grubu) ve klinik olarak stabil, anemisi olmayan 23 yenidoğan bebek (Kontrol grubu) dahil edildi. Grupların klinik ve demografik verileri Tablo 1'de verilmiştir. Transfüzyon ve Kontrol grupları arasında gestasyon haftası açısından fark saptanmazken Kontrol grubunun doğumda ve çalışma anındaki vücut ağırlığı Transfüzyon grubuna göre daha düşüktü ($p=0.01$). Kord hemoglobini, 5. dk Apgar skoru ve çalışma anındaki solunum desteği açısından gruplar arasında fark saptanmadı. Gruplar arasında serum örneklemesinin günü açısından, ki bu çalışma grubu için eritrosit transfüzyon günüydü, gruplar arasında fark saptanmadı ($p=0.43$). Transfüzyon grubunda transfüzyon öncesi Hb ve Hct değerleri kontrol grubuna göre anlamlı derecede düşüktü ($p<0.001$). Çalışma grubunun transfüzyon öncesi copeptin, NT-proBNP, ve MR-proADM düzeyleri ile kontrol grubunun düzeyleri ile kıyaslandığında da anlamlı fark saptanmadı (sırasıyla p=0,85, 0,75, 0,88). (Tablo 2). Transfüzyon grubunda transfüzyon öncesi ve sonrası copeptin, NT-ProBNP ve MR-proADM düzeyleri arasında fark saptanmadı (p değeri sırasıyla 0,44, 0,64, 0,41) (Tablo 2). Hemoglobin düzeyi 8 mg/dl altında olan hastalarda copeptin, NT-ProBNP ve MR-proADM düzeyleri Hb düzeyi >8mg/dl iken transfüzyon yapılanlar ve kontrol grubuna göre sayısal olarak yaklaşık 2 kat yüksek bulunmasına rağmen gruplar arasındaki fark istatistiksel olarak anlamlı değildi (p değeri sırasıyla 0,15, 0,47, 0,57) (Tablo 3). Çalışma grubunun semptomatik, asemptomatik alt gruplarının kontrol grubu ile birlikte olan analizinde copeptin, NT-ProBNP ve MR-proADM düzeyleri açısından fark saptanmadı (p değeri sırasıyla 0,81, 0,99, 0,93) (Tablo-4). Gestasyon haftası ile transfüzyon öncesi/sonrası copeptin, NT-proBNP,

proADM düzeyleri arasında zayıf-orta düzeyde pozitif korelasyon saptandı (sırasıyla korelasyon katsayıları ve p değerleri; copeptin (TÖ/TS) r=0,34/0,48, p= 0,019/0,017, NT-proBNP (TÖ/TS): r=0,36/0,54, p=0,012/0,006), proADM (TÖ/TS): r=0,35/0,45, p=0,014/0,026)

Tablo1. Grupların Klinik ve Demografik Özellikleri

	Transfüzyon Grubu (n=23)	**Kontrol grubu (n=24)**	**p değeri**
Gestasyon haftası*	29.0±2.29	31.2±2.65	0.08
Doğum ağırlığı (g)**	1552 (1375-2391)	1215 (885-1395)	**0.01**
Cinsiyet			
5. dk Apgar skoru**	8 (7-9)	8 (7-8)	0.21
Kord Hb (mg/dl)**	14.7 (13.9-16.8)	15.3 (13.7-16.4)	0.95
Transfüzyon öncesi Hb (mg/dl)**	8,3 (7,4-9,2)	11,2 (9,7-12,8)	**<0,001**
Transfüzyon öncesi Hct düzeyi (%)*	25,3±3,89	33,5±6,49	**<0,001**
Postnatal yaş (gün)**	20.5 (12-28)	24 (22-36.5)	0.43
Çalışma anında vücut ağırlığı (g)*	2189±729	1165±593	**0.01**
Çalışma anında solunum desteği (n)	11	5	0,69

**ortalama±SD, ** ortanca (Q1-Q3)*

Tablo 2. Transfüzyon ve Kontrol Gruplarının Hemodinamik ve Laboratuvar Verileri

	Transfüzyon Grubu				
	Transfüzyon öncesi	Transfüzyon sonrası	**Kontrol grubu**	**p1(TÖ-TS)**	**p2 (TÖ-K)**
Saturasyon (%)**	97 (96-98)	96 (96-97)	97 (96-98)	0,57	0,39
KTA (dk)**	152 (148-155)	144 (139-151)	144 (138-151)	**0,01**	**0,02**
Sistolik TA (mmHg)**	71 (64,5-75)	74 (67-78)	70 (64-76)	0,14	0,95
Diastolik TA (mmHg)**	39 (34,5-45)	40 (34-46)	39 (34-43)	0,60	0,75
Ortalama TA (mmHg)**	48 (34,5-45)	50,5 (43-57)	50 (47-53)	0,36	0,66
Perfüzyon indeksi**	1,11 (0,85-1,36)	1,27 (1,05-1,35)	1,03 (0,72-1,15)	0,15	0,28
Hemoglobin (mg/dl)**	8,3 (7,4-9,2)	12,0 (10,6-12,6)	11,2 (9,7-12,8)	**<0,001**	**<0,001**
Hematokrit (%)*	25,3±3,89	34,8±4,53	33,5±6,49	**<0,001**	**0,001**
Laktat (mg/dl)**	2,2 (1,9-3,0)	2,2 (1,7-2,8)	2,05 (1,72-2,75)	0,53	0,20
Copeptin (ng/ml)**	0,59 (0,35-3,37)	0,52 (0,31-4,28)	0,53 (0,32-1,06)	0,44	0,85
NT-proBNP (ng/l)**	95,08 (70,33-381,48)	90,7 (67,98-506,48)	100,66 (68,2-176,7)	0,64	0,75
MD-proADM (ng/l)**	24,1 (15,01-124,04)	24,7 (13,41-110,15)	23,5 (13,6-39,7)	0,41	0,88

**ortalama±SD, ** ortanca (Q1-Q3), KTA: kalp tepe atımı, TÖ: transfüzyon öncesi, TS: transfüzyon sonrası, K: kontrol*

Tablo 3. Hemoglobin 8 mg/dl altında ve üstünde olan hastaların parametreleri

	Hb<8mg/Dl (N=8)	Hb≥8 Mg/Dl (N=16)	Kontrol (N=23)	p Değeri
COPEPTİN (NG/ML)**	1,03 (0,36-24,01)	0,44 (0,20-11,18)	0,53 (0,27-49,06)	0,15
NT-PROBNP(NG/L)**	163,71 (65,64-744,77)	84,68 (44,66-866,82)	100,66 (54,72-3065,88)	0,47
MD-PROADM (NG/L)**	48,61 (10,19-965,71)	23,70 (9,39-269,29)	23,59 (9,87-1526,17)	0,57

Hemoglobin 8 mg/dl alındığında

Tablo 4. Transfüzyon Grubundaki Semptomatik ve Asemptomatik Hastalar ve Kontrol Grubu Hastalarının Parametreleri

	Semptomatik (N=13)	Asemptomatik (N=11)	Kontrol (N=23)	p Değeri
COPEPTİN (NG/ML)**	0,44 (0,20-11,18)	0,63 (0,27-24,01)	0,55 (0,27-49,06)	0,81
NT-PROBNP(NG/L)**	95,7 (44,66-866,82)	86,25 (58,71-2009,01)	101,9 (54,72-3065,88)	0,99
MD-PROADM (NG/L)**	24,6 (9,39-325,37)	21,8 (10,19-965,71)	24,1 (9,87-1526,17)	0,93

4. Tartışma

Yoğun bakım ihtiyacı olan prematüre yenidoğanlar en sık transfüzyon yapılan hasta grupları arasındadır. Doğum sonrası hemoglobindeki fizyolojik düşüş, HbF'den HbA'ya geçişte oksijen afinitesindeki değişiklikler, transfüzyonun kritik hasta bebeğe etkilerini değerlendirmekteki zorluk transfüzyon ihtiyacı olan bebeği belirlemeyi ve transfüzyon kriterlerini tanımlamayı zorlaştırmaktadır.(13-14) Transfüzyon ihtiyacı olan bebekleri belirlemede doku oksijenasyonunu dolaylı yoldan değerlendirmenin umut vaat eden bir yöntemi olan *near-infra red* spektroskopi yeterli olmamış(15), laktat düzeyi ise çok büyük değişkenlik gösterdiğinden güvenilir bulunmamıştır.(16-17)

Bu çalışmada copeptin, NT-proBNP, MR-proADM düzeylerinin eritrosit transfüzyon ihtiyacını belirlemede kullanılabilirliğini incelemek amaçlandı. Transfüzyon kararı verilen bebeklerden transfüzyon öncesi alınan copeptin, NT-proBNP, MR-proADM düzeyleri transfüzyon ihtiyacı olmayan, stabil bebeklerdeki düzeylerle karşılaştırıldığında anlamlı bir fark bulunmadı. Ayrıca çalışma grubundaki bebeklerden eritrosit transfüzyonu öncesi ve sonrasında alınan copeptin, NT-proBNP, MR-proADM düzeyleri de benzer bulundu. Transfüzyon yapılan grupta Hb cut-off değerini 8 mg/dl olarak belirlediğimizde Hb≤8mg/dl olan grupta NT-proBNP, copeptin ve MD-proADM düzeylerini Hb>8mg/dl olanlara göre daha yüksek saptandı ancak fark istatistiksel olarak anlamlı bulunmadı. Bu durum çalışmaya alınan hasta sayısının az olmasından kaynaklanmış olabilir. Özellikle yenidoğanda transfüzyon kararı ağırlıklı olarak klinik kanılara dayanmaktadır.(18) Çalışmamız da dahil literatürde anemi ile ilgili çalışmalarda kalp hızının transfüzyon yapılan grupta kontrol grubuna göre anlamlı yüksek bulunması bu nedenle sürpriz değildir. Her ne kadar kan transfüzyonu uygulamalarımızda TND'nin Transfüzyon Rehberini referans almış olsak da aneminin klinik bulgularını gösteren ancak Hb düzeyi kriterini karşılamayan bebeklerde bireyselleştirilmiş yaklaşımı benimseyerek transfüzyon yapmayı tercih etmemiz sonuçları etkilemiş olabilir.

Beyin natriüretik peptit, atrial natriüretik

peptit ile kalbin ikili natriüretik peptit sistemini oluşturmaktadır. Natriüretik peptitler atriumda volüm ve basınç artışına bağlı gelişen miyokard gerilmesinin başlattığı uyarı ile sekrete edilirler. Serum seviyeleri miyokard duvar gerimi, kardiyak iş yükü ve santral venöz basınç artışı ile korelasyon göstermektedir.(19) Willis ve ark.(20) yaptıkları çalışmada sol ventrikül disfonksiyonu ve kalp yetmezliği olmayan ciddi anemisi olan erişkin hastalarda NT-proBNP'nin yükseldiğini göstermiştir. Ancak çalışmamızda NT-proBNP düzeylerini transfüzyon öncesi, sonrası ve klinik olarak stabil, anemisi olmayan bebeklerle karşılaştırdığımızda anlamlı bir fark saptamadık. Bu çalışmada anemi grubunda hastaların yaş ortalaması 47,7 yıldır ve çalışma grubundaki hastalarda kor pulmonale, pulmoner embolizm, sepsis, atriyal fibrilasyon, akciğer kanseri ve aortik / pulmoner kapak regürjitasyonu/prolapsusunu içeren hastalık tanıları mevcuttur.(25) Yetişkin hastaların kullandığı ilaçlar ve co-morbiditeler de sonuçları değiştiren bir faktör olabilir. Literatürde perinatal dönemde ciddi anemi ve NT-proBNP düzeylerini değerlendiren tek araştırma ciddi anemisi olan hidropik fetuslarda in-utero transfüzyon öncesi ve sonrası NT-proBNP düzeylerinin değerlendirildiği bir çalışmadır.(21) Bu çalışmada Parvovirus enfeksiyonuna bağlı anemi ve hidrops gelişenlerde daha belirgin olmak üzere hidropik hastalarda NT-proBNP düzeylerinin oldukça yüksek olduğu, in-utero transfüzyon sonrasında düştüğü gösterilmiştir. Ancak hidropik hastalarda ciddi anemi, kalp yetmezliği ve buna ikincil böbrek fonksiyon bozukluğu, Parvovirusün neden olabileceği inflamasyon ve miyokardit gibi NT-proBNP düzeyinin yükselmesine neden olabilecek pek çok faktör olduğundan anemi-NT-proBNP ilişkisi hakkında bir yorum yapmak mümkün değildir.(21-22)

Hofbauer ve ark'nın(23) yaptığı deneysel çalışmada hipoksi ve fonksiyonel anemide pek çok organda ve plazmada ADM seviyesini arttığı gösterilmiştir. Anemi-ADM ilişkisini değerlendiren bir klinik çalışma literatürde mevcut değildir. Bizim çalışmamızda transfüzyon ihtiyacı olan bebeklerde öncesi/sonrası ve kontrol grubu arasında ADM düzeyi açısında da istatistiksel olarak anlamlı bir fark bulunmamıştır.

Natriüretik peptitler natriürez ve diürez ile böbrek kan akışını ve filtrasyonunu artırırken, vazopressin aquaporin-2 denilen hücre içi moleküllerin ekspresyonunu indükleyerek böbrek toplama kanalının su geçirgenliğini artırır. Bu da su tutulmasına neden olur. İntravasküler hacmin düzenlenmesinde birbirlerinin zıttı eylemlerle birlikte çalışırlar.(24) Vazopressin salgısını arttıran başlıca durumlar hipovolemi, serum osmolaritesinin düşmesi ve hiponatremidir. Mayer ve ark.'nın(25) yaptığı deneysel çalışmada vazopresinin anemi varlığında eritropoetinden bağımsız olarak eritropoezi arttırdığı gösterilmiştir. Ancak bu çalışmada genel sağlık koşulları, komorbiditeler ve ilaçlar değerlendirmeye alınmamıştır. Aynı çalışmanın hayvan modellerinde ise akut kanama sonrası vazopresin düzeyi değerlendirilmiş ve arttığı gösterilmiştir. Santral diabetes insipitus ve primer polidipsi hastalarında copeptin düzeyinin sağlıklı kontroller ile kıyaslandığı klinik bir çalışmada ise kanama, ameliyat sonrası dönem enfeksiyon gibi akut faktörlerin dışlandığı stabil anemik hastalar çalışmaya dahil edilmiş, vazopresin öncül proteini pre-proAVP'nin C-terminal segmenti olan copeptin düzeyinin anemi ile ilişkili olmadığı bulunmuştur.(26) Bu çalışma klinik olarak stabil olan hastaların dahil edilmiş olması, copeptin düzeyinin kronik anemide değerlendirilmiş olması ve sonuçları bakımından bizim çalışmamıza benzemektedir.

Tüm bebeklerde yaşamın ilk 8-10 haftası boyunca Hb düzeyi aşamalı olarak düşer.(27) Bu, yaşamın herhangi bir dönemi için akut kan kaybı ya da hastalık olmadan Hb değerinde görülebilecek en büyük değişikliktir. Sağlıklı term bebeklerde bu dönemde aneminin klinik belirti ve bulguları izlenmez ve bu düşüş fizyolojik kabul edilir. Ancak preterm bebeklerde doğum sonrası beklenen Hb düşüşü flebotomi ile kayıplar olmadan da term bebeklere göre daha hızlı ve derindir ve sıklıkla klinik anemi belirtileri eşlik eder.(28) Çalışmamızda copeptin, NT-

proBNP ve MR-proADM düzeylerinin gebelik yaşı ile korelasyon gösterdiğini saptadık. Gebelik haftası küçük olan bebeklerde copeptin, NT-proBNP ve MR-proADM düzeylerinin düşük kalması ve gebelik haftası arttıkça yükselmesi, anemiye karşı gelişecek kompanzasyon mekanizmalarının immatür olmasına bağlı olabilir ve bu durum aneminin preterm bebeklerdeki semptomatik seyrine katkıda bulunuyor olabilir. Bunun için alt grup analizlerinin de yapılabileceği daha fazla sayıda hasta içeren çalışmalara ihtiyaç vardır. Çalışmamızın en önemli kısıtlılığı dahil edilen hasta sayısının az olmasıdır. Diğer taraftan da öncesi ve sonrası verilerin kontrol grubu ile karşılaştırılması güçlü yönüdür.

5. Sonuç

Serolojik belirteçler pek çok durumda yol göstericidir ancak çalışmamızda yer alan Copeptin, NT-proBNP ve MD-proADM'in prematüre bebeklerdeki anemide, transfüzyon kararı vermede kullanışlı olmadığı kanaatine varılmıştır. Transfüzyon kriterlerindeki belirsizlik ile optimal transfüzyon stratejisini geliştirmeye yönelik araştırmalarda metodolojisinin belirlenmesindeki güçlük kısır bir döngü yaratmakta ve çalışmamızda olduğu gibi verileri yorumlamayı güçleştirmektedir. Prematüre bebeklerde doku oksijenizasyonunun bozulmaya başladığı erken dönemde vakit kaybetmeden aneminin düzeltilmesi hem hemodinamik hem de mental açıdan olumlu sonuçlanmaktadır. Sonuç olarak klinisyenin transfüzyon kararı yine hasta başında klinik ipuçlarına göre verilecektir.

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Research Article / Araştırma Makalesi

Cervical Cytology Findings in Renal Transplant Patients and Comparison of These Findings with Normal Population

Böbrek Nakli Yapılmış Hastalarda Servikal Sitoloji Bulguları ve Bu Bulguların Normal Bireylerle Karşılaştırılması

[1]Alev Ok Atılgan, [1]Merih Tepeoğlu, [1]Eda Yılmaz Akçay, [1]A.Nihan Haberal Reyhan, [2]Esra Kuşçu, [1]Handan Özdemir, [3]Mehmet Haberal

[1]Baskent University, Faculty of Medicine, Department of Pathology, Ankara, Türkiye
[2]Baskent University, Faculty of Medicine, Department of Obstetrics and Gynecology, Ankara, Türkiye
[3]Baskent University, Faculty of Medicine, Department of Transplant Surgery, Ankara, Türkiye

Abstract: Long-term immunosuppressive therapy increases the likelihood of renal transplant patients developing cervical cancer. We aimed to analyze the results of cervical cytology in renal transplant patients, compare these findings to those of the normal population, and determine the risk factors linked to the development of squamous intraepithelial lesions. Our analysis involved a retrospective study of hospital records from January 2000 to April 2018, encompassing 140 female renal transplant patients. A control group of 280 women with normal health status was selected and matched based on age and the cervical cytology procedure. The cervical cytology findings of the patients were re-evaluated using the Bethesda 2014 criteria. Of the total of 420 patients, 37 patients had epithelial cell abnormalities; including 32 (86.5%) patients in the renal transplant group and 5 (13.5%) control group ($p \leq 0.001$). Sixty-two patients had infections; including 44 (71%) patients in the renal transplant group and 18 (29%) control group ($p \leq 0.001$). We revealed that the development of squamous intraepithelial lesions was associated with factors such as having an immunologic disease as the primary renal disease, undergoing re-transplantation, and the presence of acute rejection ($p \leq 0.05$). Cervical cytology screening plays a crucial role in detecting preinvasive lesions. The incidence of epithelial cell abnormalities is significantly higher in renal transplant patients compared to the normal population. Regular cervical cytology follow-up is vital for the early detection and prevention of cervical cancer progression in transplant recipients.
Keywords: Cervical cytology, Immunosuppression, Pap smear, Renal transplantation

Özet: Uzun süreli immünsüpresif tedavi, böbrek nakli yapılan hastalarda servikal kanser gelişme olasılığını artırır. Bu çalışmada, böbrek nakli yapılan hastalarda servikal sitoloji sonuçlarını incelemeyi, bu bulguları normal popülasyonla karşılaştırmayı ve skuamöz intraepitelyal lezyon gelişimiyle ilişkili risk faktörlerini belirlemeyi amaçladık. Ocak 2000 ile Nisan 2018 tarihleri arasında, 140 kadın böbrek nakli alıcısının tıbbi kayıtlarını retrospektif olarak analiz edildi. Yaş ve servikal sitoloji prosedürü temel alınarak, normal sağlık durumuna sahip 280 kadından oluşan bir kontrol grubu seçildi ve eşleştirildi. Hastaların Pap smear bulguları, Bethesda 2014 kriterlerine göre yeniden değerlendirildi. Toplam 420 hastanın 37'sinde epitel hücre anormallikleri saptandı; bunların 32'si (%86,5) böbrek nakli grubunda ve 5'i (%13,5) kontrol grubundaydı ($p \leq 0,001$). Enfeksiyonların görüldüğü 62 hasta vardı; bunların 44'ü (%71) böbrek nakli grubunda ve 18'i (%29) kontrol grubundaydı ($p \leq 0,001$). Squamous intraepitelyal lezyon gelişiminin, hastanın primer böbrek hastalığının immünolojik bir hastalık olması, yeniden nakil olma ve akut rejeksiyon varlığı gibi faktörlerle ilişkili olduğunu saptandı ($p \leq 0,05$). Pap smear taraması, servikal preinvaziv lezyonların tespitinde önemli bir rol oynamaktadır. Epitel hücre anormalliklerinin görülme sıklığı, böbrek nakli alıcılarında normal popülasyona kıyasla belirgin şekilde daha yüksektir. Nakil alıcılarında servikal kanser ilerlemesinin erken tespiti ve önlenmesi için düzenli servikal sitoloji takibi hayati önem taşımaktadır.
Anahtar Kelimeler: Böbrek nakli, İmmunsupresyon, Pap smear, Servikal sitoloji,

ORCID ID of the authors: AOK. 0000-0001-8595-8880, MT. 0000-0002-9894-8005, EYA. 0000-0001-6831-9585 ANHR. 0000-0001-9852-9911,EK. 0000-0002-0992-6980, HÖ. 0000-0002-7528-3557, MH. 0000-0002-3462-7632

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Correspondence: Alev OK ATILGAN- Baskent University, Faculty of Medicine, Department of Pathology, Ankara, Türkiye
e-mail: aokatilgan@gmail.com

1. Introduction

Cervical cancer is one of the most common cancers in women worldwide (1). The precursor to cervical cancer is a high-grade squamous intraepithelial lesion (HSIL), typically associated with persistent human papillomavirus (HPV) infection. The majority of HPV infections naturally regress without causing cervical dysplasia. A robust immune response plays a critical role in effectively clearing HPV infections. However, long-term immunosuppressive therapy in renal transplant recipients hinders HPV clearance, leading to the progression of precancerous and cancerous lesions. Immunosuppressive drugs not only increase the likelihood of HPV infection but also contribute to DNA damage, impaired DNA repair, and reduced immune tolerance towards neoplastic cells (2,3).

Cervical carcinoma develops through the gradual accumulation of epithelial abnormalities, and routine cervical screening enables the detection of precursor lesions of cervical cancer. The Papanicolaou (Pap) smear is the main screening method used to detect cervical preinvasive and invasive lesions (4). This screening method reduces the incidence and mortality of cervical cancer in both the normal population and renal transplant recipients.

This study aimed to assess cervical cytology findings in renal transplant patients, comparing them to the normal population using the Bethesda 2014 criteria and investigate risk factors associated with squamous intraepithelial lesions (SILs) in renal transplant patients.

2. Materials and Methods

A retrospective study was conducted on the hospital records of patients who underwent renal transplant surgery between January 2000 and April 2018 at Baskent University, Ankara Hospital. The inclusion criteria for this study mandated patients to have documented gynecologic follow-up for a minimum of one year following renal transplantation and to have undergone at least one cervical cytology sample after the transplantation. A total of 140 women who had cervical cytology performed after transplantation were included in the study. Furthermore, a control group of 280 women was selected using a propensity score matching program according to the technical procedure of cervical cytology and age to ensure comparability with the study group. The control individuals did not receive any immunosuppressive treatment. All patients were aged over 18 years. The Pap smears of all patients were re-evaluated based on the Bethesda 2014 criteria (4). Clinical and pathological data, including patient age, current and past immunosuppressive regimens, history of rejection episodes and treatments, and primary disease, were reviewed, and clinical follow-up findings were documented. The donor treatment and renal transplant surgeries followed standardized procedures. The study was conducted under the ethical guidelines outlined in the 1975 Declaration of Helsinki and approved by the Ethical Review Committee of the institute (KA23/60; Date 09.05.2023).

2.1.Statistical Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (v.26.0; SPSS Inc., Chicago, IL, USA). Numerical variables were presented as mean ± standard deviation (SD). Analytical methods (Kolmogorov-Simirnov test) were used to determine whether the variables were normally distributed. Since normal distribution could not be obtained, non-parametric tests were performed. The Pearson chi-square or Fisher's exact test was used to compare the Qualitative variables and represented by numbers and percentages. The nonparametric Mann–Whitney test was used for the comparison of numerical data. The effects of clinicopathologic variables on the presence of epithelial cell abnormalities were assessed by univariate and multivariate

Cox proportional hazards regression models. For all tests, $p \leq 0.05$ was considered statistically significant.

3. Results

3.1.The Abnormal Cervical Cytology Findings in Renal Transplant Patients and the Normal Population, and Their Comparison

Figures 1 and 2 demonstrated representative microphotographs showing the epithelial abnormalities and the infectious agents.

Epithelial cell abnormalities were evaluated by analyzing Pap smear results from 140 women who underwent renal transplantation and 280 women in the control group. The mean age of patients in the renal transplant and control group was 40.37 ± 10.39 years and 40.36 ± 10.36 years (range, 20-66 years), respectively. As indicated in Table 1, out of the total 420 patients, 37 (8.8%) had epithelial cell abnormalities, with 32 (86.5%) in the renal transplant group and 5 (13.5%) in the control group ($p \leq 0.001$).

Among the patient population, seven (1.7%) individuals were diagnosed with atypical squamous cells of undetermined significance (ASC-US), with 5 (71.4%) being renal transplant group and 2 (28.6%) belonging to the control group ($p = 0.031$). Low-grade squamous intraepithelial lesion (LSIL) was detected in 25 patients (6%), including 22 (88%) renal transplant group and 3 (12%) individuals from the control group. HSIL was observed in 5 patients (1.2%), all of whom were renal transplant group, while none of the individuals in the control group showed HSIL. A statistically significant difference in epithelial cell abnormalities between the two groups was found when comparing the results to the control group ($p \leq 0.05$). Notably, no glandular cell abnormalities were detected.

Out of the 37 patients with epithelial cell abnormalities, only 10 (27.0%) underwent cervical biopsy following a Pap smear. All ten patients were renal transplant group. Among these patients, the preoperative diagnoses were ASC-US in 2 patients, LSIL in 3 patients, and HSIL in 5 patients. Among the two patients with ASC-US cytology, the histopathological findings revealed squamous metaplasia. Among the three patients with LSIL cytology, the histopathological diagnoses were LSIL in 2 patients and HSIL in 1 patient. Among the five patients with HSIL cytology, the histopathological diagnoses were HSIL in 4 patients and squamous cell carcinoma in 1 patient.

Table 1 demonstrates that out of the 420 patients, 62 (14.8%) had infections. Of these, 44 (71%) were in the renal transplant group, and 18 (29%) were in the control group ($p \leq 0.001$). Among the patient population, *Candida* infection was observed in 35 individuals (8.3%), with 28 (80%) of them belonging to the renal transplant group and 7 (20%) to the control group. *Trichomonas vaginalis* infection was detected in 3 (0.7%) patients from the renal transplant group. The incidence of *Candida* and *Trichomonas vaginalis* infection was significantly higher in the renal transplant group compared to the control group ($p \leq 0.001$, $p = 0.014$, respectively). *Herpes simplex* infection was found in only one (0.2%) patient in the renal transplant group, while *Actinomyces* infection was present in 2 individuals (0.5%) from the control group. There were no statistically significant differences between the renal transplant and control group regarding *Actinomyces* and *Herpes simplex* infections ($p = 0.316$, $p = 0.333$, respectively). Twenty-eight (6.7%) individuals had a shift in the vaginal flora suggestive of bacterial vaginosis. Of these, 12 (57.1%) patients were in the renal transplant group, and 9 (42.9%) individuals were in the control group. This difference was statistically significant ($p = 0.018$). *Chlamydia* microorganisms, reactive

changes due to intrauterine devices, and reactive changes due to radiation were not detected in either group.

Inflammatory reactive changes were observed in 50 (11.9%) individuals, including 27 (54.0%) in the renal transplant group and 23 (46.0%) in the control group. Atrophy was detected in 49 patients (11.7%), including 27 (55.1%) in the renal transplant group and 22 (44.9%) in the control group. These differences were statistically significant (p = 0.001, p = 0.001, respectively).

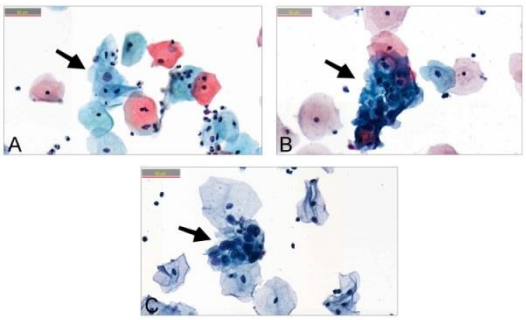

Figure 1. Representative microphotographs showing the epithelial abnormalities. A) Atypical Squamous Cells of Undetermined Significance (ASC-US). Nuclear enlargement and hyperchromasia are noted in a superficial cell. B) Low-Grade Squamous Intraepithelial Lesion (LSIL). Binucleation and koilocytosis are noted. C) High-Grade Squamous Intraepithelial Lesion (HSIL). Increased nuclear/cytoplasmic ratio and hyperchromasia are noted (Pap stain, original magnification ×400).

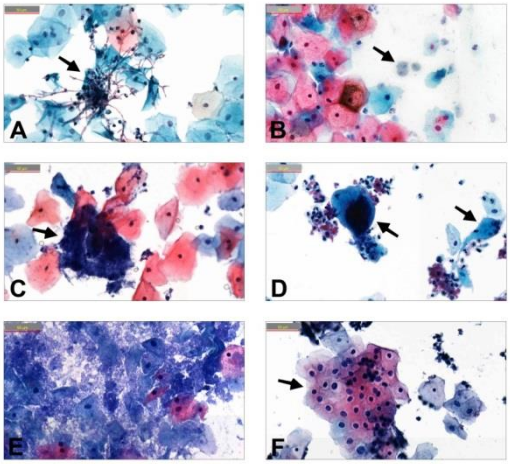

Figure 2. Representative microphotographs showing the infectious agents. A) *Candida albicans*. Fungal organisms with pseudohyphae are noted between squamous cells. B) *Trichomonas vaginalis*. Pear-shaped organisms with eccentrically located nuclei and eosinophilic cytoplasmic granules are shown. C) *Actinomyces.* Tangled clumps of filamentous organisms, often with acute angle branching, are shown as "cotton ball" clusters. D) *Herpes simplex.* A typical multinucleated cell showing the "ground-glass" appearance of the nuclei. E) Bacterial vaginosis. Shift in flora suggestive of bacterial vaginosis. Individual squamous cells are covered by a layer of coccobacilli noted as "clue cells". F) Reactive changes. Reactive squamous epithelial cells display small perinuclear halos, mild nuclear enlargement, and prominent nucleoli without any significant chromatin abnormalities (Pap stain, original magnification ×400)

Table 1. Cervical cytology findings of renal transplantation patients and normal population, and their comparison

	N (%)	Renal Transplantation Group	Control Group	*p*
	420 (100%)	140 (33.3%)	280 (66.7%)	
Age (mean ± SD) (years)		40.4 ± 10.38	40.4 ± 10.38	
Technical procedure				
Conventional cytology	272 (64.8)	77 (28.3%)	195 (71.7%)	
Liquid-based cytology	148 (35.2%)	63 (42.6%)	85 (57.4%)	
Epithelial cell abnormalities				
Absent	383 (91.2%)	108 (28.2%)	275 (71.8%)	≤ 0.001*
Present	37 (8.8%)	32 (86.5%)	5 (13.5%)	
ASC-US	7 (1.7%)	5 (71.4%)	2 (28.6%)	0.031*
LSIL	25 (6%)	22 (88.0%)	3 (12.0%)	≤ 0.001*
HSIL	5 (1.2%)	5 (100%)	0 (0%)	0.001*
Infections				
Absent	358 (85.2%)	96 (26.8%)	262 (73.2%)	≤ 0.001*
Present	62 (14.8%)	44 (71%)	18 (29%)	
Organisms				
Candida	35 (8.3%)	28 (80%)	7 (20%)	≤ 0.001*
Trichomonas Vaginalis	3 (0.7%)	3 (100%)	0 (0%)	0.014*
Actinomyces	2 (0.5%)	0 (0%)	2 (100%)	0.316
Herpes Simplex	1 (0.2%)	1 (100%)	0 (0%)	0.333
Bacterial vaginosis	22 (5.2%)	12 (57.1%)	9 (42.9%)	0.018*
Nonneoplastic findings				
Reactive changes	50 (11.9%)	27 (54.0%)	23 (46.0%)	0.001*
Atrophy	49 (11.7%)	27 (55.1%)	22 (44.9%)	0.001*

ASC-US indicates Atypical Squamous Cells of Undetermined Significance; LSIL, Low-Grade Squamous Intraepithelial Lesion; HSIL, High-Grade Squamous Intraepithelial Lesion
**Statistically significant*

3.2.The Association Between Clinicopathologic Features and Squamous Intraepithelial Lesion Development in Renal Transplant Patients

The ASC-US lesion was excluded and included in the absent group for the SIL in this section. Table 2 shows that out of 140 renal transplant patients, 22 (15.7%) were diagnosed with LSIL, and 5 (3.6%) had HSIL. The average number of cervical cytology tests performed was 4.5 ± 3.6 (range; 2-16). The mean age for patients with SIL and without SIL was 35.5 ± 8.8 years (range, 26-51) and 36.8 ± 9.0 years (range, 18-59), respectively. The two groups had no significant differences (p = 0.107). The average interval between renal transplantation and the Pap smear test for patients with SIL and without SIL was 92.98 ± 74.88 months (range, 12-301 months) and 92.66 ± 64.42 months (range, 12-329 months), respectively. The two groups had no significant differences (p = 0.814).

Out of the total 140 renal transplant patients, four patients (2.9%) underwent re-transplantation at a mean interval of 175.50 ± 70.14 months (range: 110-242 months) after their initial transplantation. Among these four re-transplanted patients, all of them (100%) were diagnosed with SIL. Additionally, SIL was found in 23 (16.9%) out of the 136 patients who had undergone transplantation only once. There was a significant association between SIL and re-transplantation (p = 0.001).

Among the patients, 35 (25%) had immunologic diseases such as glomerulonephritis, familial Mediterranean fever, and systemic lupus erythematosus, while 105 (75%) had non-immunologic diseases including vesicoureteral reflux, nephrolithiasis, pre-eclampsia, hypertension, and diabetes mellitus. Out of the 27 patients with SIL, 18 (66.7%) had immunologic diseases, while 9 (33.3%) had non-immunologic diseases. The incidence of SIL was significantly higher in patients with a

primary immunologic disease compared to those without ($p \leq 0.001$).

The majority of patients (91.4%) were treated with a regimen consisting of calcineurin inhibitors, specifically tacrolimus or cyclosporine-A, in combination with steroids. A smaller proportion of patients (8.6%) received sirolimus or mycophenolate mofetil in combination with steroids. Among the 27 patients with SIL, 25 (92.6%) were treated with a calcineurin inhibitors regimen, while 2 (7.4%) received other medications. However, there was no significant association between SIL and the immunosuppressive regimen used ($p = 0.810$). Among the patients with SIL, 14 (51.9%) had experienced acute rejection, while 13 (48.1%) had not. The incidence of SIL was higher in patients with acute rejection compared to those without ($p = 0.015$).

Out of the 140 patients, 28 (20%) had reached menopause. Among the 27 patients with SIL, 4 (14.8%) were menopausal, and 23 (85.2%) were not. However, there was no significant association between SIL and menopause status ($p = 0.453$).

Regarding cytologic findings, out of the 140 renal transplant patients, 44 (31.4%) had infections, including 28 (63.6%) with *Candida* infection, 3 (6.8%) with *Trichomonas vaginalis* infection, 12 (27.3%) with bacterial vaginosis, and 1 (2.3%) with *Herpes simplex* infection. No patients had *Actinomyces* infections. There was no significant association found between SIL and infections ($p = 0.493$).

Atrophy was detected in 27 (19.3%) patients. Among the 27 patients with SIL, 26 (96.3%) did not have atrophy, while only 1 (3.7%) had atrophy. The incidence of SIL was higher in patients without atrophy compared to those with atrophy ($p = 0.022$).

Table 2. Association between clinicopathologic features and squamous intraepithelial lesion in renal transplantation patients

Variables		**Squamous intraepithelial lesion**		*p*
	N (%)	**Present**	**Absent**	
	140 (100%)	27 (19.3%)	113 (80.7 %)	
Age (Mean ± SD) (years)		35.5 ± 8.8	36.8 ± 9.0	0.107
The mean interval time after transplantation (Mean ± SD) (months)		92.98 ± 74.88	92.66 ± 64.42	0.814
Re-transplantation				
Absent	136 (97.1%)	23 (85.2%)	113 (100%)	0.001*
Present	4 (2.9%)	4 (14.8%)	0 (0%)	
The primary disease				
Immunologic diseases	35 (25.0%)	18 (66.7%)	17 (15%)	≤ 0.001*
Non-immunologic diseases	105 (75.0%)	9 (33.3%)	96 (85%)	
Immunosuppressive Regimen				
Calcineurin inhibitors	128 (91.4%)	25 (92.6%)	103 (91.2%)	0.810
Others	12 (8.6%)	2 (7.4%)	10 (8.8%)	
Acute rejection				
Absent	95 (67.9%)	13 (48.1%)	82 (72.6%)	0.015*
Present	45 (32.1%)	14 (51.9%)	31 (27.4%)	
Menopause status				
Absent	112 (80.0%)	23 (85.2%)	89 (78.8%)	0.453
Present	28 (20.0%)	4 (14.8%)	24 (21.2%)	
Cytologic Findings				
Infection				
Absent	96 (68.6%)	20 (74.1%)	76 (67.3%)	0.493

Present	44 (31.4%)	7 (25.9%)	37 (32.7%)	
Atrophy				
Absent	113 (80.7%)	26 (96.3%)	87 (77.0%)	0.022*
Present	27 (19.3%)	1 (3.7%)	26 (23.0%)	

LSIL indicates Low-Grade Squamous Intraepithelial Lesion; HSIL, High-Grade Squamous Intraepithelial Lesion
**Statistically significant*

3.3.The Assessment of the Risk Factors for Squamous Intraepithelial Lesion Development in Renal Transplant Patients

The multivariate Cox regression analyses revealed that primary renal disease and cervical atrophy were significantly associated with the presence of SIL in the cervical cytology ($p \leq 0.001$, $p = 0.036$, respectively). The univariate Cox regression analysis showed that renal disease was significantly associated with the presence of SIL in the cervical cytology ($p \leq 0.001$) (Table 3).

Table 3. Prognostic significance of clinicopathologic features on the presence of squamous intraepithelial lesion (multivariate and univariate Cox stepwise regression analysis)

Multivariate Cox Regression Analysis				**Univariate Cox Regression Analysis**			
Variable	Hazard ratio	95% Cl	*p*-value	Variable	Hazard ratio	95% Cl	*p*-value
Re-transplantation (absent vs. present)	0.516	0.135-1.973	0.334	Re-transplantation (absent vs. present)	0.501	0.161-1.566	0.235
Primary renal disease (immunologic vs.non-immunologic)	8.744	3.671-20.883	≤0.001*	Primary renal disease (immunologic vs. non-immunologic)	7.031	3.050-16.206	≤0.001*
Immunosuppressive regimen (calcineurin inhibitors vs. others)	0.519	0.108-2.484	0.412	Immunosuppressive regimen (calcineurin inhibitors vs. others)	0.812	0.186-3.543	0.781
Acute rejection (absent vs. present)	0.971	0.371-2.543	0.952	Acute rejection (absent vs. present)	0.580	0.270-1.243	0.161
Infection (absent vs. present)	1.394	0.499-3.893	0.526	Infection (absent vs. present)	1.845	0.773-4.404	0.168
Atrophy (absent vs. present)	8.665	1.154-65.076	0.036*	Atrophy (absent vs. present)	6.645	0.891-49.563	0.065

Cl indicates Confidence interval.
**Statistically significant*

4.Discussion

Organ transplant recipients have a threefold increase in the incidence of in situ cancer compared to the normal population. Studies have shown that organ transplant recipients have a 1% incidence of invasive cervical cancer and a 3.3% incidence of cervical cancer in situ (5). Routine cervical screening plays a crucial role in detecting precursor lesions of cervical cancer. The Pap test is a convenient, affordable, and highly accurate screening method with highsensitivity and specificity. This cytologic screening test is recommended for all women, including those who have undergone transplantation. Existing guidelines for cervical cancer screening primarily emphasize the age range of 21 to 65 for women (6), but they often lack specific recommendations for immunocompromised women, including transplant patients. This gap in guidelines highlights the need for further research and consensus on appropriate screening protocols tailored to the unique needs of immunocompromised individuals.

The pathogenesis of cervical carcinoma involves the progressive accumulation of epithelial abnormalities. Consistent with previous research, the current study revealed a statistically significant increase in the risk of

epithelial cell abnormalities among renal transplant patients compared to the normal population. These findings are consistent with a study conducted by Paternoster et al., which examined 151 transplant patients and found a higher incidence of HSIL and LSIL among this population when compared to the normal population (7). Similarly, Origoni et al. conducted a study that also showed significant differences between the groups, particularly in LSIL cytology (8).

Furthermore, our study presented a case of a 47-year-old female patient diagnosed with cervical squamous cell carcinoma after HSIL cytology four months following renal transplantation. This case highlights the importance of regular cervical cancer screening and prompt follow-up in transplant recipients to detect and address any abnormal cytological findings or potential malignancies at an early stage.

Immunocompromised renal transplant recipients undergoing long-term immunosuppressive therapy face a significant risk for the presence of precancerous lesions and the development of cervical cancer (2,3,9,10). The use of immunosuppressive medications in these individuals can weaken the immune system's ability to detect and eliminate abnormal cervical cells, thereby increasing their susceptibility to HPV infection and the progression of cervical abnormalities (2,3,8). The use of calcineurin inhibitors, such as cyclosporine and tacrolimus, in long-term immunosuppressive therapy for renal transplant patients has been associated with an increased risk of carcinogenesis. This may be attributed to their potential to induce the production of cytokines that regulate factors, which play a role in cell growth and differentiation. Furthermore, these medications have been implicated in promoting metastasis, the spread of cancer cells, and angiogenesis that supports tumor growth. Consequently, calcineurin inhibitors have the potential to contribute to the development of precancerous lesions and cervical cancer in renal transplant patients. In the literature, the relationship between calcineurin inhibitors and skin cancer has been shown in renal transplant patients (11,12). We did not indicate this relationship in our series. The current study revealed that the presence of re-transplantation and acute rejection were associated with the presence of SILs in the Pap test. Besides that, most of the patients with SIL were found to have the immunologic disease as primary kidney disease. In both the multivariate and univariate Cox regression analyses, we identified that the immunologic disease as the primary renal disease was an independent risk factor for the development of SIL in renal transplantation patients. Indeed, this result is not surprising, as patients with an immunologic disease often receive immunosuppressive therapy even before undergoing transplantation.

Renal organ transplant patients frequently experience infections with HPV, which can increase the risk of developing cervical cancer (13). High-risk oncogenic types of HPV, such as HPV-16, are more commonly found in HSIL compared to LSIL, while non-oncogenic HPV types are often observed in LSIL cases. The studies have demonstrated an accelerated progression from ASC-US to LSIL or HSIL and from LSIL to HSIL or carcinoma in women infected with oncogenic types of HPV (14). Furthermore, the research conducted by Moscicki et al. indicated that the rate of regression in LSIL was solely associated with the HPV status at the current visit, while no significant association was found between LSIL regression and HPV status at baseline in their univariate analysis (15). In the study conducted by Paternoster et al. involving HPV testing, they observed a significant association between high-risk HPV infections and CIN lesions. However, no significant association was found between low-risk HPV infections and CIN lesions (7). The HPV vaccine prior to transplantation and conducting regular HPV testing are highly recommended for individuals with renal transplantation. They provide a crucial layer of protection against HPV infection, which can lead to cervical cancer.

Immunosuppression, as a notable consequence of immunosuppressive therapy, weakens the immune system and consequently increases susceptibility to

infections. The compromised immune response makes individuals more prone to acquiring various infections in the cervical region due to the decreased ability to fight off pathogens effectively. Consistent with the findings from previous study conducted in 2015 among solid organ transplant patients (kidney and liver) (16), the current study also demonstrated a higher incidence of cervical infections in renal transplant patients compared to the normal population. We revealed a significantly higher incidence of *Candida* and *Trichomonas vaginalis* infections among renal transplant patients compared to the normal population. However, our study did not reveal any significant differences between the two groups in terms of *Actinomyces* and *Herpes simplex virus* infections.

Our Pap smear cytology findings showed a change in vaginal flora that indicates bacterial vaginosis. Our study revealed notable disparities in bacterial vaginosis occurrence between the two groups. Long-term use of immunosuppressive drugs disrupts the estrous cycle and leads to decreased mucus production in the squamous epithelium, thinning, and eventually atrophy of the cervical epithelium. We observed significant differences in atrophy between the two groups, likely associated with immunosuppression due to transplantation.

Our study has several limitations. Firstly, we were unable to determine the HPV status of the transplanted women. Secondly, we did not collect data on factors such as oral contraceptive use, smoking status, and specific dosing of immunosuppressive therapy. However, we ensured that the transplanted women and control individuals were matched for the technical procedure of cervical cytology and age. The control individuals did not receive any immunosuppressive treatment.

In conclusion, our study highlights the higher susceptibility of renal transplant patients to develop cervical precancerous lesions and cervical cancer as a result of long-term immunosuppressive treatment. We observed a significant increase in the incidence of LSIL and HSIL compared to the normal population. Consequently, we recommend that Pap test screening and HPV vaccination be conducted prior to renal transplant procedures. Moreover, there is a clear necessity for a distinct cervical cancer screening program tailored specifically for immunocompromised women. Regular Pap tests and HPV tests should be performed at appropriate intervals to detect and prevent the development of precancerous lesions and cervical cancer.

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Ethics

Ethics Committee Approval: The study was approved by Baskent University Noninterventional Clinical Research Ethical Committee (Decision no: KA23/60, Date: 09.05.2023).
Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.
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Research Article / Araştırma Makalesi

Evaluation of Pediatric Cutaneous Leishmania Cases

Pediatrik Kutanöz Leishmania Olgularının Değerlendirilmesi

[1]Merve İşeri Nepesov, [2]Yalçın Kara, [2]Mahmut Can Kızıl, [3]Hilal Kaya Erdoğan, [4]Kürşat Bora Çarman, [5]Nihal Doğan, [5]Tercan Us, [2]Ömer Kılıç, [6]Ener Cagrı Dinleyici

[1]Zeynep Kamil Maternity and Children's Training and Research Hospital, Department of Pediatric İnfectious, Istanbul, Türkiye
[2]Eskisehir Osmangazi University Faculty of Medicine, Department of Pediatric İnfectious, Eskisehir, Türkiye
[3]Eskisehir Osmangazi University Faculty of Medicine, Department of Dermatology, Eskişehir, Türkiye
[4]Eskisehir Osmangazi University Faculty of Medicine, Department of Pediatric Neurology, Eskişehir, Türkiye
[5]Eskisehir Osmangazi University Faculty of Medicine, Department of Microbiology, Eskişehir, Türkiye
[6]Eskisehir Osmangazi University Faculty of Medicine, Department of Pediatric Intensive Care, Eskişehir, Türkiye

Abstract: Cutaneous Leishmaniasis (CL) is a disease caused by leishmania-type protozoans, which is transmitted by the bite of infected female phlebotomine sandflies and is characterized by ulcerated nodular lesions. Twenty-one pediatric cutaneous leishmania cases followed by pediatric infectious diseases and dermatology were included in the study. The demographic and clinical characteristics of the patients, the local or systemic treatments, and side effects were analyzed retrospectively. 14 (66%) of the patients were female and 7 (34%) were male. The mean age of the cases was 6.4 years. Fifteen of the patients were refugees (seven of the patients were from Iraq, and eight of them were from Syria). Ten of the patients (47%) had lesions only on the face, 6 (28%) were both on the face and hand, 4 (20%) were on the lower extremities. Seven patients (34%) had a single lesion, fourteen had multiple lesions and seven had more than four lesions. Amastigote was observed in the microbiological examination of skin scraping samples of 13 patients. Intralesional therapy was given to 15 patients, systemic treatment was given to 6 patients, and 2 patients refused systemic treatment. Five patient was given meglumine antimoniate, one patient was given amphotericin B. In one patient, side effects such as facial swelling, rash, and edema developed after amphotericin b, and the treatment was changed to meglumine antimoniate. Leishmaniasis is a chronic disease caused by flagellate protozoa of the genus Leishmania. especially in endemic countries. CL has become a relatively common condition all over the world due to international travel, migration, and refugees. Cutaneous Leishmania should be considered when there are chronic, painless skin lesions outside of endemic areas.
Keywords: Cutaneous Leishmania, Child, Endemic Area, Refugees

Özet: Kutanöz Leishmaniasis (KL), enfekte dişi tatarcık sineğinin ısırması ile bulaşan ve ülsere nodüler lezyonlarla karakterize, leishmania tipi protozoanların neden olduğu bir hastalık olup, dünyanın bazı bölgelerinde endemik olarak görülmektedir. Çalışmaya çocuk enfeksiyon hastalıkları ve dermatoloji tarafından takip edilen 21 pediatrik kutanöz leishmania olgusu dahil edildi. Hastaların demografik ve klinik özellikleri, aldıkları lokal veya sistemik tedaviler ve yan etkileri retrospektif olarak incelendi. Olguların 14'ü (%66) kız, 7'si (%34) erkekti. Olguların ortalama yaşı 6.4 yıldı. Hastaların 15'i mülteciydi (hastalardan yedisi Iraklı, sekizi Suriye'liydi). Hastaların 10'unda (%47) sadece yüzde, 6'sında (%28) hem yüzde hem de elde, 4'ünde (%20) alt ekstremitede lezyon vardı. Yedi hastada (%34) tek lezyon, ondördünde çoklu lezyon ve yedi hastada dörtten fazla lezyon vardı. 13 hastanın direk mikroskopik incelemesinde amastigot gözlendi. 15 hastaya intralezyonel tedavi, 6 hastaya sistemik tedavi verildi, 2 hasta sistemik tedaviyi reddetti. Beş hastaya meglumin antimoniat, bir hastaya amfoterisin B verildi. Bir hastada amfoterisin b sonrası yüzde şişlik, kızarıklık ve ödem gibi yan etkiler gelişti ve tedavi meglumin antimoniat olarak değiştirildi. Kutanöz Leishmaniasis, leishmania cinsi protozoalarının neden olduğu kronik bir hastalıktır. Uluslararası seyahat, göç ve mülteciler nedeniyle sadece endemik bölgeler değil, tüm dünyada nispeten yaygın bir durum haline gelmiştir. Endemik bölgelerin dışında kronik, ağrısız cilt lezyonları olduğunda Kutanöz Leishmania düşünülmelidir
Anahtar Kelimeler: Kutanöz Leishmania, Çocuk, Endemi, Göç, Mülteci

ORCID ID of the authors: MİN. 0000-0003-4584-1818, YK. 0000-0003-0569-1106, MCK. 0000-0002-6231-4238, HKE. 0000-0002-8172-1920, KBÇ. 0000-0002-4629-1873. 0000-0001-6103-4704, TU. 0000-0002-9772-6777, ÖK. 0000-0003-0168-4080, ECD. 0000-0002-0339-0134

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Correspondence: Yalçın KARA- Eskisehir Osmangazi University Faculty of Medicine, Department of Pediatric İnfectious, Eskisehir, Türkiye
e-mail: dryalcinkara@hotmail.com

1. Introduction

Leishmaniasis is an infectious disease caused by the obligate intracellular parasites of Leishmania protozoan microorganisms, transmitted by the bite of the vector which is a female sandfly (phlebotom)(1). According to the data of the World Health Organization (WHO), approximately 12 million people in 98 countries all over the world have been infected with leishmaniasis, and it is reported that 350 million people live with that risk (2). Approximately 50 million people in our country are at risk for this infection. Previously, a very important part of them were reported from 9 endemic provinces, namely Şanlıurfa, Diyarbakır, Mardin, Osmaniye, Adana, Hatay, Kahramanmaraş and İçel (3). However, recently, there has been an increase in cases of leishmania in non-endemic regions due to the migration of refugees from endemic regions to our country and the world due to reasons such as wars, famine, and low socioeconomic status. Our country hosts more than 4 million refugees, especially those who escaped from the civil war in Syria (4). There are three forms of Leishmaniasis which are cutaneous, mucocutaneous, or visceral (VL), depending on the leishmania species and the reservoir host's immune response (5). CL starts as an erythematous papule in the area where the fly bites and takes the form of a painless, ulcerated nodule and plaque that has a necrotic center over time (6).

Diagnosis is made by tests such as microscopic examination, culture, and PCR from clinically suspicious cases. Showing the presence of leishmania amastigotes in the light microscope is the most common diagnostic method (7). There are intralesional and systemic treatment options due to the type of Leishmania parasite, the endemic region, and the location, number, and size of the lesion. The most commonly used and oldest therapeutic agents are pentavalent antimon compounds (8). The aim of this study is to investigate the cases of pediatric cutaneous leishmaniasis seen in a non-endemic city in the central <anatolia region in the west of our country. with the increasing number of refugees in our country after war and migration. For this reason, the clinical and epidemiological characteristics and treatment regimens of the cases followed up due to CL in our hospital were evaluated retrospectively.

2. Materials and Methods

Pediatric patients under the age of 18, who were followed up with the diagnosis of CL between March 2017 and November 2021 by the Department of Pediatric Infectious Diseases and Dermatology were included in our study. The study was started after the approval of the Eskişehir Osmangazi University Ethics Committee (date:15.02.2022, number:27). The data of twenty-one pediatric patients included in the study were accessed retrospectively from the hospital automation system. Parameters such as age, gender, nationality, immigration status, country, family history, physical examination findings; location, number, and time of lesions, type of diagnosis, local or systemic treatment type, treatment duration, pharmacological agents used, side effect profile of these drugs and prognosis were examined.

Statistical analysis

Descriptive statistics are given with mean and standard deviation for numerical variables, and numbers and percentages for categorical variables. Relationships between categorical variables were tested with the chi-square test. SPSS 22.0 Windows version package program was used in the analysis. $p<0.05$ was considered as significant.

3. Results

Thirty-nine pediatric CL cases followed in our hospital were included in the study. Eighteen of 39 cases were excluded from the study because their data could not be reached. Of the remaining 21 cases, 14 (66%) were girls and 7 (34%) were boys. The mean age of the cases was 6.4 years. Fifteen (71%) of the cases were immigrants (7 Iraqi, 8 Syrian immigrants). There was only one lesion in 9 (42%) cases, multiple lesions in 12 (57%) cases, and more than four lesions in 7 (34%) cases. While 12 (57%) patients had lesions only on the face, 6 (28%) patients had lesions

on the face and extremities, and 3 (14%) patients had lesions on the lower extremities. Eleven (52%) lesions were ulcerated nodular, 9 (42) were papular, and 1 (5%) were plaque (Figure-1). The mean onset time of the lesions was 3.5 months. Amastigote was detected in the microbiological examination of 13 (61%) cases (Figure-2). Intralesional treatment was applied to 15 of the cases (71%), systemic treatment was given to 6 of them (28%), and 2 cases refused systemic treatment. The mean duration of treatment in 15 cases given intralesional therapy was 3 sessions. Meglumine antimoniate treatment was given to 5 (83%) and Amphotericin-B treatment to 1 (17%) of the 6 patients who received systemic treatment. Of the 6 patients who were given systemic treatment, two received 20 days of treatment, and four received 10 days of treatment (Table 1). Only one patient developed side effects such as swelling of the face and lips and diffuse rash after systemic treatment. For that patient amphotericin-b treatment was discontinued and meglumine antimoniate treatment was started. The mean age of the Turkish patients was higher than the Syrian and Iraqi patients (p:0.03). While intralesional treatment was applied mostly to Turkish and Iraqi nationals, the systemic treatment rate was higher in Syrian patients (p:0.02). The number of patients with more than 4 lesions in Syrian nationals was higher than in Turkish and Iraqi patients (p:0.02) (Table 2).

Figure 1. Images of Cutaneous Leishmania Cases

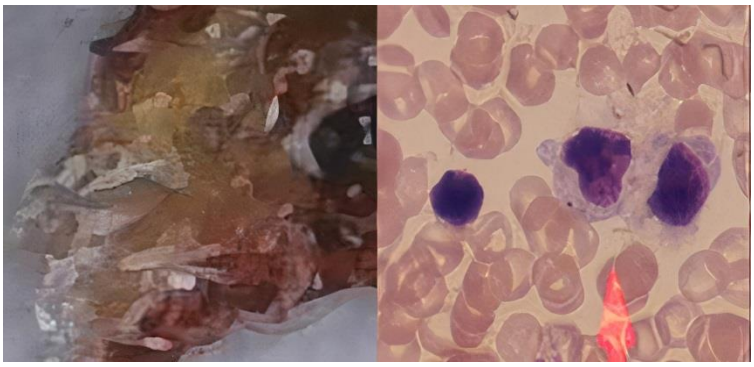

Figure 2. Nail Sign and Amastigote in microscopic examination

Table 1. Clinical distribution of all cases of cutaneous leishmania

Case Number	*Age month*	*Gender*	*Lesion Location*	*Lesion Number*	*Lesion Type*	*Lesion Time month*	*Local Treatment*	*Local Treatment Time*	*Systemic Therapy*	*Systemic Therapy Time*	*Microscopic Diagnosis*	*Nationality*	*Side Effect*
1	48	Female	Face	1	Papule	3	Yes	2	No		Amostigote	Syria	
2	132	Female	Face	1	Papule	12	Yes	2	No		Amostigote	Turkey	
3	156	Female	Face	1	Papule	6	Yes	2	No		Amostigote	Iraq	
4	24	Male	Face	1	Plaque	1	Yes	2	No		Amostigote	Iraq	
5	12	Male	Face	1	Papule	1	Yes	4	No		Amostigote	Iraq	
6	96	Female	Face	1	Papule	3	Yes	2	No		Amostigote	Turkey	
7	144	Male	Face	1	Ulcerated nodule	6	Yes	5	No		Amostigote	Syria	
8	96	Female	Face/Hand	3	Ulcerated nodule	1,5	Yes	2	No		-	Turkey	
9	84	Female	Face	3	Papule	1,5	Yes	1	Yes	20	-	Turkey	
10	168	Male	Leg	2	Papule	3	Yes	5	No		-	Turkey	
11	60	Female	Face/Hand	2	Papule	3	Yes	2	No		-	Iraq	
12	12	Female	Face	1	Ulcerated nodule	2	Yes	2	No		-	Iraq	
13	216	Male	Face	1	Ulcerated nodule	2	Yes	2	No		-	Turkey	
14	180	Male	Leg	2	Ulcerated nodule	2	Yes	2	No		-	Iraq	
15	18	Female	Face	7	Ulcerated nodule	2	No		Yes	20	Amostigote	Iraq	
16	60	Female	Face/Eyelid Body	6	Ulcerated nodule	6	No		Refuse		Amostigote	Syria	Edema/ Rash
17	48	Female	Face/Leg	5	Ulcerated nodule	2	No		Refuse		Amostigote	Syria	
18	24	Male	Face/Ear/ Neck	5	Ulcerated nodule	2	Yes	1	Yes	10	Amostigote	Syria	
19	48	Female	Face Body	5	Ulcerated nodule	3	No		Yes	10	Amostigote	Syria	
20	60	Female	Face	6	Ulcerated nodule	3	No		Yes	10	Amostigote	Syria	
21	24	Female	Leg	5	Papule	3	No		Yes	10	-	Syria	

Table 2. Clinical and epidemiological features of cutaneous leishmania cases

	Total n:21 (%)	Turkish Patients n:6 (%)	Syrian Patients n:8 (%)	Iraqi Patients n:7 (%)	p
Age (year)	6.4 (1-18)	11 (7-18)	4.7 (2-12)	5.5 (1-15)	**0.03**
Gender					0.7
Female	14 (66)	4 (67)	6 (75)	4 (57)	
Male	7 (33)	2 (33)	2 (25)	3 (43)	
Lesion Location					0.6
Face	12 (57)	4 (67)	3 (38)	5 (72)	
Leg	3 (14)	1 (17)	1 (12)	1 (14)	
Multiple	6 (28)	1 (17)	4 (50)	1 (14)	
Lesion Number					0.4
Single	9 (43)	3 (50)	2 (25)	4 (57)	
Multiple	12 (57)	3 (50)	6 (75)	3 (42)	
>4 lesions	7 (33)	0 (50)	6 (75)	1 (14)	
Lesion Type					0.3
Papule	9 (43)	4 (67)	2 (25)	3 (43)	
Plaque	1 (5)	0 (0)	0 (100)	1 (14)	
Ulcere-nodule	11 (53)	2 (33)	6 (75)	3 (43)	
Lesion Time (month)	3.6	3.8	3.5	2.5	0.1
Local Treatment	15 (71)	6 (100)	3 (38)	6 (86)	**0.02**
Systemic Treatment	6 (28)	1 (17)	4 (50)	1 (14)	**0.05**
Microscopic Diagnosis (Amostigote)	13 (62)	2 (33)	7 (88)	4 (57)	0.09

4. Discussion

CL is a parasitic disease that is endemic in nearly 80 countries around the world, including the Southeast regions of our country. While almost all of the approximately 1.5 million new cases per year were reported from these endemic regions in the past, cases have been reported from all countries in recent years due to wars, famine, and migration (9). Our country hosts more than 4 million refugees, especially from endemic regions such as Syria and Iraq. Kaman et al. reported 16 pediatric CL cases from Ankara province, which is not one of the endemic regions of our country (10). In our study, we found 21 pediatric CL cases in Eskişehir, which were not endemic leishmaniasis. This, in parallel with the recent literature, supports that the frequency of CL cases has increased in non-endemic regions after wars and migrations (11,12).

In our study, pediatric CL was more common in girls than boys. In the study of Cömert et al. and Kireçci et al., CL was more common in girls, while in the study of Kaman et al., it was more common in boys (10,13-14). The fact that CL cases are more common in girls in immigrants can be explained by the fact that more women work in open areas such as fields and gardens. In our study, CL lesions were most commonly found on the face, followed by the feet and hands. Similarly, Kaya et al. and Kaman et al. reported that CL lesions were most common in the face and neck region (10-11). We attributed this to the fact that sandflies infect more open areas such as the face and neck.

In our study, 57% of the cases had multiple lesions. The number of cases with more than four lesions in Syrian nationals was higher than in Turkish and Iraqi patients (p:0.02). Contrary to our study, the number of cases with a single lesion was higher in studies conducted in India, Iran, and Pakistan (15,16). In the study of Aksoy et al. and Kaya et al. from our country, the number of lesions was higher in Syrian patients than in Turkish patients, as in our study (11,17). This may be due to the lack of facilities such as shelters and hygiene for Syrian refugees. In our study, ulcerated nodular lesions were present in 53% of the cases. The most common lesion type was reported as papule in the study of Layegh et al., plaque in the study of Bari et al., and ulcerated nodule in the study of Aksoy et al. (17-19). In our study, ulcerated nodules were more common in Syrian patients, whereas papular lesions were more common in Turkish patients. This may be due to the delay in admission to the hospital and the infected type of leishmania.

In the study of Aksoy et al., it was reported that intralesional treatment was more common, and in the study of Kaman et al., cases who were given systemic treatment were more frequent (10,17). In our study, 71% of the cases were given intralesional and 28% systemic treatment. The rate of intralesional treatment was higher in Turkish cases and the systemic treatment rate was higher in Syrian cases. This can be explained by the fact that in our study, the number of lesions in Syrian nationals was higher and they were not eligible for local treatment.

Although the basis of systemic therapy is pentavalent antimonial; It has been reported that amphotericin-b is an effective and alternative treatment modality in the presence of serious side effects, in cases that do not respond to treatment, and in the presence of multiple lesions (20-23). Similarly, in our study, meglumine antimonate was the most commonly used systemic therapy, and liposomal amphotericin B treatment was used in one patient. The main limitations of the study are the small number of cases and the inability to perform microbiological typing of the leishmania subspecies.

The most common and easily accessible method for the diagnosis of cutaneous leishmania is to detect amastigotes in direct microscopic examination from samples taken from suspicious lesions. Molecular methods such as PCR, which directly show the causative agent and can be identified, are other important diagnostic methods. In our study, amastigotes were seen in the microscopic examination of 61% of the cases,

but PCR or culture could not be performed in any of the cases. Similarly, Altınel et al. diagnosed 82.7% of cutaneous leishmaniasis cases by microscopic and pathological examination of smear samples taken from the lesion (24). In the most recent studies conducted in our country, Gürses et al. and Nalçacı et al. emphasized the importance of newly developed molecular methods in the diagnosis and typing of Leishmania (25,26). In our study, only microscopic examination was used in diagnosis and not molecular methods, which is one of the limitations of our study.

As a result, CL cases have become a public health problem for non-endemic regions as a result of migration from endemic regions to non-endemic regions due to war, famine, and economic reasons. CL should be kept in mind as a diagnosis, especially in long-lasting ulcerated nodular and papular lesions. It is important to detect the lesions early and to give intralesional and systemic treatment depending on the location and number of the lesions, especially in foreign patients. In addition, priority should be given to measures such as hygiene and cleaning measures, fighting against vectors, and increasing shelter options for the control of the disease.

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Ethics

Ethics Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Ethical Committee (Approval Date/ Number: 15.02.2022/27).
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Research Article / Araştırma Makalesi

COVID-19 Pandemisi Öncesi Kanserli Çocukların Akut Solunum Yolu Viral Enfeksiyonlarının Epidemiyolojisi

Epidemiology of Acute Respiratory Viral Infections of Children with Cancer Before the COVID-19 Pandemic

[1]Ersin Töret, [1]Uğur Tokdemir, [1]Zeynep Canan Özdemir, [1]Berra Nur Aksakal, [2]Ömer Kılıç, [3]Tercan Us, [3]Gül Durmaz, [1]Özcan Bör

[1]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Çocuk Hematoloji ve Onkolojisi Bilim Dalı, Eskişehir, Türkiye
[2]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Çocuk Enfeksiyon Hastalıkları Bilim Dalı, Eskişehir, Türkiye
[3]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Tıbbi Mikrobiyoloji, Eskişehir, Türkiye

Abstract: Children with cancer became a major high-risk group during the COVID-19 pandemic. It has become difficult for patients to reach practical and safe care and treatment all over the world. The late diagnosis of many childhood cancers was driven by limited access to healthcare due to the pandemic and fears of COVID-19 that prevented parents from making an early medical assessment of their child's symptoms. Acute respiratory diseases are an important cause of morbidity and mortality in children with cancer, regardless of the COVID-19 pandemic and were seen less frequently in the pandemic during the lockdown and distant education period in comparison to the time before the pandemic in children with cancer. Acute respiratory viral infections frequently cause febrile neutropenia attacks in children under five years of age. A three year retrospective cross-sectional study was performed in a tertiary care university hospital. Children with cancer who presented to the Department of Pediatric Hematology and Oncology with the diagnosis of acute respiratory viral infection were included in the study if they had available results of multiplex polymerase chain reaction (PCR) of nasopharyngeal aspirate samples. The qualitative detection of 18 respiratory viruses and four bacterias were detected by the real-time multiplex polymerase chain reaction. Sixty-six patients with 93 acute respiratory viral infection were included in this study. Seventy of 93 (75%) samples were positive for at least one pathogen. The most common three viruses were HRV, Influenza H1N1, and Influenza H1N3, respectively. Other than COVID-19, the risk of severe acute respiratory viral infections are always important in children with cancer and during the pandemic, hygiene measures and social restrictions caused a reduction in the number of acute respiratory viral infection. This study is critical because it shows the distribution of agents in children with cancer who had acute viral upper respiratory tract infections in the near term before the pandemic.
Keywords: COVID-19, Childhood Cancers, Febrile Neutropenia, Respiratory İnfections

Özet: COVID-19 pandemisi sırasında kanserli çocuklar yüksek riskli gruplardan biri oldular. Hastaların kolay vegüvenli hasta bakımına, daha önemlisi tedaviye ulaşması tüm dünyada zorlaştı. Pandemi nedeniyle sağlık hizmetlerine sınırlı erişim ve ebeveynlerin çocuklarındaki semptomların erken tıbbi değerlendirilmesini engelleyen COVID-19 korkusu birçok çocukluk çağı kanserinin geç teşhisine neden oldu. Akut solunum yolu enfeksiyonları, COVID-19 pandemisinden bağımsız olarak kanserli çocuklarda önemli bir hastalık ve ölüm nedenidir. Bu enfeksiyonlar, pandemi öncesine göre pandemi döneminde sokağa çıkma yasağı ve uzaktan eğitim nedeniyle daha az görüldü. Akut solunum yolu viral enfeksiyonları beş yaşın altındaki çocuklarda sıklıkla febril nötropeni ataklarına neden olur. Üç yıllık retrospektif kesitsel nitelikte olan bu çalışma üçüncü basamak bir üniversite hastanesinde yapıldı. Çocuk Hematoloji ve Onkoloji Bilim Dalı'nda akut solunum yolu viral enfeksiyonu tanısı alan kanserli çocuklar, nazofaringeal aspirat örneklerinde multipleks polimeraz zincir reaksiyonu (PCR) ile etken saptandıysa çalışmaya dahil edildi. Multipleks polimeraz zincir reaksiyonu ile on sekiz solunum virüsünün ve dört bakterinin kalitatif tespiti için test çalışıldı. Akut viral üst solunum yolu atağı geçiren 66 hasta bu çalışma dahil edildi. Doksan üç örneğin 70'i (%75) en az bir patojen için pozitifti. En yaygın üç virüs sırasıyla HRV, Influenza H1N1 ve Influenza H1N3'dü. COVID-19 dışında, kanserli çocuklarda ciddi akut solunum yolu viral enfeksiyonu riski her zaman önemlidir ve pandemi sırasında hijyen önlemleri ve sosyal kısıtlamalar, akut solunum yolu viral enfeksiyonu sayısında azalmaya neden olmuştur. Bu çalışma pandemi öncesi yakın dönemin akut viral üst solunum yolu enfeksiyonu geçiren kanserli çocuklarda etken dağılımı göstermesi nedeniyle önemlidir.
Anahtar Kelimeler: COVID-19, Çocukluk Çağı Kanserleri, Febril Nötropeni, Solunum Yolu Enfeksiyon

ORCID ID of the authors: ET. 0000-0002-6379-8326, UT, 0000-0002-8500-4304, ZCÖ. 0000-0002-9172-9627, BNA. 0000-0002-3703-2474, ÖK 0000-0003-0168-4080, TU. 0000-0002-9772-6777, GD. 0000-0002-4534-8620, ÖB. 0000-0002-1662-3259

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Correspondence: Ersin TÖRET-- Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Çocuk Hematoloji ve Onkolojisi Bilim Dalı, Eskişehir, Türkiye
e-mail: drersintoret@hotmail.com

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1. Introduction

The first case of COVID-19 was detected in Turkey when the World Health Organisation (WHO) proclaimed a COVID-19 pandemic on March 11, 2020. Children with cancer are among the high risk groups for COVID-19 because of immunosuppression treatment due to anti-cancer therapy. The current outbreak of COVID-19 caused an unheard-of global threat to the practical and safe care for children with cancer. Moreover, the late diagnosis of many childhood cancers were due to limited access to healthcare due to the pandemic and fear of infection which prevented parents from seeking early medical evaluation of symptoms in their child (1-3).

Febrile neutropenia (FN) is one of the most common acute side effects of pediatric cancer treatment and the mortality due to FN has dramatically declined due to the widespread use of broad-spectrum antibiotics. Acute respiratory viral infections (ARVIs) frequently cause FN attacks in children under five years of age. Even if cancer patients are not neutropenic, due to the ongoing immunosuppression, infections are likely to be severe (4-6). Acute respiratory diseases are an important cause of morbidity and mortality in children with cancer, regardless of the COVID-19 pandemic. The non-COVID-19 ARVIs were seen less frequently in the pandemic during the lockdown and distant education period in comparison to the time before the pandemic in children with cancer (7,8).

This study aimed to evaluate the distribution of respiratory viruses which caused ARVI in children with cancer before the COVID-19 pandemic.

2. Materials and Method

A three year (January 2019 to February 2020) retrospective cross-sectional study was performed in a tertiary care university hospital in Turkey after obtaining approval from the local ethics committee. Children with cancer who presented to the Department of Pediatric Hematology and Oncology with the diagnosis of acute respiratory viral infection were included in the study if they had available results of multiplex polymerase chain reaction (PCR) of nasopharyngeal aspirate samples. The clinical records were obtained from the medical records.

Acute respiratory viral infection (ARVI) was described as the presence of cough with fever (fever; at least one episode of fever, measured or reported, with axillary temperature> 38°C (based on one measurement) or 37.5°C (based on two measurements with a 1-hour interval) for less than two weeks with at least one or more of the following signs or symptoms: coryza, cough, sore throat, and/or gastrointestinal symptoms.

Respiratory samples taken from each nasopharyngeal aspirate and one from the nasopharyngeal swab were collected from all patients enrolled in the study. Within an utmost period of 4 hours after collection, the specimens were blended and annexed to a ringer lactate solution to a total of 4 mL. After homogenization, the specimens (approximately 1 mL) were allocated into aliquots in cryotubes, previously identified and stored in liquid nitrogen, and stored at -80 ◦C. In the Medical Microbiology Laboratory, the DNA, and total RNA nucleic acids were extracted from samples using the extraction Kit.

The sensitivity and specificity were followed up by standard quality control for molecular diagnostics. The qualitative detection of 18 respiratory viruses (adenovirus (ADV), coronavirus (NL63, 229E, OC43, and HKU1), human metapneumovirus (hMPV A/B), human rhinovirus (HRV), enterovirus; influenza A (H1, H1N1, and H3), influenza B, Middle East Respiratory Syndrome–related Coronavirus (MERS-Cov), parainfluenza (PIV1, 2, 3, and 4), respiratory syncytial virus (RSV A/B), and four bacterias (*Bordatella Parapertussis, Bordatella Pertussis,Chlamydia Pneumoniae, and Mycoplasma Pneumoniae)* were detected by the real-time multiplex polymerase chain reaction.

Data were analysed using the Statistical Package for the Social Sciences (SPSS)

program, version 17.0 (SPSS Inc., Chicago, IL, USA). Non-parametric descriptive statistics were calculated. A p-value<0.05 was considered significant. Approval for the study was obtained by Eskisehir Osmangazi University Non-interventional Clinical Research Ethics Committee.

3. Results

Sixty-six patients (44 males, M: F= 2:1) with ARVI were included in this study. Forty-one (62%) of them were diagnosed with hematologic malignancy (leukemia or lymphoma), 14 (21%) of them were with solid tumors and 11 (17%) of them were with bone marrow failure (isolated neutropenia or pancytopenia). The most common complaints in 93 episodes of 66 patients were cough, coryza, and fever. Seventeen applications were only due to fever. Patients were admitted to the hospital with a mean of 1.8 ± 1.4 days (range 0-6 days) following the onset of fever.

Seventy of 93 (75%) samples were positive for at least one pathogen. The most common three viruses were HRV, Influenza H1N1, and Influenza H1N3, respectively (Table 1). The coexistence of two pathogens were detected in 15 (16%) samples (Table 2). A bacterial agent was not detected in any of the samples. The mean age of patients was 5.3 ± 4.3 years (range, 6 months to 17.5 years).

Adenovirus (ADV), Coronavirus (Cor-NL63, Cor-229E, Cor-OC43, Cor-HKU1), Human metapneumovirus (hMPV A/B), Human rhinovirus (HRV), Enterovirus; Influenza A (H1, H1N1, and H3), Influenza B, Middle East Respiratory Syndrome–related Coronavirus (MERS-Cov), Parainfluenza (PIV1, 2, 3, and 4), Respiratory syncytial virus (RSV A/B). months to 17.5 years). The distribution of positive tests by season were 46 (66%) in winter, 12 (17%) in spring, 1 (1%) in summer, and 11 (16%) in autumn.

As an antiviral agent, oseltamivir was utilized in 42 of the 93 (45%) episodes of ARVI. In 28 of 42 (66%) episodes, influenza was the causative agent (influenza A H1N1 n:17, H3 n:6, and influenza B n:5). Also, four cases with a negative nasale sample had used oseltamivir. Seventeen (18%) cases were supported with the replacement of intravenous immunoglobulin (IVIg). Pulmonary findings as increased respiratuar rate, breath sounds louder than normal, crackles, and other anormalities in physical examination were detected in 35 (38%) of the 93 episodes. Oxygen therapy, admission to an intensive care unit, and need for mechanical ventilation were not required in any of the episodes.

4. Discussion

The pandemic of COVID-19 is one of the most critical global challenges faced in the last months. However, other than COVID-19, the risk of severe ARVIs are always important in children with cancer (10, 11). In this study, we evaluated the distribution of respiratory viruses which caused ARVI in children with cancer before the COVID-19 pandemic. Patients with fever were admitted to the hospital within an average of 48 hours. The most common symptoms (cough, coryza and fever) of patients were similar to that observed in the previous studies (12,13).

In Marcone et al study (14), viral diagnosis was achieved in 361 (83.2%) hospitalized patients and 115 (61.8%) outpatients. Aydin Koker et al (15) reported that they detected an agent for acute viral respiratory infections in 219/560 (39.1%). Also, coinfection with two viruses was detected in 45/219 (20.5%) of episodes (8). In another study, coinfections were reported 36 out of 326 (5.5%) severe acute lower respiratory tract infections (16). In our study, we obtained 70 out of 93 (75%) samples which were positive for at least one pathogen and the coexistence of two pathogens were detected in 15 (16%) samples. The ARVIs are frequent in cold seasons; autumn and winter (13). Similar to previous studies, the most common test positivity was detected during the winter months in this study.

Table 1. Distribution of pathogens identified by moleculer tests

Pathogens	Cases with single detection	Cases with co-detection	Total number of cases (%)
ADV	4	-	4 (5)
Cor-NL63	1	1	2 (3)
Cor-229E	1	-	1 (1)
Cor-OC43	3	-	3 (4)
Cor-HKU1	2	-	2 (3)
HMPV A/B	4	-	4 (5)
HRV	21	3	24 (27)
Entero V.5	-	-	-
InfA-H1	19	1	20 (23)
InfA-H1N1	-	1	1 (1)
InfA-H3	6	1	7 (8)
InfB	5	-	5 (6)
MERS-Cov	-	-	-
PIV-1	1	-	1 (1)
PIV-2	-	-	-
PIV-3	-	1	1 (1)
PIV-4	1	2	3 (4)
RSV-A/B	2	5	7 (8)

Adenovirus (ADV), Coronavirus (Cor-NL63, Cor-229E, Cor-OC43, Cor-HKU1), Human metapneumovirus (hMPV A/B), Human rhinovirus (HRV), Enterovirus; Influenza A (H1, H1N1, and H3), Influenza B, Middle East Respiratory Syndrome–related Coronavirus (MERS-Cov), Parainfluenza (PIV1, 2, 3, and 4), Respiratory syncytial virus (RSV A/B).

Table 2. Combination of identified combinations among co-detection of all respiratory pathogens

	ADV	Cor-NL63	Cor-229E	Cor-OC43	Cor-HKU1	HMPV A/B	HRV	Entero V.	InfA H1	InfA H1N1	InfA H3	InfB	MERS-Cov	PIV1	PIV2	PIV3	PIV4	RSV A/B
ADV	NA	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
Cor-NL63	-	NA	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-
Cor-229E	-	-	NA	-	-	-	1	-	-	-	1	-	-	-	-	-	-	-
Cor-OC43	-	-	-	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cor-HKU1	-	-	-	-	NA	-	-	-	-	-	-	-	-	-	-	-	-	-
HMPV A/B	-	-	-	-	-	NA	-	-	-	-	-	-	-	-	-	-	-	-
HRV	-	-	-	-	-		NA	-	-	-	-	-	-	-	-	-	-	-
Entero V.	-	-	-	-	-	-	-	NA	-	-	-	-	-	-	-	-	-	-
InfA-H1	-	-	-	-	-	-	1	-	NA		-	-	-	-	-	-	-	-
InfA-H1N1	-	-	-	-	-	-	1	-	-	NA	-	-	-	-	-	-	-	-
InfA-H3	-	-	-	-	-	-	-	-	-	-	NA	-	-	-	-	-	-	-
InfB	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-	-	-	-
MERS-Cov	-	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-	-	-
PIV-1	-	-	-	-	-	-	-	-	-	-				NA	-	-	-	-
PIV-2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-
PIV-3	-	-	-	-	-		1	-	-	-	-	-	-	-	-	NA	-	-
PIV-4	-	-	-	-	-	-	1	-	-	1	-	-	-	-	-	-	NA	
RSV-A/B	-	-	-	1	-	1	-	-	1	1	-	1	-	-	-	-	-	NA

Adenovirus (ADV), Coronavirus (Cor-NL63, Cor-229E, Cor-OC43, Cor-HKU1), Human metapneumovirus (hMPV A/B), Human rhinovirus (HRV), Enterovirus; Influenza A (H1, H1N1, and H3), Influenza B, Middle East Respiratory Syndrome–related Coronavirus (MERS-Cov), Parainfluenza (PIV1, 2, 3, and 4), Respiratory syncytial virus (RSV A/B).

The three viruses most frequently detected in children with ARVI were unsorted HRV, RSV, and influenza subtypes (14-16). In this study, we most frequently detected HRV, influenza subtypes, and RSV, respectively.

The seasonal prevalence of influenza infections in children with cancer, closely parallels the community wide prevalence. However, influenza infection remains a significant cause of morbidity and mortality in these patients. As a well known precept, respiratory infection management occurs with providing the patient with supportive care and utilizing antiviral therapy to whose in need. Neuraminidase inhibitors are recommended as a first-line medication for the treatment or prophylaxis of influenza infections in the immunocompromised population(17-19). Also, as an adjuvant treatment, intravenous immunoglobulin (IVIG) are used to support the immune system in some severely ill patients (20). In this study, 45% of the cases were given oseltamivir, while 18% were given IVIG.

In Marcone et al. (14) study, the clinical findings were significantly serious in the inpatients than the outpatients. Aydin Koker et al. (15) reported that the pulmonary findings were seen in 28% of the patients and patients with acute leukemia were more vulnerable to pneumonia than children with solid tumors. In this study, pulmonary findings were detected in 38% of the cases. This may be related to the higher number of patients with acute leukemia compared to other diagnoses. But we are happy that oxygen therapy, admission to an intensive care unit, and need for mechanical ventilation were not required in any of the episodes.

In summary, we have seen a decrease in ARVI due to viral factors other than COVID-19 in patients during the pandemic. In this period, hygiene measures and social restrictions caused a reduction in the number of ARVI. Before the pandemic, we found that influenza subtypes and HRV were the most commonly detected viruses in children with cancer similar to the healthy population. The lack of a need for intensive care and the absence of patient loss was pleasing. This study is critical because it shows the distribution of agents in children with cancer who had acute viral upper respiratory tract infections in the near term before the pandemic.

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Ethics

Ethics Committee Approval: The study was approved by Eskisehir Osmangazi University Non-interventional Clinical Research Ethical Committee (Decision no: 04, Date: 14.07.2020).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis**.**

Author Contributions:

Idea/concept: E.T., Z.C.Ö., Ö.K., Design: E.T., T.U., G.D., Ö.B. Data Collection: U.T, B.A. Data Processing: E.T., U.T. Analysis/Comment: T.U., G.D., Ö.B, Literature research/review: E.T., Ö.K. Writing: E.T., B.A.

All authors discussed the results and contributed to the final manuscript.

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Research Article / Araştırma Makalesi

Endoscopic Ear Surgery : 7 Years of Single Center Experience

Endoskopik Kulak Cerrahisi: 7 yıllık Tek Merkez Deneyimi

Ercan Kaya , Şaziye Armağan İncesulu , Mehmet Özgür Pınarbaşlı , Furkan Kaya *

Eskisehir Osmangazi University, Faculty of Medicine, Department of Otorhinolaryngology, Eskisehir, Türkiye.

***This study was presented as a poster at Sanal Congress of Turkish National Otolaryngology-Head and Neck Surgery; Nov 26–28, 2020.**

Abstract: This study aims to share our clinic's endoscopic ear surgery experiences and create a guide for future, more detailed studies. The data of patients who were operated on endoscopically or in combination with a microscope were collected between 2015 and 2022 years retrospectively. The data of 70 patients who had ear surgery with an endoscopic or combined approach with a microscope in our clinic were included in this study. The patients were divided into four groups. The type-1 tympanoplasty group (26 cases) was followed for an average of 16.3 months. The mean follow-up period of 9 cases in the middle ear exploration and ossiculoplasty group was 13.4 months. The case group of 18 people who were operated on for cholesteatoma was followed up for an average of 17.7 months. The stapedectomy case group (17 patients) was followed up for a mean of 14.9 months. Significant improvement was observed in the air-bone gap. Considering the increasing use of endoscopy in otology, we believe that its advantages over the traditional microscopic approach in pathologies limited to the middle ear should be supported by further studies.
Keywords: Endoscopy, Otology, Neurotology, Middle Ear

Özet: Bu çalışmanın amacı, kliniğimizin endoskopik kulak cerrahisi deneyimlerini paylaşmak ve sonrasında daha detaylı çalışmalar için kılavuz oluşturmaktır. Araştırmada retrospektif olarak kliniğimizde 2015-2022 yılları arasında; endoskopik veya mikroskopla kombine olarak opere olan bireylerin verileri, hastane veri tabanından toplanmıştır. Araştırmaya kliniğimizde endoskopik veya mikroskopla kombine yaklaşımla kulak operasyonu olmuş 70 hastanın verileri dahil edilmiştir. Temelde yapılan cerrahinin niteliğine göre hastalar dört gruba ayrılmıştır. Tip-1 timpanoplasti olan gruptaki 26 vaka ortalama 16,3 ay takip edilmiştir. Eksplorasyon ve işitme rekonstrüksiyonu yapılan gruptaki 9 vakanın takip ortalama süresi 13,4 aydır. Kolesteatom nedeniyle opere edilen 18 kişilik vaka grubu ise ortalama 17,7 ay takip edilmiştir. Stapedetomi yapılan 17 kişilik vaka grubu ise ortalama 14,9 ay takip edilmiş olup hava ve kemik yolu arasındaki gapte ortalama 16,7 desibellik kazanç sağlanmıştır. Endoskopinin KBB pratiğinde giderek yaygınlaşması ve otoloji alanındaki kullanımı düşünüldüğünde, orta kulağa sınırlı patolojilerde geleneksel mikroskobik yaklaşıma göre avantajlarının ileri çalışmalarla desteklemesi gerektiği kanaatindeyiz.
Anahtar Kelimeler: Endoskopi, Otoloji, Nörotoloji, Orta Kulak

ORCID ID of the authors: EK. 0000-0002-9961-0313, ŞAİ. 0000-0001-8467-5950, MÖP. 0000-0003-1486-9551, FK. 0000-0001-7216-5187,

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Correspondence: Furkan KAYA - Eskisehir Osmangazi University, Faculty of Medicine, Department of Otorhinolaryngology, Eskisehir, Türkiye
e-mail: kaya.furkan105@gmail.com

1. Introduction

Although endoscopy in otolaryngology practice dates back to the 1960s, its use in treatment and follow-up became widespread in the 90s. High-quality endoscopes and new technologies have triggered endoscope usage, especially in ear surgery [1].

Although the endoscope has a disadvantage, such as one-handed use, absence of binocular vision, and potential thermal damage to surrounding tissues due to the endoscope's heat effect; it provides better control over areas such as sinus tympani and hypotympani, where sufficient surgical vision cannot be achieved microscopically. In addition, because of the minimally invasive approach to the middle ear, the decrease in postoperative morbidity and contribution to better wound healing cannot be ignored[1,2].

Although the microscope is still considered the main instrument for ear surgery today, endoscopic middle ear approaches are gaining importance, especially in isolated and limited pathologies[1,2].

This study shares the experiences of our clinic regarding endoscopic ear surgery. We aim to create a database for further studies to compare the advantages and disadvantages of endoscope use in ear surgery.

2. Materials and methods

The data of patients who were operated on only with the transcanal endoscopic approach or the combined approach with the microscope were collected retrospectively between 2015 and 2022 years. The patients were selected from those who were operated on through the external auditory canal with a standard 0°, 3.0 mm rigid endoscope by a single experienced surgeon. Age, previous ear surgery history, preoperative and postoperative physical examination findings, changes in preoperative and postoperative complaints, preoperative and postoperative audiological data, postoperative follow-up period, discharge time, and preoperative radiological findings were evaluated parameters.

Physical examinations of all patients were performed with an otoscope or microscope in the preoperative and postoperative first month under policlinic conditions. Preoperative and postoperative first-month audiological evaluations of all patients were performed. The mean of the hearing levels at 0.5, 1, 2, and 4 kHz were used as the pure tone average [3].

The Ethics Committee of Eskişehir Non-Interventional Clinical Research Ethics approved this study on 16.06.2020(04).

Analysis of all data was performed by using SPSS 23. Statistical program (SPSS Inc, Chicago, Illinois). Descriptive analyses were performed. Audiologic results were compared by using the Wilcoxon signed rank test for dependent groups. The probability value of $p<0,05$ was accepted as the level of significance.
The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

3. Results

These results include the data of 70 patients who underwent otological surgery with an endoscopic approach or the combined approach with a microscope in our clinic between 2015 and 2022. Patients whose external auditory canal skin was elevated as a tympanomeatal flap and operated under general anesthesia were included in the study group. Patients who were operated on under local anesthesia or whose external auditory canal skin was not elevated as a flap were excluded from this study. The patients were divided into four groups, namely, type 1 tympanoplasty, middle ear exploration and ossiculoplasty, chronic otitis media with cholesteatoma, and stapedetomy(Table 1).

There were 26 cases in the type-1 tympanoplasty group; the mean age was 37(range 14-65 years), and the mean follow-up was 16.3(range 7-26) months. Among the perforated tympanic membranes, 3 were posterior marginal, 2 were anterior marginal,

4 were central, 7 were subtotal, and 10 were total perforated(Table 2). During the follow-up, the success rate of the graft membrane was 84.6%. In half of the cases, tragal cartilage; in the other half, temporalis muscle fascia was used as a graft. The mean preoperative air-bone gap(ABG) significantly decreased from 25.1±7.45 to 17.08±7.09 dB postoperatively($p<0.05$-Wilcoxon signed rank test)(Table 3). During the follow-up period, in the pure tone audiometry performed in the postoperative first month, 7.3 decibels(dB) ABG closure was detected compared to the preoperative period. Only one patient described a short-term tinnitus and fullness sensation, which later regressed spontaneously in the follow-ups. No postoperative complications were reported in the remaining patients. All patients were discharged within one day. There was no additional pathology except tympanic membrane perforation in the preoperative computed tomography(CT) scan.

There were 9 cases in the middle ear exploration and ossiculoplasty group; the mean age was 28.3(range 14-49 years), and the mean follow-up was 13.7(range 8-20) months. The primary ossicular defect was detected in 6 cases, and after ossiculoplasty with bone cement, 29 dB mean ABG closure was achieved in pure tone audiometry($p<0.05$-Wilcoxon signed rank test) (Table 3)**.** One case was operated on suspicion of perilymph fistula after trauma, and no fistula was observed during the case. Two cases were revision tympanosclerosis cases and a second look together with ossiculoplasty was performed. No complications occurred except for one patient who had a temporary taste disorder. The mean discharge time of cases was 1.3 days. There was no additional pathology in the preoperative CT scan**.**

There were 18 cases in the chronic otitis media with cholesteatoma group; the mean age was 32.8(range 7-62 years), and the mean follow-up was 17.7(range 6-36) months. Five cases were combined with a microscope, and 13 cases were performed with the endoscope only. Two cases were congenital cholesteatoma, and 16 cases were acquired cholesteatoma. Two congenital cholesteatomas were Potsic stage 4[4]. In the group of acquired cholesteatoma; 4 of them were Stage 3, 6 of them were Stage 2, and 6 of them were Stage 1 according to EANO / JOS cholesteatoma classification[5](Figure 1). Half of the cases were revision cases and there was a history of previous cholesteatoma surgery. 94%(17/18) of the cases showed no recurrence suspicion with a physical examination during the postoperative follow-up period. In only one of the cases, revision was needed with the suspicion of recurrence. In one of the cases, facial paralysis developed in the preoperative period, and because of that surgery was planned as an emergency. The patient's facial paralysis completely resolved with medical treatment in the postoperative period. In one of the cases, vertigo developed in the preoperative period, because of that surgery was planned as an emergency with suspicion of labyrinthine fistula. The labyrinthine fistula was also repaired in this case with a combine approach, and no vertigo was reported in the postoperative period. One case was operated bilaterally at 6-month intervals with a preliminary diagnosis of bilateral congenital cholesteatoma. The petrous apex cholesteatoma was excised with a combined approach in two cases. Two patients with petrous apex cholesteatoma had House-Brackmann grade 6 facial paralysis preoperatively, and their facial paralysis continued in the postoperative period. No additional complications were reported during the follow-up of the cases. The mean discharge time of the patients was 2.3 days. All patients had preoperative CT and diffusion magnetic resonance imaging (MRI) scans to map cholesteatoma.

There were 17 cases in the stapedetomy group; the mean age was 38.7 (range 23-60 years), and the mean follow-up was 14.9(range 6-24) months. The mean preoperative air-bone gap(ABG) significantly decreased from 29.6±7.83 to 9.35±3.23 dB postoperatively($p<0.05$-Wilcoxon signed rank test) (Table 3). Mean 20.2 dB ABG closure was achieved compared to the preoperative period in the pure tone audiometry performed in the postoperative 1st month. In 13 of the 17 cases, 10 dB or below ABG was achieved in the postoperative period. In all cases, the ABG was below 20 dB in the postoperative period. There was a complaint of persistent

tinnitus during the follow-ups in one case. Five cases described post-operative short-term mild to moderate vertigo. The patient with the complaint of persistent tinnitus had a history of tympanoplasty. Tympanosclerosis which was detected intraoperatively was thought to be the main reason for the tinnitus in this patient. Revision surgery was planned in the second month postoperatively, considering piston dislocation in one patient. No complications were observed in the remaining patients in the postoperative period. The mean discharge time of the patients was 2.7 days. Otosclerosis findings of varying severity were found in all patients except the patients with tympanosclerosis in the preoperative CT scan (Table 4).

Table 1. Number of the patients

Surgery type	***Number of patients***
Type 1 tympanoplasty	26
Exploration	9
Cholesteatoma	18
Stapedetomy	17

Table 2. Perforation sizes and sites

Perforation site	***Number of the patients***
Posterior marginal	3(2 small*, 1 medium)
Anterior marginal	2(2 small)
Central	4(1 small, 2 medium, 1 large)
Subtotal	7
Total	10

***small: <25% of the tympanic membrane size, medium 25%-50% of the tympanic membrane size, large 50%-75% of the tympanic membrane size, >75% classified as total or subtotal perforation*

Table 3. Preoperative and postoperative ABG thresholds

Group	**Preoperative ABG**	**Postoperative ABG**	**Test statistics**	**p**
Type 1 tympanoplasty (n=26)	25.1±7.45 db	17.08±7.09 db	Wilcoxon	<0.001
Exploration (n=9)	44,3±11.96 db	15,29±10.23 db	Wilcoxon	<0.001
Otosclerosis (n=17)	29.6±7.83 db	9.35±3.23 db	Wilcoxon	<0.001

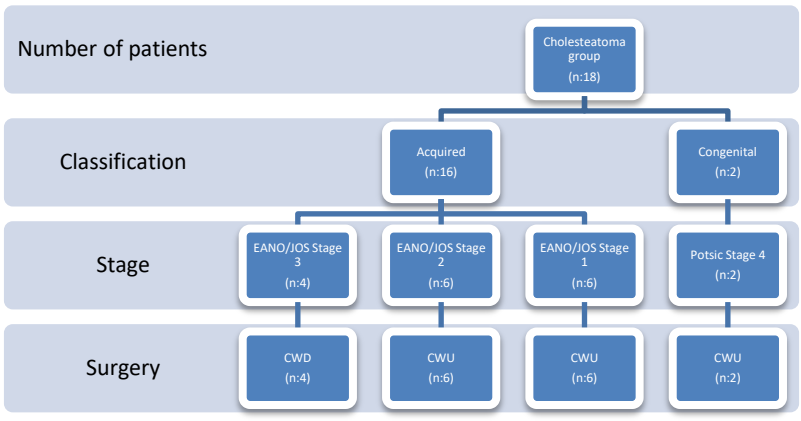

Figure 1. Cholesteatoma group

CWU: Canal Wall Up mastoidectomy
CWD: Canal Wall Down mastoidectomy

4. Discussion

In the group who had endoscopic type 1 tympanoplasty performed, a graft success rate(84.6%)was achieved parallel to the literature during follow-ups. A low complication rate and 7.3 dB mean ABG closure in the pure tone audiometry performed in the postoperative first month is in line with the current endoscopic type 1 tympanoplasty literature[6]. There is no significant difference between the two methods in graft success rate, complication rate, and hearing gain in studies comparing the traditional microscope with the endoscope; therefore, endoscopic type-1 tympanoplasty can be considered a reliable method[6-8].

The exploration and hearing reconstruction group results align with the existing literature with a 29 dB mean ABG closure. In five of our cases, there was a history of head trauma, and in four cases, we detected a separation in the ossicular chain (between incus and stapes). In one of the children, there was no history of trauma; therefore, congenital incudostapedial joint separation was the diagnosis for this patient. The perilymphatic fistula was not detected intraoperatively in the patient with suspected perilymphatic fistula secondary to trauma. Considering that the endoscope provides better surgical vision over the oval and round windows, we can assume that the endoscope is superior to the microscope in terms of perilymphatic fistula repair[9]. In two cases, hearing reconstruction was not performed to avoid additional complications due to extensive tympanosclerosis affecting the oval window floor. Although the advantages of the endoscopic approach over the microscopic approach should be supported by more research, especially in isolated ossicular pathologies; we believe that the endoscopic method will be preferred in the future in terms of surgical view and approach [10,11].

Although the follow-up period of our clinic is limited in the case series of endoscopic cholesteatoma surgery, the recurrence rate of 6% in an average follow-up of 17.7 months is in line with the existing endoscopic cholesteatoma surgery literature. Recurrence rates vary between 2% and 25% in different studies, depending on the follow-up period and surgical technique [12]. It has been reported in different studies that recurrence rates are higher in Canal Wall Up (CWU) techniques compared to Canal Wall Down (CWD) mastoidectomy after a single surgery in the microscopic approach[12]. Different studies state that endoscopic approaches are more successful in recurrence than microscopic CWU mastoidectomy techniques in cholesteatomas confined to the middle ear [12]. It has been shown that the endoscope provides better surgical vision than the microscope, especially in the sinus tympani and epitympanic areas, and therefore the endoscope prevents residual cholesteatoma in such areas [13]. The advantage of the minimally invasive approach provided by the endoscope in congenital cholesteatoma cases cannot be ignored, especially in the pediatric age group [14]. In terms of complication rates, the case series of our clinic is approximately the same as the literature data. Although the limited follow-up period in our clinic is disadvantageous in this study, it is clear that more reliable data can be obtained in future studies. Recurrence rates in cholesteatoma surgery may differ depending on the follow-up period, surgical method, and technique. We believe that the combined use of an endoscope and microscope is more successful than the microscopic approach alone in terms of long-term recurrence rates, and this will be further supported by future studies [15,16].

An acceptable 20.2 dB mean ABG closure was achieved in the endoscopic stapedetomy group. In 70% (12/17) of the patients, an air-bone gap of 10 dB or less in the postoperative period can be considered successful in terms of stapes surgery. In different studies; postoperative ABG of 10 dB or less, varies between 72.1% and 94.2% in the microscopic stapedotomy techniques[17]. Our clinic's postoperative complication rates align with the literature [17,18]. We believe that the advantages of the endoscope over the microscope in protecting the corda tympani and scutum during stapedotomy can be studied with future work. Especially the complication rates in long-term follow-ups and the differences between the microscopic

approach and the endoscopic approach should be supported by further studies[18,19]. The two major limitations of this study are that relatively small sample size and being retrospective. The main disadvantage of this retrospective study is the lack of control of the datas. Duration of surgery could be significant data for endoscope versus microscope comparison. Evaluation of the potential chorda tympani injury and disturbances of the taste also could be significant data for the success of endoscopic surgery. Duration of surgery and injury of the chorda tympani have been evaluated since 2021 as our clinical approach. In this context, this study can not give any data for the potential damage of the chorda tympani and the duration of surgery because of its retrospective nature.

5. Conclusion

Although the use of endoscopy in otological surgery is still at an early stage compared to microscopy; the endoscope has been accepted as a safe and successful surgical procedure with the proper indication in the field of otology. Although endoscope has disadvantages such as single-hand use and the heat effect, its use will gradually increase parallel to the developing technology. We believe that the advantages of endoscopes in pathologies limited to the middle ear should be supported by further studies, especially in terms of postoperative discharge time, complication rate, and surgical success.

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Ethics

Ethics Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Ethical Committee (Approval Date/ Number: 16.06.2020/04
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Research Article / Araştırma Makalesi

Fournier Gangreni'nde Vakum Yardımlı Kapama (Vak)'nın Yara İyileşmesi ve Greft Uyumu Üzerine Etkisi

The Effect of Vacuum-Assited Closure (VAC) on Wound and Graft Healing in Fournier's Gangrene

Burhan Baylan, Recep Uzun

Afyonkarahisar Sağlık Bilimleri Üniversitesi, Tıp Fakültesi, Üroloji Anabilim Dalı, Afyonkarahisar, Türkiye

Özet: Fournier Gangreni (FG), perineal, perianal veya genital bölgeleri etkileyen agresif bir nekrotizan fasiit olarak tanımlanmıştır. FG'de nekrotik dokuların erken dönemde agresif ve tam cerrahi debridmanı yapılmalıdır. FG'nin tedavisinde VAK ve konvansiyonel pansumanu karşılaştırarak, başlangıç cerrahisi ile greftleme arasında geçen süre ve greftleme sonrası sekonder debritman gereksinimi açısından incelemeyi amaçladık. 2015- 2023 yılları arasında Üroloji Kliniği'mizce FG tanısı konularak cerrahi tedavi uygulanan ve greft ile doku kapama yapılmış 48 hastanın verileri retrospektif incelendi. Hastaların klinik, patofizyolojik özellikleri, predispozan faktörler, VAK veya konvansiyonel pansuman kullanımı, greft kaybı sayıları, hastanede kalış süreleri kaydedildi. VAK ve konvansiyel pansuman yapılan gruplar karşılaştırılmalı değerlendirildi. Fournier Gangreni tanısı ile takip ve tedavi edilen toplam 48 hastanın 25'inde (%52) postoperatif dönemde VAK pansuman kullanılırken, 23'ünde (%48) konvansiyonel pansuman kullanılmıştı. Ortalama hastanede yatış süreleri, VAK grubunda 28 gün , konvansiyonel grupta 48 gün olarak tespit edilmiş ve VAK grubunda anlamlı olarak daha kısa saptandı. (p = 0.008). VAK grubunda 2 hastada , konvansiyonel pansuman yapılan hasta grubunda 6 hastada greft ile kapama sonrası sekonder debritman gerekli olduğu tespit edildi. Greft kaybı oranları VAK pansuman yapılan grupta, konvansiyonel pansuman yapılan gruba göre istatistiksel anlamlı daha azdı. FG 'de VAK tedavisi yara iyileştirmesini hızlandırmakta, hastanede kalış süresini kısaltmakta ve greft ile doku kapama sonrası ikincil cerrahi girişim oranlarını azaltmaktadır
Anahtar Kelimeler: Fournier gangreni, VAK, konvansiyonel pansuman, Greft

Abstract: Fournier's Gangrene (FG) has been described as an aggressive necrotizing fasciitis that affects the perineal, perianal, or genital areas. Aggressive and complete surgical debridement of necrotic tissues should be performed in the early period in FG. We aimed to compare VAC and conventional dressing in the treatment of FG in terms of the time elapsed between initial surgery and grafting and the need for secondary debridement after grafting. The data of 48 patients who were diagnosed with FG by our Urology Clinic between 2015 and 2023, underwent surgical treatment and graft tissue closure were retrospectively analyzed. Clinical, pathophysiological features, predisposing factors, use of VAC or conventional dressings, number of graft losses, length of hospital stay were recorded. VAC and conventional groups were evaluated comparatively Of the total 48 patients who were followed up and treated with Fournier's Gangrene, 25 (52%) used VAK dressing in the postoperative period, while conventional dressing was used in 23 (48%). The mean length of hospital stay was 28 days in the VAC group, 48 days in the conventional group and significantly shorter in the VAC group. (p = 0.017). It was determined that secondary debridement was required after graft closure in 2 patients in the VAK group and in 6 patients in the conventional dressing group. Graft loss rates were statistically significantly less in the VAC dressing group than in the conventional dressing group. VAC treatment in FG accelerates wound healing, shortens hospital stay, and reduces secondary surgical intervention rates after tissue closure with grafting.
Keywords: Fournier's gangrene, VAC, conventional dressing, Graft

ORCID ID of the authors: BB. 0000-0002-5509-7140, RU. 0000-0002-0841-8757

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Correspondence: Burhan BAYLAN - Afyonkarahisar Sağlık Bilimleri Üniversitesi, Tıp Fakültesi, Üroloji Anabilim Dalı, Afyonkarahisar, Türkiye
e-mail: baylanburhan@gmail.com

1. Giriş

Fournier Gangreni (FG) perineal, perianal ve/veya genital bölgeleri etkileyen agresif nekrotizan fasiit olarak ilk defa 1883'te tanımlanmış ve halen aynı tanımlama kullanılmaktadır. FG, obliteratif endarterit ve subkutan arterlerin trombozu ile karakterize nekrotizan, yumuşak doku enfeksiyonudur. Akut başlangıç, hızlı progresyon ve % 20-30'luk oldukça yüksek mortalite oranı ile karakterizedir.(1-5)

FG etyopatogenizinde deri, üretra veya rektumdan kaynaklı polimikrobiyal etiyoloji öngörülmüştür.(6,7) Ayrıca diyabet, kronik alkolizm, insan immün yetmezlik virüsü, steroid kötüye kullanımı, sitotoksik ilaçlar, lenfoproliferatif hastalık, malnütrisyon ve düşük sosyo-ekonomik durum gibi birçok predispozan faktör FG oluşumu ile ilişkilendirilmiştir.(8,9)

Avrupa Üroloji Birliği (EAU) Ürolojik Enfeksiyonlar kılavuzuna göre, gecikmiş ve/veya yetersiz cerrahinin yüksek mortaliteye neden olabileceğinden, ilk yaklaşımın nekrotik dokunun agresif, tam ve erken (< 24 saat) cerrahi debridman olması gerektiği belirtilmiştir.(10)

Acil ampirik parenteral antibiyotik tedavisi verilmeli ve amikrobiyolojik kültür sonuçlarına göre tekrar düzenlenmelidir. FG'nin komşu dokulara hızlı ilerlemesi cerrahi debritman sonrası dokularda geniş defektler bırakabilmektedir. Bununla birlikte FG debritman sonrası, sık pansuman ve flep veya cilt greftlerine ihtiyaç duyabilecek karmaşık yara kapanma süreçleri gelişebilmektedir. (11)

Postoperatif açık yara bakımı için farklı protokoller bildirilmiştir, ancak bunların etkinliği uygun şekilde analiz edilmemiştir ve mevcut kılavuzlarda çok düşük bir kanıt düzeyi göstermektedir(10). FG'de vakum yardımlı kapama (VAK) tedavisinin rolüne ilişkin kanıt eksikliği (kanıt düzeyi 4) mevcuttur.(10)

Çalışmamızın amacı, FG'nin yara tedavisinde VAK'ın konvansiyonel pansumanlara karşı rolünü, cerrahi debritman ile greftleme arasında geçen süre ve greftleme sonrası sekonder debritman gerekliliği açısından karşılaştırmayı amaçladık.

2. Gereç ve Yöntem

Üniversitesi Klinik Araştırmalar Etik Kurulu'nun 2023/146 sayılı etik kurul onayı alınarak 2015- 2023 yılları arasında Üroloji Kliniği'mizce FG tanısı konularak cerrahi tedavi uygulanan ve greft ile doku kapama yapılmış 48 hastanın verileri retrospektif olarak incelendi. Hastaların klinik ve patofizyolojik özelliklerine ilişkin cinsiyet, yaş, predispozan faktörler, FG'nin kaynağı, ilk başvurudaki kan sonuçları, hastanede kalış süresi, cerrahi işlemlerin tipi ve sayısı, VAK veya konvansiyonel pansuman kullanımı, ilk debridmandan yaranın kapanmasına kadar geçen süre ve greftleme sonrası sekonder debritman gereksinim sayıları kaydedildi. VAK, cerrahi debridmandan hemen sonra cerrahın klinik yargısına dayanarak kullanılmıştı. VAK ile belirlenen negatif basınç değeri, bir sonraki pansuman değişikliğine kadar 75-125 mmHg'de uygulanmıştı. Her VAK değişikliği için, yaralar sağlıklı ve canlı doku görünene kadar ameliyathanede anestezi altında seri olarak debride edilmişti. Toplanan tüm veriler VAK kapama uygulanan ve konvansiyonel pansuman yapılan 2 farklı grup arasında karşılaştırılmalı olarak değerlendirildi.

İstatistiksel analiz

Veri analizi, IBM SPSS Statistics ver. 25.0 yazılımı (IBM Corporation, Armonk, NY, ABD) kullanılarak gerçekleştirilmiştir. Kategorik değişkenler mutlak ve göreceli yüzde frekansları ile özetlenmiş ve Fisher exact testi ile bağımsız gruplar arasında karşılaştırılmıştır. Wilcoxon runk sum testi ile bağımsız gruplar arasında karşılaştırıldı.

3. Bulgular

FG tanısı ile cerrahi debritman ve doku greftleme yapılan toplam 48 hastanın 25'inde (%52) postoperatif dönemde VAK pansuman kullanılırken, 23'ünde (%48) konvansiyonel pansuman kullanılmıştır. Hastaların özellikleri ve demografik özellikleri Tablo 1'de listelenmiştir. Tedavi edilen hastaların tümü erkek cinsiyetti. VAK veya konvansiyonel

pansuman ile tedavi edilen hastaların demografik özellikler ve predispozan faktörler açısından istatistiksel anlamda benzerdi.

Her iki grupta preoperatif dönem kan analizleri incelendiğinde C-reaktif protein, sedimentasyon ve albumin gibi kan sonuçları açısından istatistiksel olarak anlamlı bir fark bulunmadı. (Tablo 1)

Tüm hastalara başvurudan sonraki ilk 12 saat içinde cerrahi radikal debridman uygulanmıştı.

Testis ve/veya spermatik kordun etkilenmesi nedenli 48 hastanın 7'sinde tek taraflı, 4'ünde bilateral orşiektomi uygulanmıştı. 8 hastada perineal bölgeye uzanımlı FG nedenli perineal saha debritmanı, 4 hastada inguinal bölgeye uzanım nedenli inguinal saha debritmanı uygulanmıştı. VAK ve konvansiyonel pansumanlı hastalarda uygulanmış cerrahi yaklaşımlar Tablo 2'de listelenmiştir.

Ortalama hastanede yatış süreleri, VAK grubunda 28 gün (16-51), konvansiyonel grupta 48 gün (35-66.5) olarak tespit edilmiş ve VAK grubunda anlamlı olarak daha kısa saptanmıştır. (p=0.008). İlk debridmandan itibaren greftleme ile yara kapanmasına kadar geçen medyan süre, VAK tedavisi ile yönetilen FG'li hastalarda 23 gün (12–36), konvansiyonel grupta ise 45 gün (30–60) olarak tespit edildi. VAK grubunda bu süre istatistiksel anlamlı kısaydı (p=0.009) (Tablo 3).

Her iki grupta greftleme sonrası takiplerinde greft enfeksiyonu veya greft nekrozu nedenli cerrahi debritman gerektirme sayıları karşılaştırıldı. VAK grubunda 25 hastanın 2'sinde, konvansiyonel pansuman yapılan hasta grubunda ise 23 hastanın 6'sında gerekli olduğu tespit edildi. Greft kaybı oranlarının VAK pansuman yapılan grupta, Konvansiyonel pansuman yapılan gruba göre istatistiksel anlamlı daha az olduğu gözlenmiştir (p=0.002) (Tablo 3).

Tablo 1. FG tanılı hastaların demografik özellikleri

Karakteristik ve demografik özellikler	**VAK pansuman** n=25	**Konvansiyonel Pansuman** N=23	**P değer**
Yaş,yıl (n=48)	63 (50-75)	66 (58-72)	0,421
Predispozan Faktörler			
Obezite	5	2	0,036
Diyabet	23	21	0,314
Hipertansiyon	18	15	0,393
Yatağa bağımlı	4	1	0,023
Sigara	10	7	0,671
Alkolizm	8	4	0,089
Steroid kullanımı	3	2	0,866
Böbrek yetmezliği	2	1	0,376
Pelvik radyoterapi öyküsü	1	0	0,075
Fournier kaynağı			
Ürogenital bölge	20	17	
Anorektal bölge	10	11	
Ürogenital ve anorektal bölge	5	5	
Kan analizleri			
C Reaktif Protein	148,5 (80,1-165,3)	158,7 (92,3-169,7)	0,154
Sedimentasyon	46,3 (38,4-62,7)	49,4 (29,7-64,5)	0,140
Albümin	2,8(2,2-3,3)	2,6(2-2,6)	0,132

Tablo 2. FG'de cerrahi debritman ile eş seanslı uygulanan cerrahi prosedürler

Cerrahi yaklaşımlar	VAK pansuman	Konvansiyonel Pansuman
Skrotal cerrahi	23	20
Tek taraf orşiektomi	5	2
Bilateral orşiektomi	2	2
Perineal cerrahi	5	3
İnguinal cerrahi	2	2

Tablo 3. FG'de cerrahi sonrası döneme ilişkin istatistiksel karşılaştırma

	VAK pansuman	Konvansiyonel Pansuman	P değer
Hastanede kalış süresi (gün)	28 (16-51)	48 (35-66.5)	0.008
İlk debritman ve greftleme arası süre (gün)	23 (12–36)	45 (30–60)	0.009
Greftleme sonrası sekonder debritman gerekliliği	2 (2/25)	6 (6/23)	0.002

4. Tartışma

FG, subkutan arterlerin obliteratif bir endarteriti olup, deri ve subkutan dokunun kangreni ile sonuçlanır. (12) FG agresif polimikrobiyal enfeksiyondur. [8, 10]. Gecikmiş ve/veya yetersiz cerrahinin daha yüksek mortaliteye yol açabileceğinden cerrahi debridmanın erken ve agresif olması gerekmektedir.[8, 10, 13]. Yanaral ve ark çalışmasındaVAK'ın konvansiyonel pansumana göre daha az pansuman değişikliği, daha az ağrı ve daha fazla hareketlilik sunarak etkili olduğunu bildirmiştir [14].

VAK uygulanan hastalar bazı çalışmalarda hastanede kalış sürelerinin daha uzun olduğunu bildirmişlerdir [15-17], ancak bazı yazarlar zıt verileri tanımlamışlardır [18, 19] Bizim çalışmamızda hastanede yatış süreleri, VAK grubunda, konvansiyonel pansuman yapılan gruba göre anlamlı olarak daha kısa saptanmıştır.

Lacovelli ve ark yaptığı çalışmada yara kapanmasının tamamlanması için gereken sürelere bakıldığında, VAK ile veya VAK'sız yaklaşımla tedavi edilen vakalar arasında anlamlı bir fark göstermedi. (20) Bizim çalışmamızda ise bu çalışmadan farklı olarak İlk debridmandan yaranın doku greftleme ile kapanmasına kadar geçen medyan süre, VAK tedavisi ile yönetilen FG'li hastalarda konvansiyonel gruba göre istatistiksel anlamlı kısaydı.

Bildiğimiz kadarıyla literatürde çalışmamıza benzer çalışma bulunmamakta ve diğer çalışmalardan farklı olarak greftleme sonrası takiplerinde cerrahi debritman gerektirme oranları karşılaştırılmıştır. Greft kaybı oranlarının VAK pansuman yapılan grupta, konvansiyonel pansuman yapılan gruba göre istatistiksel anlamlı daha az olduğu gözlenmiştir.

Çalışmanın limitasyonları retrospektif tasarım olması ve örneklem büyüklüğü, nadir patoloji için 48 vaka ile sınırlıdır, ancak istatistiksel bir bakış açısıyla, sınırlı analiz yapılabilmiştir. Prospektif randomize klinik çalışma, VAK'ın FG yönetimindeki rolünü daha iyi açıklığa kavuşturmaya yardımcı olacaktır. Ne yazık ki, hastaları prospektif olarak randomize etmek de zordur, çünkü bu tipik olarak acil bir durumdur ve ayrıntılı, kapsamlı anamnez ve bir çalışmaya kaydolmaya izin vermeyebilir.

5. Sonuç

FG'nin yönetimi son derece zordur. FG hastalarında VAK tedavisi güvenli ve etkili bir teknik gibi görünmektedir. VAK tedavisi yara iyileştirmesini hızlandırmakta ve hastanede kalış süresini kısaltmaktadır. Doku grefti kapama uygulanan hastalarda ikincil cerrahi girişim oranlarını azaltmaktadır. Sonuçlarımızı doğrulamak için daha büyük çalışmalara ihtiyaç vardır.

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Research Article / Araştırma Makalesi

Assessment of Ergonomic Working Conditions and Stress Perceptions of Office Workers: A University Example

Büro Çalışanlarının Ergonomik Çalışma Koşulları ve Stres Algılarının Değerlendirilmesi: Bir Üniversite Örneği

Feyza Nehir Öznur Muz, Ali Kılınç, Mine Tepetaş, Alaettin Ünsal, Didem Arslantaş

Eskişehir Osmangazi University Faculty of Medicine Department of Public Health, Eskişehir, Türkiye

Abstract: The necessity of organizing the working conditions of a workplace in a way that is suitable for employees and that they can easily do their jobs brings ergonomics to the forefront in terms of occupational health and safety. It is aimed to determine the perception of ergonomic working conditions and the stress levels of a university's office workers. This cross-sectional study was conducted among 530 office workers of a university. The Ergonomic Working Conditions Scale (EWCS) was used to determine the perception of ergonomic working conditions, and the Perceived Stress Scale (PSS), was used to determine stress perception levels. Mann-Whitney U, Kruskal-Wallis tests, Spearman correlation and Multiple linear regression analyses were used. Participants ages ranged between 19-60 years with a mean of 37.2±8.9 years. The participants' scores on the EWCS ranged between 36-130, with a mean score of 83.6±14.2 points. It was found that there was a weak negative correlation between the scores obtained from the EWCS and the scores obtained from PSS (r= -0.167, p=0.001). As a result of multiple linear regression analysis, it was found that age, gender, working time and ergonomic arrangement of working conditions by the employee were associated with the scores obtained from the EWCS (F=4318, p<0.001). It was found that the perceptions of university office workers about the ergonomic conditions of the working environment were at a moderate level. As the level of perception of the employees about ergonomic conditions increased, the level of perceived stress decreased.
Keywords: Ergonomics, Stress, Office Worker, University

Özet: Bir işyerinin çalışma koşullarının çalışanlara uygun ve işlerini rahatlıkla yapabilecekleri şekilde düzenlenmesi gerekliliği, iş sağlığı ve güvenliği açısından ergonomiyi ön plana çıkarmaktadır. Bu çalışmada bir üniversitenin büro çalışanlarının ergonomik çalışma koşulları algısı ve stres algısı düzeylerinin belirlenmesi amaçlanmıştır. Bu kesitsel çalışma, bir üniversitenin 530 büro çalışanında gerçekleştirilmiştir. Ergonomik çalışma koşulları algısını belirlemek için Ergonomik Çalışma Koşulları Ölçeği (EÇKÖ) ve stres algısı düzeylerini belirlemek için Algılanan Stres Ölçeği (ASÖ) kullanılmıştır. Mann-Whitney U, Kruskal-Wallis testleri, Spearman korelasyon ve Çoklu doğrusal regresyon analizleri kullanılmıştır. Katılımcıların yaşları 19-60 arasında değişmekte olup ortalama 37.2±8.9 yıl idi. Katılımcıların EÇKÖ puanları 36-130 arasında değişmekte olup, ortalama puan 83.6±14.2'dir. EÇKÖ'den elde edilen puanlar ile ASÖ'den elde edilen puanlar arasında negatif yönde zayıf bir korelasyon olduğu bulundu (r=-0.167, p=0.001). Çoklu lineer regresyon analizi sonucunda yaş, cinsiyet, çalışma süresi ve kendisi tarafından çalışma koşullarının ergonomik olarak düzenlenmesi durumları ile EÇKÖ'den alınan puanların ilişkili olduğu saptandı (F=4318, p<0,001). Üniversite büro çalışanlarının çalışma ortamının ergonomik koşullarına ilişkin algılarının orta düzeyde olduğu bulunmuştur. Çalışanların ergonomik koşullara ilişkin algı düzeyi arttıkça algılanan stres düzeyi de azalmaktadır.
Anahtar Kelimeler: Ergonomi, Stres, Büro Çalışanı, Üniversite

ORCID ID of the authors: FNÖM.0000-0001-8747-9867, AK. 0000-0002-0577-8570 . MT. 0000-0003-4747-7220,AÜ. 0000-0001-8353-1605,,DA. 0000-0002-5263-3710,

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Correspondence: Feyza Nehir ÖZNUR MUZ - Eskişehir Osmangazi University Faculty of Medicine Department of Public Health, Eskişehir, Türkiye
e-mail: feyzanehir@yahoo.com

1. Introductions

Work offices are places where they spend an important part of the day for those working in both the private sector and public institutions and organizations. For people who spend more time at work than at home, it is known that workplace working conditions have a direct impact on the productivity of the employee. The necessity of organizing these workplace working conditions in a way that is suitable for employees and that they can do their jobs easily brings ergonomics to the forefront in terms of occupational health and safety (1).

Ergonomics, also known as human factors engineering and design, aims to adapt work to people and each person to their own work. It is essential to implement practices that prioritize the health and productivity of employees. The aim of ergonomics is not only to eliminate risk factors that are important for occupational accidents and occupational diseases, but also to increase the well-being and performance of employees by ensuring occupational safety and improving working conditions in the workplace (2).

Ergonomic conditions of workplaces can be organized in many ways such as anthropometric, physiological, psychological, informational and safety. Employees may be exposed to many physical, chemical, biological and psychosocial risk factors in the workplace (3). While these risk factors may negatively affect the health and therefore work efficiency of employees, the presence of plants and flowers in the same environment and colorful and vivid paintings on the walls may make employees feel more comfortable psychologically (4).

An institutionalized workplace should carefully complete the arrangements to be made for its employees by considering all these methods. In the occurrence of occupational musculoskeletal disorders observed physically due to working conditions in the office environment, problems such as incorrect sitting posture, overloading of muscles due to repetitive static movements, use of incorrect equipment, failure to select ergonomic equipment suitable for the body structure/anthropometric dimensions of the person or failure to adjust mechanisms according to personal body characteristics must be overcome (5). In other words, workplace working conditions should be designed and organized by taking into account the anthropometric characteristics of the employees.

In order for individuals to work in harmony, prioritizing not only physical but also mental health, and organizing the environment and system to suit the individual, so that they can do their job easily, will not only increase the performance of employees, but also reduce the pressure and stress burden on them (6,7).

As a matter of fact, stress is defined as an introverted reaction that people show against situations that they perceive as a threat or difficulty and it is seen as a factor known to have many negative effects on human health (8). Despite this, studies evaluating the relationship between stress and perception of ergonomic conditions are insufficient in the literature. In our study, it was aimed to determine the level of perception of ergonomic working conditions, to examine some variables thought to be related to this perception, and to evaluate the level of stress perception of Eskisehir Osmangazi University office workers.

2. Materials and Methods

The study is a cross-sectional study, conducted on office workers of a university between March 01 - April 29, 2022. Eskisehir Osmangazi University has 13 faculties, 2 colleges, 5 vocational schools, 4 institutes and affiliated units. There are a total of 821 clerical staff working throughout the university and it was aimed to reach all of them in our study. Ethical and administrative approvals were obtained for the study A total of 291 people who were not present at the workplace during the data collection period (n=64) and who refused to participate in the study (n=227) were excluded from the study. The study group consisted of 530 people (64.6%).

A questionnaire form prepared by utilizing the literature was used for data collection in the study (9–11). After visiting the office workers in the units where they worked and informing them about the subject and purpose of the study, verbal consent was obtained from those who agreed to participate in the study. The questionnaires were completed by office workers under the supervision of the research team in approximately 15-20 minutes. The dependent variable of the study was the perception of ergonomic working conditions, while the independent variables were age, gender, presence of chronic disease, physical disability, current position and working time in the workplace and perceived stress level.

The 'Ergonomic Working Conditions Scale' developed by Oskaloglu and Cati was used to determine the perception levels of the study group regarding ergonomic working conditions. The scale consists of 26 questions and total scores can vary between 26-130. As the scores increase, it is accepted that working conditions are perceived as more ergonomic (11). 'Perceived Stress Scale' was used to determine stress levels. The scale was developed by Cohen et al. in 1983 and the Turkish validity and reliability study was conducted by Eskin et al. in 2013. The scale consists of 10 questions and it is accepted that the perceived stress level increases as the scores increase (12).

The data obtained were evaluated in SPSS V20.0 statistical package program. Kolmogorov-Smirnov test was used for the conformity of measurable data to normal distribution. Mann-Whitney U test, Kruskal-Wallis test and Spearman correlation and Multiple linear regression analysis (enter method) were used for analysis. For linear regression analysis, logarithmic transformation was performed to approximate the normal distribution of some variables. $p<0.05$ was accepted as statistical significance value.

3. Results

The study group consisted of 339 (64.0%) females and 191 (36.0%) males. Their ages ranged between 19-60 years, with a mean of 37.2 ± 8.9 years. The "Ergonomic Working Conditions Scale" scores of the participants ranged from 36 to 130, with a mean score of 83.6 ± 14.2 (median: 84). The scores of female employees were lower than the scores of male employees (p=0.001). The distribution of the Ergonomic Working Conditions Scale scores of the study group according to some sociodemographic characteristics is given in Table 1.

Table 1. Distribution of the Ergonomic Working Conditions Scale scores of the study group according to some sociodemographic characteristics

Sociodemographic Characteristics	**n**	**%**	**Ergonomic Working Conditions Scale Score** Median (Min-Max)	**Statistical Analysis** z / KW; p
Age (years)				
≤ 30	134	25.3	83.5 (36-130)	
31-40	201	37.9	84.0 (52-130)	1.938; 0.379
≥41	195	36.8	86.0 (44-127)	
Gender				
Female	339	64.0	82.0 (36-130)	**3.454; 0.001**
Male*	191	36.0	86.0 (44-130)	
Marital Status				
Married	328	61.9	85.0 (36-130)	1.784; 0.074
Single	202	38.1	83.5 (37-130)	
Education Status				
High school and below	222	41.9	85.5 (37-130)	0.680; 0.496
University graduate and above	308	58.1	84.0 (36-130)	

Position Classification				
Manager / consultant	26	4.9	87.5 (37-122)	
Constable	240	45.3	86.0 (44-130)	4.834; 0.081
Secretary / service staff	264	49.8	83.0(36-130)	
History of Chronic Disease				
No	412	77.7	85.0 (36-130)	1.377; 0.169
Yes	118	22.3	82.0 (47-126)	
Physical Disability Status				
No	494	93.2	84.0 (36-130)	0.374; 0.708
Yes	36	6.8	83.5 (45-114)	
Total	530	100.0	84.0 (36-130)	

** statistically significant group (p<0.05)*

Four hundred thirty two (81.5%) of the employees reported that their employers had not made arrangements for ergonomic conditions. The total working time in the current job of 159 (30%) of the study group was 5 years or less. The scores of this group were lower than the other groups (p=0.009). While 23.2% of the participants stated that they had not heard of the definition of ergonomics before, only 21.6% of those who had heard of it reported that their workplaces were organized for ergonomic conditions. The distribution of the scores obtained by the participants from the Ergonomic Working Conditions Scale according to some factors thought to be related to ergonomic working conditions is given in Table 2.

Table 2. Distribution of the Ergonomic Working Conditions Scale scores of the study group according to some factors thought to be related to ergonomic working conditions

Some factors related to ergonomic working conditions	**n**	**%**	**Ergonomic Working Conditions Scale Score** Median (Min-Max)	**Statistical Analysis** z / KW; p
Total Working Time At Current Job (Years)				
5 and below*	159	30.0	80.0 (36-130)	
6-10	127	24.0	86.0 (52-114)	**9.414; 0.009**
11 and above	244	46	85.5 (44-130)	
Hearing The Concept Of Ergonomics				
No	123	23.2	86.0 (37-130)	0.982; 0.326
Yes	407	76.8	84.0 (36-130)	
Attending An Event On Ergonomics In The Last 1 Year				
No	506	95.5	84.0 (36-130)	1.848; 0.065
Yes	24	4.5	90.5 (49-130)	
Ergonomic Organization Of Working Conditions By The Employer In The Last 1 Year				
No	432	81.5	83.0 (36-127)	**3.455; 0.001**
Yes*	98	18.5	88.5 (52-130)	
Ergonomic Organization Of Working Conditions By Oneself In The Last 1 Year				
No	263	49.6	83.0 (36-127)	**2.434; 0.015**
Yes*	267	50.4	86.0 (45-130)	
Total	530	100.0	84.0 (36-130)	

** statistically significant group (p<0.05)*

The scores of the study group on the Perceived Stress Scale ranged 0-37, with a mean of 20.8 ± 4.7 (median: 21) points. There was a very weak negative correlation between the office workers' scores on the Ergonomic Working Conditions Scale and their scores on the Perceived Stress Scale (p=0.001, r=-0.167). The distribution of the Ergonomic Working Conditions and Perceived Stress Scale scores of the study group is given in Figure 1.

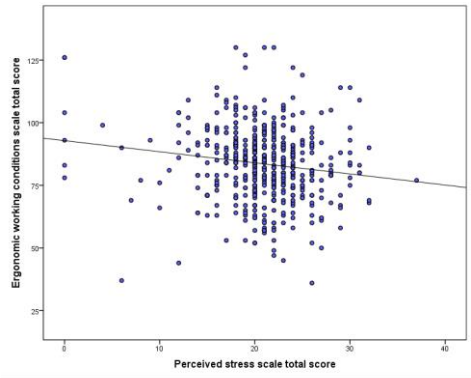

Figure 1. The distribution of the ergonomic working conditions and perceived stress scale total scores of the study group.

As a result of multiple linear regression analysis (enter method), it was found that age, gender, duration of employment and ergonomic organization of working conditions by oneself were associated with the scores obtained from the EWCS (F=4318, p<0.001).

The results of multiple linear regression analysis of the total scores obtained from the ergonomic working conditions scale with the variables considered to be related to ergonomics are given in Table 3.

Tablo 3. Multiple linear regression analysis results of the ergonomic working conditions scale total score and variables thought to be related to ergonomics

Sociodemographic Characteristics and Related Variables	**EWCS Total score**		
	Standartize β	**Unstandartize β (%95 GA)**	**p**
Age	-0.122	-0.086 (-0.173—0.00)	**0.049**
Gender	0.109	0.017 (0.004—0.031)	**0.014**
Marital Status	-0.019	-0.002 (-0.014—0.009)	0.667
Duration Of Employment	0.165	0.015 (0.004 —0.025)	**0.007**
Position Classification	-0.045	-0.006 (-0.017 — 0.006)	0.312
Attending An Event On The Topic	0.078	0.029 (-0.003 — 0.061)	0.179
Ergonomic Organization Of Working Conditions By Oneself	0,088	0,014 (0,000 — 0,027)	**0,050**
Ergonomic Organization Of Working Conditions By The Employer	0.092	0,018 (0,000 — 0,036)	0.076
Perceived Stress Scale Scores Total Score	-0,066	-0,05 (-0,117 — 0,015)	0,129
R^2	0,06		
F	4318		**<0,001**

4. Discussion

Although it is known that ergonomics makes life easier to the extent that it is more harmonized with the environment, many workplaces and employers may ignore the regulation of ergonomic conditions for different reasons. The office workers in the study group perceived their ergonomic conditions as moderate level. As the university is a public institution, the administration has strict rules to follow for office spaces, which may prevent office workers from taking the initiative to improve their working conditions.

Work life and the time spent in workplaces occupy almost one third of a person's life (13). Healthy and safe working environments to be provided for human beings, who are the cornerstone of the existence of businesses, increase the contribution of the employee to the structure in which he/she works. Determining the ergonomic conditions of the working environment is a priority for the arrangements that can be made. Similar to our study, Polat et al. measured the level of perception of the conditions and found that the conditions were perceived at a moderate level (14).

As individuals get older, they can be expected to be more selective about ergonomic working conditions in order to cope with health problems more easily. In our study, although no relationship was found between the age groups of office workers and ergonomic working conditions in the univariate analysis, age affected the perception of ergonomic working conditions in the multiple linear regression model. Güneş et al. reported that there was no difference between age groups and ergonomic working conditions (15), and Costa and Sartori reported that ergonomic conditions worsened as the age of employees increased (16).

Although women are actively participating in working life today, the fact that working conditions are designed according to men's anthropometric characteristics and lifestyle may cause women's perception of ergonomic working conditions to be lower. This is also supported by the fact that women are more sensitive to working conditions due to their physiological characteristics (muscle strength, cardiovascular function, aerobic work capacity, pregnancy, childbirth, etc.). In our study, in parallel with this, it was found that the level of perception of ergonomic working conditions was better among men than women. In a study conducted by Güler et al. on the evaluation of ergonomic conditions, it was reported that women complained more about negative ergonomic working conditions (17). In another study conducted by Güneş and Ceylan, it was reported that women were employed under more unfavorable ergonomic conditions than men (15). In this context, our study is in parallel with other studies in the literature.

It is known that ergonomic working conditions directly affect the physical health of the individual and that desk workers frequently experience musculoskeletal disorders (18). Therefore, it is possible that office workers with physical disabilities evaluate the ergonomics of working conditions as worse. However, in our study, no difference was found between those with and without physical disabilities in terms of the level of perception of ergonomic working conditions. Belgen et al. reported that employees with physical disabilities were employed under worse ergonomic conditions (19). Similar results have been reported in different studies in the literature (20,21).

It can be expected that office workers who have been working in the same workplace for a long time will be more conscious about ergonomics with the experience they have gained in the workplace, and even adopt the environment more and make various arrangements themselves, so that their working conditions will be more ergonomic. In this study, it was found that those with less total working time in their current job had worse perceptions of ergonomic working conditions. While a similar result was reported in the study by Pirvu et al. (22), a positive correlation between working time and the degree of satisfaction with ergonomic

conditions was reported in the study by Parmaksız et al. (23).

Employees who heard the concept of ergonomics and subsequently conduct research on the subject are expected to have more knowledge about the ergonomics. Although there was no difference between those who have heard of ergonomics and those who have not in terms of the level of perception about ergonomic working conditions in our study, it is possible that the workers who have this awareness will organize their working environments accordingly and work in more ergonomic conditions. It is an expected result that those who personally make ergonomic arrangements in their workplaces think that their conditions are better. In this context, in this study, it was found that those who made arrangements for ergonomic conditions by themselves in the last year had better perceptions of ergonomic working conditions. In some studies, it was reported that those who had previously heard the concept of ergonomics worked under more ergonomic conditions (24,25). Similarly, some studies reported that personal arrangements made in the workplace environment created more ergonomic working conditions (26,27). It can be said that the different results reported may be due to the fact that the studies were conducted in societies with different sociocultural structures and/or the measurement methods used in the evaluation of the conditions were different.

In this study, it was found that office workers who reported that the employer had made arrangements for ergonomic conditions within the last year had better perceptions of ergonomic working conditions. In addition, although no statistically significant difference was found, it can be said that employees who are managers or consultants have better perceptions of ergonomic working conditions ($p=0.081$). The fact that the people who should make the necessary arrangements regarding ergonomics are already managers and consultants may have led to this result. As a matter of fact, it is included in many employment contracts that appropriate arrangements should be made by the employer. In studies, it has been reported that productivity increases at the level where employee conditions are improved by employers' ergonomic working conditions regulations and if these principles are not applied, conditions deteriorate and employee health and productivity are negatively affected (28,29).

Ergonomics plays a very important role in the protection and development of not only physical but also mental health among employees. It is known that good ergonomic conditions such as proper body posture, well-lit environment, and regulation of the temperature of the working environment reduce perceived stress in office workers (30). In our study, it was found that there was a very weak negative correlation between the perceived ergonomic conditions of the working environment of office workers and their perceived stress levels. Although a negative relationship between stress and ergonomic working conditions is expected (31), it has also been reported that no relationship was found between ergonomic working conditions and stress levels (32). One of the reasons for the different results reported in various studies may be that ergonomic conditions differ between sectors.

The limitations of this study include the fact that it was a cross-sectional study, that it was a single-center study and that the scale used only measured how individuals perceived ergonomic working conditions. The answers given are subjective and may change according to the conditions of the day and the participant's willingness to participate in the study.

5. Conclusion

It can be said that the perceptions of university office workers about the ergonomic conditions of the working environment are at a moderate level. The fact that women interpreted the conditions as worse in the study suggested that the conditions may have been designed and organized according to the male gender, as in male-dominated societies. It was observed that the perception of ergonomic working conditions was better

when ergonomic arrangements were made by the employee himself or by his employer. As the level of perception of ergonomic working conditions increased, the level of perceived stress decreased.

It may be useful to organize the working environment in the university in terms of ergonomics and to inform the employees about the subject. Office ergonomics trainings can be given to employees and employers and incentives can be provided for necessary ergonomic arrangements. It would be useful for future research to conduct more comprehensive studies to reveal the relationship between perceptions of ergonomic conditions and stress level.

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Ethics

Ethics Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Noninterventional Ethical Committee (Approval Date/ Number: 05.04.2022/70

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Research Article / Araştırma Makalesi

Real-Life Data on the Use of Omalizumab in Patients with Severe Asthma and Chronic Urticaria and Mepolizumab in Patients with Severe Asthma: A Retrospective Study

Astım ve Kronik Ürtikerli Hastalarda Omalizumab'ın ve Şiddetli Astım Hastalarında Mepolizumab'ın Kullanımına İlişkin Gerçek Yaşam Verileri: Geriye Dönük Bir Çalışma

[1]Pamir Cerci, [2]Tuba Erdogan

[1] Division of Immunology and Allergy, Department of Internal Medicine/ Eskisehir City Hospital, Eskisehir, Türkiye
[2] Division of Immunology and Allergy, Baskent University, Faculty of Medicine, Ankara, Türkiye

Abstract: This study aimed to assess the real-life effectiveness of omalizumab and mepolizumab in patients with severe asthma and chronic spontaneous urticaria (CSU), explicitly examining changes in IgE levels and eosinophil counts during treatment. This retrospective study involved patients with severe asthma or CSU treated with biologic agents, including omalizumab and mepolizumab. The primary outcome measures were serum IgE levels, eosinophil counts, urticaria activity scores (UAS), and asthma control test scores (ACT). We studied 61 patients with severe asthma or chronic urticaria treated with biological agents. Patients with asthma exhibited a significant reduction in the median annual attack rate from 4 to 0 with omalizumab ($p<0.001$) and from 6 to 1 with mepolizumab ($p<0.001$). Eosinophil counts, and ACT scores significantly decreased with mepolizumab ($p<0.001$). Six patients who transitioned from omalizumab to mepolizumab did not experience severe asthma attacks in the first six months following the treatment switch. Patients with CSU showed a significant response to omalizumab ($p<0.001$). We observed significant improvements in various markers, including total IgE levels, eosinophil counts, UAS, and ACT scores, indicating that these treatments can effectively manage the symptoms of both conditions. These findings underscore the potential benefits of using these treatments as effective therapeutic options.
Keywords: Asthma, Mepolizumab, Omalizumab, Total IgE, Urticaria

Özet: Bu çalışmanın amacı, şiddetli astım ve kronik spontan ürtiker (CSU) hastalarında omalizumab ve mepolizumab'ın gerçek yaşam etkinliğini değerlendirmek, özellikle tedavi sırasında IgE seviyelerindeki ve eozinofil sayılarındaki değişiklikleri incelemekti. Bu geriye dönük çalışma, biyolojik ajanlarla, omalizumab ve mepolizumab dahil olmak üzere tedavi edilen şiddetli astım veya CSU hastalarını içermektedir. Birincil sonuç ölçümleri serum IgE seviyeleri, eozinofil sayıları, ürtiker aktivite puanları (UAS) ve astım kontrol testi puanları (ACT) idi. Veriler istatistiksel yazılım kullanılarak analiz edildi ve Wilcoxon işaretli sıra testi kullanılarak karşılaştırıldı. Biyolojik ajanlarla tedavi edilen şiddetli astım veya kronik ürtikerli 61 hastayı inceledik. Astımlı hastalar, omalizumab ile yıllık ortalama atak oranında 4'ten 0'a ($p<0.001$) ve mepolizumab ile 6'dan 1'e ($p<0.001$) önemli bir azalma gösterdi. Eozinofil sayıları ve ACT puanları mepolizumab ile önemli ölçüde azaldı ($p<0.001$). Omalizumab'dan mepolizumab'a geçiş yapan altı hasta, tedavi değişikliğinin ilk altı ayında şiddetli astım atakları yaşamadı. CSU'lu hastalar omalizumab'a önemli bir yanıt gösterdi ($p<0.001$). Toplam IgE seviyeleri, eozinofil sayıları, UAS ve ACT puanları da dahil olmak üzere çeşitli belirteçlerde önemli iyileşmeler gözlemledik, bu da bu tedavilerin her iki durumun semptomlarını etkili bir şekilde yönetebileceğini göstermektedir. Bu bulgular, bu tedavilerin etkili terapötik seçenekler olarak kullanılmasının potansiyel faydalarını vurgulamaktadır.
Anahtar Kelimeler: Astım, Kronik Ürtiker, Mepolizumab, Omalizumab, Immünglobulin E

ORCID ID of the authors: PA.0000-0002-0844-6352, TE. 0000-0002-3143-2442

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Correspondence: Pamir ÇERÇİ-- Division of Immunology and Allergy, Department of Internal Medicine/ Eskisehir City Hospital, Eskisehir, Türkiye
e-mail: pamir.cerci@saglik.gov.tr

1. Introduction

Biological therapy agents, such as omalizumab and mepolizumab, have become cornerstone treatments in recent years, offering significant improvements in the quality of life for patients with severe asthma and chronic spontaneous urticaria (CSU) (1, 2). These agents present an alternative to systemic corticosteroids, effectively controlling symptoms and enhancing patients' well-being. Omalizumab, a humanized monoclonal antibody, is approved for treating moderate to severe allergic asthma and CSU. It functions by binding to circulating free immunoglobulin E (IgE) antibodies, thereby reducing IgE-mediated immune responses pivotal to CSU pathogenesis (3, 4). A study evaluating response rates, baseline IgE levels, and total IgE levels after omalizumab treatment in patients with CSU found that alterations in IgE levels can predict the outcome of omalizumab treatment (5). In another study, Tamer et al. demonstrated that omalizumab reduced serum total eosinophil levels in a significant proportion of CSU patients, indicating that serum eosinophil count might be a valuable marker for guiding treatment decisions (6).

A study investigating changes in serum total IgE in severe asthmatics over one year with measurements repeated every two months reported that most of the variability was due to differences between patients, while the within-patient variability in total IgE levels was quite limited (7). Another study reported that the response to omalizumab is better predicted by the ratio of total IgE levels at week four to baseline levels, especially in patients with a ratio exceeding 2 (8). Furthermore, omalizumab has been linked to improved lung function and reduced eosinophil counts in patients with uncontrolled asthma (9). However, not all patients achieve symptom control and reduced exacerbations with omalizumab. The OSMO study indicated that patients with uncontrolled severe eosinophilic asthma (SEA) who switch from omalizumab to mepolizumab might experience notable improvements in asthma control and reduced exacerbations (10). An exploratory post hoc analysis of the OSMO study showed that patients with high baseline eosinophil levels might benefit from switching to mepolizumab from omalizumab, resulting in improved asthma control, quality of life, and fewer exacerbations (11).

Mepolizumab, another biological agent, inhibits interleukin-5 (IL-5) and is approved for treating SEA in adults and children aged six and above. It reduces blood eosinophil levels, a key contributor to asthma pathogenesis (12). This approach has been shown to improve asthma control and reduce the frequency of exacerbations (13, 14). Both post hoc analyses and prospective clinical studies indicate that baseline blood eosinophil counts can predict disease morbidity and identify patients likely to benefit most from mepolizumab (15, 16).

Given the profound impact of these biological agents on patient outcomes, there is a growing interest in understanding their clinical efficacy and safety. This study aims to gather real-life data on omalizumab in patients with severe allergic asthma and CSU, and mepolizumab in patients with SEA. Additionally, it seeks to assess changes in IgE levels and eosinophil counts during these treatments.

2. Materials and Methods

2.1 Study design and participants

This multicenter, retrospective study encompassed 36 adults with severe persistent asthma treated with omalizumab or mepolizumab and 25 patients with CSU treated with omalizumab. Six patients with severe persistent allergic asthma unresponsive to omalizumab underwent a wash-out period of three months before transitioning to mepolizumab. The primary objective was to assess changes in IgE concentrations and peripheral eosinophil counts. The secondary objective aimed to gather real-life data on the efficacy of these biological agents.

Atopy was assessed using skin prick tests and specific IgE measurements, with the puncture method employed. A mean wheal diameter ≥ 3mm compared to the negative control was considered positive. Specific IgE levels were determined using ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) for

prevalent allergens, with levels ≥ 0.35 kU/L indicating positivity.

CSU and asthma were diagnosed based on the EAACI/GA²LEN/EDF/WAO and Global Initiative for Asthma (GINA) guidelines, respectively (17, 18). CSU was identified by the recurrence of wheals, angioedema, or both for over six weeks, while asthma was determined through a combination of clinical history, physical examination, and spirometry findings, with severe asthma characterized as uncontrolled despite maximum medication adherence or exacerbation upon dose reduction.

Patients with CSU had been previously treated with high-dose oral antihistamines for at least 24 weeks but remained symptomatic despite treatment. Total IgE levels, eosinophil counts, eosinophil percentages, and urticaria activity scores were evaluated before and during omalizumab therapy. Clinical response and disease severity were evaluated using the UAS7, calculated from the weekly urticaria activity score (17). Medical records of the patients were reviewed retrospectively.

The administration of mepolizumab and omalizumab was sanctioned based on the criteria delineated in the Turkey Social Security Institution Health Application Communique. Criteria for omalizumab administration included severe persistent allergic asthma, body weight between 20-150 kg, sensitization to at least one perennial allergen, and serum IgE levels between 30-1500 IU/ml, and to have shown an inadequate response to high-dose corticosteroid, long-acting beta 2 agonist and/or leukotriene receptor antagonist therapy. The dose was determined by pre-treatment total IgE level and body weight. For mepolizumab, criteria included uncontrolled asthma requiring regular systemic steroid use for at least six months despite high-dose inhaled corticosteroids and long-acting beta-agonist inhalers for at least one year and an eosinophil count of ≥300 cells/µl (≥150 cells/µl for patients on regular systemic steroids). Patients with a history of omalizumab failure and an eosinophilic phenotype were switched to mepolizumab treatment. Clinical parameters, such as the Asthma Control Test (ACT) score, blood eosinophil count, and the frequency of asthma exacerbations, were obtained through a retrospective review of patient records. An exacerbation was characterized as a deterioration of asthma symptoms that necessitated oral corticosteroids (OCS) for at least three days per week and led to a significant decline in the asthma control test (ACT) score.

Routine screenings conducted during patient visits to various outpatient clinics in our hospital were used to assess total IgE levels and eosinophil counts. Total IgE levels and eosinophil counts were assessed when patients did not receive systemic steroids. Throughout the omalizumab and mepolizumab treatment period, changes in patients' regular controller medications, such as inhaled therapies, antihistamines, and leukotriene receptor antagonists, were adjusted based on individual patient needs and clinical responses. The time points are approximate, labeled as '6-month', '12-month', and '24-month'.

The Non-Interventional Clinical Research Ethics Committee of Eskişehir Osmangazi University, Turkey, approved this study (Approval Date: 13.07.2021, Approval Number: 2021 – 279/13).

2.2 Statistical Analysis

The data were inputted into the Statistical Package for Social Sciences software version 22.0 (SPSS Inc; Chicago, IL, USA) and analyzed using the same program. The Kolmogorov-Smirnov test was employed to determine the normality of the data distribution. For non-normally distributed data, median values were used. The mean and standard deviation (SD) of continuous variables were used to express data at baseline and after treatment with biological medications. The Wilcoxon two-sample test was used to compare results before and after treatment for comparative analyses of continuous variables. Comparisons among more than two groups were analyzed by Repeated Measures ANOVA. Categorical data were evaluated using the appropriate chi-square or Fisher's exact test. A P value of <.05

was considered to indicate statistical significance. Friedman's test was used for comparing time-varying effects. The standard deviations were reported as mean +- SD, and p-values below 0.001 were reported as p<0.001.

3. Results

We included 61 patients (57.4% female, median age 46 years). Among the participants, 59% (n=36) were administered a biological agent to treat severe asthma, and the remaining 41% (n=25) were treated with omalizumab for CSU. Of the patients receiving biologics for severe asthma, 19 were treated with omalizumab and 11 with mepolizumab. Six patients, initially treated with omalizumab, transitioned to mepolizumab due to an inadequate response to the initial treatment. The median treatment duration was 24 months for patients treated with omalizumab and 12 months for those treated with mepolizumab. Among the 36 patients who received a biological agent for asthma, 74.2% had allergic rhinitis, and 44.4% had chronic rhinosinusitis with nasal polyps (CRSwNP). Out of these, 28 patients were allergen-sensitive, while eight were non-atopic. These data are presented in Figure 1 and Table 1.

Table 1. Baseline Characteristics of Study Participants with Severe Asthma

	Treatment (n=36)		
	OMA	**Mepo**	**All Asthma Patients**
Number (n.)	25	11	36
Age, mean (SD) years	48.4 ± 15.0	51.8 ±10.6	49.5 ± 13.8
Female, n. (%)	13 (52.0%)	7 (63.6%)	20 (55.6%)
Sensitization to respiratory allergens (%)	25 (100%)	3 (27.3%)	28 (77.7%)
Allergic rhinitis, n. (%)	22 (88.0%)	3 (27.3%)	25 (69.4%)
CRSwNP, n. (%)	9 (36.0%)	7 (63.6%)	16 (44.4%)
Duration of asthma, mean (SD) years	8.4 ± 4.3	5.9 ± 3.2	7.6 ± 3.8
ACT score (Initial), mean (SD)	14.0 ± 3.1	13.2 ±3.7	13.8 ± 3.5
Exacerbation in the previous year, median (min.-max.)	4.0 (2-16)	6.0 (1-14)	5.0 (1-16)
Eosinophils (cell/µL) (Initial), mean (SD)	417.1 ± 347.8	2004.2 ± 1962.9	902.0 ± 450.4
Total IgE (kU/L) (Initial), median (min.-max.)	428.0 (42.4-2500.0)	504.0 (17.1-3095.0)	504.0 (17.1-3095.0)
Treatment duration, mean (SD) months	47.0 ± 36.8	15.0 ± 8.6	8.5 ± 6.1

Abbreviations: OMA, Omalizumab; Mepo, Mepolizumab; SD, Standard Deviation; µL, Microliter; kU/L, kilounits per liter; IgE, Immunoglobulin E.

Among the 25 patients receiving omalizumab for chronic idiopathic urticaria, 20% had allergic rhinitis, and 16% had asthma. Out of these, seven patients were allergen-sensitive, while 18 were categorized as non-atopic based on skin prick and specific IgE tests. These data are presented in Table 2.

Table 2. Baseline Characteristics of Study Participants with Chronic Spontaneous Urticaria

Treatment (n=25)	**Omalizumab**
Age, mean (SD) years	37.8 ± 13.6
Female, n. (%)	15 (60.0%)
Sensitization to any respiratory allergen (%)	7 (28.0%)
Duration of CSU, mean (SD) months	20.9 ± 8.5
UAS7 score (Initial), mean (SD)	33.5 ± 6.7
Eosinophils (cell/µL) (Initial), mean (SD)	164.3 ± 138.0
Total IgE (kU/L) (Initial), median (min.-max.)	166 (24.2-2109.0)
Treatment duration, mean (SD) months	20.9 ± 8.5

Abbreviations: n, Number; CSU, Chronic Spontaneous Urticaria; SD, Standard Deviation; µL: Microliter; kU/L, kilounits per liter; IgE, Immunoglobulin E; UAS7, Urticaria activity score-7.

The median annual attack rate for patients with asthma receiving omalizumab was 4 (minimum-maximum: 2-16). Post-treatment, this rate decreased to a median of 0 (minimum-maximum: 0-11) ($p<0.001$). Before treatment, patients with asthma receiving mepolizumab had a median annual attack rate of 6 (minimum-maximum: 1-14). This decreased to a median of 1 (minimum-maximum: 0-4) after treatment ($p<0.001$).

Patients with CSU showed a significant response to omalizumab treatment, especially at the 12 and 24-month marks, as evidenced by comparing the UAS-7 before and after treatment (Figure 2). Among these patients, 11 continued with omalizumab treatment as their symptoms consistently recurred upon treatment interruption but were manageable with continued therapy. In contrast, nine patients discontinued treatment after a median duration of 12 months (6-36) and did not experience urticaria attacks in the following period. We could not obtain current status information for three patients due to their absence from follow-up visits over the past six months. For two patients unresponsive to the standard 300mg dose of omalizumab given every 28 days, the dosage was adjusted to 450mg. Upon analysis without differentiating by diagnosis, we observed that the median IgE levels of all patients undergoing omalizumab treatment increased over the treatment duration (Figure 3).

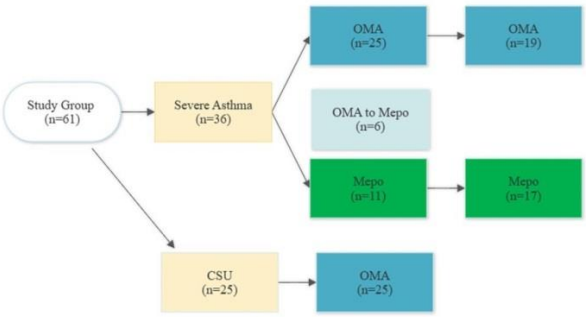

Figure 1. Flowchart of Patient Allocation and Treatment (OMA: Omalizumab, Mepo: Mepolizumab) Of the 61 patients in the study, 36 received a biological agent for severe asthma, with 19 treated with omalizumab and 11 with mepolizumab. Six patients initially received omalizumab but switched to mepolizumab due to an inadequate response. The remaining 25 patients were treated with omalizumab as a biological agent for chronic urticaria.

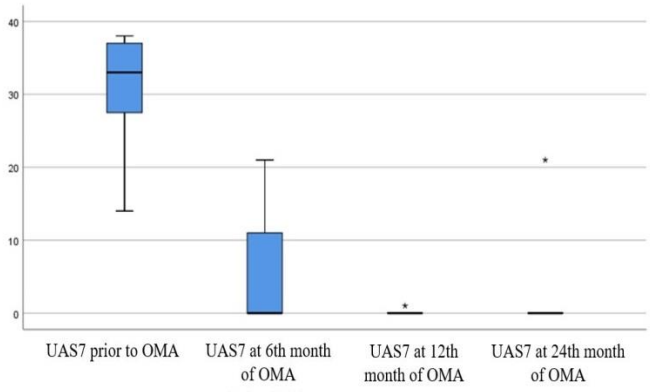

Figure 2. Change in Urticaria Activity Score Following Omalizumab Treatment. The graph shows the change in urticaria activity score (UAS) at different time points before and after treatment with omalizumab in patients with chronic idiopathic urticaria. The UAS ranges from 0 to 42, with higher scores indicating greater disease activity. The data are presented as mean ± standard deviation (SD) for each time point. The scores at 12 and 24 months after treatment were significantly lower than those at baseline, indicating a significant improvement in disease activity following omalizumab treatment.

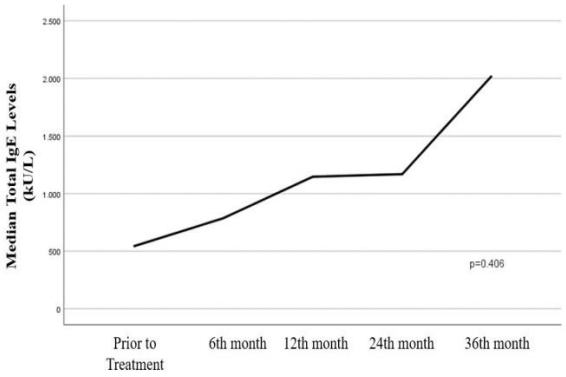

Figure 3. Median IgE Levels in Patients Treated with Omalizumab Over Time. Median IgE levels were measured at baseline and 6-month intervals during treatment with omalizumab. The line shows the median IgE levels (in kU/L) over time for all patients receiving omalizumab, regardless of diagnosis. A non-significant increase in median IgE levels over time was observed (p=0.406).

Table 3 showcases the variations in total IgE levels, eosinophil counts, percentages, and asthma control scores for the 17 patients with severe asthma treated with mepolizumab. While the patient's serum total IgE levels did not show a statistically significant alteration, there was a notable reduction in eosinophil counts and an enhancement in ACT scores ($p<0.001$). Six of the patients who transitioned from omalizumab to mepolizumab did not encounter severe asthma flare-ups in the initial six months post-switch. However, two patients began experiencing exacerbations after the sixth month of treatment. The attack frequency diminished for the other four patients. For those transitioning from omalizumab to mepolizumab, the median interim was three months (minimum-maximum: 2-6). For these five patients, the annual exacerbation rates averaged 12.5 ± 5.1 prior to initiating omalizumab, 7.3 ± 3.7 while on omalizumab, and 1.6 ± 1.5 during mepolizumab therapy.

Table 3. Changes in Total IgE, Eosinophil Levels, and Asthma Control Test Scores in Patients Treated with Mepolizumab

	Prior to Treatment		**3. month**		**6. month**		**12. month**		**24. month**		
	N	Median (Min-Max)	N	Median (Min-Max)	N	Median (Min-Max)	N	Median (Min-Max)	N	Median (Min-Max)	P*
Total IgE	17	504 (17-3095)	8	373 (30-1941)	14	150 (35-1404)	9	80 (18-1527)	4	239 (23-493)	0,706
Eos. x10^3	17	1080 (290-7414)	11	120 (70-786)	12	220 (50-410)	9	90 (50-400)	4	90 (70-160)	**<0.001**
ACT Score	16	13 (9-22)	15	22 (18-25)	12	24 (17-25)	9	25 (20-25)	4	24 (24-25)	**<0.001**

**p: Friedman's test (The analysis did not include the 24th month due to the low number of patients)*
Abbreviations: ACT, Asthma Control Test; Eos, Eosinophil; IgE, Immunoglobulin E.

Table 4 outlines the changes in total IgE levels, eosinophil counts, and asthma control test scores for patients with severe asthma undergoing omalizumab treatment. Significantly, there was a minor yet statistically relevant rise in the patient's serum total IgE levels ($p=0.029$), while eosinophil counts remained consistent with no marked variation ($p=0.887$). Clinically, the ACT scores displayed a pronounced enhancement, signaling improved asthma management, a statistically significant change ($p<0.001$).

Table 4. Changes in Total IgE, Eosinophil Levels, and Asthma Control Test Scores in Patients Treated with Omalizumab

	Prior to Treatment		3. month		6. month		12. month		24. month		
	N	Median (Min-Max)	N	Median (Min-Max)	N	Median (Min-Max)	N	Median (Min-Max)	N	Median (Min-Max)	P*
Total IgE	25	428.0 (42.0-2500.0)	18	530.5 (54.0-2900.0)	17	610.0 (76.0-3100.0)	16	681.5 (90.0-3500.0)	16	568.5 (67.0-4115.0)	**0.029**
Eos. x10^3	25	450.0 (70-1200.0)	18	400.0 (30.0-1100.0)	17	450.0 (100.0-1200.0)	16	410.0 (100.0-1400.0)	16	350.0 (50.0-1000.0)	0.887
ACT Score	25	14 (9-19)	18	17 (15-24)	17	20 (14-25)	16	21 (9-25)	16	23.5 (11-25)	**<0.001**

**p: Friedman's test*
Abbreviations: ACT, Asthma Control Test; Eos, Eosinophil; IgE, Immunoglobulin E.

Within our study cohort, we noted two instances of breast cancer and one case of chronic lymphocytic leukemia (CLL) among those treated with omalizumab. It is crucial to highlight that no definitive association existed between these malignancies and omalizumab treatment. For the two patients diagnosed with breast cancer, omalizumab treatment was not discontinued. Both patients were apprised of the situation, and after detailed discussions, they gave their informed consent to persist with the treatment. Conversely, the patient diagnosed with CLL had their treatment halted due to the necessity of chemotherapy.

4. Discussion and Conclusion

Our study emphasizes the efficacy of omalizumab for patients with severe allergic asthma and CSU, and mepolizumab for SEA management. These insights add to the expanding literature endorsing these biological agents.

We observed marked enhancements in clinical outcomes, especially among patients with elevated total IgE levels and eosinophilic inflammation. Ertas et al. proposed that serum total IgE levels might forecast the omalizumab response in CSU patients. Specifically, those with diminished serum IgE levels had a notably reduced likelihood of therapy responsiveness (5). Although our research did not identify a statistically significant uptick in IgE levels, we contend that an IgE increase does not inherently align with clinical decline. This perspective is congruent with Ertas et al.'s findings. Beyond its efficacy, our data highlighted a significant drop in eosinophil counts and diminished intrasubject variability in total IgE concentrations among omalizumab-treated patients. These findings align with previous research on the drug's mechanism of action (9, 19). Omalizumab is recognized for its selective targeting of Th2 inflammation, proficiently reducing eosinophil counts in both blood and sputum samples (20-22). Nevertheless, the precise mechanism underlying omalizumab's reduction of eosinophil counts remains debatable. It is hypothesized that the drug may have a direct effect or that reduced IgE levels and T-cell-derived cytokines may trigger eosinophil apoptosis (23). Omalizumab has been shown to improve asthma symptom control, enhance the quality of life, and reduce exacerbation rates in appropriately selected patients with persistent allergic asthma (24-26). In line with our observation of omalizumab's efficacy in diminishing the annual attack rate for severe allergic asthma patients, a recent real-world Turkish study showcased that integrating omalizumab into the standard care regimen led to marked reductions in oral corticosteroid usage, asthma medication inhalers, and short-acting rescue meds. This also correlated with fewer hospitalizations, emergency room visits, and unscheduled outpatient appointments (27). This study further highlighted the cost-effectiveness of omalizumab, underscoring its clinical, quality of life, and economic benefits in treating severe allergic asthma (27).

Our findings also advocate for mepolizumab as a potent treatment option for patients with severe asthma. By inhibiting IL-5, mepolizumab curtails eosinophil counts, mitigates airway inflammation, and augments lung functionality in severe asthma patients.

We observed a significant decrease in eosinophil counts in patients treated with mepolizumab, a finding consistent with previous studies that have demonstrated the drug's effectiveness in reducing eosinophilic inflammation in patients with severe asthma (14, 15, 24, 25).

For those with severe asthma, therapies involving omalizumab and mepolizumab notably curtailed asthma exacerbation rates, resonating with prior research (3, 4, 28). Our study also demonstrated that treatment with mepolizumab was associated with a significant reduction in eosinophil counts, which correlated with improved asthma control, as evidenced by higher ACT scores. These findings are consistent with previous studies demonstrating the efficacy of mepolizumab in reducing exacerbation rates and improving asthma control in patients with SEA (5, 6, 15, 29). However, in our research, mepolizumab-treated patients did not exhibit a marked shift in serum total IgE levels. This finding aligns with previous studies, which also reported that mepolizumab does not significantly influence IgE levels (24).

Multiple studies propose that patients with elevated baseline blood eosinophil counts or accompanying nasal polyps might reap enhanced clinical advantages by transitioning straight from omalizumab to mepolizumab (10, 11). Our study found that transitioning from omalizumab to mepolizumab for some patients with severe asthma resulted in observable clinical improvements. This finding aligns with previous studies suggesting the potential clinical benefits of switching to mepolizumab in patients who do not respond to omalizumab (11, 27).

Consistent with previous studies, omalizumab treatment has significantly reduced urticaria activity scores among CSU patients (25, 26). Our study also demonstrated that continued treatment with omalizumab was necessary to maintain symptom control in some patients, as discontinuation of treatment led to symptom recurrence in some cases. Furthermore, some patients required an increased dose of omalizumab to achieve symptom control, which aligns with previous studies reporting that higher doses may be necessary for some patients (7).

Our research identified two breast cancer cases and one chronic lymphocytic leukemia instance among omalizumab-administered patients. The relationship between omalizumab and malignancy has been a topic of interest in the medical community. A 5-year observational study involving 5007 omalizumab-treated and 2829 non-omalizumab-treated patients found similar incidence rates of primary malignancies between both groups (30). A disproportionality analysis within VigiBase identified 1380 reports of neoplasms associated with omalizumab, suggesting a potential association with a higher risk of malignancies (31). Contrarily, a Danish National Patient Registry study found no difference in cancer incidence rates between participants treated with omalizumab and those not treated (32). An analysis of pooled data from randomized, double-blind, placebo-controlled asthma trials further supported the lack of association between omalizumab use and malignancy (33). Given the mixed evidence, it is crucial to approach omalizumab cautiously, especially in patients with a history of cancer.

There are inherent limitations in our study that warrant consideration during interpretation. Its retrospective nature might infuse bias since data was not gathered prospectively, and treatment choices were not randomized. Given our study's retrospective design and the impediments from the COVID-19 pandemic, we could not undertake a quality-of-life evaluation. Such an assessment might have offered more profound insights into treatment impacts on daily living. Our limited sample size could curtail the extrapolation of our insights to a more expansive patient demographic with severe asthma and CSU. Additionally, the lack of a control group prevents us from making definitive conclusions about the efficacy of these treatments. Lastly, the unavailability of routine pulmonary function tests (PFTs), attributed to COVID-19 constraints, might constrain our lung function evaluation. However, some studies suggest that PFT parameters may not change significantly with

the treatments used in our study (14, 34). Therefore, although the lack of PFTs may limit our assessment of lung function, we believe our study still provides essential insights into the effectiveness of omalizumab and mepolizumab.

In conclusion, our findings support the effectiveness of omalizumab and mepolizumab in reducing asthma attacks and improving symptoms in patients with severe asthma and CSU. While baseline eosinophil and IgE levels may offer some insight into the clinical response, our data suggest that comprehensive clinical evaluation is necessary for monitoring treatment. Further research is needed to confirm these findings and better understand these treatments' long-term safety and efficacy.

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Ethics

Ethics Ethics Committee Approval: The study was approved by Eskisehir Osmangazi University Noninvasive Ethical Committee (Approval Date/ Number: 13.07.2021 /13)

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

Author Contributions: Idea/concept: P.C., T.E., Design: P.C., T.E., Data Collection: P.C., T.E., Data Processing: P.C., T.E., Analysis/Comment: P.C., T.E., Literature research/review: P.C., Writing: P.C., All authors discussed the results and contributed to the final manuscript.

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Research Article / Araştırma Makalesi

Retropubik Radikal Prostatektomi Operasyonunda Peroperatif Kanama Miktarını ve Kan Transfüzyonu İhtiyacını Etkileyen Faktörler

Factors Affecting Peroperative Bleeding Amount and Need for Blood Transfusion in Retropubic Radical Prostatectomy Operation

[1]Osman Gerçek, [1]Veli Mert Yazar, [1]Murat Cengizhan Atik, [2]Kutay Topal

[1]Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi, Üroloji Anabilim Dalı, Afyonkarahisar, Türkiye
[2]Afyonkarahisar Devlet Hastanesi, Üroloji Kliniği, Türkiye

Abstract: Intraoperative blood loss is one of the important complications of radical prostatectomy. Appropriate perioperative risk stratification may reduce the possibility of intraoperative blood transfusion. In this study, we aimed to reveal the risk factors that may cause bleeding. 180 patients who were diagnosed with prostate cancer by conventional transrectal ultrasonography biopsy (TRUS-Bx) and underwent retropubic radical prostatectomy (RP) were included in our study. The relationship between the mean blood loss during the operation and the clinical and pathological findings of the patient was examined. Factors that could affect the amount of bleeding and predict the amount of bleeding before the operation were tried to be revealed. The time between TRUS-Bx and RP was statistically significantly longer in patients with a large amount of bleeding (p=0.005). When the level of peroperative bleeding was compared with the TRUS-Bx and RP ISUP scores, both TRUS-Bx and RP ISUP values were statistically significantly higher in patients with high bleeding (>845 cc) (respectively; p=0.024, p<0.001). A 1-unit increase in the TRUS-Bx ISUP score was associated with an increase of 100.04 cc in the amount of peroperative bleeding. In the logistic regression analysis, the most important predictor for the amount of perioperative bleeding was RP ISUP grade (p=0.003). In high-stage patients, bleeding occurs more during the operation. In patients with an ISUP grade and a high biopsy tumor percentage, more careful dissection may reduce the amount of perioperative bleeding. It should be kept in mind that the cancer stage may be higher than the biopsy pathology in patients with a large amount of intraoperative bleeding.
Keywords: Prostate cancer, Bleeding, Prostatectomy

Özet: İntraoperatif kan kaybı radikal prostatektominin önemli komplikasyonlarından biridir. Perioperatif uygun risk sınıflamasının yapılması intraoperatif kan transfüzyonu ihtimalini azaltabilir. Biz bu çalışmada kanamaya neden olabilecek risk faktörlerini ortaya koymayı amaçladık. Çalışmamıza konvansiyonel transrektal ultrasonografi biyopsi (TRUS-Bx) ile prostat kanseri tanısı konulan ve retropubik radikal prostatektomi (RP) operasyonu gerçekleştirilen 180 hasta dahil edildi. Operasyonda gerçekleşen ortalama kan kaybı ile hastanın klinik ve patolojik bulgularının ilişkisi incelendi. Kanama miktarına etki edebilecek ve operasyon öncesi kanama miktarını öngörebilecek faktörler ortaya konulmaya çalışıldı. Kanama miktarı fazla olan hastalarda TRUS-Bx ile RP arasında geçen süre istatistiksel anlamlı olarak daha uzundu (p=0.005). Peroperatif kanama düzeyi ile TRUS-Bx ve RP ISUP skorlarının karşılaştırıldığında, kanama miktarı yüksek olan (>845 cc) hastalarda hem TRUS-Bx hem de RP ISUP değerleri istatistiksel olarak anlamlı daha yüksek izlendi (sırasıyla; p=0,024, p<0,001). TRUS-Bx ISUP skorunda 1 birimlik artış, peroperatif kanama miktarında 100.04 cc artışla ilişkili bulunmuştur. Lojistik regresyon analizinde peroperatif kanama miktarı için en önemli prediktör RP ISUP derecesiydi (p=0,003). Yüksek evre hastalarda operasyon sırasında kanama daha çok olmaktadır. ISUP derecesi ve biyopsi tümör yüzdesi yüksek olan hastalarda daha dikkatli bir diseksiyon, peroperatif kanama miktarını azaltabilir. Intraoperatif kanama miktarı fazla olan hastalarda kanser evresinin biyopsi patolojisine göre daha yüksek olabileceği unutulmamalıdır.
Anahtar Kelimeler: Prostat kanseri, Kanama, Prostatektomi

ORCID ID of the authors: OG. 0000-0002-8710-7171, VMY. 0000-0001-7885-1401, MCA. 0009-0001-6698-6007, KT. 0000-0001-7501-7251

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Correspondence: Osman GERÇEK-- Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi, Üroloji Anabilim Dalı, Afyonkarahisar, Türkiye
e-mail: osmangercek1989@hotmail.com

1. Giriş

Radikal prostatektomi klinik olarak lokalize prostat kanseri tedavisinde ana tedavi yöntemlerinden biridir. Radikal prostatektomide amaç, onkolojik olarak uzun dönemde en iyi sonuçları almak ve aynı zamanda erektil potans, üriner kontinans gibi fonksiyonel sonuçların korunmasıdır. Radikal prostatektomi operasyonu; açık, laparoskopik ve robotik olarak uygulanabilir. Halen intraoperatif kan kaybı radikal prostatektominin önemli komplikasyonlarından biridir (1). Prostatın zengin venöz ağından dolayı radikal retropubik prostatektomide kan kaybı fazla olmaktadır (2). Radikal prostatektomide ortalama olarak 450-750 ml kan kaybı olmaktadır. Hastalara %3.4-%3.8 oranında intraoperatif olarak kan transfüzyonu yapılmaktadır (3, 4). İntraoperatif kan transfüzyonunun alerji, enfeksiyon, hemoliz ve koagülopati gibi komplikasyonları mevcuttur (5, 6). Ayrıca kan transfüzyonu sonrası kanser rekürrensi, akut böbrek yetmezliği veya mortalite meydana gelebilir (7, 8). Perioperatif uygun risk sınıflamasının yapılması intraoperatif kan transfüzyonu ihtimalini azaltabilir. Yüksek kan kaybı ihtimali olan hastalarda daha dikkatli bir diseksiyon ve operasyon öncesi uygun kan hazırlığının yapılması olası komplikasyonları en aza indirmek için önemli gözükmektedir. Biz bu çalışmada kanamaya neden olabilecek risk faktörlerini ortaya koymayı amaçladık.

2. Gereç ve Yöntem

Bu çalışma Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi Hastanesi Üroloji Kliniği'nde yapılmıştır. Çalışmada örneklem büyüklüğü hesaplanmamış olup evrenin tamamına ulaşılmaya çalışılmıştır. Etik onay alındıktan sonra (Afyonkarahisar Sağlık Bilimleri Üniversitesi Klinik Araştırmalar Etik Kurulu, 2011-KAEK-2, 2023/351) verileri retrospektif olarak kaydettik. Çalışmamız Helsinki Deklarasyonu ilkelerine uygun olarak yapıldı.

Çalışmamıza, Mayıs 2017-Haziran 2023 tarihleri arasında üroloji polikliniğinde PSA yüksekliği, dijital rektal muayenede (DRM) şüpheli bulgu veya multiparametrik prostat manyetik rezonans görüntülemede (MpMR) malignite şüphesi saptanan, konvansiyonel transrektal ultrasonografi biyopsi (TRUS-Bx) ile prostat kanseri tanısı konulan ve açık retropubik radikal prostatektomi (RP) operasyonu gerçekleştirilen 180 hasta dahil edildi. Laparoskopik radikal prostatektomi yapılan hastalar çalışmaya dahil edilmedi. 8 hastanın operasyonu kullandığı antikoagülan veya antiagregan kesilmeden gerçekleştirildiği için çalışma dışı bırakıldı. Çalışmamıza lokal veya lokal ileri prostat kanseri nedeniyle ilk tedavi seçeneği cerrahi planlanan hastalar dahil edildi. Daha önce prostat kanseri veya başka nedenle pelvik radyoterapi, hormonoterapi veya kemoterapi alan ve bilinen kanama bozukluğu olan hastalar çalışma dışı bırakıldı.

Yaş, PSA (ng/ml), transrektal prostat hacmi (cc), PSA dansitesi, DRM bulguları, TRUS-Bx ISUP (International Society of Urological Pathology) derecesi, TRUS-Bx pozitif kor oranı, TRUS-Bx ortalama tümör hacmi, RP tümör lokalizasyonu, RP ISUP derecesi, RP tümör yüzdesi, TRUS-Bx ile RP arasında geçen süre, operasyon süresi (dk), operasyonda ortalama kan kaybı (cc), ekstrakapsüler yayılım, seminal vezikül invazyonu (SVI), lenfovaskülerinvazyon (LVI) perinöralinvazyon (PNI), cerrahi sınır pozitifliği, pelvik lenf nodu diseksiyonu (PLND) yapılıp yapılmadığı ve lenf nodu pozitifliği tarandı ve kaydedildi. TRUS-Bx ortalama tümör yüzdesi pozitif korların tümör yüzdeleri toplanıp, pozitif kor sayısına bölünerek hesaplandı. Gleason derecesinin RP'de artışı upgrade olarak belirtildi. Briganti nomogramı ile bireyselleştirilmiş lenf nodu pozitifliği riski yüksek olan (≥%5 ve üzeri) veya multiparametrik prostat manyetik rezonans görüntülemede (MpMR) ve Gallium (^{68}Ga) labeled prostatespecific membrane antigen positron emission tomography/computed tomography'de (PSMA-PET/CT) pozitif lenf nodu saptanan hastalara genişletilmiş pelvik lenf nodu diseksiyonu (ePLND) işlemi gerçekleştirildi (9, 10).

Hastaların RP operasyonu sırasında ortalama kan kaybı ve kan transfüzyonu yapılıp yapılmadığı kaydedildi. Çalışmamıza dahil edilen hastaların operasyon sırasında

kaydedilen ortalama kan kaybı değeri olan 845 cc'den az ve çok kanama olmak üzere 2 grup oluşturuldu. Postoperatif ihtiyacı olan hastalara kan transfüzyonu gerçekleştirildi. Postoperatif majör kanama veya hemodinamik instabilite nedeniyle tekrar opere edilen hastamız olmadı. Tüm operasyonlar benzer tecrübeye sahip cerrahlar tarafından, desenden teknik kullanılarak gerçekleştirildi.

Operasyonda gerçekleşen ortalama kan kaybı ile hastanın klinik ve patolojik bulgularının ilişkisi incelendi. Kanama miktarına etki edebilecek ve operasyon öncesi kanama miktarını öngörebilecek faktörler ortaya konulmaya çalışıldı.

İstatistiksel Analiz

Çalışma verilerinin istatistiksel analizi bilgisayar ortamında IBM SPSS (Statistical Package for the Social Sciences) version 20.0 programı ile yapıldı. Değişkenlerin normal dağılıma uygunluğu Kolmogorov-Smirnov (K-S) testi kullanılarak incelendi. İkili grupların karşılaştırılmasında; normal dağılım gösteren parametreler için Student's T testi, anormal dağılım gösteren parametreler için Mann-Whitney U testi uygulandı. Çok gözlü çapraz tabloların değerlendirilmesi Ki-kare testi ya da Fisher Exact testi ile yapıldı. Operasyonda ortalama kan kaybı ile farklı parametreler arası ilişkiler yerine göre Spearman korelasyon testi ve Pearson korelasyon testi ile değerlendirildi. Ortalama kan kaybının ortalama değeri olan 845 cc altı ve üstü kanama olarak 2 grup oluşturularak; kanama miktarını öngörmedeki bağımsız prediktörler enter yöntemi ile Binary lojistik regresyon analizi kullanılarak incelendi. Model uyumu için Hosmer-Lemeshow testi kullanıldı. $p<0,05$ olduğunda sonuçlar istatistiksel olarak anlamlı kabul edildi.

3. Bulgular

Çalışmaya dahil edilen 172 hastanın ortalama yaşı 65.08±5.63 olup gruplar arasında anlamlı fark saptanmadı (p=0.111). PSA, PSA dansitesi, prostat hacmi, TRUS-Bx pozitif kor oranı, TRUS-Bx ortalama tümör yüzdesi, operasyon süresi, RP tümör yüzdesi ve hacmi açısından gruplar arasında istatistiksel anlamlı fark yoktu (sırasıyla; p=0.803, p=0.491, p=0.084, p=0.647, p=0.069, p=0.059, p=0.131, p=0.278). Kanama miktarı fazla olan hastalarda TRUS-Bx ile RP arasında geçen süre istatistiksel anlamlı olarak daha uzundu (p=0.005) (Tablo 1).

DRM bulguları, RP tümör lokalizasyonu, SVI, LVI, PNI, PLND yapılmış olması ve lenf nodu pozitifliği açısından gruplar arasında istatistiksel anlamlı fark izlenmedi (sırasıyla; p=0.876, p=0.501, p=0.930, p=0.314, p=0.286, p=0.128, p=0.414). RP patoloji spesmenlerinde; tümör derecesi upgrade olan, extrakapsüler yayılımı olan, cerrahi sınır pozitifliği olan hastalarda istatistiksel olarak daha fazla kanama izlendi (p=0.001, p=0.022, p=0.014) (Tablo 2).

Peroperatif kanama düzeyi ile TRUS-Bx ve RP ISUP skorlarının karşılaştırıldığı çok gözlü çapraz tabloda; en sık karşılaşılan ISUP derecesi 1 olup, kanama miktarı yüksek olan (>845 cc) hastalarda hem TRUS-Bx hem de RP ISUP değerleri istatistiksel olarak anlamlı daha yüksek izlendi (sırasıyla; p=0,024, p<0,001) (Tablo 3).

Belirteçler arasında yapılan korelasyon analizinde peroperatif kanama miktarı ile TRUS-Bx ISUP, RP ISUP, Bx-RP arası geçen süre, TRUS-Bx tümör yüzdesi, RP tümör yüzdesi arasında anlamlı ve pozitif bir korelasyon olduğu saptandı (sırasıyla; r=0.266 p<0.001, r=0.447 p<0.001, r=0.269 p<0.001, r=0.192 p=0.012, r=0.151 p=0.048). Birbiriyle korele olduğu düşünülen diğer belirteçler tabloda ayrıntılı olarak belirtildi (Tablo 4).

TRUS-Bx ISUP skorunun, peroperatif kanama miktarına anlamlı düzeyde ve pozitif yönlü etkisi olduğu hipotezine dayanılarak iki veri lineer regresyon analizi (enter yöntemiyle) ile incelendi. Model istatistiksel olarak anlamlıydı (F=12.95, p<0.001) ve anlamlı oto-korelasyon sorunları olmadan (Durbin-Watson=1.72) peroperatif kanama miktarındaki varyansın %7.1'ini açıklayabildi. Doğrusal regresyon analizinde, TRUS-Bx ISUP skorunun peroperatif kanama miktarının tahmin etmede etkili bir belirteç olduğu saptandı. Standartize edilmiş regresyon katsayılarına (β) göre; TRUS-Bx ISUP skorunda 1 birimlik artış, peroperatif kanama miktarında, 681.87 cc sabit değerinin üzerinde

100.04 cc artışla ilişkili bulunmuştur (Tablo 5).

Peroperatif kanama miktarını etkileyen; radikal prostatektomi patoloji materyalinde olası bağımsız prediktörlerin sonuca en fazla katkısı olanı belirlemek için Binary lojistik regresyon analizi uygulandı. Peroperatif kanama miktarını öngören model anlamlıydı ($\chi2(8) = 6.538$, $p = 0.587$) ve reenkarserasyondaki varyansın %22'sini açıklayabiliyordu (Nagelkerke R2 = 0.220). Model kanaması düşük olanların %74.7'sini, kanama miktarı yüksek olanların %58.8'ini (toplamda %66.9) doğru tahmin etmişti. Peroperatif kanama miktarı için en önemli prediktör RP ISUP derecesiydi (p=0,003) (Tablo 6).

Tablo 1. Grupların Demografik, Klinik ve Patolojik Verileri

	Kanama Miktarı<845cc N=89	**Kanama Miktarı>845cc N=85**	**p**
Yaş (yıl)	65.76±5.55	64.39±5.65	0.111
PSA (ng/ml)	9*	8.03*	0.803
PSA Dansitesi (%)	20*	22.3*	0.491
Prostat Hacmi (cc)	45.62±22.96	40.89±24.47	0.084
TRUS-Bx Pozitif Kor Oranı (%)	34.80±23.67	37.17±25.86	0.647
TRUS-Bx Ortalama Tümör Yüzdesi (%)	32.44±22.85	38.15±22.64	0.069
Operasyon Süresi (dk)	132.47±25.23	142.76±32.53	0.059
TRUS-Bx ile RP arasında geçen süre (gün)	48.46±26.62	64.65±41.20	**0.005**
RP Tümör Yüzdesi (%)	10*	15*	0.131
RP Tümör Hacmi (cc)	2.84*	3.84*	0.278

(:median, PSA: prostat spesifik antijen, TRUS-Bx: Transrektal ultrasonografi-biyopsi, RP: radikal prostatektomi)*

Tablo 2. Grupların Demografik, Klinik ve Patolojik Verileri

	Kanama Miktarı < 845cc N=89 n %	**Kanama Miktarı > 845cc N=85 n %**	**p**
DRM			
Benign	44 (50.6)	44 (51.8)	0.876
Malign	43 (49.4)	41 (48.2)	
Upgrade			
Yok	74 (85.1)	54 (63.5)	**0.001**
Var	13 (14.9)	31 (36.5)	
RP Tümör Lokalizasyon			
Sağ	9 (10.3)	6 (7.1)	0.501
Sol	8 (9.2)	5 (5.9)	
Bilateral	70 (80.5)	74 (87)	
Extrakapsüler Yayılım			
Yok	55 (63.2)	45 (52.9)	**0.022**
Var	32 (36.8)	40 (47.1)	
SVI			
Yok	65 (74.7)	64 (75.3)	0.930
Var	22 (25.3)	21 (24.7)	
LVI			
Yok	71 (81.6)	64 (75.3)	0.314
Var	16 (18.4)	21(24.7)	
PNI			
Yok	47 (54)	39 (45.9)	0.286
Var	40 (46)	46 (54.1)	
Cerrahi Sınır Pozitifliği			
Yok	69 (79.3)	53 (62.4)	**0.014**
Var	18 (20.7)	32 (37.6)	
PLND			
Yapılmadı	50 (57.5)	39 (45.9)	0.128
Yapıldı	37 (42.5)	46 (54.1)	

Lenf Nodu Pozitifliği			
Yok	70 (80.5)	64 (75.3)	0.414
Var	17 (19.5)	21 (24.7)	

(DRM: dijital rektal muayene, RP: radikal prostatektomi, SVI: seminal vezikül invazyonu, LVI: lenfovasküler invazyon, PNI: perinöralinvazyon, PLND: pelvik lenf nodu diseksiyonu)

Tablo 3. Hastaların Biyopsi ve Radikal Prostatektomi ISUP Skorları ile Operasyon Kanama Miktarının İlişkisi

	Kanama Miktarı < 845cc N=89 n %	**Kanama Miktarı > 845cc N=85 n %**	**p**
TRUS-Bx ISUP			
1	65 (74.7)	43 (50.6)	**0.024**
2	12 (13.8)	23 (27.1)	
3	5 (5.7)	9 (10.6)	
4	5 (5.7)	9 (10.6)	
5	0 (0)	1 (1.2)	
RP ISUP			
1	56 (64.4)	28 (32.9)	**<0.001**
2	20 (23)	26 (30.6)	
3	7 (8)	14 (16.5)	
4	3 (3.4)	13 (15.3)	
5	1 (1.1)	4 (4.7)	

(TRUS-Bx: Transrektal ultrasonografi-biyopsi, RP: radikal prostatektomi, ISUP: International Society of Urological Pathology)

Tablo 4. Demografik ve klinik Verilerin Korelasyon Analizi

		Kanama Miktarı (cc)	**PSA (ng/ml)**	**Prostat Hacmi (cc)**	**TRUS-Bx ISUP**	**RP ISUP**	**Bx-RP Geçen Süre**	**Bx Pozitif Kor Oranı**	**Bx Tümör Yüzdesi**	**RP Tümör Yüzdesi**	**Op. Süresi (dk)**
Kanama Miktarı	r										
	p										
PSA (ng/ml)	r	0.041									
	p	0.595									
Prostat Hacmi (cc)	r	-0.131	0.063								
	p	0.088	0.414								
TRUS-Bx ISUP	r	0.266	0.264	-0.71							
	p	**<0.001**	**<0.001**	0.356							
RP ISUP	r	0.447	0.416	0.027	0.707						
	p	**<0.001**	**<0.001**	0.723	**<0.001**						
Bx-RP Geçen Süre	r	0.269	0.045	-0.49	0.008	0.026					
	p	**<0.001**	0.554	0.523	0.921	0.735					
Bx Pozitif Kor Oranı	r	0.60	0.328	-0.125	0.310	0.329	0.093				
	p	0.438	**<0.001**	0.103	**<0.001**	**<0.001**	0.224				
Bx Tümör Yüzdesi	r	0.192	0.312	-0.142	0.251	0.385	0.183	0.578			
	p	**0.012**	**<0.001**	0.063	**0.001**	**<0.001**	**0.016**	**<0.001**			
RP Tümör Yüzdesi	r	0.151	0.389	-0.090	0.324	0.432	-0.008	0.494	0.539		
	p	**0.048**	**<0.001**	0.239	**<0.001**	**<0.001**	0.916	**<0.001**	**<0.001**		
Op. Süresi (dk)	r	0.130	0.117	-0.009	0.238	0.217	0.057	-0.108	-0.016	0.108	
	p	0.089	0.125	0.911	**0.002**	**0.004**	0.458	0.157	0.839	0.157	

(PSA: prostat spesifik antijen, TRUS-Bx: Transrektal ultrasonografi-biyopsi, RP: radikal prostatektomi, Op: operasyon)

Tablo 5. TRUS-Bx ISUP Skoru ile Peroperatif Kanama Miktarının Lineer Regresyon Analizi

Değişkenler	**B**	**Standart hata**	**β**	**t**	**p**	**%95 Güven Aralığı**
(Sabit)	681.87	52.89	-	12.89	**<0.001**	577.45to786.29
Kanama Miktarı (cc)	100.04	27.79	0.266	3.60	**<0.001**	45.18 to154.91

Bağımlı değişken: Peroperatif kanama miktarı (cc)

R:0.266 **$R^{2:}$0.071** **F: 12.95** **p<0.001** **Durbin-Watson: 1.72**

(TRUS-Bx: Transrektal ultrasonografi-biyopsi

Tablo 6. Peroperatif Kanama Miktarına Etki Eden Radikal Prostatektomi Patoloji Bulgularının Lojistik Regresyon Analizi

Risk Faktörü	**Peroperatif Kanama Miktarı (cc)**	
	RR (%95 GA)	**p değeri**
RP ISUP	1.264-3.124	**0.003**
Upgrade	0.618-3.632	0.371
RP Tümör Lokalizasyonu	0.606-1.890	0.814
RP Tümör Hacmi (cc)	0.982-1.010	0.544
RP Tümör Yüzdesi	0.973-1.022	0.835
Extrakapsüler Yayılım	0.676-3.674	0.293
SVI	0.089-0.816	0.020
LVI	0.398-2.729	0.932
PNI	0.313-1.522	0.358
Cerrahi Sınır Pozitifliği	0.713-4.664	0.210
PLND Yapılması	0.660-3.855	0.300
Lenf Nodu Pozitifliği	0.271-2.080	0.582

(RP: radikal prostatektomi, ISUP: International Society of Urological Pathology, SVI: seminal vezikül invazyonu, LVI: lenfovasküler invazyon, PNI: perinöral invazyon, PLND: pelvik lenf nodu diseksiyonu, RR: estimated relative risk showed by odds ratio, GA: güven aralığı)

4. Tartışma ve Sonuç

Cerrahi operasyonların en önemli sorunlarından birisi operason sırasında veya sonrasında meydana gelen kanamadır. Radikal prostatektomi gibi büyük cerrahi prosedürler için de bu sorun geçerlidir. Peroperatif kanama cerrahi alanı kirletmekte ve cerrahın işini zorlaştırmaktadır (11). İntraoperatif kanama operasyon süresini uzatmakta ve morbiditeyi artırmaktadır. Radikal prostatektomi operasyonunda, kanamayı durdurmak için kullanılan hemostatik girişimler nörovasküler demete hasar verebileceğinden dolayı postoperatif fonksiyonel sonuçları olumsuz etkilemektedir (12). Radikal prostatektomi sırasında kanamanın odağı değişkenlik gösterebilir. Genellikle venöz yapıların yaralanmasına bağlı meydana gelir. Ayrıca lenfadenektomi yapıldığı sırada hipogastrik arterin dallarının yaralanmasına bağlı da kanama görülebilir (13).

Yapılan çalışmalarda radikal prosatektomi sırasında kanamayı etkileyen birden fazla faktör tespit edilmiştir. Bunlar arasında; cerrahın deneyimi, intraperitonel veya ekstraperitoneal yaklaşımın seçilmesi, nörovaskülerin demetin korunması, genel anestezi uygulanması, neoadjuvan hormonoterapi uygulanması, prostat boyutu, vücut kitle indeksi ve operasyon süresi sayılabilir (11, 14, 15, 16).

Bazı araştırmacılar radikal prostatektomi yapılacak olan hastaların peroperatif kan transfüzyonu ihtiyacı için prediktif faktörler üzerinde çalışmalar yapmışlardır. Dash ve arkadaşlarının yaptığı çalışmada, radikal prostatektomi yapılan 1123 hastanın prospektif incelemesinde hastaların %9.3'ünde kan transfüzyonu ihtiyacı olmuştur. Bu çalışmada prostat hacmi, cerrahın deneyimi, genel anestezi uygulanmış olması ve neoadjuvan hormonoterapi uygulamasını peroperatif kan transfüzyonu yapılmasını etkileyen faktörler olarak belirtmişlerdir (16).

Chan ve arkadaşları yaptığı bir çalışmada prostat volümü büyük olan hastalarda kanamanın daha fazla olduğunu göstermişlerdir (17). Bizim çalışmamızda prostat biyopsisindeki tümör yüzdesi , ISUP derecesi ve biyopsi ile cerrahi arasında geçen süre peroperatif kanamayı etkileyen faktörler olarak bulunmuştur. Diğer çalışmaların aksine çalışmamızda prostat hacmi ile kanama arasında istatiksel olarak anlamlı bir fark saptanmadı.

Çalışmamızda peroperatif kanama miktarının fazla olduğu hastaların radikal prostatektomi patoloji spesmenlerinde ekstrakapsüler yayılım ve cerrahi sınır pozitifliğinin istatiksel olarak anlamlı şekilde fazla olduğu saptanmıştır. Bu durum, yüksek evre hastalarda kanama miktarının daha fazla olması ve dolayısıyla bu hastalarda ekstrakapsüler yayılım ve cerrahi sınır pozitifliğinin daha fazla beklenmesi ile açıklanabilir.

Eroğlu ve arkadaşları 290 hasta üzerinden yaptıkları bir çalışmada, transrektal biyopsi ile radikal prostatektomi arasında süre uzadıkça tümör evresinde yükselme olduğunu saptamışlardır (18). Bizim çalışmamızda ise biyopsi ile cerrahi arasında süre uzadıkça peroperatif kanama miktarının arttığını saptadık. Bu süre uzadıkça tümör evresinin artmasına bağlı olarak veya biyopsi sonrası meydana gelen periprostatik fibrozisin diseksiyonu zorlaştırabileceğini ve buna bağlı olarak mikrokanamaların artabileceği düşünülebilir.

Bir çok malignitede yeni damar oluşumları meydana gelmektedir. Tümör hücreleri büyümek ve metastaz yapmak için ya normal damarlardan ya da yeni oluşan damarsal yapılardan sisteme geçmektedir (19, 20). Bizim çalışmamızda da biyopsi spesmenlerinde tümör yüzdesi arttıkça peroperatif kanama miktarında artış meydana geldiği saptanmıştır. Bu korelasyonun tümör yüzdesi arttıkça neovaskülarizsyonun artmasına ve buna bağlı olarak peroperatif kanamayı etkilemesinden kaynaklandığı düşünülebilir.

Çalışmamızın bazı kısıtlamaları bulunmaktadır. Bu kısıtlılıklar; tek merkezli bir çalışma olmasına bağlı olarak hasta sayısının az olması ve kanama miktarı

ölçümünde intraoperatif anestezi tarafından hesaplanan miktar kullanılması sayılabilir. Bu hesaplamada idrar, lenf ve yıkama sıvıları toplam miktardan düşülmüş olsa da değerlendirme subjektif olabilmektedir. Çalışmamızın güçlü yanları ise; iyi bir hasta kaydı tutulmasına bağlı olarak cerrahi ve patolojik verilerin uygun olarak tespit edilmesi, operasyonların yakın cerrahi tecrübeye sahip cerrahlar tarafından yapılması ve lojistik regresyon analizi, lineer regresyon analizi gibi istatistiksel yöntemlerin kullanılmasıdır. Daha yüksek hasta serileriyle ve farklı cerrahi yöntemlerle yapılacak olan çalışmaların literatüre katkı sağlayacağını düşünmekteyiz.

Sonuç olarak radikal prostatektomi planlanan, prostat biyopsisi patolojisinde ISUP derecesi yüksek saptanan hastalarda preoperatif uygun kan hazırlığının yapılmasını önermekteyiz. ISUP derecesi ve biyopsi tümör yüzdesi yüksek olan hastalarda daha dikkatli bir diseksiyon, peroperatif kanama miktarını azaltabilir. Intraoperatif kanama miktarı fazla olan hastalarda kanser evresinin biyopsi patolojisine göre daha yüksek olabileceği unutulmamalıdır.

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Research Article / Araştırma Makalesi

Demographic Features And Allergic Sensitization of Patients with Respiratory Symptoms

Solunumsal Semptomları olan Hastaların Demografik Özellikleri ve Alerjik Duyarlılıkları

Müge Olgaç

Division of Immunology and Allergic Diseases, Seyrantepe Hamidiye Etfal Research Hospital, Istanbul, Turkiye

Abstract: The prevalence of allergic airway diseases are increasing worldwide. Adressing the responsible allergen is crucial to take precautions and treat patients. The aim of this study is to evaluate the demographic and clinical features of patients with suspected respiratory allergies. Medical reports of adult patients admitted to outpatient clinic of immunology and allergic diseases were retrospectively screened. Patients those had at least one of the following complaints and/or symptoms of rhinorhea, nasal itching, sneezing, nasal obstruction, shortness of breath, chest tightness, phlegm, cough, itchy eyes were recruited to study. Demographic and clinical features were recorded. Atopy status was determined with skin prick test and/or serum specific IgE levels. Of the 986 patients recruited, majority was female (73.32%). 70.38 % patients had rhinitis, 14.40 % had patients rhinitis and asthma, 3.54 % patients had asthma, 11.66% patients had nonspesific airway symptoms. Atopy was determined in 426 (43.20 %) patients, house dust mite (HDM) and Parietaria were the most frequent allergens. Almost half of the patients with rhinitis and asthma were atopic (48.32%, 51.97%, respectively). Patients those had hypersensitivity to Parietaria, a weed pollen, had perennial symptoms. In conclusion, detection of underlying cause of airway diseases is an important step in managing the disease. In this study HDM and Parietaria were the most frequently determined allergens, both yielded perennial symptoms revealing the importance of continuous treatment through the year.
Keywords: Allergic rhinitis, Asthma, House dust mite, Parietaria, Respiratory allergies, Skin prick test

Özet: Alerjik havayolu hastalıklarının prevalansı tüm dünyada artmaktadır. Hastaların tedavilerini ve gereken önlemleri belirlemek için sorumlu alerjeni saptamak önemlidir. Bu çalışmada respiratuar alerji şüphesi olan hastaların demografik ve klinik özelliklerinin araştırılması amaçlanmıştır. İmmunoloji ve alerji hastalıkları polikliniğine başvurmuş erişkin hastaların tıbbi kayıtları retrospektif olarak incelendi. Burun akıntısı, burun kaşıntısı, hapşırma, burun tıkanıklığı, nefes darlığı göğüste sıkışma, balgam çıkarma, öksürük, göz kaşıntısı gibi semptom ve/veya yakınmalardan en az biri olan hastalar çalışmaya dahil edildi. Hastaların demografik ve klinik özellikleri kaydedildi. Atopi durumu deri prik testleri ve/veya serum spesifik IgE tayini ile yapıldı. Çalışmaya dahil edilen 986 hastanın çoğu (%73.32) kadındı. Hastaların %73.38'inde rinit, %14.4'ünde rinit ve astım, %3.54'ünde astım, % 11.66'sında nonspesifik havayolu semptomları bulunmaktaydı. 426 (%43.20) hasta atopikti, ev tozu akarı ve Parietaria en sık saptanan alerjenlerdi. Rinit ve astım hastalarının yaklaşık yarısında atopi mevcuttu. (sırasıyla %48.32, %51.9). Bir yabani ot poleni olan Parietaria'ya karşı aşırıduyarlılık tespit edilen hastalarda yakınmalar perennialdi. Sonuç olarak havayolu hastalığı altta yatan sebebini bulmak hastalık yönetimi için önemli bir basamaktır. Bu çalışmada evtozu akarı ve Parietaria en sık saptanan alerjenler olup, her ikisi de perennial yakınmalara sebep olmaktadır. Bu bulgu, tedavinin yıl boyu devam etmesinin önemini göstermektedir.
Anahtar Kelimeler: Alerjik rinit, Astım, Ev tozu akarı, Parietaria, Havayolu alerjileri, Deri prik test

ORCID ID of the authors: M:O. 0000-0001-7802-4326

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Correspondence: Müge OLGAÇ - Division of Immunology and Allergic Diseases, Seyrantepe Hamidiye Etfal Research Hospital, Istanbul, Turkiye
e-mail:drmugeolgac@yahoo.com.tr

1. Introduction

Indoor and outdoor allergens are proteins that may induce IgE synthesis in sensitive patients. Sensitization to indoor and outdoor allergens together with exposure is a risk factor for allergic airway diseases such as asthma and allergic rhinitis(AR) (1).

Asthma is a chronic respiratory disease characterized by variable symptoms of wheezing, cough, shortness of breath, chest tightness with a marked heterogeneity in aetiology, pathophysiology and clinical aspects (2), based on clinical features and pathophysiological mechanisms different asthma subtypes have been identified. These subtypes of certain clusters with similar demographic, clinical and pathophysiological characteristics are called asthma phenotypes (3, 4).

Allergic asthma is most easily recognized asthma phenotype that may be associated with family history and concomitant other allergic diseases such as allergic rhinitis, atopic dermatitis, eczema food/drug allergies (2).

Rhinitis is defined as having at least one of the symptoms: rhinorrhea, nasal itching and nasal congestion. When rhinitis is induced by an immunoglobulin IgE-mediated inflammation of the nasal mucous membranes following allergen exposure it is defined as AR (5, 6).

The prevalence of allergic airway diseases are increasing worldwide, yielding a substantial socioeconomic loss and deterioration in the quality of life for patients. In order to reduce burden of allergic diseases, early disease diagnosis, taking precautions, and effective treatment are necessary (7, 8).

The primary aim of this study was to evaluate the demographic and clinical features of patients referred to outpatient clinic of immunology and allergy with complaints and/or symptoms of airway diseases. Secondary aim of was to determine the presence of atopy and clinical compatibility of sensitized allergens by means of symptomatology and seasonal pattern.

2. Materials and Methods

2.1 Study Design

Medical reports of adult patients who admitted to an outpatient clinic of Allergy and Immunology Department between January 2021–June 2022 were retrospectively screened. Patients those had at least one of the following complaints and/or symptoms such as rhinorhea, nasal itching, sneezing, nasal obstruction, shortness of breath, chest tightness, phlegm, cough, itchy eyes were recruited to study. Demographic and clinical features were reported.

Atopy was defined as at least 1 positive skin prick test (SPT) result or positive specific IgE (ssIgE) to common aeroallergens. A positive skin prick test was defined as a mean wheal diameter at least 3 mm larger than the negative control with surrounding erythema (9). SsIgE positivity was defined as a value of 0.35 kU/L or more (10). Polysensitization was defined if more than one allergen was present.

The visual analogue scale (VAS) were used to assess the severity of AR. VAS symptom scores ranged from “nasal symptoms, not at all bothersome” (0 cm) to “nasal symptoms, extremely bothersome” (10 cm). VAS below 5cm were defined as mild rhinitis and those equal to or above 5 cm defined as moderate/severe rhinitis. AR is also defined as seasonal and/or perennial according to distribution of symptoms throughout the year (5, 11).

The degree of asthma control was assessed with the Asthma Control Test (ACT). Having an ACT score of less than 20 was defined as uncontrolled asthma and asthma severity is assessed from the level of treatment required to control symptoms and exacerbations (2, 12).

Patients with any data lacking were not included to the study.

Ethical approval was obtained from the Seyrantepe Hamidiye Etfal Sağlık

Uygulamaları ve Araştırma Merkezi Ethics Committee (Date: 07/05/2022, No.3606).

2.2. Statistical analysis

Statistical analysis was performed by SPSS.25 version. Categorical variables were summarized as frequencies and percentages. Continuous variables were given as mean and standard deviations or median (IQR) according to the distribution of the data. The Wilcoxon test was used for comparison of data that were not normally distributed. Mann- Whitney U test and Kruskal-Wallis test was conducted to evaluate the different groups. In all analyses, p values less than <0.05 were considered as statistically significant.

3. Results

3.1. Clinical and demographic features of the patients

3009 patients were screened and 986 patients found eligible to the study. The ages of patients ranged from 18 to 82 years (mean: 36.74± 13.37 years) and 723(73.32%) patients were female. 694 (70.38 %) patients had rhinitis, 142 (14.40 %) had patients rhinitis and asthma, 35 (3.54 %) patients had asthma, 115 (11.66%) patients had nonspesific airway symptoms and were not diagnosed as neither asthma nor rhinits. Of the 115 patients, 50 patients had chronic cough without any concomitant allergic or occupational airway disease. Others had various complaints/ symptoms such as posterior rhinnorhea, phlegm, conjuctivitis, sore throat frequent pharyngitis.

Of the rhinitis patients, 404 (48.32 %) patients were atopic and were defined as AR patients as stated above. According to AR severity classification, 119 patients (29.45 %) had mild AR, while 285 patients (70.54 %) had moderate-severe AR. Symptoms were perennial in 358 (88.61 %) patients and 37 (9.15%) of them were having seasonal exacerbations, 46 (11.38 %) patients had only seasonal AR.

51.97% of asthmatic patients had positive allergy tests and they were defined as allergic asthma patients. According to severity of asthma 147(83.52%) patients had mild asthma, 20 (11.36%) patients had moderate asthma, 10 (5.68%) patients had severe asthma.

Childhood onset of symptoms were detected in 15.21 % of all patients.

3.2. Atopy status and distribution of allergen sensitization

Atopy was detected in 426 (43.29 %) patients, house dust mite (HDM) was the most frequent allergen (33.87 %), while pollen hypersensitivity was detected in 14.80 %, mold in 5.37% and animal dander in 2.83 % of the patients. Having a positive SPT/ssIgE with 2 or more allergens is defined as polysensitization. 134 (13.59 %) patients were polysentisized, making 31.45 % of the atopic patients.

The distribution of aeroallergen hypersensitivity in atopic patients were shown in Table1.

Table 1. The distribution of aeroallergen hypersensitivity in atopic patients.

	Name of Allergen	Number of patients (%)
House dust mite allergens	Dermatophagoides Pteronyssinus	331 (33.6)
	Dermatophagoides Farinae	321 (32.6)
Pollen allergens	Grass	57 (5.8)
	Grass-cereal	27 (2.7)
	Tree pollens	39(4)
	Wall pelitory	68 (6.9)
Mold allergens	Alternaria Alternata	44 (4.5)
	Aspergillus Fumigatus	36 (3.7)
Animal dander allergens	Cat	25 (2.5)
	Dog	10 (1)

Atopy didn't differ between genders. Atopic patients were significantly younger than nonatopic patients. The age group with the highest allergen positivity was between 18 to 40 years old group.

When atopy was evaluated according to initial diagnosis it was observed that patient with nonspesific airway symptoms were nonatopic (p <0.001) and atopy was more frequently observed in patients those are initially diagnosed as asthma and rhinitis together (p=0.024).

The comparison of clinical and demographic characteristics of atopic and non atopic patients were shown in Table 2.

Table 2. The comparison of clinical and demographic characteristics of atopic and non-atopic patients

		Atopic patients, n (%)	**Nonatopic patients, n (%)**	**p**
Gender	Male	123 (46.8)	140 (53.2)	NS
	Female	300 (41.5)	423 (58.5)	
Childhood onset		89 (59.3)	61 (40.7)	<0.001
Age, mean		32.96±11.22	39.58 ±14.1	<0.001
Age groups	18-40 years	322 (52.1)	296 (47.9)	NS
	40-60 years	89 (29.5)	213 (70.5)	<0.001
	60 < years	12 (18.2)	54 (81.8)	<0.001
Initial diagnosis	Rhinitis	320 (41.6)	374 (53.9)	NS
	Asthma	11 (31.4)	24 (68.6)	NS
	Rhinitis+ asthma	82 (57.7)	60 (42.3)	0.02
	None	10 (8.7)	105 (91.3)	<0.001
Asthma	Mild	72 (49)	75 (51)	NS
	Moderate-Severe	20 (66.3)	10 (33.3)	

Polisensitization can effect distribution of symptoms' seasons, particularly in favour of perennial pattern. To eliminate this contoversy, seasonal patterns of symptoms according to sensitized allergens are evaluated in monosensitized patients. This evaluation demonstrated that patients with DHM, mold, wall-pellitory (Parietaria) and cat/dog hypersensitivity had perennial symptoms, while Patients with grass, and tree pollen hypersensitivity had seasonal symptoms (table 3).

Table 3. Distribution of seasonal pattern of symptoms in monosensitized patients

	Seasonal symptoms, n of patients	**Perennial symptoms, n of patients**	**p**
House dust mite	1	222	<0.001
Parietaria	8	20	<0.001
Grass Pollen	8	2	<0.001
Tree Pollen	6	3	<0.001
Mold	0	19	
Animal dander	0	9	

The frequency of HDM hypersensitivity in asthma and rhinitis were 44.63 % and 38.15% respectively (p= 0.001, <0.001 respectively). When HDM hypersensitivity is assesed in allergic asthma and allergic rhinitis, frequency of HDM hypersensitivity are 81.05 % and 78.21 % respectively (p= <0.001, p=<0.001 respectively).

4. Discussion

Respiratory allergic diseases yields an important burden for patients by means of socioeconomic loss and reduction in the quality of life. Identifying the allergen responsible for the disease is important to take precautions and managing these diseases accordingly. In our study, more than a half of the patients had a disease in allergic nature and/or deteriorated by environmental exposures. Atopy was detected in 43.20 % of patients, and the frequency of atopy is higher in patients initially diagnosed as asthma and rhinitis together (p=0.024). The strong correlation between allergic asthma and allergic rhinitis as comorbidities is often interpreted as an evidence for underlying sensitization, which in turn comprimises the term respiratory allergic disease (2, 13).

The most common allergen was HDM (33.87%). European Community Respiratory Health Survey (14) detected an overall prevalence of 21 % sensitization to HDM, which is a lower prevalance compared to this study. The higher prevalance in this study can be explained by the increased prevalance of HMD hypersensitivity in warm an humid climates.

Parietaria is the second most frequent allergen detected in this study, which is considerable since Parietaria is one of the most important causes of pollen allergies in Mediterranean region. Parietaria has a peculiar value, in particular for its long lasting duration of pollination, even some doctors accept it as a perennial allergen (15, 16). Ariano R et al. demonstrated that the Parietaria season has tended to be prolonged, and its pollen count has tended to increase over time (17). In a 10 year lasting study conducted in Italy, Parietaria polination was found to be 6-7 months on average, with two main peaks seen: an important peak during mid-spring and a lower peak during early fall (18). Due to long lasting pollination, the impact of Parietaria on clinical symptoms for sensitive patients may last longer that symptoms may not be named as seasonal. In this study, when seasonal patterns of symptoms are evaluated for Parietaria sensitive patients, it is found that perennial pattern is significantly more frequent than seasonal pattern.

Animal dander hypersensitivity were the least frequent allergens in this study. This low frequency might be attributed to the fact that SPT or ssIgE for cat and dog wasn't routinely performed unless a patient had any complaints and/or exposure suggesting pet allergy. Nevertheless the frequency of pet allergy in Turkey is lower when compaired to European countries and the US which might be explained by low pet ownership rate in our country (19, 20).

Age was an important discriminating factor for atopy (2). In this study, atopic patients were significantly younger than nonatopic patients. It was observed that allergen positivity decreased with increasing age. Although very low in frequency atopy can be detected also in geriatric patients.

31.59 % of the atopic patients were polysensitized. Cross reactions between allergens may cause false positivity yielding false identification of polysensitization. Component resolved diagnosis (CRD) allows a detailed molecular profiling of the polyclonal IgE repertoire of the allergic patient thus are useful in discriminating polysensitization (21). Since CRD wasn't performed in this study, there may be false polysensitizations. This is a potential limitation of this study.

5. Conclusion

Present study investigated allergen sensitivity of patients with symptoms suggesting respiratory allergy. Patients having nonspesific symptoms without an initial diagnosis of rhinitis or asthma tend to be nonatopic. HDM is the most frequently detected allergen and symptoms are mainly perennial. This finding reveals the importance of continuos treatment throughout

the year in order to control symptoms and reduce inflammation.

Secondly, Parietaria sensitive patients had perennial distribution of symptoms. In light of this finding Parietaria can be considered as a perennial allergen, but further studies with larger series are needed to clarify seasonal pattern of Parietaria.

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Ethics

Ethics Ethics Committee Approval: The study was approved by Hamidiye Etfal Research Hospital Ethical Committee (Approval Date/ Number: 05.07.2022/3606)
Author Contributions: Idea/concept: M.O. Design: M.O. Data Collection: M.O. Data Processing: M.O. Analysis/Comment: M.O. Literature research/review: M.O. Writing: M.O. All authors discussed the results and contributed to the final manuscript.
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Research Article / Araştırma Makalesi

The Effect of Back Massage Applied to Palliative Care Patients on Sleep Quality and Pain

Palyatif Bakım Hastalarına Uygulanan Sırt Masajının Uyku Kalitesi ve Ağrıya Etkisi

[1]Hilal Durmaz, [2]Sevil Pamuk Cebeci

[1]Eskişehir Osmangazi University/ Institute of Health Sciences, Fundamentals of Nursing Department, Eskişehir, Türkiye
[2]Eskişehir Osmangazi University/ Faculty of Health Sciences, Fundamentals of Nursing Department, Eskişehir, Türkiye

Abstract: This study was conducted between November 2021 and April 2022 to examine the effect of back massage applied to palliative care patients receiving inpatient treatment in the palliative care service of a hospital in Bilecik, Turkey on sleep quality and pain. A pretest-posttest control group randomized experimental design was used. A total of 52 volunteer patients, 26 in experimental and 26 in control groups, were recruited. A Patient Identification Form, the Pittsburgh Sleep Quality Index, and the McGill Pain Scale-Short Form were used to collect data. The experimental group was given an 18-minute a day back massage for seven days by the researcher. To evaluate the effect of the back massage, the Pittsburgh Sleep Quality Index and the McGill Pain Scale-SF were filled out. At the end of the 7th day, intra- and inter-group differences were examined. The statistical significance was accepted as $p<0.05$. Both groups were equivalent regarding some individual characteristics (age, gender, level of education, and medical diagnosis). The seven-day follow-up results regarding the experimental and control group patients' sleep and pain indicated a significant difference between the groups in favor of the experimental group after the 4th day ($p <.001$). A statistically significant difference was found between patients' mean sleep quality scores according to 2*2 MIX ANCOVA test results both in interaction ($F(1,50)= 15.899$, $p<.001$, $\eta^2=.016$) and between groups ($F(1,50)= 27.271$, $p<.001$, $\eta^2=.10$). There was a statistically significant difference between patients' mean pain scores according to 2*3 MIX ANOVA test results regarding both measurement time ($F(1,50)= 7.619$, $p<.001$, $\eta^2=.013$) and interaction ($F(1,50)= 48.751$, $p<.001$, ($\eta^2=.083$). In this study, a back massage was applied to palliative care patients for seven days, and there was a statistically significant increase in patients' sleep quality and decrease in pain levels starting from the 4th day of the application.
Keywords: Back massage, palliative care, sleep quality, pain, holistic care, nursing care

Özet: Çalışma, palyatif bakım hastalarına uygulanan sırt masajının uyku kalitesi ve ağrıya etkisini incelemek amacıyla, Kasım 2021- Nisan 2022 tarihleri arasında Türkiye'de Bilecik ilinde bir hastanenin palyatif bakım servisinde yatarak tedavi gören hastalar ile yapıldı. Ön test-son test kontrol gruplu desene sahip randomize kontrollü deneysel çalışma olarak planlandı. Örneklemi 26 deney, 26 kontrol olmak üzere toplam 52 gönüllü hasta oluşturdu. Deney grubuna 7 gün boyunca her gün 18 dk. süreyle araştırmacı tarafından sırt masajı uygulandı. Deney grubuna uygulanan sırt masajının etkisini değerlendirmek için Pittsburgh Uyku Kalitesi İndeksi, McGill Ağrı Ölçeği-Kısa Formu doldurduldu. 7. Günün sonunda grup içi ve gruplar arası farklar incelendi. İstatistiksel anlamlılık düzeyi $p<0.05$ kabul edildi. Deney ve kontrol grubunun sosyo-demografik özellikleri incelendiğinde, her iki grubun yaş, cinsiyet, eğitim durumu, tıbbi tanı gibi bireysel özellikler bakımından benzer olduğu görüldü. Deney ve kontrol gruplarındaki hastaların uykuya ve ağrıya ilişkin 7 günlük izlem sonuçları incelendiğinde; her iki grup arasında 4. günden sonra deney grubu lehine anlamlı farklılaşma başlamıştır ($p<.001$). Hastaların uyku kalitesi puan ortalamaları karşılaştırıldığında; 2*2 MİX ANCOVA test sonuçlarına göre; hem etkileşimde ($F(1,50)= 15.899$, $p<.001$, $\eta^2=.016$), hem de gruplar arasında ($F(1,50)= 27.271$, $p<.001$, $\eta^2=.10$) istatistiksel olarak anlamlı farklılık bulundu. Hastaların ağrı puan ortalamaları karşılaştırıldığında; 2*3 MİX ANOVA test sonuçlarına göre hem ölçüm zamanı ($F(1,50)= 7.619$, $p<.001$, $\eta^2=.013$), hem de etkileşimde ($F(1,50)= 48.751$, $p<.001$, $\eta^2=.083$) istatistiksel olarak anlamlı farklılık bulundu. Bu çalışmada, palyatif bakım hastalarına 7 gün boyunca sırt masajı uygulanmış, uygulamanın 4. gününden itibaren hastaların uyku kalitesinde istatistiksel açıdan anlamlı artış ve ağrı düzeylerinde ise anlamlı azalış olduğu belirlenmiştir.
Anahtar Kelimeler: Sırt masajı, palyatif bakım, uyku kalitesi, ağrı, holistik bakım, hemşirelik bakımı

ORCID ID of the authors: H.D. 0000-0002-7267-0041, SPC. 0000-0002-3788-5784

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Correspondence: Sevil PAMUK CEBECİ-- Eskişehir Osmangazi University/ Faculty of Health Sciences, Fundamentals of Nursing Department, Eskişehir, Türkiye

e-mail: sevil.pamukcebeci@ogu.edu.tr

1. Introduction

Palliative care is intended to improve the quality of life of terminally ill patients, who have reached the last stage of their lives due to their illness and whose recovery is not possible, and ensure a peaceful death (1). Palliative care, according to the definition of the World Health Organization (WHO), aims at improving physical (pain, movement restrictions, weight problems, etc.) and psycho-social (anxiety, depression, death anxiety, etc.) state related to a disease in life-threatening situations faced by individuals and their environment. It is defined as care that improves the quality of life of the individual and his/her environment through early diagnosis, treatment, and evaluation (2). The most frequent problem in palliative care, where individualized care is most intensively applied, is pain (3). Pain is an unpleasant emotional experience caused by damage due to physiological changes in tissues (4). The main indicator of the quality of nursing care is to manage patients' pain and suffering well and improve their quality of life (5). Treatment and care of pain requires the combination of pharmacological and non-pharmacological approaches (6). Pharmacological treatments include oopoids, nonopoids, and adjuvant analgesics. Nonpharmacological applications can be listed as massage applications, relaxation techniques, hypnosis, acupressure, and acupuncture (7). Thanks to massage, one of the most used holistic care methods, the pain caused by contracted and tense muscles is relieved and reduced (8). In addition to relaxing the muscles, it also reduces pain by facilitating the oxygenation of tissues and the body's release of endorphins (9).

Another common complaint in palliative care patients is insomnia (10). Sleep affects quality of life and is among the life activities necessary for the individual to be physically and spiritually healthy (11,12). Sleeping disorders include difficulty falling asleep, difficulty staying asleep, early morning waking or poor sleep, and non-restorative sleep (12,13). Sleep quality is also linked to pain (13). Poor sleep quality causes decreased tolerance to pain. Sleep provided by pharmacological applications does not provide the quality of normal sleep and even reduces sleep quality (14). It is reported that massage and relaxation techniques are effective in the management of sleep disorders (14). Massage is one of the oldest care methods used to relieve many ailments (15). It is seen that there are limited studies in the literature on back massage application in palliative care patients. This research was planned as a randomized controlled experimental study with a pre-test - post-test control group design to examine the effect of back massage applied to palliative care patients on sleep quality and pain. It is thought that this study will contribute to increasing the use of massage by caregivers and support further studies in this field.

2. Materials and Methods

2.1. Purpose and type of the research

This research was planneded as a randomized controlled experimental study with a pre-test-post-test control group design to examine the effect of back massage applied to palliative care patients on sleep quality and pain.

2.2. Research Hypotheses

H_1: Back massage applied to palliative care patients has a positive effect on sleep quality.

H_2: Back massage applied to palliative care patients has a pain-relieving effect.

2.3. Sample of the research

The study consisted of palliative care patients who received inpatient treatment in the Palliative Care Service of a Training and Research Hospital in Bilecik, Turkiye, between November 2021 and April 2022. The sample included palliative care patients who voluntarily agreed to participate in the study, needed palliative care, and met the

research criteria. A power analysis was performed on the GPower 3.1 software to determine the sample size. The analysis was based on the data of the *"Randomized controlled trial of the effectiveness of using back massage to improve sleep quality among Taiwanese insomnia postpartum women"* study. As a result, the sample size was calculated as a total of 52 patients, including 26 patients in each group, based on a power value of 95% and a CI of 95%. Considering some attrition, 28 patients were included in both groups. One patient had to leave the experimental group because she could not tolerate the massage application, and another patient was excluded because she had impaired consciousness during the study phase. Two patients from the control group were excluded from the study due to early discharge and transfer to another hospital. The study was completed with 52 patients, including 26 in the experimental and 26 in the control group. The trial was registered with the ClinicialTrials.gov PRS (Protocol Registration and Results System) (Protocol number: NCT05168514).

2.4. Research inclusion criteria

- Having no communication problem, especially with accurately expressing pain and sleep status, and communicating cognitively, affectively, and verbally,

-Being over 18 years of age,

-Accepting to receive inpatient treatment in the palliative care service for at least 7 days,

- Not reacting negatively to any touch-oriented intervention, such as massage,

- Having complete tissue integrity in the area to be massaged.

2.5. Randomization Method

The Random Integer Generator method was used under the Numbersalt heading on the random.org website to divide all patients who met the research criteria into experimental and control groups. Eligible patients were referred to the study coordinator. After giving the necessary information to the patients, the study coordinator randomly assigned them to the "experimental" and "control" groups through random numbers generated on the website https://www.random.org/.

Total number of patients = Experimental group + Control group

(N) 52 = (n) 26 + (n) 26

2.6. Data collection tools

A Patient Identification Form, the Pittsburgh Sleep Quality Index, and the McGill Pain Scale-Short Form were used.

Patient Identification Form: The patient identification form was prepared by the researchers to determine participants' socio-demographic characteristics.

Pittsburgh Sleep Quality Index: Buysse et al. developed the Pittsburgh Sleep Quality Index (PSQI) (16). The validity and reliability study of the scale in Turkish was carried out by Ağargün et al. (17). The PSQI is a 19-item scale that is used to evaluate sleep quality. Each item is scored between 0 and 3. The scale consists of seven subsections that are used to evaluate objective sleep quality, sleep latency, time spent asleep, sleep habits, sleep disorders, use of sleeping pills, and loss of daytime functionality. By summing the scores from these subsections, a PSQI score between 0 and 21 is obtained. A PSQI total score that is greater than 5 indicates that the individual's sleep quality is inadequate, with a sensitivity of 89.6% and a specificity of 86.5% and that there is a severe sleep disorder in at least two out of seven areas or moderate sleep disorder in three (16,17).

McGill Pain Scale - Short Form: McGill Pain Scale-Short Form was developed by Melzack (18). The Turkish validity-reliability study of the scale was conducted by Yakut et al. (19). The short form of the McGill Pain Scale provides information about the sensory dimension, intensity, and felt effects of pain. In this regard, the scale has three dimensions. The first part

includes 15 descriptive items expressing the characteristics of pain. Of these 15 items, 11 are used to assess the sensory dimension of pain, and 4 are used to evaluate the perceptual dimension. These items are rated with expressions indicating intensity between 0 and 3 (0 = none, 1 = mild, 2 = moderate, 3 = excessive). In the first part, the sensory pain score is between 0 and 33, the perceptual pain score is between 0 and 12, and the total pain score is between 0 and 45. An increase in the total score indicates an increase in pain. In the second part, there are five-word groups ranging from "mild pain" to "unbearable pain" to determine the intensity of pain felt by the patient. In the third part, the patient's instantaneous pain intensity is evaluated through visual comparison (18,19).

2.7. Ethical approval

Ethical approval for the study was obtained from Eskisehir Osmangazi University Non-interventional Clinical Research Ethical Committee (Ref.nr: 2021/04). Institutional permission (Ref. nr: 2021/28) was obtained from the institution where the study was conducted. Voluntary informed consent forms were obtained from the participants, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

2.8. Application of Research

In the study data collection began after obtaining the necessary institutional and ethical permissions. During admission, the research coordinator explained the purpose, scope, duration, and method of the research to the patients who came to the institution where the research was conducted and met the research criteria. Then, verbal and written permission was obtained from patients (or their legal guardians) who agreed to participate in the study voluntarily. Volunteer patients were assigned to experimental and control groups via randomization by the research coordinator. In the research, the nurse among the researchers applied all the back massages to be given to the experimental group. This nurse had acquired massage application skills during undergraduate and postgraduate education, was authorized as a massage practitioner by national laws and regulations (20), and had no other massage training. The guideline specified in the study protocol was followed to ensure equal application among patients. Data forms for both groups were filled out by the research coordinator. The final analysis was done using the data set by a statistician who did not know the participants.

Study protocol

Patients assigned to both groups filled out the "Patient Identification Form", "Pittsburgh Sleep Quality Index", and "McGill Pain Scale - Short Form" as a pre-test on the first day.

No massage was applied to the control group. Treatment and care practices in the routine of the palliative care clinic continued.

The experimental group was given a massage by the researcher nurse for 18 minutes a day for 7 days.

The massage application sequence was performed as effleurage, petrissage, friction, percussion, and vibration and ended with effleurage again.

Each massage maneuver took 3 minutes.

Liquid petroleum jelly was used as a massage solution.

The Pittsburgh Sleep Quality Index and the McGill Pain Scale-Short Form were filled out to evaluate sleep quality and pain after massage. In this way, the application took 7 days.

Back massage application and filling out of the scales were performed before an analgesic agent was administered to the patients (before 10:00 in the morning).

The scales were completed by the control group simultaneously with the experimental group.

Application guidelines for back massage

1. The patient is informed about the application before the massage application is initiated.

2. The materials required for massage application are brought.

3. A screen is placed around the bed to protect patient privacy.

4. The door of the room where the patient is located is closed.

5. The nurse removes her/his rings and washes hands.

6. Since the back massage is applied to the upper extremity, the patient's upper underwear is removed and he/she is placed in the prone position. The legs and hips are covered with a sheet.

7. The bed height is adjusted to a level that will not tire the massage nurse.

8. The nurse takes some liquid petroleum jelly in the palm of his/her hand to reduce friction and relax the body during the massage. In order not to irritate the patient, it should be warmed by holding it in the palm of the hand for a while.

9. Massage is started with the first manipulation movement, the effleurage maneuver.

10. Back massage is continued with petrissage, friction, percussion, and vibration maneuvers.

11. Three minutes are allocated for each maneuver.

12. Massage application is terminated with effleurage.

13. The nurse should observe skin integrity or redness while applying back massage.

14. After the application, the nurse removes the excess lotion (liquid petroleum jelly) with a towel.

15. The patient is dressed.

16. The patient is given a suitable position to rest after the massage.

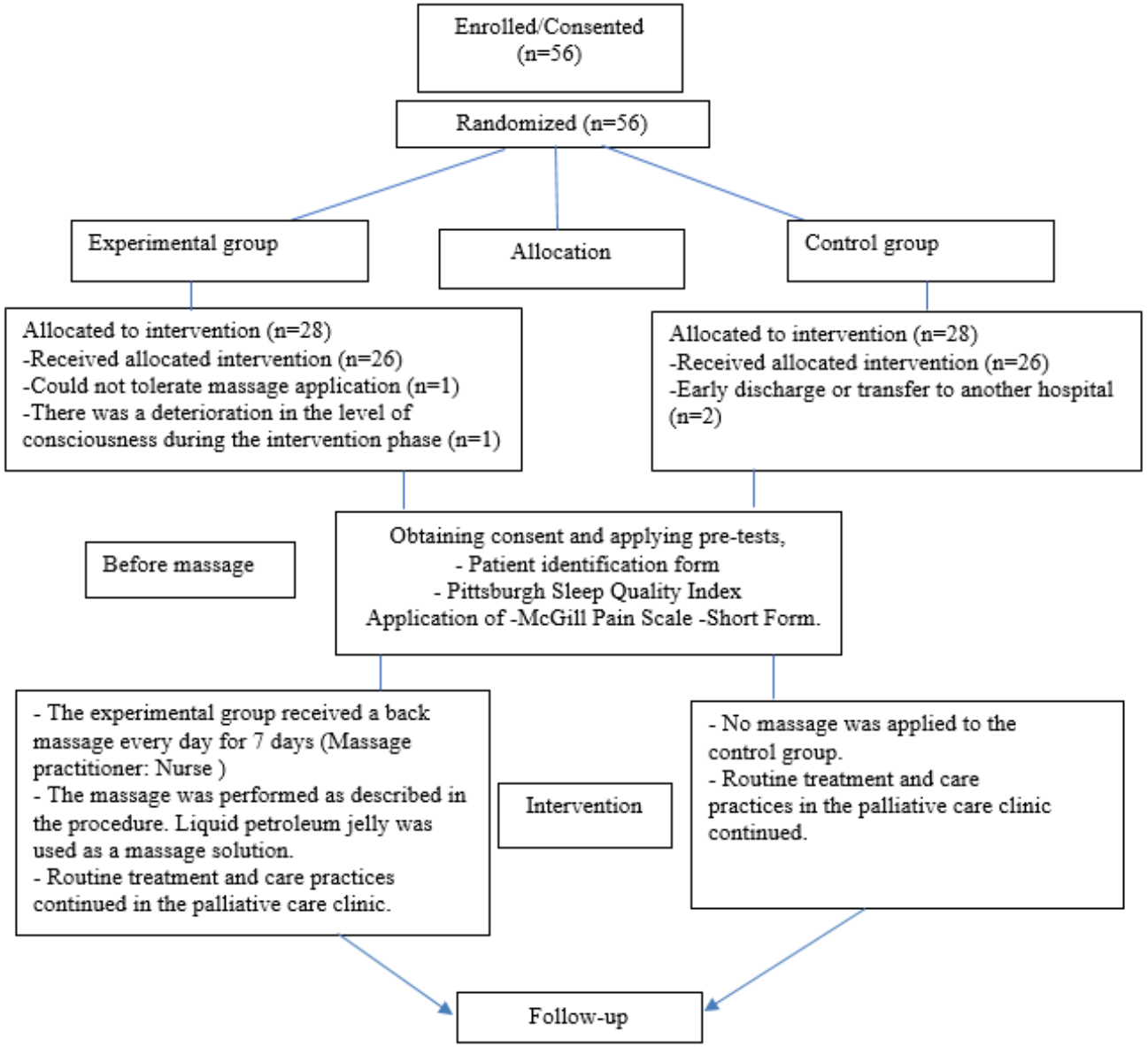
17. At the end of the massage, the nurse washes his/her hands.

18. Used materials are removed.

19. The application is recorded on the patient's observation sheet (11).

2.9. Data analysis

Evaluation of the data was done on the Statistical Package for Social Sciences (SPSS) 22.0 software. Descriptive statistical methods, such as frequency, percentage, mean, and SD, were used in data analysis. The suitability of the data for normal distribution was tested with the Shapiro-Wilk test. Since the data showed a normal distribution, 2*2 MIX ANCOVA, Post hoc Tukey Test, and 2*3 MIX ANOVA parametric tests were used.


Enrolled/Consented (n=56)
Randomized (n=56)
Experimental group
Allocation
Control group
Allocated to intervention (n=28)
-Received allocated intervention (n=26)
-Could not tolerate massage application (n=1)
-There was a deterioration in the level of consciousness during the intervention phase (n=1)
Allocated to intervention (n=28)
-Received allocated intervention (n=26)
-Early discharge or transfer to another hospital (n=2)
Before massage
Obtaining consent and applying pre-tests,
- Patient identification form
- Pittsburgh Sleep Quality Index
Application of -McGill Pain Scale -Short Form.
- The experimental group received a back massage every day for 7 days (Massage practitioner: Nurse)
- The massage was performed as described in the procedure. Liquid petroleum jelly was used as a massage solution.
- Routine treatment and care practices continued in the palliative care clinic.
Intervention
- No massage was applied to the control group.
- Routine treatment and care practices in the palliative care clinic continued.
Follow-up

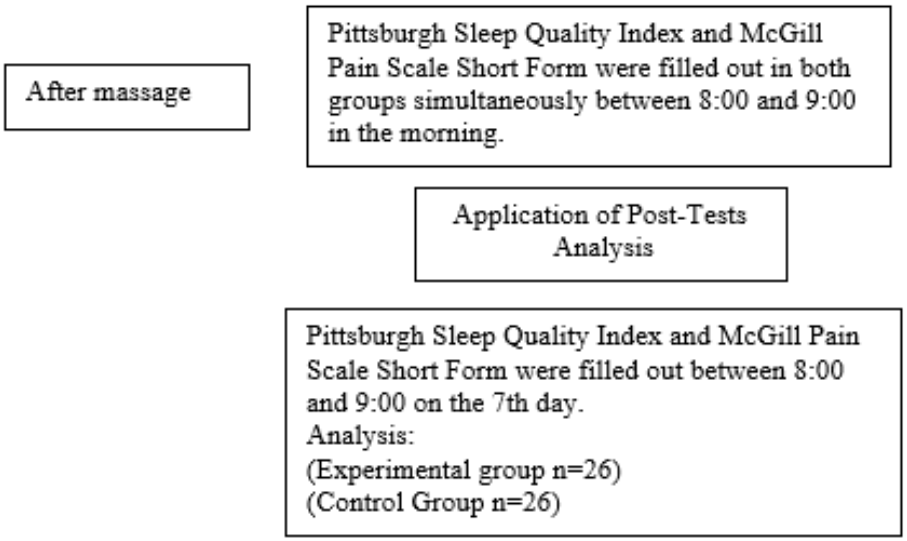


Figure 1. Study flow chart

3. Results

When the distribution of socio-demographic characteristics between the groups was examined, it was seen that the mean age of the patients in the experimental group was 63.7, 53.8% were male, 42.3% were married, 38.4% were primary school graduates, 34.6% were retired, and that 71.2% had cancer. The average age of the patients in the control group was 60.7, 53.8% were male, 61.5% were married, 42.3% were secondary school graduates, 34.6% were retired, and that 88.4% had cancer. Both groups were found to be equivalent in terms of individual characteristics, such as age, gender, educational status, and medical diagnosis (Table 1).

Table 1. Findings regarding the descriptive statistics of the scales

Variables	**Experimental group (n=26)**		**Control group (n=26)**	
Age Mean±SD/ Min-Max	63.731±*9.648*	(48-84)	60.731±12.880	(30-78)
	n	**%**	**n**	**%**
Gender				
Female	12	46.154	12	46.154
Male	14	53.846	14	53.846
Marital status				
Single	15	57.692	10	38.461
Married	11	42.308	16	61.538
Educational Status				
Primary school	10	38.461	7	26.923
Middle School	5	19.231	11	42.308
High school	9	34.615	4	15.385
Higher education	2	7.692	4	11.538
Job				
Unemployed	7	26.923	8	30.769
Civil servant	3	11.538	2	7.692
Employee	7	26.923	7	26.923
Retired	9	34.615	9	34.615

Since parametric tests were used in the research, normal conditions were examined. Statistics on sleep quality and pain level variables were given (Table 2). All variables of the study were distributed normally in the experimental and control groups, and skewness and kurtosis values were within a normal range, as shown by Shapiro-Wilk test results. Histograms and Q-Q plots were examined, and normality was observed. Additionally, means, standard deviations, and highest and lowest values regarding sleep quality and pain levels were given (Table 2).

Table 2. Findings on the descriptive statistics of the scales

	Pittsburgh1		Pittsburgh4		Pittsburgh7		McGill1		McGill4		McGill7	
	Experimental Group	**Control Group**	**Experimental Group**	**Control Group**	**Experimental Group**	**Control Group**	**Experimental Group**	**Control Group**	**Experimental Group**	**Control Group**	**Experimental Group**	**Control Group**
Distortion	-0.662	-0.309	-0.487	-0.270	-0.385	-0.040	-0.580	0.213	-0.534	0.464	-0.169	0.650
Kurtosis	0.410	0.071	-0.173	0.168	-0.555	-0.233	-0.450	-0.068	-1.178	-0.540	-1.029	-0.266
Shapiro-Wilk	0.944	0.978	0.964	0.976	0.967	0.978	0.951	0.976	0.895	0.956	0.939	0.944
Shapiro-Wilk (p value)	0.170	0.823	0.477	0.786	0.539	0.828	0.242	0.791	0.062	0.325	0.130	0.167
Lowest value	7.000	6.000	5.000	7.000	1.000	9.000	13.000	14.000	8.000	25.000	5.000	25.000
Highest value	21.000	21.000	21.000	21.000	21.000	21.000	54.000	52.000	49.000	53.000	50.000	57.000

When the 7-day follow-up results regarding sleep quality in the experimental and control group palliative care patients were examined, it was seen that differentiation began between both groups after the 4th day. The positive effect of back massage on sleep quality in the experimental group was observed on the 4th day of the massage application. At the same time, sleep quality started to increase. An increase in the total score on the "Pittsburgh Sleep Quality Index (PSQI)" indicates that sleep quality is inadequate. The PSQI score of the experimental group started to decrease after the 4th day, showing that sleep quality started to increase. In the control group where back massage was not applied, the PSQI total score started to increase from the 4th day, meaning a slight decrease in sleep quality was observed. On days 5-6-7 of the massage application, the difference in PSQI scores of both groups widened, and it was observed that the sleep quality of the patients in the experimental group increased significantly (Figure 1).

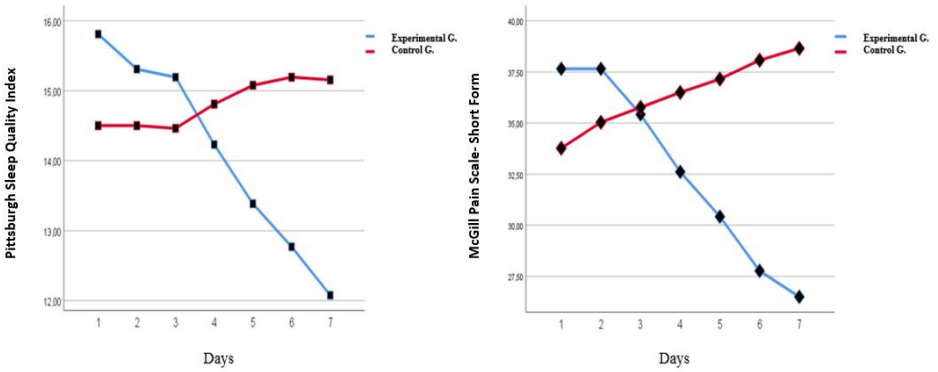


Figure 1. Findings related to sleep quality in experimental and control group patients

Figure 2. Findings related to pain score in experimental and control group patients

When the 7-day follow-up results regarding the pain score in the experimental and control group palliative care patients were examined, it was observed that the day when the pain-reducing effect of the back massage application began to be seen in the experimental group was the 4th day of the massage application. In the control group that did not receive back massage, there was a slight increase in pain scores. An increase in the total score obtained from the McGill Pain Scale indicates that the patient's pain also increases. On days 5-6-7, the difference in pain scores of both groups widened, and while the pain scores of the control group increased, the pain scores of the patients in the experimental group decreased significantly (Figure 2).

When the mean sleep quality scores of the experimental and control groups were compared, statistically significant differences were found both in interaction ($F(1.50)= 15.899$, $p<.001$, $\eta^2=.016$) and between groups ($F(1.50)= 27,271$, $p<.001$, $\eta^2=.10$) according to the 2*2 MIX ANCOVA test results (Table 3). The post hoc Tukey Test was performed to find the difference in sleep quality (Table 4). The sleep quality curve is shown in Figure 3.

Table 3. 2*2 Mix ANCOVA analysis results of sleep quality

Source of variance	**KT**	**Sd**	**KO**	**F**	**p**	**η^2**
Intra-group						
Measurement time	0.062	1	0.062	0.026	0.872	0.000
Measurement time ✻ group	**37.329**	**1**	**37.329**	**15.899**	**.001**	**0.016**
Measurement time✻ Pittsburgh1	0.588	1	0.588	0.251	0.619	0.000
Residual	115.046	49	2.348			
Inter- group						
Group	**237.804**	**1**	**237.804**	**27.271**	**.001**	**0.102**
Pittsburgh1	1.078.967	1	1.078.967	123.734	.001	0.464
Error	427.283	49	8.720			

Pittsburgh1: Pittsburgh Sleep Quality Index (PSQI)

Table 4. Post hoc test results of sleep quality

Measurement time	**Grup**		**Measurement time**	**Group**	**Mean difference**	**SE**	**df**	**t**	**p_{tukey}**
DAY4	Experimental		DAY7	Experimental	**2.125**	**0.429**	**49.000**	**4.953**	**.001**
DAY4	Control	-	DAY7	Control	**-0.317**	**0.429**	**49.000**	**-0.739**	**.881**
DAY4	Experimental	-	DAY4	Control	**-1.860**	**0.460**	**49.000**	**-4.047**	**.001**
DAY7	Experimental	-	DAY7	Control	**-4.302**	**0.820**	**49.000**	**-5.246**	**.001**

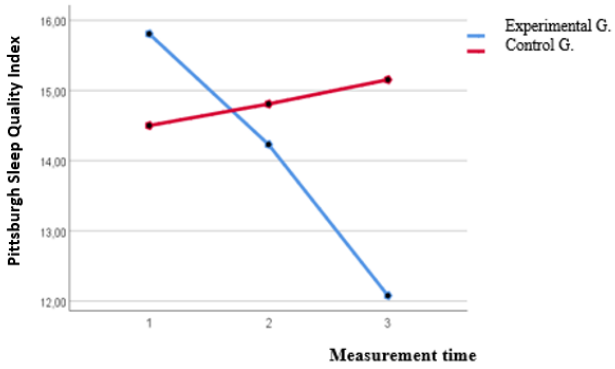


Figure 3. Sleep quality measurement results for day 1, 4, and 7 in experimental and control group patients

Firstly, the examination of the intra-group results showed that there was a significant increase in sleep quality in the experimental group from the 4th day to the 7th day (p <.001). In the control group, there was no significant change in sleep quality between the 4th and 7th days (p>.001, Table 4).

The examination of the inter-group results showed that the sleep quality of the patients in the experimental group increased significantly on the 4th and 7th days (p<.001, Table 4).

When the mean pain scores in the experimental and control groups were compared, both measurement time (F(1,50)= 7.619, p<.001, η^2=.013) and interaction (F(1, 50)= 48.751, p<.001, η^2=.083) difference was found according to the 2*3 MIX ANOVA results (Tablo 5). The post hoc Tukey Test was performed to find the difference in sleep quality (Table 6). The mean pain score curve is shown in Figure 4.

Table 5. 2*3 Mix ANOVA analysis results of the pain score

Source of variance	**KT**	**Sd**	**KO**	**F**	**p**	**η^2**
Intra-group						
Measurement time	**261.397**	**2**	**130.699**	**7.619**	**< .001**	**0.013**
Measurement time ✻ group	**1.672.551**	**2**	**836.276**	**48.751**	**< .001**	**0.083**
Error	1.715.385	100	17.154			
Inter- group						
Group	640.103	1	640.103	2.023	0.161	0.032
Error	15.824.154	50	316.483			

Table 6. Post hoc test results of the pain dimension

Measurement time	**Group**		**Measurement time**	**Group**	**Mean difference**	**SE**	**df**	**t**	**p_{tukey}**
DAY1	Experimental	-	**DAY4**	Experimental	**5.038**	**0.908**	**50.000**	**5.548**	**.001**
DAY4	Experimental	-	**DAY7**	Experimental	**6.115**	**1.099**	**50.000**	**5.565**	**.001**

DAY1	Experimental	-	**DAY7**	Experimental	**11.154**	**1.388**	**50.000**	**8.037**	**.001**
DAY1	Control	-	**DAY4**	Control	**-2.731**	**0.908**	**50.000**	**-3.00**	**0.045**
DAY1	Experimental	-	DAY1	Control	**3.885**	**2.794**	**50.000**	**1.391**	**0.732**
DAY4	Experimental	-	DAY4	Control	**-3.885**	**3.003**	**50.000**	**-1.29**	**0.787**
DAY7	Experimental	-	DAY7	Control	**-12.154**	**3.188**	**50.000**	**-3.81**	**0.005**

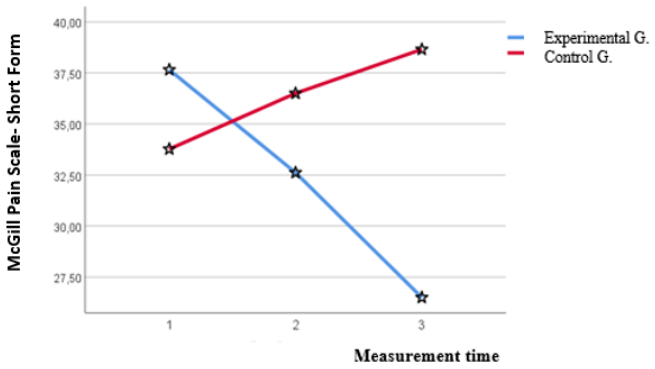


Figure4. The measurement results of the pain score on the 1st, 4th, and 7th days in the experimental and control group patients

Firstly, the examination of the intra-group results indicated that there was a decrease in the mean pain score in the experimental group from day 1 to day 4 (p = .001, Table 6). Also, it was observed that there was a decrease in the mean pain score from the 4th day to the 7th day in the experimental group (p = .001, Table 6). Finally, it was observed that there was a decrease in the mean pain score in the experimental group from day 1 to day 7 (p=.001, Table 6). In the control group, there was no change in pain scores, but an increase in pain scores was observed from day 1 to day 4 (p=.045, Table 6).

When we looked at the results between groups, on the first day of the back massage applied to the experimental group, there was no difference between the experimental and control groups (p=.732, Table 6). When the pain scores on the 4th day were examined, a difference began to occur in the pain scores of the experimental group (Figure 4). The day when the pain started to decrease was the 4th day of the back massage application. Finally, the pain score decreased in the experimental group on the 7th day (p=.005, Table 6).

4. Discussion

Massage application has been accepted as one of the most popular complementary care methods used in palliative care centers, especially in recent years (21). There is ongoing research into whether this method does not harm the clinical course of the patient, but its benefit needs to be confirmed, as well (22). The purpose of this study was to examine the effect of back massage applied to palliative care patients on sleep quality and pain.

Considering the 7-day follow-up findings regarding the sleep quality of the experimental and control groups in this study, the back massage applied showed its effect from the 4th day, and the sleep quality of the experimental group increased. In the remaining 3 days, the sleep quality of the experimental group continued to increase, while it decreased in the control group. This shows the positive

effect of back massage applied to palliative care patients on sleep quality. As a result, the hypothesis (H_1) "Back massage applied to palliative care patients has a positive effect on sleep quality" was confirmed. The back massage showed its effect on the 4th day of the application, and the effect continued to increase over time. As can be understood from this result, at least 4 days of application is required to see the positive effect of massage application. In the study of Kashani and Kashani, it was stated that there was a significant relationship between massage therapy application and sleep quality (23). In the study of Miladinia et al., it was reported that back massage significantly reduced sleep disturbance, pain, and fatigue and improved sleep quality over time (24). In the study by Ünal and Akpınar', foot reflexology and back massage were applied twice a week for 4 weeks, and as a result, it was stated that foot reflexology and back massage improved the sleep quality of hemodialysis patients (25). Other studies in the literature have shown statistically and clinically significant effects of massage on sleep (26-28). The literature supports the results of our study.

When we looked at the findings regarding the pain scores of palliative care patients in the experimental and control groups, the mean McGill Pain Scale scores in the experimental group remained similar on the 1st and 2nd days but decreased from the 3rd day. According to the 7-day follow-up findings regarding the mean pain scores of the experimental and control groups, the back massage applied showed its effect from the 4th day, and the pain of the patients in the experimental group decreased. In line with these results, the hypothesis (H_2) that "Back massage applied to palliative care patients has a pain-relieving effect" was accepted. The back massage showed its effect on the 4th day of the application and it continued to increase over time. At least 4 days of application is required to see the pain-relieving effect of massage application. In the study of Büyükyılmaz and Aştı, it was found that relaxation techniques and back massage applied for 3 days were effective in reducing pain and anxiety (29). In the study by Han and Lee, in which the effect of back massage on the degree of pain, anxiety, and sleep quality was examined, it was stated that the level of pain decreased significantly and sleep quality increased significantly, compared to the first day after surgery (30). As a result of Mok and Woo's research, it was reported that slow-stroke back massage reduced anxiety and shoulder pain (31). When other studies in the literature were examined, the effect of massage on pain was evaluated and a significant difference was reported in favor of massage (24, 27, 31-35). The results of our research were in parallel with the literature. Some studies in the literature support the view that the effect of massage on pain is limited (22, 36, 37). We believe that this difference in the literature may be due to factors, such as diversity in study populations, diagnostic differences, the presence of patients with metastatic pain, the inclusion of patients with depression and psychosocial disorders in the sample groups, and differences in research methods.

Another striking point in our research findings was that the sleep quality of palliative care patients, whose pain decreased, increased simultaneously. On the 4th day of the back massage application, the pain level decreased statistically and clinically significantly, and the sleep quality of the patients, whose pain decreased, began to increase. Similar studies in the literature showed that reduced pain levels had a positive effect on patients' physiological parameters, such as insomnia, depression, and anxiety levels and this supports our study finding (27, 30, 32,38,39).

5. Conclusion

In conclusion, the study showed that back massage application improved sleep quality and reduced pain in palliative care patients. The most visible effect of the back massage was on the 4th day of the application. By the 7th day, it was observed that the positive effect gradually increased. Studies in which massage is applied for a longer period with larger sample groups are recommended. The cost of the application is low and its effect is high. We believe that caregivers of palliative care patients can use massage more effectively.

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Ethics

Ethics Committee Approval: The study was approved by Eskisehir Osmangazi University Non-interventional Clinical Research Ethical Committee (Decision no: 04, Date: 07.09.2021).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

Conflict of Interest: This research was produced from the Master's Thesis. Supported by Eskisehir Osmangazi University Scientific Research Projects Coordination Unit (Project Number: TYL-2022-2284). The authors have no other financial disclosures to share. ClinicialTrials.gov PRS Protocol Registration and Results System, Protokol no: NCT05168514

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Research Article / Araştırma Makalesi

Evaluation of the Effect of Health Indicators on Life Expectancy at Birth and Years of Life Lost in European Union Countries and Türkiye: A Panel Data Analysis.

Türkiye ve Avrupa Birliği Ülkelerinde Doğumda Beklenen Yaşam Süresi ve Ölüme Bağlı Kaybedilen Yıllar Üzerine Etkili Sağlık Göstergelerinin Belirlenmesi: Bir Panel Veri Analizi

[1]Emrah Atay, [2]Selma Metintaş, [3]Fatih Çemrek, [4]Elgiz Askeroğlu

[1]Eskişehir Tepebaşı District Health Directorate, Eskisehir, Türkiye
[2]Eskişehir Osmangazi University Faculty of Medicine Department of Public Health, Eskisehir, Türkiye
[3]Eskişehir Osmangazi University, Faculty of Science, Department of Statistics Eskisehir, Türkiye
[4]Giresun University, Faculty of Arts and Sciences, Department of Statistics, PhD Student in Statistics Program, Giresun, Türkiye

Abstract: The aim of the study is to evaluate the effect of selected health indicators on life expectancy at birth (LEAB) and years of potential life lost (YPLL) in Türkiye and European Union (EU) countries with data of 2000-2017 period. The study is an ecological research with panel data analysis (PDA). Four panels are modeled as health care use, health equipment, health resources and health risks. LEAB and YPLL which are in health status category were considered as dependent variables. It was found that an increase in the child vaccination rates, number of Magnetic Resonance Imaging devices (MRI), health spending, number of doctors and number of nurses had an increasing effect on LEAB, while an increase in the child vaccination rate, length of hospital stay, hospital discharge rates, number of Computed Tomography (CT) devices and MRIs, health spending and number of doctors had a decreasing effect on YPLL. In addition, an increase in smoking prevalence rate, alcohol consumption and obesity prevalence rate had a decreasing effect on LEAB, while an increase in smoking prevalence rate and obesity prevalence rate had an increasing effect on YPLL. Analyzing the data of health indicators with modern statistical approaches such as Panel Data Analysis (PDA) can help to guide for determining interventions, strategies and projections in health services.
Keywords: Health Indicators, Panel Data Analysis, Health Status

Özet: Çalışmanın amacı, 2000-2017 dönemi verileri ile Türkiye ve Avrupa Birliği (AB) ülkelerinde seçilmiş sağlık göstergelerinin doğuşta beklenen yaşam süresi (DBYS) ve ölüme bağlı kaybedilen potansiyel yıllar (YPLL) üzerindeki etkisini değerlendirmektir. Çalışma ekolojik nitelikte bir panel veri analizi (PVA) araştırmasıdır. Sağlık hizmeti kullanımı, sağlık ekipmanları, sağlık kaynakları ve sağlık riskleri olmak üzere dört panel modellenmiştir. Sağlık durumu kategorisinde yer alan DBYS ve YPLL bağımlı değişkenler olarak kabul edilmiştir. Bulgulara bakıldığında çocuk aşılama oranları, Manyetik Rezonans Görüntüleme (MRI) cihazı sayısı, sağlık harcamaları, doktor ve hemşire sayısındaki artışın DBYS üzerinde artırıcı bir etkiye sahip olduğu; çocuk aşılama oranı, hastanede kalma süresi, hastane taburculuk hızı, Bilgisayarlı Tomografi (BT) cihazı ve MRI sayısı, sağlık harcamaları ve doktor sayısındaki artışın ise YPLL üzerinde azaltıcı bir etkiye sahip olduğu saptandı. Bununla birlikte sağlık riskleri panelindeki sigara içme prevelans hızı, alkol tüketim miktarı ve obezite prevelans hızındaki artışın DBYS üzerinde azaltıcı etkisi olduğu; sigara içme prevelans hızı ve obezite prevelans hızındaki artışın ise YPLL üzerinde artırıcı etkiye sahip olduğu saptandı. Sağlık göstergelerine ait verilerin Panel Veri Analizi (PVA) gibi modern istatistiksel yaklaşımlarla analiz edilmesi sağlık hizmetlerinde müdahale, projeksiyon ve stratejileri belirlemede yol gösterici olabilir.
Anahtar Kelimeler: Sağlık göstergeleri, Panel Veri Analizi, Sağlık Düzeyi

ORCID ID of the authors: EA. 0000-0002-6581-8626, SM. 0000-0002-5002-5041, FÇ. 0000-0002-6528-7159, EA. 0000-0001-5883-5527

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Correspondence: Emrah ATAY-- Eskişehir Tepebaşı District Health Directorate, Eskisehir, Türkiye
e-mail: emraha06@gmail.com

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1. Introduction

The importance of organisation and planning to maintain the health status of community has been clearly understood in today's world. Health policy makers are also in search of accurate and reliable health indicators in order to reveal the health status and to make projections for the future.

Determining the health levels of populations with multifactorial structure has become much more difficult in terms of data collection, analysis and interpretation because a health indicator may measure a certain cituation directly, it may suggest the fact relatively and also interact with other indicators and co-factors. In this respect, identifying health indicators in the targeted area and investigating their impact on health outcomes is a process that needs to be carefully planned and executed. Also it is important using well confirmed, valid and reliable indicators as reference in both of identification of population health studies and development of new indicators studies (1-3).

In this context, two of important health indicators among health planners for determining health status are "Life Expectancy at Birth" (LEAB) and "Years of Potential Life Lost" (YPLL). Life expectancy at birth which includes the entire life course is a key criterion for assessing community health (4,5). YPLL is an estimate of the average number of years of a person who would have lived if he or she had not died prematurely. Therefore, it is a measure of premature mortality (6-8). In today's world, mortality and rates tend to evaluate the most common causes of death in the elderly. On the other hand, since YPLL also gives due weight to deaths among younger people so this makes it a valuable the indicator among those who wish to highlight to causes of death that occur throughout the population regardless of age (6-9).

The aim of the study is to evaluate the health indicators determined by international organizations that may be associated with life expectancy at birth and the years lost due to premature death in Türkiye and European Union countries with Panel Data Analysis (PDA) in a multivariate model.

2. Materials and Methods

This is an ecological study with Panel Data Analysis (PDA) of selected health indicators of EU countries and Türkiye using the Organization for Economic Cooperation and Development (OECD), Our World in Data and The Institute for Health Metrics and Evaluation Global Health Data Exchange (IHME-GHDx) platform's databases between 2000-2017 (10-12). Ethical approval was obtained from Eskişehir Osmangazi University Non-Invasive Clinical Researches Ethics Committee dated 06/08/2019 and with decision number 20.

2a.Determination of Health Indicators

The dependent and independent variables of the study are determined on the basis of OECD Health Data classification pattern (10). The OECD Health data classifies the health indicators in 5 main topics and each topic includes various variables. While modelling the panels, the first 4 main topics with given parameters are defined as independent variables and the last one (Health Status) including 2 parameters is defined as dependent variables as it is seen in below.

- ***Health care use:*** Child vaccination rates, length of hospital stay, hospital discharge rates (10).
- ***Health equipment:*** Hospital beds, Computed Tomography (CT) scanners, Magnetic Resonance Imaging (MRI) units (10).
- ***Health resources:*** Health spending, number of doctors, number of nurses (10).
- ***Health risks:*** Smoking prevalence rate, alcohol consumption, obesity prevalence rate (10).

- ***Health status:*** Life Expectancy at Birth (LEAB), Years of Potential Life Lost (YPLL) (10).

According to this map, the panels were configured to investigate the effect of selected independent variables on LEAB and YPLL dependent variables respectively.

2b. Variable Definitions and Details

Life Expectancy at Birth: The LEAB data were taken from the OECD Health Database (13,14). It is defined as the average number of years a person can expect to live if they experience the age-specific mortality rates prevalent in a given country and a given year. This indicator is measured as years (13,14).

Years of Potential Life Lost: The YPLL data were obtained from the IHME-GBDx database. The source defines it as: *"YPLL or YLL is the years lost due to premature death and is calculated by subtracting the age at death from the longest possible life expectancy"* (15). This indicator can be expressed in hundreds of thousands and even millions but presented with its eigenvalue in the relevant table and included in PDA as logarithmic transformation value so the results as interpreted as amount of percentage.

Child Vaccination Rates: In the OECD Health Database, child vaccination rate is presented under two subheadings: one for "measles" and one for "diphtheria-pertussis-tetanus"(16). In this study, data for the diphtheria-pertussis-tetanus were used and the unit of the indicator is percentage of children at around age 1. (16).

Length of Hospital Stay: This parameter refers to the average of days patients stay in hospital. *"The total number of days stayed by all inpatients during a year divided by the number of patients admitted or discharged"* is the explanation of measuremet (17). It is highlighted that day cases are excluded (17). There are two separate data sets for acute care cases and for childbirth without complications (17). The data for acute care cases were used in this study.

Hospital Discharge Rates: Hospital discharge rates reflects the number of patients who has spent at least one night in hospital and left after threatment or receiving care (18). The details about indicator is explained as "*the deaths that occur in hospital after inpatient care is included but same-day discharges are usually excluded. This parameter is measured per 100,000 inhabitants"* (18).

Hospital Beds: According to source of this data, curative (or acute) care beds, rehabilitative care beds, long-term care beds and other beds in hospitals are components of total hospital beds (19). The unit of parameter is total hospital beds per 1000 inhabitants (19).

Computed Tomography (CT) Scanners: It is presented as a total and also 2 sub-categories which split between hospitals *(primarily inpatient facilities)* and ambulatory care providers *(primarily outpatient facilities).* The measure for this indicator is the number of equipment per 1,000,000 inhabitants (20). The data of total is used in the study.

Magnetic Resonance Imaging (MRI) Units: The measure for this indicator is the number of equipment per 1,000,000 inhabitants. It is presented as a total and also 2 sub-categories which split between hospitals *(primarily inpatient facilities)* and ambulatory care providers *(primarily outpatient facilities)* (21). The data of total is used in the study.

Health Spending: In OECD Health Database, this parameter is seperated into government/compulsory, voluntary and out-of-pocket payment subcategories and also there is the total category. The data of total category with the unit defined as *"percentage of health expenditures in gross domestic product (GDP)"* are used in the study (22).

Number of Doctors and Nurses: The measure unit of these indicators are the number of doctors per 1000 inhabitants and the number of nurses per 1000 inhabitants (23,24).

Smoking Prevalence Rate: Smoking status is defined as the population aged 15 years and older who report smoking every day (25). In the study, data on this indicator were obtained from Our World in Data and the total category is used (25).

Alcohol Consumption: Data on alcohol consumption are taken from the OECD database (26). The age group of this indicator is people who are 15 or older and indicator reflects the annual sales of pure alcohol in liters per person in defined age group (26).

Obesity Prevalence Rate: The data for this indicator were obtained from Our World in Data database and the data of people who are 18 years or older in the population were used (27).

2c. Derivation of Data and Missing Data Assessment

Missing data is an important problem for researches and there are various methods to deal with it (28,29). For this reason, the countries and categories with minimum missing data were determined. If an indicator or country contains huge missing data which limits the use of other indicators or countries in same panel, that country or indicator was excluded. Also if there is no data for Türkiye in a category it is excluded from the relevant panel concept as well. In the study, 18 observations for the period 2000-2017 constitute the time series of the countries, and countries with more than one third (33%) of these (i.e. 7 or more missing value) were excluded from the study. For countries with 6 or less missing observation, the missing data were completed by taking into account the location and sequentiality of the missing data and the country's course for that parameter in related period. So the data used in PDA are consisted of complete or completed with suitable methodology like overall mean, nearest neighbour mean, increasing or decreasing trend of segmental part or overall. The data of smoking prevalence rate were obtained from Our World in Data platform, where the data between 2000 and 2010 are presented as three-point data for 2000, 2005 and 2010 years. In the completion of the data between the years 2000-2005, the missing data were completed by dividing the change amount between these two points by the number of years, and the data between 2005-2010 were similarly calculated by dividing the change amount between these two points by the number of years. Since the United Kingdom was an EU country during the study period, it was included in the panels.

2d. Constructing the Panels

It was given the numbers from 1 to 4 to the panels due to category name based on independent variables which are configured coherent with OECD Health Database pattern. For each panel, if the dependent variable is LEAB, it is added “A” label and if the dependent variable is YPLL, it is added “B” label.

At this point, the Panel 1 includes child vaccination rates, length of hospital stay, hospital discharge rates as independent variables and the panel which investigates the effect of these independent variables on LEAB dependent variable is named as Panel 1A, the panel which investigates the effect of these parameters on YPLL dependent variable is named as Panel 1B. Same configuration applied to all other panels too. Panel 2 includes hospital beds, Computed Tomography (CT) scanners, Magnetic Resonance Imaging (MRI) units as independent variables. It is named as Panel 2A for LEAB and Panel 2B for YPLL as dependent variable. Panel 3 includes health spending, number of doctors, number of nurses as independent variables. It is named as Panel 3A for LEAB and Panel 3B for YPLL as dependent variable. Panel 4 includes smoking prevalence rate, alcohol consumption, obesity prevalence rate as independent variables. It is named as Panel 4A for LEAB and Panel 4B for YPLL as dependent variable.

2e. Statistical Analysis

Time series data refers to data collected on a variable or situation based on a time period such as days, months, years, seasons (30-34). The horizontal cross-sectional data refers to the type of data formed by combining data obtained from different units at a certain point in time (30-34). In these two approaches, analyses are conducted separately and the results can not be interpreted as single common and blended result. Panel data is a type of data that combines both the data of

units and time series. Panel Data Analysis (PDA) is a 2-dimensional analysis in which these two are evaluated together. The advantage of this analysis is that the data belonging to a certain number of units in a certain time interval can be evaluated together in a single analysis and the results can be interpreted in a single common way (30-34).

In the study, time series data of countries are presented as descriptive statistics in the form of mean, standard deviation, median, minimum-maximum values and range *(Appendix 1 to 6)*. For the PDA, which constitutes the core of the study, a decision tree was adopted after an extensive literature review. The analysis consists of 5 steps and is given below respectively:

Step 1: It is tested the correlation between units in the panel data and the homogeneity/heterogeneity of the time series in the panel data. Swamy S test was used to test homogeneity and Pesaran CD Test was used to test correlation.

Step 2: The stationarity of the panel data was tested with unit root tests according to the result of the previous step.

Step 3: It is performed cointegration test in the panel data. Before the cointegration test, some steps were applied to analyse correlation in the whole dataset. After this process, the Westerlund (2016) Cointegration Test was used for cointegration test.

Step 4: Unobserved effects, fixed/random effects, correlation, autocorrelation and heteroskedasticity tests were performed in the panel data.

Step 5: Based on the previous findings, the process of determining the results with the appropriate estimator was performed. Parks-Kmenta estimator, Arellano Froot and Rogers estimator or Driscoll-Kraay estimator were used as estimators under matching conditions.

PDA was performed by R for Windows version 3.6.3 (35). In all steps of PDA, $p \leq 0.05$ was considered statistically significant based on 95% confidence interval and 5% margin of error.

3. Results

When the data of countries in the study are evaluated with LEAB perspective, the average with standard deviation (±SD) of 24 countries for the 2000-2017 period was 78.36 (±3.22) years. The top value for LEAB was observed in Spain with 83.40 years in 2016 and 2017, while the lowest value was observed in Latvia with 69.90 years in 2000. The country with the widest range recorded between 2000 and 2017 in Estonia with 7.30 years, followed by Türkiye with 7.00 years. At this point, the narrowest range belongs to Sweden with 2.80 years. *(See Appendix 1)*

When the 24 countries in the panels were evaluated with YPLL perspective, the average of the countries with SD for the 2000-2017 period was 3,466,956.63 (±3,837,599.77). The top value for YPLL was observed in Germany in 2000 with 14,283.797 and the lowest value belonged to Luxembourg in 2008 with 60,347. In the selected time period of 2000-2017, Türkiye has the widest range with 3,068,115, while Luxembourg has the narrowest range with 7885. *(See Appendix 1)*

Panel 1

The model constructed with the independent variables of child immunization rates, length of hospital stay and hospital discharge rate. The effect of these variables on each of the LEAB and YPLL dependent variables in Panel 1 is given in Table 1. The Panel 1 consists of 21 countries, 18 observations for each country for the period 2000-2017 and 378 values in total. *(See Appendix 2)*

Table 1. Parks-Kmenta Estimator results for Panel 1A and Panel 1B.

Panel 1A (Parks-Kmenta Estimator)				**Panel 1B (Parks-Kmenta Estimator)**			
Dependent Variable: LEAB **Observations:** 378 – **Countries:** 21				**Dependent Variable:** YPLL **Observations:** 378 – **Countries:** 21			
Independent Variable	**Coefficient**	**SE***	**Probability p**	**Independent Variable**	**Coefficient**	**SE***	**Probability p**
Child Vaccination Rates	0.030465	0.013059	**0.020**	Child Vaccination Rates	-0.023018	0.000219	**<0.001**
Length of Hospital Stay	-0.109689	0.096915	0.258	Length of Hospital Stay	-0.043226	0.005736	**<0.001**
Hospital Discharge Rates	-0.000036	0.000039	0.346	Hospital Discharge Rates	-0.000036	1.80e-07[a]	**<0.001**
Probability of Model (p) = 0.035				**Probability of Model (p)= <0.001**			

* *Standard Error*
a: 1.80x10^{-7}

The model is significant in both Panel 1A (p=0.035) and Panel 1B (p<0.001). In the Panel 1A each 1-unit value increase in the child vaccination rates variable shows an increase of approximately 0.03 units value in LEAB. In Panel 1B, a 1-unit value increase in the number of child vaccination rates variable leads to a decrease of approximately 0.02% in YPLL, and a 1-unit value increase in the length of hospital stay variable leads to a decrease of approximately 0.04% in YPLL, a 1-unit value increase in the hospital discharge rates variable leads to a decrease of approximately 0.00004% in YPLL.

Panel 2

The model is created with the independent variables which are hospital beds, Computed Tomography (CT) scanners, Magnetic Resonance Imaging (MRI) units. The effect of these parameters on each of the dependent variables of LEAB and YPLL in Panel 2A and 2B is given in Table 2. The Panel 2 consists of 20 countries, 18 observations for each country for the period 2000-2017 and 360 values in total. *(See Appendix 3)*

Table 2. Arellano-Froot and Rogers estimator results Panel 2A and Panel 2B.

Panel 2A (Arellano-Froot and Rogers Estimator)				**Panel 2B (Arellano-Froot and Rogers Estimator)**			
Dependent Variable: LEAB **Observations:** 360 - **Countries:** 20				**Dependent Variable:** YPLL **Observations:** 360 – **Countries:** 20			
Independent Variable	**Coefficient**	**SE***	**Probability p**	**Independent Variable**	**Coefficient**	**SE***	**Probability p**
Hospital Beds	-0.533810	0.315653	0.107	Hospital Beds	0.045875	0.040408	0.107
Computed Tomography (CT) Scanners	-0.071940	0.059144	0.239	Computed Tomography (CT) Scanners	-0.112106	0.036694	**0.002**
Magnetic Resonance Imaging (MRI) Units	0.187039	0.659370	**0.011**	Magnetic Resonance Imaging (MRI) Units	-0.034273	0.013404	**0.011**
Probability of Model (p)= <0.001				**Probability of Model (p)= <0.001**			

* *Standard Error*

The model is significant in both Panel 2A ($p<0.001$) and Panel 2B ($p<0.001$). In the Panel 2A each 1-unit value increase in the number of Magnetic Resonance Imaging (MRI) units variable leads to an increase of approximately 0.19 units of value in LEAB. In Panel 2B, a 1-unit value increase in the number of Computed Tomography (CT) scanners variable leads to a decrease of approximately 0.11% in YPLL, and a 1-unit increase in the number of Magnetic Resonance Imaging (MRI) units variable leads to a decrease of approximately 0.03% in YPLL.

Panel 3

The model is created with the independent variables which are health spending, number of doctors and number of nurses. The effect of these parameters on each of the dependent variables of LEAB and YPLL in Panel 3A and 3B is given in Table 3. The Panel 3 consists of 20 countries, 18 observations for each country for 2000-2017 period and 360 values in total. *(See Appendix 4)*

Table 3. Results of Driscoll-Kraay estimator for Panel 3A, Arellano-Froot and Rogers estimator for Panel 3B.

Panel 3A (Driscoll-Kraay Estimator)				**Panel 3B (Arellano-Froot ve Rogers Estimator)**			
Dependent Variable: LEAB **Observations: 360 - Countries: 20**				**Dependent Variable: YPLL** **Observations: 360 - Countries: 20**			
Independent Variables	**Coefficient**	**SE***	**Probability p**	**Independent Variables**	**Coefficient**	**SE***	**Probability p**
Health Spending	0.351369	0.136035	**0.019**	Health Spending	-0.183185	0.944482	**0.050**
Doctors	3.217506	0.253237	**<0.001**	Doctors	-0.413797	0.131901	**0.002**
Nurses	0.244775	0.070105	**0.003**	Nurses	0.004583	0.097868	0.963
Probability of Model (p)= <0.001				**Probability of Model (p)= <0.001**			

** Standard Error*

The model is significant in both Panel 3A ($p<0.001$) and Panel 3B ($p<0.001$). In the Panel 3A each 1-unit value increase in health spending variable shows an increase of approximately 0.35 units of value in LEAB, each unit value increase in the number of doctors variable shows an increase of approximately 3.22 units of value in LEAB and each unit increase in the number of nurses variable leads to an increase of approximately 0.25 units value in LEAB. In Panel 3B each 1-unit value increase in health spending leads to a decrease of approximately 0.18% in YPLL and each 1-unit value increase in the number of doctors leads to a decrease of approximately 0.41% in YPLL.

Panel 4

The model is created with the independent variables which are smoking prevalence rate, alcohol consumption, obesity prevalence rate. The effect of these parameters on each dependent variables LEAB and YPLL in Panel 4A and 4B is given in Table 4. The Panel 4 consists of 24 countries, 18 observations for each country for the period 2000-2017 and 432 values in total. *(See Appendix 5)*

Table 4. Parks-Kmenta estimator results Panel 4A and Panel 4B.

Panel 4A (Parks-Kmenta Estimator)				**Panel 4B (Parks-Kmenta Estimator)**			
Dependent Variable: LEAB **Observations** 432 - **Countries:** 24				**Dependent Variable:** YPLL **Observations:** 432 – **Countries:** 24			
Independent Variables	**Coefficient**	**SE***	**Probability p**	**Independent Variables**	**Coefficient**	**SE***	**Probability p**
Smoking Prevalence Rate	-0.02607	8.74e-06[a]	**<0.001**	Smoking Prevalence Rate	0.022265	0.006824	**<0.001**
Alcohol Consumption	-0.00030	0.000029	**<0.001**	Alcohol Consumption	-0.009134	0.008150	0.262
Obesity Prevalence Rate	-0.00158	0.000020	**<0.001**	Obesity Prevalence Rate	0.237553	0.011680	**0.042**
Probability of Model (p)= <0.001				**Probability of Model (p) = 0.007**			

a: 8.74x10^{-6}
** Standard Error*

The model is significant in both Panel 4A ($p<0.001$) and Panel 4B ($p=0.007$). In the Panel 4A each 1-unit value increase in the smoking prevalence rate leads to a decrease of approximately 0.026 units of value in LEAB, a 1-unit value increase in the amount of alcohol consumption leads to a decrease of approximately 0.0003 units of value in LEAB, and a 1-unit value increase in the obesity prevalence rate leads to a decrease of approximately 0.0015 units value in LEAB. In Panel 4B each 1-unit increase in the smoking prevalence rate variable leads to an increase of approximately 0.02% in YPLL and each 1 unit increase in the obesity prevalence rate leads to an increase of approximately 0.24% in YPLL.

4. Discussion

In the study, the determination of health indicators that may be associated with the LEAB and YPLL was based on data from European Union countries and Türkiye. It was found that the increase in child immunization rates, number of MRIs, health spending, number of doctors and nurses parameters were associated with the increase on LEAB, whereas the increase in smoking prevalence rate, alcohol consumption, obesity prevalence rate parameters were inversely associated. On the other hand, it is detected that increase in child immunization rates, length of hospital stay, hospital discharge rates, number of CT and MRIs, health spending, number of doctors parameters were associated with the decrease on YPLL, while increase in smoking prevalence rate and obesity prevalence rate parameters were associated with the increase on YPLL. Considering the overall, it is understood that the health indicators which may be associated with LEAB and YPLL overlap in most areas.

Vaccination is a proven tool for controlling and eliminating life-threatening infectious diseases, and childhood vaccination against vaccine-preventable diseases is considered one of the most cost-effective programs to reduce child mortality and morbidity worldwide. In Panel 1 of the study, the child vaccination rate indicator was found to prolong LEAB and decrease YPLL. In a PDA conducted by Mohan et al. with data of OECD countries between 1990 and 2002, it was reported that an increase in the vaccination rates of children in terms of measles have relation with increasing the LEAB and decreasing the infant mortality (36).

The interpretation of length of stay is complex situation. The evaluation of relationship between length of stay and quality of care is not easy because length of hospital stay is determined by an intertwined, multiple network of supply and demand that operates

at macro and micro levels (37,38). In Panel 1 of the study, the effect of length of hospital stay on LEAB could not be demonstrated, but its effect on YPLL was significant and an increase in length of hospital stay leads to a decrease in YPLL. It can be interpreted that diseases with long diagnosis and treatment processes require longer hospital stays, and therefore, as the time spent in the hospital increases, it can be interpreted as having a decreasing effect on the YPLL by allowing both accurate diagnosis and adequate treatment for these diseases. In the literature, it could not seen a study that addresses the effect of this parameter on health outcomes with PDA using a similar model to our study.

The hospital discharge rates variable which is also located in Panel 1 represents valuable data and is used in many fields including various government agencies, individual health service providers, consumer organizations, health insurers, policy makers, researchers and the private sector (39). In the study, no significant finding was found on the effect of hospital discharge rate on LEAB, but when the effect on YPLL was analyzed, it was found that an increase in hospital discharge rate leads to a decrease YPLL.

CT and MRI devices have been introduced to the health service as a result of the development and successful partnership between technology and medical science and they managed to decrease the time gap between diagnosis and treatment in some conditions . In Panel 2, it was found that the increase in the number of MRIs per capita leads to an increase LEAB, while the increase in the number of CT and MRIs per capita leads to a decrease YPLL. In a PDA study conducted by Mohan et al. using data from OECD countries between 1990 and 2002, it was reported that there is significant relation between the use of CT and increase in LEAB (36).

In Panel 3 of the study, it was found that the increase in health spending leads to an increase in LEAB and decrease in YPLL. It was reported that health expenditures had a significant positive relationship with LEAB using 2006-2010 data from 108 developing countries by Hassan et al. (40). In a PDA study conducted by Makuta et al. using data from 43 sub-Saharan African countries between 1996 and 2011, it was reported that public health expenditures had a significant effect on infant mortality and LEAB (41). Rahman et al. reported that total health expenditures, public health expenditures and private health expenditures did not have a significant relationship with LEAB in their PDA study conducted with data from 1995-2014 for 15 countries in South and South East Asia (42). In the PDA study conducted by Novignon et al. in 44 sub-Saharan African countries with data for the period 1995-2010, it was reported that health expenditures have relation with increasing the LEAB, decreasing the infant mortality and overall mortality (43). In a PDA study conducted by Rad et al. in Eastern Mediterranean Countries with data for the period 1995-2010, it was reported that there was a relation between health expenditures and reducing infant mortality (44).

Also in Panel 3, it was found that the increase in the number of doctors and nurses lead to an increase the LEAB. On the other hand, an increase in the number of doctors leads to a decrease the YPLL, but there was no significant relationship between the number of nurses and YPLL. In the literature, the effects of health workforce on health outcomes are also examined and the positive effect of the number of physicians and nurses per a certain number of people on health outcomes is emphasized (45-49). As an ecological finding, it has been suggested that a 1% increase in the supply of primary care physicians can reduce mortality by 0.08 per 100,000 population (47). In the PDA study conducted by Mohan et al. in 25 OECD countries with data from 1990-2002, it was reported that the number of physicians per 1000 persons had a significant effect on LEAB and mortality (36).

In the study it was found that increase in smoking rate leads to a decrease LEAB and increase YPLL. In a PDA study conducted by Kennelly et al. with data from 19 OECD countries, smoking was reported to have an

effect on LEAB and mortality (50). In a PDA study conducted by Poças et al. with 1980-2004 data from 17 OECD countries, it was reported that smoking was reported to have a negative effect on life expectancy (51). In another study conducted by Poças et al. on life expectancy at the age of 65 years and older, using PDA data from 20 EU countries for 1990-2016, smoking was reported to have a negative effect on life expectancy at the age of 65 years and older (52).

In the study, it is found that increase in alcohol consumption leads to a decrease LEAB but no significant relationship was found between it and YPLL. In a PDA study conducted by Kennelly et al. it was reported that alcohol use had a negative effect on LEAB in men, but there was no significant relation between alcohol use and LEAB in women (50). In a PDA study conducted by Poças et al. using 1980-2004 data from 17 OECD countries, it was reported that alcohol use negatively affected life expectancy (51). In another study which is conducted by Poças et al. with a PDA on life expectancy at the age of 65 years and older, this time using 1990-2016 data from 20 EU countries, it is reported that alcohol use had a negative effect on life expectancy at the age of 65 years and older (52). In a PDA study conducted by Mohan et al. with data from OECD countries between 1990 and 2002, there was no significant relation reported between alcohol use and LEAB (36).

In the study, it was found that the increase in the obesity rate in individuals aged 18 years and over, leads to a decrease in LEAB and an increase YPLL. Although there are many studies in the literature showing the effects of obesity on LEAB and YPLL using different methodologies, it could not be found a study examining the situation with PDA method as in our study.

5. Conclusions

The results show that despite the great and rapid progress in technology and medical science, the number of doctors is the factor that has the greatest impact on both LEAB and YPLL. This finding once again shows the indispensability and importance of the health professionals and human labor force. Another important result is the demonstration that cost-effective interventions like child immunization rates, fight against smoking, decrasing alcohol use and obesity prevalence can prolong LEAB and reduce YPLL.

Limitations

The study has some limitations depending on the research category and the methodology. The first of these is missing data issue. Obtaining the data which represents the whole of a country on a subject is a very challenging process, so even the reports presented by international organizations like WHO, OECD contain missing data. While forming the panels in the study, some countries or variables had to be left out of the panel due to missing data. This situation negatively affected the representation or reflection capacity of the PDA results in terms of the both some countries and variables.

On the other hand, the fact that these data are presented through multiple steps as a result of comprehensive and complicated studies by international organizations causes the data presented to be one or a few years behind. For this reason, 2017 data could be used as the most up-to-date and completed data for parameters included in the study period.

Before considering the results in total, it should be taken into account that the study was conducted in EU countries and Türkiye, which are at a better level of development than some of other continents or regions of the world.

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Ethics

Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Non-Invasive Clinical Researches Ethics Committee (Decision no: 20, Date: 06.08.2019).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was an ecological research with panel data analysis (PDA) and data is derived from databases of international organizations and platforms**.**

Author Contributions:

Idea/concept: E.A., S.M., F.Ç., Design: E.A., S.M., F.Ç., E.A., Data Collection: E.A., S.M., F.Ç., Data Processing: E.A., S.M., F.Ç., E.A., Analysis/Comment: E.A., S.M., F.Ç., E.A., Literature research/review: E.A., S.M., F.Ç., E.A., Writing: E.A., S.M., F.Ç., E.A.

All authors discussed the results and contributed to the final manuscript.

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Appendix 1. Descriptives of Life Expectancy at Birth (LEAB) and Years of Potential Life Lost (YPLL) dependent variables for the 24 countries between 2000 and 2017.

Countries	Life Expectancy at Birth (Years)						Years of Potential Life Lost					
	Mean	SD	Median	Min	Max	Range	Mean	SD	Median	Min	Max	Range
Austria	80.25	1.14	80.45	78.20	81.70	3.50	1215052.00	36548.99	1197520.50	1180700.00	1307087.00	126387.00
Belgium	79.86	1.23	80.00	77.80	81.60	3.80	1673634.33	59701.85	1665433.00	1590582.00	1794854.00	204272.00
Czechia	77.18	1.41	77.35	75.10	79.10	4.00	1931649.50	98742.38	1917968.00	1805074.00	2096597.00	291523.00
Denmark	79.02	1.46	78.90	76.90	81.20	4.30	882403.00	64569.39	885232.00	794794.00	977005.00	182211.00
Estonia	74.61	2.57	74.70	70.90	78.20	7.30	327689.72	55278.23	323677.00	258510.00	414710.00	156200.00
Finland	79.92	1.26	80.00	77.70	81.70	4.00	832226.78	27196.65	836775.00	779662.00	884470.00	104808.00
France	81.22	1.28	81.45	79.20	82.80	3.60	8631339.00	312429.82	8594607.50	8223334.00	9149309.00	925975.00
Germany	79.95	0.98	80.25	78.20	81.20	3.00	13482094.80	383896.30	13321593.00	13023853.00	14283797.00	1259944.00
Greece	80.26	0.93	80.35	78.60	81.50	2.90	1685472.28	24183.21	1684146.50	1642284.00	1738660.00	96376.00
Hungary	74.19	1.40	74.30	71.90	76.20	4.30	2514487.11	216994.57	2531290.50	2135071.00	2844750.00	709679.00
Ireland	79.83	1.64	80.25	76.60	82.20	5.60	518882.50	27179.95	514040.50	491745.00	587815.00	96070.00
Italy	81.67	1.10	81.65	79.90	83.30	3.40	8425276.56	293445.53	8385271.00	8004592.00	8992530.00	987938.00
Latvia	72.27	1.86	72.30	69.90	74.80	4.90	625835.11	91038.10	622944.00	501394.00	742503.00	241109.00
Lithuania	72.91	1.45	72.50	70.90	75.60	4.70	865335.94	88383.70	869485.00	736464.00	1018124.00	281660.00
Luxembourg	80.31	1.69	80.65	77.80	82.80	5.00	63802.33	2394.11	63672.50	60347.00	68232.00	7885.00
Netherlands	80.30	1.28	80.65	78.20	81.80	3.60	2244285.28	102953.21	2195613.00	2140679.00	2426415.00	285736.00
Poland	76.00	1.34	75.75	73.80	78.00	4.20	7512011.61	262580.71	7601766.50	7088683.00	7931141.00	842458.00
Portugal	79.44	1.54	79.60	76.90	81.50	4.60	1721984.83	126794.51	1708036.00	1550211.00	1946096.00	395885.00
Slovakia	75.26	1.33	75.15	73.40	77.30	3.90	1048081.28	45434.76	1068117.50	972249.00	1100287.00	128038.00
Slovenia	78.89	1.84	79.20	76.10	81.30	5.20	333426.89	25754.93	330043.50	296797.00	371803.00	75006.00
Spain	81.60	1.42	81.70	79.30	83.40	4.10	5912087.67	221795.61	5932984.00	5630693.00	6367578.00	736885.00
Sweden	81.26	0.91	81.40	79.70	82.50	2.80	1300653.17	46718.97	1304179.00	1242777.00	1378603.00	135826.00
Türkiye	74.51	2.44	74.00	71.10	78.10	7.00	10244071.30	937490.13	9745364.00	9495542.00	12563657.00	3068115.00
United Kingdom	79.94	1.20	80.10	77.90	81.40	3.50	9215176.17	435016.51	9176545.50	8636537.00	10039307.00	1402770.00
Total	78.36	3.22	79.20	69.90	83.40	13.50	3466956.60	3837599.77	1663399.50	60347.00	14283797.00	14223450.00

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

Appendix 2. Descriptives of child vaccination rates, length of hospital stay and hospital discharge rates independent variables for the 21 countries forming Panel 1 between 2000 and 2017.

Countries	Child Vaccination Rates (%)						Length of Hospital Stay (Days)						Hospital Discharge Rates (Per 100,000 inhabitants)					
	Mean	**SD**	**Median**	**Min**	**Max**	**Range**	**Mean**	**SD**	**Median**	**Min**	**Max**	**Range**	**Mean**	**SD**	**Median**	**Min**	**Max**	**Range**
Austria	86.96	4.83	85.50	81.00	98.00	17.00	6.81	0.38	6.75	6.40	7.60	1.20	26777.61	966.30	26814.50	24926.00	28115.00	3189.00
Belgium	97.38	1.61	98.00	95.00	99.00	4.00	7.41	0.54	7.30	6.60	8.20	1.60	16752.50	408.12	16931.00	16003.00	17242.00	1239.00
Czechia	97.71	1.11	97.95	95.80	99.00	3.20	6.86	0.83	6.70	5.80	7.90	2.10	20878.27	795.66	20609.50	19814.00	22366.00	2552.00
Estonia	94.03	0.87	94.00	92.80	95.90	3.10	6.08	0.51	6.00	5.50	7.30	1.80	17696.22	1011.18	17636.00	15639.00	19554.00	3915.00
Finland	97.38	2.65	98.00	89.00	99.00	10.00	6.92	0.24	7.00	6.40	7.20	0.80	18868.61	1673.82	18637.50	16424.00	21349.00	4925.00
France	97.93	1.00	98.00	96.10	99.00	2.90	5.73	0.18	5.70	5.40	6.10	0.70	17444.88	813.22	17193.50	16363.00	18954.00	2591.00
Germany	95.31	2.25	96.00	90.00	98.00	8.00	8.43	0.83	8.25	7.50	10.10	2.60	23276.11	2020.49	23464.50	19961.00	25686.00	5725.00
Greece	96.88	3.28	99.00	89.00	99.00	10.00	5.61	0.28	5.55	5.20	6.20	1.00	16838.22	3695.54	18171.00	8270.00	20636.00	12366.00
Hungary	99.86	0.08	99.80	99.80	100.00	0.20	6.12	0.55	5.90	5.50	7.10	1.60	22243.94	2331.79	21091.50	19494.00	25330.00	5836.00
Ireland	91.56	4.25	93.35	83.00	95.50	12.50	6.11	0.31	6.10	5.60	6.50	0.90	13500.94	312.12	13572.50	12863.00	14026.00	1163.00
Italy	94.66	2.26	95.40	87.00	97.00	10.00	6.79	0.11	6.80	6.70	7.00	0.30	14305.94	1990.00	14382.00	11597.00	17713.00	6116.00
Luxembourg	98.94	0.23	99.00	98.00	99.00	1.00	7.42	0.15	7.40	7.20	7.80	0.60	17030.55	1259.67	17167.00	15050.00	18859.00	3809.00
Netherlands	96.47	0.97	96.70	93.90	97.80	3.90	6.66	1.24	6.55	5.00	9.00	4.00	10389.61	1016.94	10064.00	9125.00	12219.00	3094.00
Poland	98.46	0.66	98.65	96.40	99.00	2.60	7.33	0.50	7.40	6.60	7.90	1.30	15397.64	1694.33	15549.00	13259.00	18152.00	4893.00
Portugal	96.70	1.83	98.00	93.20	98.60	5.40	8.72	0.24	8.75	8.30	9.40	1.10	8866.77	304.78	8914.00	8453.00	9271.00	818.00
Slovakia	98.41	1.16	99.00	96.00	99.40	3.40	7.04	0.60	6.95	6.20	8.40	2.20	19142.77	501.22	19116.00	18368.00	20252.00	1884.00
Slovenia	94.91	1.64	95.00	91.00	97.00	6.00	6.28	0.52	6.50	5.50	7.10	1.60	16794.50	1244.33	17004.00	14392.00	18457.00	4065.00
Spain	96.56	0.91	96.60	94.80	98.00	3.20	6.46	0.38	6.45	6.00	7.10	1.10	10461.77	352.34	10456.00	9906.00	11099.00	1193.00
Sweden	98.16	0.61	98.00	97.00	99.00	2.00	6.03	0.38	6.15	5.60	6.60	1.00	15762.00	585.18	15930.50	14014.00	16251.00	2237.00
Türkiye	90.64	9.29	96.00	68.00	98.00	30.00	4.61	0.77	4.10	3.90	5.80	1.90	12908.33	3445.00	13687.50	7712.00	17115.00	9403.00
United Kingdom	92.94	1.66	92.50	91.00	95.00	4.00	6.55	0.67	6.25	5.90	7.90	2.00	13064.22	181.63	13050.50	12767.00	13354.00	587.00
Total	**95.80**	**4.16**	**97.00**	**68.00**	**100.00**	**32.00**	**6.67**	**1.05**	**6.60**	**3.90**	**10.10**	**6.20**	**16590.55**	**4591.69**	**16831.00**	**7712.00**	**28115.00**	**20403.00**

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

Appendix 3. Descriptives of the number of hospital beds, Computed Tomography (CT) scanners, Magnetic Resonance Imaging (MRI) units independent variables for the 20 countries forming Panel 2 between 2000 and 2017.

Countries	Hospital Beds (Per 1000 inhabitants)						Computed Tomography (CT) Scanners (Per 1,000,000 inhabitants)						Magnetic Resonance Imaging (MRI) Units (Per 1,000,000 inhabitants)					
	Mean	**SD**	**Median**	**Min**	**Max**	**Range**	**Mean**	**SD**	**Median**	**Min**	**Max**	**Range**	**Mean**	**SD**	**Median**	**Min**	**Max**	**Range**
Austria	7.67	0.14	7.68	7.37	7.95	0.58	28.87	1.23	29.36	26.09	30.02	3.93	17.45	3.36	18.24	10.98	22.96	11.98
Belgium	6.19	0.32	6.20	5.66	6.72	1.06	15.76	4.89	13.84	10.50	23.92	13.42	9.10	2.18	10.49	6.03	11.78	5.75
Czechia	7.22	0.43	7.25	6.63	7.80	1.17	13.67	1.71	13.78	9.65	16.12	6.47	5.23	2.53	5.37	1.66	9.44	7.78
Estonia	5.49	0.59	5.43	4.69	7.04	2.35	12.49	5.56	14.97	4.62	19.78	15.16	6.92	4.60	7.86	1.24	13.68	12.44
Finland	5.99	1.33	6.41	3.28	7.54	4.26	18.38	4.00	19.42	13.27	24.51	11.24	17.84	5.34	15.67	9.85	27.05	17.20
France	6.84	0.66	6.78	5.98	7.97	1.99	11.66	3.38	10.96	7.01	17.36	10.35	6.91	3.92	6.24	1.65	14.21	12.56
Germany	8.41	0.32	8.29	8.00	9.12	1.12	31.00	3.50	31.19	24.61	35.34	10.73	24.69	6.47	24.37	14.32	34.71	20.39
Greece	4.59	0.26	4.73	4.20	4.93	0.73	29.92	4.60	31.14	22.97	36.13	13.16	19.03	5.29	20.88	11.86	26.91	15.05
Hungary	7.41	0.44	7.18	6.98	8.16	1.18	7.34	0.93	7.25	5.68	9.19	3.51	2.88	0.68	2.79	1.76	4.70	2.94
Ireland	4.13	1.46	3.91	2.54	6.13	3.59	13.76	3.62	14.62	8.08	19.14	11.06	10.28	3.32	10.43	5.75	15.18	9.43
Italy	3.77	0.49	3.74	3.17	4.71	1.54	29.73	4.30	31.40	21.13	34.71	13.58	19.66	6.91	20.82	7.76	28.66	20.90
Latvia	6.93	1.16	7.25	5.57	8.77	3.20	24.41	10.54	24.78	8.87	39.13	30.26	6.64	4.90	7.18	0.52	13.90	13.38
Lithuania	7.41	0.56	7.25	6.56	8.83	2.27	15.78	6.21	14.94	6.57	23.76	17.19	5.51	4.41	4.61	0.29	12.37	12.08
Luxembourg	5.64	0.69	5.52	4.66	6.86	2.20	24.18	3.68	25.14	16.77	28.38	11.61	10.61	3.69	11.87	2.26	14.06	11.80
Netherlands	4.16	0.49	4.29	3.28	4.92	1.64	9.60	3.35	10.57	4.57	13.75	9.18	9.61	2.96	10.67	5.80	13.02	7.22
Poland	6.62	0.09	6.63	6.42	6.80	0.38	11.45	4.62	11.63	4.42	17.33	12.91	3.92	2.60	3.32	0.79	7.93	7.14
Slovakia	6.55	0.70	6.56	5.75	7.86	2.11	13.24	3.35	13.76	7.84	17.88	10.04	5.53	2.67	6.13	1.11	9.56	8.45
Slovenia	4.74	0.26	4.64	4.49	5.40	0.91	11.24	2.21	11.95	7.63	15.00	7.37	7.12	2.53	6.90	3.00	11.61	8.61
Türkiye	2.59	0.11	2.60	2.45	2.81	0.36	10.23	3.84	11.15	4.16	14.77	10.61	6.41	3.96	8.29	0.56	11.01	10.45
United Kingdom	3.27	0.56	3.29	2.54	4.08	1.54	8.11	1.42	7.57	5.35	10.82	5.47	6.24	1.01	6.00	4.54	7.79	3.25
Total	**5.79**	**1.72**	**5.96**	**2.45**	**9.12**	**6.67**	**17.04**	**8.84**	**14.43**	**4.16**	**39.13**	**34.97**	**10.08**	**7.18**	**8.58**	**0.29**	**34.71**	**34.42**

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

Appendix 4. Descriptives of health spending, number of doctors and number of nurses independent variables for the 20 countries forming Panel 3 between 2000 and 2017.

Countries	Health Spending (% of GDP)						Number of Doctors (Per 1000 inhabitants)						Number of Nurses (Per 1000 inhabitants)					
	Mean	**SD**	**Median**	**Min**	**Max**	**Range**	**Mean**	**SD**	**Median**	**Min**	**Max**	**Range**	**Mean**	**SD**	**Median**	**Min**	**Max**	**Range**
Austria	9.89	0.42	9.88	9.20	10.37	1.16	4.60	0.43	4.64	3.85	5.18	1.33	6.29	0.45	6.41	5.55	6.85	1.30
Belgium	9.66	0.87	9.93	8.00	10.56	2.56	2.93	0.07	2.92	2.83	3.08	0.25	9.55	0.91	9.37	8.27	11.22	2.95
Czechia	6.72	0.61	6.74	5.72	7.81	2.09	3.75	0.42	3.57	3.37	4.89	1.52	8.00	0.11	8.03	7.61	8.11	0.50
Denmark	9.58	0.76	9.81	8.10	10.67	2.57	3.54	0.38	3.61	2.91	4.10	1.19	9.66	0.27	9.69	9.29	10.03	0.74
Estonia	5.61	0.68	5.74	4.70	6.62	1.92	3.21	0.20	3.27	2.78	3.47	0.69	6.10	0.22	6.15	5.64	6.41	0.77
Finland	8.64	0.87	8.72	7.14	9.77	2.64	2.87	0.31	2.77	2.50	3.39	0.89	13.11	1.29	13.48	10.71	14.44	3.73
France	10.75	0.69	10.85	9.58	11.58	2.00	3.32	0.03	3.32	3.26	3.37	0.11	8.33	1.20	8.05	6.66	10.48	3.82
Germany	10.62	0.51	10.59	9.89	11.37	1.49	3.69	0.35	3.58	3.25	4.25	1.00	11.38	1.02	11.27	9.99	13.13	3.14
Hungary	7.30	0.41	7.23	6.78	8.12	1.34	3.06	0.20	3.09	2.68	3.34	0.66	6.08	0.35	6.20	5.28	6.51	1.23
Latvia	5.75	0.29	5.71	5.40	6.24	0.84	3.06	0.17	3.13	2.69	3.23	0.54	4.90	0.34	4.87	4.51	5.61	1.10
Lithuania	6.25	0.44	6.19	5.51	7.36	1.85	3.97	0.31	3.88	3.63	4.56	0.93	7.48	0.14	7.50	7.25	7.71	0.46
Luxembourg	6.27	0.76	6.32	5.20	7.35	2.15	2.64	0.26	2.71	2.15	2.98	0.83	10.52	1.61	11.07	7.38	11.97	4.59
Netherlands	9.54	0.88	9.63	7.71	10.58	2.88	2.99	0.41	2.89	2.44	3.79	1.35	11.66	0.71	11.66	10.29	12.83	2.54
Poland	6.13	0.35	6.21	5.30	6.59	1.29	2.26	0.09	2.23	2.14	2.43	0.29	5.11	0.16	5.17	4.75	5.28	0.53
Slovakia	6.73	0.83	6.87	5.30	7.95	2.65	3.34	0.10	3.35	3.04	3.47	0.43	6.20	0.53	6.06	5.65	7.44	1.79
Slovenia	8.21	0.37	8.14	7.51	8.74	1.23	2.49	0.28	2.40	2.15	3.10	0.95	8.02	0.82	7.95	6.85	9.92	3.07
Spain	8.29	0.91	8.66	6.77	9.17	2.40	3.58	0.27	3.61	3.13	3.88	0.75	4.76	0.60	4.88	3.54	5.74	2.20
Sweden	9.19	1.35	8.35	7.37	10.98	3.61	3.69	0.39	3.71	3.02	4.27	1.25	10.57	0.43	10.76	9.62	10.94	1.32
Türkiye	4.81	0.42	4.93	4.14	5.53	1.40	1.60	0.18	1.62	1.30	1.87	0.57	1.48	0.35	1.43	1.06	2.07	1.01
United Kingdom	9.14	0.93	9.50	7.28	10.05	2.77	2.50	0.27	2.60	1.98	2.81	0.83	8.39	0.44	8.38	7.83	9.15	1.32
Total	**7.95**	**1.91**	**7.93**	**4.14**	**11.58**	**7.44**	**3.16**	**0.71**	**3.21**	**1.30**	**5.18**	**3.88**	**7.88**	**2.86**	**7.74**	**1.06**	**14.44**	**13.38**

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

Appendix 5. Descriptives of smoking prevalence rate, alcohol consumption and obesity prevalence rate independent variables for the 24 countries forming Panel 4 between 2000 and 2017.

Countries	Smoking Prevalence Rate (%)						Alcohol Consumption (Liters per Year)						Obesity Prevalence Rate (%)					
	Mean	SD	Median	Min	Max	Range	Mean	SD	Median	Min	Max	Range	Mean	SD	Median	Min	Max	Range
Austria	37.88	6.37	37.02	28.49	49.10	20.61	12.52	0.41	12.50	11.90	13.70	1.80	17.13	2.05	17.10	14.00	20.58	6.58
Belgium	32.21	3.05	32.00	27.74	37.40	9.66	10.63	0.77	10.45	9.40	12.20	2.80	19.65	1.69	19.65	17.00	22.45	5.45
Czechia	34.25	0.06	34.30	34.10	34.30	0.20	11.77	0.24	11.80	11.40	12.10	0.70	23.52	1.77	23.40	21.00	27.08	6.08
Denmark	27.12	6.32	26.50	18.30	38.30	20.00	11.10	1.61	10.70	9.10	13.10	4.00	16.95	1.89	16.90	14.00	20.11	6.11
Estonia	35.07	2.73	34.98	31.05	39.60	8.55	11.73	1.46	11.85	9.00	14.80	5.80	19.30	1.27	19.25	17.40	21.34	3.94
Finland	24.49	3.06	24.34	19.92	29.70	9.78	9.38	0.67	9.30	8.40	10.50	2.10	19.37	1.82	19.45	16.40	22.20	5.80
France	33.66	0.73	33.68	32.58	34.90	2.32	12.67	0.79	12.55	11.60	14.10	2.50	18.83	1.92	18.80	15.80	22.01	6.21
Germany	32.50	1.77	32.47	28.01	35.30	7.29	11.54	0.57	11.35	10.80	12.90	2.10	19.40	2.02	19.35	16.30	22.73	6.43
Greece	47.81	3.25	47.53	43.40	53.50	10.10	8.01	0.95	8.25	6.40	9.20	2.80	21.83	2.13	21.80	18.50	25.34	6.84
Hungary	35.23	3.46	35.06	30.05	41.10	11.05	11.91	1.04	11.65	10.60	13.30	2.70	22.97	2.34	22.85	19.60	26.92	7.32
Ireland	30.22	4.38	29.93	24.23	37.80	13.57	12.35	1.38	11.95	10.60	14.50	3.90	20.79	3.13	20.70	16.00	25.98	9.98
Italy	24.96	0.94	24.90	23.55	26.50	2.95	8.08	0.99	7.75	7.00	9.80	2.80	17.61	1.64	17.65	15.00	20.22	5.22
Latvia	37.51	0.50	37.35	36.92	38.80	1.88	9.89	1.68	10.15	6.70	12.60	5.90	21.47	1.46	21.40	19.30	23.91	4.61
Lithuania	31.94	2.35	31.79	28.43	35.90	7.47	12.91	1.48	13.20	9.70	14.70	5.00	24.00	1.58	23.95	21.60	26.63	5.03
Luxembourg	28.36	3.77	28.11	22.30	34.70	12.40	12.12	0.66	11.95	11.30	13.40	2.10	19.39	2.27	19.40	15.80	23.07	7.27
Netherlands	31.01	3.84	30.75	25.80	37.70	11.90	9.23	0.62	9.50	8.20	10.10	1.90	16.98	2.47	17.05	13.00	20.89	7.89
Poland	33.49	4.19	33.13	27.40	40.70	13.30	9.79	0.94	10.20	7.80	10.80	3.00	20.36	1.88	20.30	17.50	23.50	6.00
Portugal	24.10	1.07	24.03	22.54	25.90	3.36	11.30	1.01	11.50	9.50	12.80	3.30	17.46	2.38	17.45	13.70	21.29	7.59
Slovakia	30.59	0.60	30.40	30.05	32.10	2.05	10.38	0.45	10.20	9.70	11.20	1.50	18.03	1.68	17.95	15.50	20.87	5.37
Slovenia	24.45	1.40	24.39	22.26	26.80	4.54	11.10	0.99	11.00	9.50	13.50	4.00	17.69	1.71	17.65	15.10	20.57	5.47
Spain	33.84	3.37	33.98	28.77	39.50	10.73	10.70	0.99	10.75	9.20	12.40	3.20	21.19	1.83	21.15	18.30	24.17	5.87
Sweden	24.69	4.46	24.39	18.17	32.30	14.13	6.96	0.34	7.00	6.20	7.40	1.20	17.69	2.02	17.60	14.60	21.03	6.43
Türkiye	32.12	3.71	31.88	26.64	38.40	11.76	1.42	0.10	1.40	1.20	1.60	0.40	27.34	3.35	27.25	22.20	32.80	10.60
United Kingdom	29.14	5.28	28.73	21.36	38.20	16.84	10.37	0.76	10.25	9.40	11.60	2.20	23.41	3.06	23.35	18.60	28.38	9.78
Total	**31.53**	**6.27**	**31.51**	**18.17**	**53.50**	**35.33**	**10.33**	**2.58**	**10.80**	**1.20**	**14.80**	**13.60**	**20.10**	**3.35**	**19.80**	**13.00**	**32.80**	**19.80**

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

Case Report / Olgu Sunumu

Clear Cell Sarcoma of the Kidney: A Remarkably Uncommon Case Report

Böbreğin Berrak Hücreli Sarkomu: Oldukça Nadir Bir Olgu Sunumu

[1]Emel Tekin, [1]Osman Furkan Mülkem, [2]Ersin Töret

[1] Eskisehir Osmangazi University Faculty of Medicine Department of Pathology, Eskisehir, Turkiye
[2]Eskişehir Osmangazi University, Faculty of Medicine, Department of Pediatric Hematooncology, Eskisehir, Turkiye

Abstract: Clear cell sarcoma of the kidney (CCSK) is one of the most common malignant renal neoplasms in childhood, although it is quite rare. Its incidence peaks around the age of 3 and it is twice as common in males. We present a rare case of CCSK showing a rare histopathological pattern in terms of age and gender. A 7-month-old female patient presented with complaints of vomiting, abdominal swelling, and diarrhea. Imaging analysis revealed a mass in the right kidney, and right radical nephrectomy was performed, considering Wilms tumor (WT). There was a solid gray-white mass that completely filled the kidney, with a maximum dimension of 8.5 cm, macroscopically. The samples obtained showed intratubular structures within the tumor and kidney parenchyma in limited areas at the periphery. The tumor had a normochromic monotonous nucleus with occasional clear cytoplasm and mostly exhibited a palisade-like arrangement pattern. In the differential diagnosis, with blastemal WT and Ewing sarcoma being the primary considerations, the positivity of CyclinD1 markers, negativity of other markers, and morphological characteristics were evaluated in favor of CCSK with a palisaded Schwannian pattern. The patient was put on an intensive chemotherapy process, but was lost after relaps at weet 24. CCSK is seen in a similar age group as WT but is distinguished by its rarity and relatively worse prognosis. Histopathologically, it most commonly presents in a myxoid pattern and least commonly in anaplastic pattern. The palisaded schwannian type seen in our case is recorded at a rate of 11%. No spesific diagnostic marker has been identified immunohistochemically, but the overexpression of markers such as CyclinD1, BCOR, and EZH2 is reported to be helpful in diagnosis. Due to its high metastatic potential and limited treatment options, further research is needed to understand the molecular nature of the disease.
Keywords: Clear cell sarcoma of the kidney, Case report, Rare tumor of the childhood, Malignant renal tumor of the childhood

Özet: Böbreğin berrak hücreli sarkomu (BBHS) oldukça nadir görülmekle birlikte çocukluk çağının en sık görülen malign böbrek neoplazilerinden biridir. İnsidansı 3 yaş civarında pik yapmakta olup erkek cinsiyette 2 kat daha sık görülmektedir. Nadir bir yaş ve cinsiyette nadir bir histopatolojik patern gösteren BBHS olgusu sunduk. 7 aylık kız hasta kusma, karında şişlik ve ishal şikayeti ile başvurdu. Yapılan görüntüleme analizinde sağ böbrekte kitle saptanması üzerine Wilms tümörü (WT) düşünülerek sağ radikal nefrektomi uygulandı. Makroskopik olarak en büyük boyutu 8,5 cm olan böbreğin tamamını dolduran solid gri-beyaz kitle mevcuttu. Alınan örneklerde tümör içerisinde entrape tübül yapıları ve periferde sınırlı alanlarda böbrek parankimi seçilmekteydi. Tümör normokromatik monoton nükleuslu yer yer şeffaf sitoplazmalı ve çoğunlukla palizat benzeri dizilim paterninde idi. Ayırıcı tanıda başta blastemal WT ve Ewing sarkomu da düşünülerek yapılan belirteçlerden SiklinD1 pozitifliği, diğer markırların negatifliği ve morfolojik özellikleri ile olgu palizatlanan schwannian paternde BBHS lehine değerlendirildi. Olgu yoğun kemoterapi sürecine alındı ancak 24. hafta relaps sonrası kaybedildi. BBHS, WT ile benzer yaş grubunda görülmekle birlikte oldukça nadir olması ve nispeten daha kötü prognozlu olması ile ayrılmaktadır. Histopatolojik olarak en sık miksoid, en az anaplastik paternde karşımıza çıkmaktadır. Olgumuzda görülen palizatlanan schwannian tip ise %11 oranında kaydedilmiştir. İmmunohistokimyasal olarak spesifik tanı koydurucu bir belirteç henüz tanımlanmamış olup SiklinD1, BCOR, EZH2 gibi markırların overekspresyonunun tanıya yardımcı olduğu bildirilmektedir. Metastaz potansiyeli yüksek ve tedavi alternatifi kısıtlı olması nedeni ile hastalığın moleküler doğasını anlamak için yeni araştırmalara ihtiyaç vardır.
Anahtar Kelimeler: Böbreğin şeffaf hücreli sarkomu, olgu sunumu, Çocukluk çağının nadir tümörü, çocukluk çağı malign böbrek tümörü

ORCID ID of the authors: ET. 0000-0001-7297-9869 OFM. 0000-0001-9875-1985 ET. 0000-0002-6379-8326

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Correspondence: Emel TEKİN - Eskisehir Osmangazi University Faculty of Medicine Department of Pathology, Eskisehir, Turkiye
e-mail: emelyaldir@gmail.com

1. Introduction

Clear cell sarcoma of the kidney (CCSK) is a rare kidney tumor that often appears in the early years of life. It constitutes approximately 2.8% of primary childhood kidney tumors (1). However, its incidence is reported as 0.2 per million in the overall group of childhood cancers (2). CCSK is dominant in males and more often between the ages of 2-3 years (male to female ratio of 2.63) (3). It is extremely rare in infants younger than 6 months and young adults.

Orginially called ‘’Bone-metastasizing renal tumor of childhood’’ in 1978 (4), in has a high potential for malignancy. It is known to have a worse prognosis compared to Wilms tumor (WT), which is more commonly encountered in the same age group (3). We presented an extremely rare histopathological subtype and clinical case of CCSK.

2. Case Report

A 7-month-old girl presented to the hospital with complaints of vomiting, abdominal distension, and diarrhea that had been ongoing for a month. During the physical examination, a mass was palpated in the right side of the abdomen. Abdominal ultrasound revealed a solid mass with a size of approximately 8 cm, originating from the medial parenchyma of the right kidney and showing an exophytic extension into the abdomen with widespread arterial and venous vascularity, as well as a heterogeneous internal structure and smooth contours. A mass was confirmed on magnetic resonance imaging, and compression of the inferior vena cava and right renal vein was present in the vicinity of the mass. However, no trombus was detected within the vascular lumen. Based on clinical and imaging analysis results, the patient underwent a right radical nephrectomy and was sent to the pathology laboratory with a preliminary diagnosis of WT. Macroscopically, a heterogeneous mas with smooth margins and dimensions of 8.8x8.5x8 cm was observed, consisting of gray-white and grey-brown areas that covered the entire surface of the kidney on the cut section. Capsule seemed intact. Numerous samples were taken from different areas. Histopathologically, the tumor consisted of cells with sharp borders that were separated from the renal parenchyma, which was focally selected in microscopic foci around the tumor. Most of these cells had small to medium-sized uniform nuclei with irregular nuclear membranes and focal clear cytoplasm arranged in a schwannoma-like pattern (Figure 1). There were numerous mitotic figures in the background. Additionally, angioinvasion was observed (Figure 2). Vimentin, Bcl-2, CyclinD1, CD99, CD56, INI1, and FLI1 were diffusely positive, whereas WT-1, SMA, EMA, CK AE1-AE3, PAX8, Synaptophysin, Chromogranin A, Myo-D1, CD57, Neurofilament, NSE, S100, Myogenin, Desmin, ALK-1, and CD34 were negative, indicating differential diagnosis from WT and other childhood kidney tumors. The Ki-67 proliferation index was around 40% (Figure 3). Based on the histopathological and immunohistochemical findings, the case was diagnosed as a CCSK with palisading Schwannian histological subtype. Therefore, the patient was treated according to the National Wilms Tumor Study Group 5th version (NWTS-V) protocol. Abdominal radiotherapy was administered from the 10th week of the 24-week treatment. Despite being in remission at the 6th and 18th weeks, abdominal and cerebral metastases were detected at the end of the treatment. Unfortunately, the patient, who deviated from the protocol, passed away within one month.

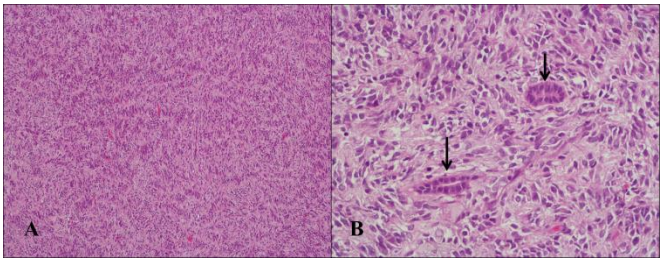

Figure 1. Verocay body-like palisading of neoplastic cells, H&E, X40 (A), abundant mitotic figures are observed in the tumoral infiltration composed of uniform hypochromatic nuclei, and there are also entrapped renal tubular structures (black arrow) in between, H&E, X200 (B)

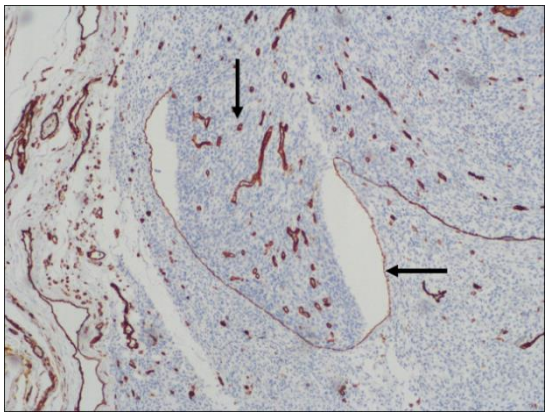

Figure 2. Vascular invasion of tumor cells, CD31, immunohistochemistry, X100

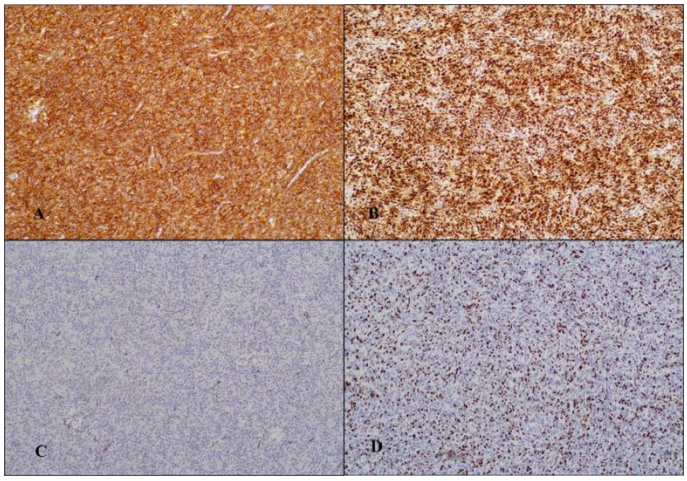

Figure 3. The tumor shows positivity for CD56 (A) and Cyclin D1 (B), negativity for WT1 (C), and Ki-67 proliferation index of 40% (D), immunohistochemistry, X40

3. Discussion

CCSK ranks second among childhood kidney malignancies. Approximately 90% of tumors in this group are composed of WT (1, 5). The most common symptoms observed in patients are abdominal pain, distension or mass, nausea, vomiting, weight loss, subfebrile fever, hamaturia, and anemia. It is known for its aggressive clinical behavior and late recurrence (6). WT is the most important differential diagnosis for CCSK. While WT shows different incidences according to ethnic groups, such a characteristic has not been

identified for CCSK. Genetic factors are thought to play a major role in its pathogenesis.

CCSK can present with a wide range of histopahological morphologies. The described patterns and frequencies include myxoid (50%), sclerosing (35%), cellular (26%), epitheloid (trabecular or acinar type) (13%), palisading verocay bodies (11%), spindle cell (7%), storiform (4%), and anaplastic (2.6%), with patterns frequently coexisting within the tumor (7). Classical morphology consists of cell nests or cords separated by thin and branching fibrovascular septa, giving a ‘’chicken-wire’’ appearance. Cord cells contain clear cytoplasm and monotonous round-to-oval-shaped nuclei with fine chromatin and indistinct nucleoli. Hypochromatic finely dispersed chromatin is an important cytologic feature helpful in distinguishing this tumor from mimickers (8). Differentiating CCSK, especially blastemal WT, congenital mesoblastic nephroma, rhabdoid tumor, primitive neuroectodermal tumor, extra-skeletal Ewing's sarcoma and neuroblastoma is important for the correct treatment protocol and prognostic approach (9). WT has an early tendency to metastasize, classically spreads to lymph nodes, lungs, and liver, but bone metastasis is rare. WT can have a bilateral onset in 5% of cases, but such a feature has not yet been reported for CCSK. In contrast to WT, no relationship has been shown between CCSK and congenital anomalies (10).

There is no spesific immunohistochemical marker identified for CCSK. It shows positivity with Vimentin and weak positivity with Actin. Negativity for EMA, Desmin, S100, WT1, CD56, CD99, Synaptophysin, CKAE1-AE3, CAM5.2 supports the diagnosis (8, 11). The overexpression of CyclinD1 has been detected in recent times and it is recommended as an auxiliary diagnostic tool (12). Although BCOR positivity has been suggested to be supportive, negative cases with molecularly proven diagnosis have also been reported (13). In some recent molecular studies, it has been found that the tumor exhibits overexpression of EZH2 messenger RNA (14).

The treatment protocol consists of systemic chemotherapy and local radiotherapy in addition to radical surgery (15). The prognosis has improved in recent times with the application of more intensive chemotherapy or radiotherapy, but the need for alternative targeted therapies persists due to the toxic effects of intensive therapy. Relapse is observed in approximately 16% of patients within 17 months of diagnosis. The most common sites of relapse are the brain, lungs, and bones, and the prognosis after relapse is quite poor (16).

This case was in a rarer age group and gender compared to the cases in the literature, and it had a rare histopathological pattern, palisaded variant like schwannoma. It is a challenging diagnosis clinically, radiologically, and histopathologically, and it is necessary to differentiate it from mimickers due to its poor prognostic features. Molecular investigations are recommended for cases that cannot be ruled out with immunohistochemical markers for clarification of the diagnosis.

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Ethics

Informed Consent: The authors declared that informed consent form was signed by the patient.

Copyright Transfer Form: Copyright Transfer Form was signed by the authors.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices: ET, OFM, ET. Concept: ET. Design: ET, OFM. Data Collection or Processing: ET, OFM, ET. Analysis or Interpretation: ET, ET. Literature Search: ET, OFM. Writing: ET, OFM.

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Case Report / Olgu Sunumu

Jejunal Divertikülozis- Tanısal Laparotominin Yeri

Jejunal Diverticulosis- The Place of Diagnostic Laparotomy

Arda Şakir Yılmaz, Bartu Badak

[1]Sivrihisar İlçe Devlet Hastanesi Genel Cerrahi Kliniği, Eskişehir, Türkiye
[2]Eskişehir Osmangazi Üniversitesi, Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Eskişehir, Türkiye

Özet: Jejunoileal divertiküloz, sıklıkla asemptomatik seyir gösteren ince bağırsağın divertiküler hastalığıdır. Divertiküler hastalık, esas olarak kolonu etkileyen nispeten yaygın bir hastalık olmasına rağmen daha az ölçüde sırasıyla ince bağırsağın farklı kısımlarını; duodenumu, jejunumu ve ileumu da etkileyebilir. Toplumda nadir görülen bu hastalık, gelişebilecek komplikasyonlar nedeniyle tanı ve tedavisinin iyi bilinmesi gerekmektedir. Jejunal perforasyon en sık görülen komplikasyondur. Bunun dışında obstrüksiyon ve divertiküler kanama da görülebilmektedir. Hastalık tanısı koymak, semptomların spesifik olmaması ve görüntüleme gereksinimi veya acil laparotomi sırasında anlaşılması nedeniyle oldukça zordur. Biz de bu olgu ile tanınması oldukça zor ve tedavi seçenekleri iyi bilinmeyen bu hastalık konusunda tedavi yaklaşımını göstermeye çalıştık.
Anahtar Kelimeler: Divertiküloz, Bağırsak, Küçük, Karın, Akut

Abstract: Jejunoileal diverticulosis is a diverticular disease of the small intestine with a frequently asymptomatic course. Although diverticular disease is a relatively common disease affecting mainly the colon, to a lesser extent it can also affect different parts of the small intestine; duodenum, jejunum, and ileum respectively. This disease is rare in the community and its diagnosis and treatment should be well known due to the complications that may develop. Jejunal perforation is the most common complication. Obstruction and diverticular bleeding may also occur. Diagnosis of the disease is very difficult due to non-specific symptoms and the need for imaging or recognition during emergency laparotomy. In this case report, we tried to demonstrate the treatment approach for this difficult to diagnose and poorly understood disease.
Keywords: Diverticulosis, Intestine, Small, Abdomen, Acute

ORCID ID of the authors: AŞY. 0000-0003-1269-0814, BB. 0000-0003-3465-8719

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Correspondence: Arda Şakir YILMAZ - Sivrihisar İlçe Devlet Hastanesi Genel Cerrahi Kliniği, Eskişehir, Türkiye
e-mail: dr.ardayilmaz@hotmail.com

1. Giriş

Jejunoileal divertiküloz (JID), musküler tabaka olmaksızın mukoza ve seroza çıkıntıları olan yalancı divertiküller olarak tanımlanmaktadır. Toplum prevelansı %0.1 olan nadir bir hastalıktır. Genellikle asemptomatik bir hastalık olup, herhangi bir nedenle yapılan görüntüleme veya ameliyat sırasında tesadüfen saptanır. (1, 2) Ancak nadir durumlarda jejunal divertikülozis; divertikülit, perforasyon ve obstrüksiyon gibi komplikasyonlarla da karşımıza çıkabilmektedir.(3, 4)

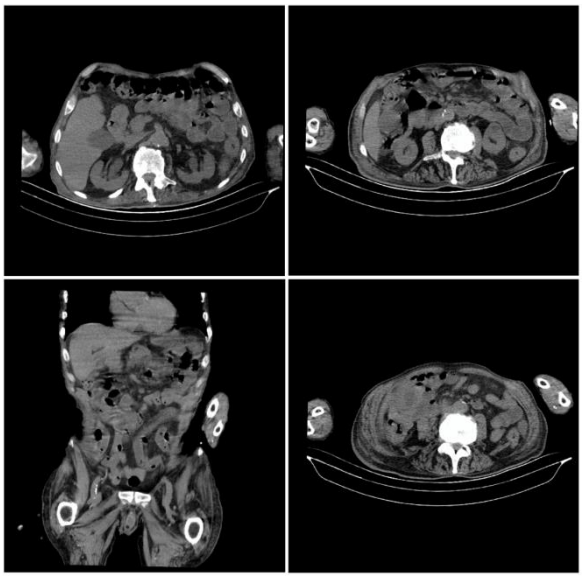
Biz de ishal ve şiddetli karın ağrısı şikâyeti ile başvuran, laparotomi sırasında jejunal divertiküloz saptanan bir olguyu görüntüler eşliğinde sunmayı amaçladık.

2. Olgu Sunumu

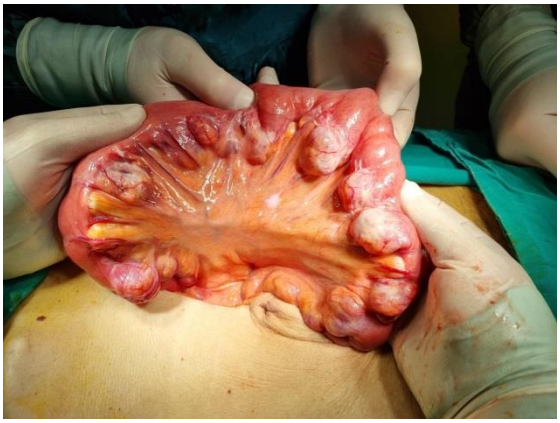
87 yaşında erkek hasta yaklaşık 3 gündür başlayan ishal, gittikçe artan kıvrandırıcı tarzda karın ağrısı olması nedenli acil servise başvurmuş. Bilinen kronik hastalık öyküsü bulunmayan, yaklaşık 15 yıl önce benign prostat hiperplazisi nedenli opere olan hastanın sürekli kullandığı herhangi bir ilacı bulunmuyor. Acil serviste yapılan fizik muayenede bilinç bulanıklığı mevcut, nörolojik motor defisit yok ve karın muayenesinde akut batın bulguları saptanmış. Çalışılan kan parametrelerinde hemoglobin 11.5 g/dl, lökosit 14200 uL, C-reaktif protein 158.8 mg/L, kreatinin 1.32 mg/dl, üre azotu 42.5 mg/dl, kalsiyum 7.48 mg/dl; kan gazında pH 7.17, laktat 2.2 mmol/L, bikarbonat 4 mmol/L, baz eksisi -23.8 mmol/L olarak ölçülmüş. Bunun üzerine perforasyon şüphesiyle hastaya abdomen bilgisayarlı tomografi (BT) çekilmiş. BT'nin yorumunda ince bağırsak mezosu kalın ve ödemli görünümde, karın içi minimal sıvı, superior mezenterik arterde akut-kronik ayrımı yapılamayan trombüsden bahsedilmiş (Resim 1). Ardından akut batın ve mezenter iskemi ön tanısı ile genel cerrahi kliniğine konsülte edilmiş.

Tarafımızca yeniden değerlendirilen hasta, acil cerrahi müdahale amacıyla yoğun bakıma yatırıldı. Bilgilendirilmiş onamlarının alınmasının ardından hasta ameliyata alındı. Orta hat insizyon ile laparotomi sonrası eksplorasyonda; karın içi reaksiyonel minimal sıvı görüldü, fakat bağırsaklarda herhangi bir perforasyon veya iskemiye rastlanmadı. Mikroperforasyon açısından tüm bağırsak segmentleri ayrıtılı incelendi. Treitz'dan itibaren 150 cm.'lik segmentte yaklaşık 30 adet divertikül, aynı segment bağırsak mezosunda kalınlaşma (panniküllit) ve milimetrik lenfadenopatiler izlendi (Resim 2). Ayrıca sigmoid kolonunun 20 cm.'lik kısmında yine divertiküller izlendi (Resim 3). Ancak herhangi bir mikroperforasyona rastlanmadı. Ardından karın içi bol izotonik solüsyonlar ile yıkandı ve batın uygun şekilde kapatılarak ameliyata son verildi.

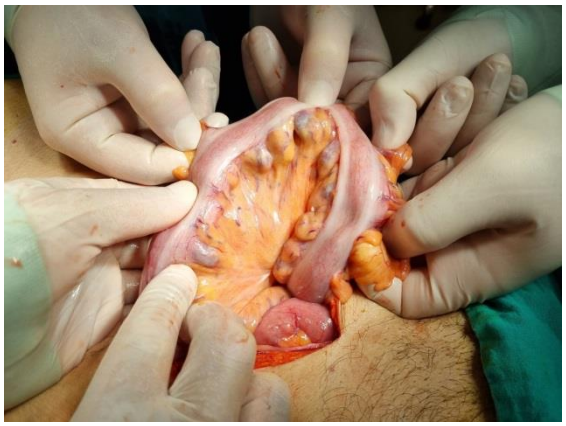
Ameliyat sonrası yoğun bakıma alınan ve entübe halde takibe alınan hasta, enfeksiyon hastalıklarına danışıldı. İmipenem tedavisi başlanan hastanın takiplerinde halen akut faz reaktanlarının yüksek seyretmesi, vitallerinin hipovolemik ve taşikardik olması nedenli yeniden enfeksiyon hastalıklarına konsülte edildi. Enfeksiyon hastalıklarının yeni önerisi ile meropenem ve vankomisin tedavisine geçildi. Tedavi sonrası takiplerinde akut faz yanıtı azalan, vitalleri düzelen hasta extübe edildi. Bilinç durumu da düzelen hasta, yaklaşık 10 gün sonra şifa ile taburcu edildi.



Şekil 1. İnce bağırsak mezosunda kalınlaşma ve ödem (BT görünümü)



Şekil 2. Jejenumda divertiküloz görünümü



Şekil 3. Sigmoid kolonda divertiküloz görünümü

3. Tartışma

Jejunoileal divertiküloz ilk olarak 1794'te Somerling tarafından, ardından 1809'da Astley Cooler tarafından tanımlanmış ve tüm ince barsak divertikülozlarının sadece %18'ini oluşturan nadir bir hastalıktır.(5, 6) Divertiküler hastalık, esas olarak kolonu etkileyen nispeten yaygın bir hastalıktır, ancak daha az ölçüde sırasıyla ince bağırsağın farklı kısımlarını; duodenumu, jejunumu ve ileumu da etkileyebilir.(7, 8)

Semptomatik ince barsak divertikülozu olan 208 hastanın retrospektif bir incelemesinde, divertiküllerin yüzde 79'u duodenumda, yüzde 18'i jejunum veya ileumda ve yüzde 3'ünde ise her üç segmentte yer aldığı saptanmıştır.(1) İnce barsak divertikülü olan hastaların %60'ında aynı anda kolon divertikülü vardır.(9, 10) Bizim hastamızda da yoğunluk olarak jejenumda divertiküllerin yoğun olmasına rağmen eş zamanlı sigmoid kolonda da divertikülleri mevcuttu.

Etiyolojisi, kolon kaynaklı divertikülüza benzer şekilde, bağırsak duvarındaki vasa recta penetrasyonuna bağlı yapısal zayıflık ile ilişkilidir. Bu zayıf noktalardan kas tabakası boyunca mukoza, submukoza ve seroza çıkıntıları gelişerek mezenterik barsak duvarında ince duvarlı pulsiyon tipi divertiküller oluşur.(11, 12)

Hastaların %40'ı asemptomatik olmasına rağmen, prezentasyonlar genellikle spesifik olmayan, belirsiz semptomlar şeklindedir.(6) Erken evre tanı genellikle görüntüleme ile tesadüfen veya başka nedenlerle intraoperatif olarak konur. Altın standart görüntüleme yöntemi kontrastlı BT'dir. JID, klinik duruma ve başvuru anındaki komplikasyonlara bağlı olarak konservatif veya cerrahi olarak yönetilebilir.(11)

Jejunum ve ileumda bulunan divertiküller, duodenal olanlardan daha az görülür, ancak komplikasyon gelişme şansı çok daha yüksektir. Jejunal perforasyon en sık görülen komplikasyondur, ancak obstrüksiyon ve divertiküler kanama da görülebilir.(13, 14) Genel olarak, hastaların yaklaşık %10'unda komplikasyon gelişebilmektedir.(10)

JID genellikle yaşamın altıncı veya yedinci on yılındaki yaşlı erkek popülasyonunu etkiler ve hastanın geçmişte kolonik divertiküler hastalığı varsa risk artar. Ayrıca çalışmalar, divertiküler hastalığın aileden geçtiğini göstermektedir.(5) Kesin etiyoloji hala bilinmemekle birlikte, bazı çalışmalar intestinal diskinezi, peristalsis anormalliği ve yüksek intraluminal basınç gibi divertiküloz gelişme riskini artıran risk faktörlerini göstermektedir.(15)

Lokal inflamasyon bulguları, dilatasyon ve bağırsak mezosunda kalınlaşması ile birden fazla alanla ilişkili ekstraluminal sıvı varlığı hastamızdaki ana bulgulardı.

JID'nin yönetimi, klinik duruma ve başvuru anındaki komplikasyonların varlığına bağlı olarak medikal veya acil laparotomi şeklinde olabilmektedir. Örneğin, non-perfore lokalize peritonit durumunda, invaziv cerrahi girişime gitmeden önce geniş spektrumlu antibiyotiklerle medikal tedavi, barsak istirahati ve lokalize intraperitoneal toplama için perkütan görüntü kılavuzluğunda aspirasyon denenebilir.(5, 6, 11) Bununla birlikte, jeneralize peritonit veya tıbbi tedavinin başarısız olduğu komplike JID'de kesin tedavi olarak segmental barsak rezeksiyonu ve anastomoz yapılabilir.

Son olarak, mevcut rapor, ince barsak divertikülozunun tanı ve tedavisinde yer alan zorluklar hakkında bilgi vermektedir. JID, akut karın ağrısı ile başvuran yaşlı hastaları değerlendirirken gözden kaçırılmaması gereken nadir bir durumdur. Erken tanı önemlidir ve cerrahi kararı vermek için BT taramaları son derece yararlıdır. Ameliyathanede bağırsağın dikkatli bir şekilde değerlendirilmesi, cerrahi ekibin bağırsak rezeksiyonunun farklı uzantılarına ve hatta gerektiğinde deviasyona karar vermesine yardımcı olacaktır. JID, normal ince barsak patolojisinin nadir ve ilginç bir varyasyonudur. Sadece potansiyel olarak ölümcül klinik etkileri nedeniyle değil, aynı zamanda ortaya çıkardıkları patofizyolojik muamma nedeniyle de oldukça dikkat çekmektedir. Fizyolojik olarak rahatsız edici bir invaziv araştırmadan ziyade konservatif

bir yaklaşıma yönlendirilebileceğinden, cerrahlar bu hastalığın varlığına karşı yeterince uyanık olmalıdır.

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Etik Bilgiler

Aydınlatılmış Onam: Hastaya aydınlatılmış onam formu imzalatıldığı beyan edilmiştir.

Telif Hakkı Devir Formu: Tüm yazarlar tarafından Telif Hakkı Devir Formu imzalanmıştır.

Hakem Değerlendirmesi: Hakem değerlendirmesinden geçmiştir.

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Derleme / Review

Lung fibrosis molecular mechanisms

Akciğer Fibrozisinin Moleküler Mekanizmaları

Ayşe Koçak Sezgin

Kutahya Health Sciences University, Faculty of Medicine, Department of Medical Biochemistry, Kutahya, Türkiye

Abstract: Lung fibrosis is a highly heterogeneous and life-threatening disease in patients. Studies on the molecular pathogenesis of lung fibrosis have more often focused on the mechanisms regulating the increase of extracellular matrix and collagen. Although these studies have been conducted in this way, many different new studies are also being conducted. These studies have focused more on the mechanisms regulating fibroblast activation and differentiation, how fibrosis starts and how it progresses. In this review, especially the molecular mechanisms of lung fibrosis are emphasized and examined.
Keywords: Lung fibrosis, lung fibrosis pathology, molecular mechanism

Özet: Akciğer fibrozisi oldukça heterojen ve yaşamı tehdit eden bir hastalıktır. Akciğer fibrozisinin moleküler patogenezi üzerine yapılan çalışmalar daha çok hücre dışı matriks ve kollajen artışını düzenleyen mekanizmalara odaklanmıştır. Bu çalışmalar var olsa da, birçok farklı yeni çalışma da yapılmaktadır. Bu çalışmalar daha çok fibroblast aktivasyonunu ve farklılaşmasını düzenleyen mekanizmalara, fibrozisin nasıl başladığına ve nasıl ilerlediğine odaklanmaktadır. Bu derlemede özellikle akciğer fibrozisinin moleküler mekanizmaları üzerinde durulmuş ve mekanizmaları incelenmiştir.
Anahtar Kelimeler: Akciğer fibrozisi, akciğer fibrozisi patolojisi, moleküler mekanizma

ORCID ID of the authors: AKS. 0000-0002-1510-2937

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Correspondence- Ayşe Koçak SEZGİN- Kutahya Health Sciences University, Faculty of Medicine, Department of Medical Biochemistry, Kutahya, Türkiye
e-mail: ayse.kocaksezgin@ksbu.edu.tr

1. Introduction

Lung fibrosis, which occurs in patients with alveolar fibrosis, is quite resistant to treatment and has a high mortality. In patients, this process includes the progression of fibrosis in the lung, respiratory distress, and irreversible serious damage to the lung. Although the etiology of lung fibrosis is not yet known, idiopathic pulmonary fibrosis (IPF), a serious disease form, is predicted to live maximum 6 years after diagnosis (1).

Lung Fibrosis Pathology

Studies on lung fibrosis and responsible molecular mechanisms are ongoing. The fibrotic process can arise from many different etiologies. In particular, patients with acute respiratory distress syndrome (ARDS) (2) experience an increase in many factors leading to lung fibrosis. In other patients with pulmonary fibrosis, irradiation to the chest may occur from environmental factors such as exposure to asbestos or silica. Although very rare, lung fibrosis can develop very rapidly with unknown damage and this is mostly IPF. The pathology that causes lung fibrosis has become more complex over the years. Over the years, the number of cellular and molecular hypotheses of the disease has increased. In lung fibrosis, age-related loss of function occurs at the molecular, cellular and tissue levels (3, 4).

Lung Fibrosis and Molecular Mechanisms

Wound healing and fibrosis, effective in lung fibrosis, are characterized by complete inflammation, tissue injury, myofibroblast transformation, fibroblast migration, extracellular matrix deposition (ECM), and ECM remodeling. These pathological processes cannot be considered independent of each other and are mechanisms that trigger each other, thus exacerbating fibrosis. Fibrosis, characterized by these mechanisms, can occur in many vital organs such as the skin, lung, and liver, and plays an active role in many diseases. During fibrosis, fibroblasts, immune, epithelial, and endothelial cells are very actively involved (5, 6). Many environmental factors, such as exposure to organic and inorganic harmful compounds, infection, smoking, cause damage to the lung epithelium. It is here that tissue healing is activated in response to the damaged lung tissue. This process actually facilitates the repair of lung tissue and its transformation and adaptation to damage (7). In all fibrotic processes, the underlying mechanism of fibrosis is not fundamentally different, although the etiologies or causes of occurrence may differ. In summary, cellular fibrosis is mainly characterized by abnormal deposition of ECM components, especially collagen. There is an age-dependent irreversible breakdown of lung fibrosis as described above. In lung fibrosis, age-dependent inability to repair damaged tissue, resolve fibrosis, tissue scarring, disruption of tissue homeostasis and ultimately organ damage (8). In lung fibrosis, it can be said that the degree of damage and pathology increases with aging in the damaged lung. Under normal lung injury conditions, alveolar epithelial cell 2s (AEC2s) are replaced by proliferating and differentiating AEC2 cells and some stem cells, and new vessel formation, coagulation, migration and transformation of fibroblast cells, collagen synthesis in endothelial cells are stimulated. Chemokines such as transforming growth factor (TGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) are involved in this entire fibrotic process. In the development of lung injury, inflammation is increased and levels of interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), which are characterized by inflammation, are increased. The whole process creates an environment that favors alveolar regeneration and lung tissue remodeling (9).

TGF-β cytokine is mainly involved in lung fibrosis. The TGF-β family are multifunctional cytokines that exist in three isoforms: TGF- β1, TGF- β2 and TGF- β3. The molecular and biological activities of the three isoforms differ from each other, but TGF- β1 plays a dominant role in pulmonary fibrosis (10). In the extracellular matrix, TGF-β plays very important roles and is the most

important promoter of the entire fibrotic process. It is also considered the most potent chemotactic factor for immune cells such as monocytes and macrophages. In monocytes and macrophages, TGF- β activates the release of cytokines such as PDGF, IL-1, basic FGF (bFGF) and TNF-α and automatically regulates its own cascade (10). TGF-β is increased in the lung tissue of patients with IPF (11) and increases in TGF-β generation are consistently observed in rodents with bleomycin-induced pulmonary fibrosis (12). TGF-β is increased in the lung tissue of patients with idiopathic pulmonary fibrosis (11) and increases in TGF- β generation is consistently observed in rodents with bleomycin-induced pulmonary fibrosis (12). The TGF-β Smad cascade is actively involved from the membrane to the nucleus (13). In this pathway, activated TGF-β receptors are translocated to the nucleus by regulating other Smad proteins, leading to the phosphorylation of Smad-2 and Smad-3.

One study shows that Smad-3 deficiency attenuates bleomycin-induced pulmonary fibrosis in mice (14) and that the inhibitor Smad-7 prevents phosphorylation of Smad-2 and Smad-3 through activated TGF-β's receptors (15, 16). In lung fibrosis, TGF-β1 is considered the most important chemokine. AEC2s produce TGF-β1 following actin-myosin-mediated cytoskeletal contractions induced by the unfolded protein response (UPR) following six integrins activation. αvβ6 integrin & TGF- β1 pathway, a pathway ready to recognize damaging stimuli, is actually a molecular sensing mechanism (17). In lung fibrosis, it is the most important profibrotic mediator that activates the profibrotic cascade, triggers myofibroblast transformation, promotes epithelial-mesenchymal transition (EMT), circulating fibrocyte recruitment, fibroblast activation, and proliferation and epithelial cell apoptosis, epithelial cell migration, and production of pro-angiogenic factors (17).

In lung fibrosis, another important factor is PDGF. It increases the proliferation of fibroblasts while inducing ECM synthesis. Alveolar macrophages with IPF produce higher amounts of PDGF-B mRNA and protein level (18, 19). Impaired PDGF levels have been observed in animal models, particularly in AEC2 and mesenchymal cells (20). PDGF-B transgenic mice have been observed to develop lung disease characterized by diffuse emphysematous lung lesions and inflammation/fibrosis in focal areas (21).

In another study, intratracheal instillation of recombinant human PDGF-B in rats produces fibrotic lesions in blood vessels and airways (22). In a bleomycin-induced experimental mouse model, gene transfer of the extracellular domain of the PDGF receptor ameliorated pulmonary fibrosis (23). Insulin-like growth factor (IGF)-1, which promotes fibroblast proliferation, has also been observed to work synergistically with PGDF (24).According to this study, alveolar macrophages from patients with IPF expressed higher levels of IGF-1 mRNA and protein than normal alveolar macrophages (24, 25).

In normal fibroblasts, after stimulation with TGF-β, increased phosphorylation of JAK-2 was observed to induce subsequent activation of STAT-3 and transcription of collagen. Selective inhibition of JAK-2 blocks TGF-β-induced collagen release in vitro and prevents experimental fibrosis *in vivo* (26). However, different studies may show that tumor cells and fibroblasts can become resistant to JAK-2 inhibitors in long-term treatment, which is essential for chronic fibrotic diseases (27, 28). This resistance is not due to somatic mutations but to transactivation of JAK-2 by JAK-1 and subsequent activation of downstream signaling through STAT proteins (27, 28). This escape mechanism may be blocked by simultaneous inhibition of JAK-1 and JAK-2 or by co-treatment with JAK-2 and heat shock protein-90 (HSP-90) inhibitors, which have promising antifibrotic effects in murine models of skin and lung fibrosis (28).

Epithelial-mesenchymal transition (EMT) is the pathological phenomenon in lung fibrosis in which epithelial cells lose their normal phenotype and profibrogenic markers such as α-smooth muscle actin (α-SMA), fibroblast-specific protein 1 (FSP1), collagen type 1 and fibronectin are highly secreted (29). Some studies have demonstrated the capacity of

alveolar epithelial cells to trans-differentiate into fibrogenic myofibroblasts (30, 31).
In lung fibrosis, EMT stimulation is initiated by overexpression of TGF- β by damaged epithelial and endothelial cells as well as macrophages and fibroblasts, thus leading to a positive cycle of stimulation. With the induction of EMT, SMAD activation occurs in the "canonical" TGF- β signaling pathway (32). In addition, another pathway that promotes fibrosis is the "non-canonical" TGF-β signaling involving the extracellular signal-regulated kinase (ERK) pathway, which leads to EMT trans-differentiation (32).
Furthermore, EMT induction is mediated by the cross-interaction of TGF-β1 with the canonical WNT/β-catenin pathway (33), through the interplay of WNT and TGF-β signaling pathways, β-catenin accumulates in the nucleus and promotes EMT in alveolar epithelial cells (34) , resulting in the transformation of alveolar cells into myofibroblasts characterized by ECM deposition and fibrosis. It is also known that EMT pathogenesis is linked to autophagy of alveolar epithelial cells, leading to fibrosis and other lung pathologies (35). Hedgehog signaling, an important regulator of tissue repair and EMT, is involved during fibrosis (36, 37). In the lung, normally, Hedgehog signaling ensures fibroblast normalization and maintains homeostasis (36). However, in pathological states of the lung, Hedgehog signaling is too overactive, as shown in bleomycin-induced lung fibrosis, and blocking hedgehog epithelium-fibroblast trans-differentiation can attenuate experimental pulmonary fibrosis (38, 39, 40). Fibroblast growth factor receptors (FGFR-1, -2) have been found to be elevated in myofibroblast cells, which are fibrosis cells, and in patients with IPF. Also, basic fibroblast growth factor (bFGF) plays a role in lung fibrosis. In alveolar macrophages are a dominant source of bFGF in intra-alveolar fibrotic areas following acute lung injury (41). In a study of IPF, mast cells were found to be the predominant bFGF-producing cells and bFGF levels correlated with bronchoalveolar lavage cellularity and severity of gas exchange abnormalities (42).
In fibrosis, there is resistance to apoptosis and this process exacerbates fibrosis. Activation of the PI3K-AKT-mTOR signaling pathway reduces autophagy in fibrosis (43), and inhibition of EF2K and p38 MAPK signaling reduces autophagy, which in turn reduces lung fibroblast apoptosis (44). In the lung, this suppression of apoptosis and autophagy also exacerbates fibrosis and increases inflammation.
In our knowledge, all over these molecular regulation of lung fibrosis, inflammation is so active and activator of fibrosis. In lung fibrosis, fibroblast proliferation and myofibroblasts, lymphocytic cytokines are active and act profibrotic. The role of Th-1, Th-2 and Th-17 T-cells in pulmonary fibrosis is known. The Th1 T-cell subset produces IL-1, TNF- α, PDGF and TGF- β1 and has clear profibrotic effects. Th-2 and Th-17 responses appear to be more important in the pathogenesis of IPF. They lead to direct activation of certain interleukins (IL-4, IL-5, IL-13) and fibroblasts (45-47).

2. Conclusions

In conclusion, lung fibrosis is a serious life-threatening lung disease. Although many pathways involved in lung fibrosis are known, its etiology and pathology are not yet fully understood. Many molecular pathways in lung fibrosis exhibit heterogeneous behavior and there is a therapeutic need. The large number of therapeutic interventions suggests that in the near future there may be more specific therapeutic options for the disease.

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Letter to the Editor / Editöre Mektup

Donor-related EDTA dependent pseudothrombocytopenia after allogeneic stem cell transplantation. Can it be real?

Allojeneik Kök Hücre Nakli Sonrası Gelişen Donör Kaynaklı EDTA'ya Bağlı Pseudotrombositopeni. Gerçek olabilir mi?

Hava Üsküdar Teke, Eren Gündüz

Eskisehir Osmangazi University Faculty of Medicine, Hematology Department, Eskisehir, Türkiye

Abstract: Hematopoietic stem cell transplantation (HSCT) may take place in the form of an autologous or allogeneic transplant depending on the indication for transplantation. Because of the myeloablative conditioning regimens preceding HSCT, deep thrombocytopenia is experienced by most of the stem cell recipients in whom replenishment of leukocytes and platelets is expected within the first month following the transplantation. Prolonged thrombocytopenia, on the other hand, usually develops as a delayed complication of allogeneic stem cell transplantation (allo-SCT) and is associated to the source of stem cells, quantity of the infused CD34+ cells, graft-versus-host-disease (GVHD), insufficient engraftment, relapse of the malignancy, microangiopathy, alloimmunisation, medications, or viral infections. In an attempt to explain pathogenesis leading to post-HSCT thrombocytopenia, two main theories have been proposed. First one is the peripheral destruction caused by anti-platelet antibodies, splenic sequestration, or other factors. The latter blames insufficient platelet generation due to impaired thrombopoiesis. Nevertheless, most of the clinical conditions arise with overlapping of both mechanisms.Here we present a pseudothrombocytopenia case induced by donor-related ethylene-diamine-tetra-acetic acid (EDTA) as an unanticipated cause of thrombocytopenia to which most recipients of allo-SCT are prone to.
Keywords: EDTA, Allogeneic Stem Cell Transplantation

Özet: Hematopoietik kök hücre nakli (HKHN) endikasyona göre otolog veya allojeneik yapılabilir. Derin trombositopeniler, myeloablatif hazırlama rejimlerine bağlı olarak genellikle tüm hastalarda görülür. Lökositlerin ve trombositlerin yenilenmesi nakilden sonraki ilk ay içinde beklenir.. Uzun süreli trombositopeni, genellikle allojeneik kök hücre nakli sonrası hastalarda geç komplikasyon olarak görülür. Bu durum, kök hücre kaynağına, infüze edilen CD34+ hücrelerin miktarına, graft versus host hastalığına, engrafman yetmezliğine, altta yatan malignitenin nüksüne, mikroanjiyopatiye, alloimmünizasyona, ilaçlara veya viral enfeksiyonlara bağlanmaktadır. HKHN sonrası trombositopeninin patogenezi için iki ana teori ileri sürülmüştür, ilki anti-trombosit otoantikorları, splenik sekestrasyon veya diğer faktörler nedeniyle periferik yıkım; ikincisi ise, trombosit üretiminin, bozulmuş trombopoez nedeniyle yetersiz olmasıdır. Bununla birlikte, çoğu klinik durum, iki mekanizmanın üst üste çakışması ile karşımıza çıkar.Bu yazıda alloKHN sonrası beklenen bir durum olan trombositopeninin beklenmeyen bir nedeni olarak 'donör kaynaklı EDTA'ya bağlı pseudotrombositopeni' vakası sunulmuştur.
Anahtar Kelimeler: EDTA, Allojeneik kök hücre nakli

ORCID ID of the authors: HÜT. 0000-0002-4434-4580, EG. 0000-0001-7455-2949

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Correspondence- Hava ÜSKÜDAR TEKE- Eskisehir Osmangazi University Faculty of Medicine, Hematology Department, Eskisehir, Türkiye
e-mail: havaus@yahoo.com

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1. To the editor

Hematopoietic stem cell transplantation (HSCT) may take place in the form of an autologous or allogeneic transplant depending on the indication for transplantation. Because of the myeloablative conditioning regimens preceding HSCT, deep thrombocytopenia is experienced by most of the stem cell recipients in whom replenishment of leukocytes and platelets is expected within the first month following the transplantation. Prolonged thrombocytopenia, on the other hand, usually develops as a delayed complication of allogeneic stem cell transplantation (allo-SCT) and is associated to the source of stem cells, quantity of the infused CD34+ cells, graft-versus-host-disease (GVHD), insufficient engraftment, relapse of the malignancy, microangiopathy, alloimmunisation, medications, or viral infections. In an attempt to explain pathogenesis leading to post-HSCT thrombocytopenia, two main theories have been proposed. First one is the peripheral destruction caused by anti-platelet antibodies, splenic sequestration, or other factors. The latter blames insufficient platelet generation due to impaired thrombopoiesis. Nevertheless, most of the clinical conditions arise with overlapping of both mechanisms (1-3).

Here we present a pseudothrombocytopenia case induced by donor-related ethylene-diamine-tetra-acetic acid (EDTA) as an unanticipated cause of thrombocytopenia to which most recipients of allo-SCT are prone to.

A 39-year-old male patient visited emergency care on March 2018 complaining of chest pain and high fever lasting for the last 3 days. On his physical examination, pale conjunctivas and tachycardia was noted. Cardiac enzymes were tested due to chest pain of the patient which revealed increased troponin-T and CK-MB levels. Therefore, the patient was hospitalized at the ward of cardiology upon diagnosis of acute coronary syndrome and myocarditis. On admission, his test results were hemoglobin: 13.1 g/dL, leukocyte: 13800/mm3, absolute neutrophile count (ANC): 10900/mm3, platelet: 64000/mm3, C-reactive protein: 100 mg/dL, and erythrocyte sedimentation rate (ESR): 117 mm/h. Echocardiography showed EF: 60%, minimal mitral regurgitation, with a normal coronary angiography. Colchicine and ibuprofen were initiated for the patient based on diagnosis of myocarditis and then he was discharged to home. During his follow-ups conducted by the cardiology outpatient department, the patient was referred to the outpatient department of hematology as he developed anemia and deepening thrombocytopenia. Peripheral blood smear of the patient showed myeloblasts featuring with Auer rods. Preliminary diagnosis of acute leukemia was considered, and bone marrow aspiration/biopsy was performed. Bone marrow aspirate of the patient was composed of 25% myeloblasts with Auer rods. The diagnosis of acute myeloid leukemia (AML)-M2 was then established and thereupon 7+3 regimen of remission-induction chemotherapy was applied. A post-treatment bone morrow exam was performed to check the patient's response to the first course of chemotherapy which indicated a blast ratio of 8%. As complete remission was not achieved, second course of 7+3 regimen was applied. Complete remission was attained through the second 7+3 regimen. After complete remission, the patient underwent allogeneic stem cell transplantation from a fully compatible sibling in July 2018 because of primary resistance and variable t (8; 21) positivity. At post-transplant Day 100, the patient's test results were hemoglobin: 13.4 g/dL, leukocyte: 7800/mm3, ANC: 4200/mm3, and platelet: 165000/mm3. Bone marrow exam was negative for t(8;21) abnormality, and cytogenetic analysis was normal. In February 2019, 8 months after allo-SCT, his test results were hemoglobin: 14.3 g/dL, leukocyte: 8410/mm3, ANC: 3260/mm3, and platelet: 23000/mm3. At that time, patient had a negative medical history for any other herbal or medical treatment. Blood smear of the patient was prepared, showing clumped platelets. Complete blood count of the patient's donor resulted as hemoglobin: 16.7 g/dL, leukocyte: 5300/mm3, ANC: 2600/mm, platelet: 22000/mm3, and query in his past medical history elicited known EDTA-induced pseudothrombocytopenia.

Consequently, EDTA-induced pseudothrombocytopenia of the patient subsequent to allo-SCT was considered to be donor-derived (peripheral blood smear findings of the patient and donor were given in Figure). A retrospective analysis of the patient's former investigations figured out health checkup tests done in 2009. At that time, his hemoglobin: 15.3 g/dL, leukocyte: 10000/mm3, ANC: 6800/mm3, platelet: 196000/mm3, and peripheral blood smear was normal.

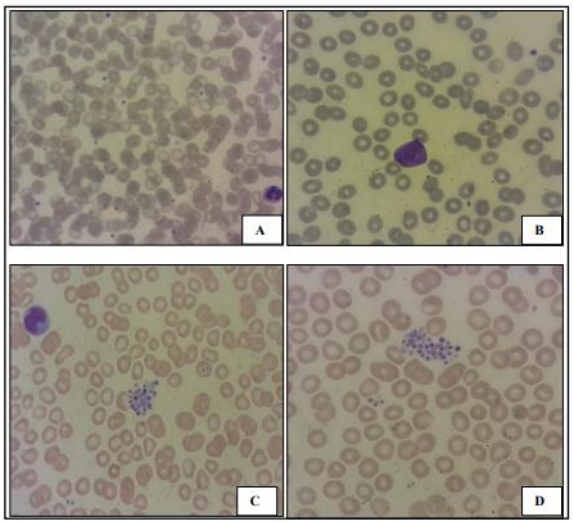

Figure. The patient's peripheral smear results by time **A.** Peripheral smear from a routine checkup in 2009, with normal results **B.** Peripheral smear of blasts in March 2018 when AML was diagnosed **C.** Peripheral smear of pseudothrombocytopenia due to donor-related EDTA 8 months after allogeneic stem cell transplantation. **D.** The donor's peripheral smear, EDTA-induced pseudothrombocytopenia

Prolonged thrombocytopenia following HSCT usually develops as a delayed complication of allo-SCT (1). EDTA-induced pseudothrombocytopenia is not a likely cause of thrombocytopenia following allo-SCT and may very rarely occur in association with medication (2). When our patient was evaluated for thrombocytopenia developed in the 8th month of post-transplant, it was found that he did not take any medicine in her interrogation. Peripheral blood smear was evaluated for relapse which was the preliminary diagnosis. No relaps was detected, clumped platelets were seen. The cause of thrombocytopenia was pseudothrombocytopenia due to EDTA. When the patient was further assessed to address the reason causing EDTA-induced pseudothrombocytopenia, no secondary cause was identified. On the other hand, his donor had experienced EDTA-induced pseudothrombocytopenia leading to the conclusion that the patient's clinical picture was originating from his donor.

As a result, this is the first case of donor-related EDTA-induced pseudothrombocytopenia in the literature. Donor-related EDTA-induced pseudothrombocytopenia should be listed as a rare etiological cause of thrombocytopenia occurring following allo-SCT.

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Ethics

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