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# **Retrospective Evaluation of Children with Influenza Infection**

# Gripli Çocukların Retrospektif Değerlendirilmesi

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#### Abstract

**Objective:** This study aimed to review the general characteristics of influenza and evaluate the clinical and laboratory characteristics of patients with influenza hospitalized in our unit.

**Methods:** This is a retrospective, descriptive study. Between 01.01.2017 and 01.07.2020; 124 patients hospitalized with flu-like illness symptoms and found to have influenza virus in the respiratory viral panel were included in the study.

**Results:** The mean age of the patients was 4.85±3.94 years, of which 27 (21.8%) were less than 2 years old, 42 (33.9%) were between 2 and 5 years old, and 55 (44.4%) were older than the 5-year-old age group. Although many patients were at high risk of influenza, only 3 (2.4%) were vaccinated. The most common complaints at presentation were fever (n=121, 97.6%) and cough (n=109, 87.9%). Respiratory distress was more common in patients <2 years compared with the other age groups (p=0.046; p=0.002). Underweight and overweight/obese patients required more intensive care admissions than normal weight patients (p=0.003 and p=0.001, respectively). Of all patients, 116 (93.5%) recovered without sequelae, 4 (3.2%) died.

**Conclusion:** Although influenza infection is an important problem in terms of morbidity and mortality among children with respiratory tract infections, our vaccination rates are not sufficient even in high-risk groups. Influenza is a significant and serious disease, especially in children <2 years. Obese and malnourished patients may require more frequent intensive care admissions.

Keywords: Influenza, pediatric, flu vaccine

#### Öz

**Amaç:** Bu çalışmada influenza virüsün genel özelliklerinin gözden geçirilmesi, kliniğimizde yatırılarak izlenmiş influenza hastalarının klinik ve laboratuvar özelliklerinin değerlendirilmesi amaçlanmıştır.

**Yöntem:** Çalışmamız retrospektif, tanımlayıcı bir çalışmadır; 01.01.2017-01.07.2020 tarihleri arasında, grip benzeri hastalık semptomlarıyla yatırılarak izlenen ve solunum yolu viral panelinde influenza virüs saptanan 124 hasta çalışmaya dahil edilmiştir.

**Bulgular:** Hastaların yaş ortalaması 4,85±3,94 yıldı, bunların 27'si (%21,8) <2 yaş, 42'si (%33,9) 2-5 yaş ve 55'i (%44,4) >5 yaş grubundaydı. İnfluenza açısından riskli grupta çok sayıda hasta olmasına rağmen sadece 3'üne (%2,4) influenza aşısı yapılmıştı. En sık başvuru yakınmaları ateş (n=121, %97,6) ve öksürüktü (n=109, %87,9). Solunum sıkıntısı <2 yaş hastalarda diğer yaş gruplarına göre daha sıktı (p=0,046; p=0,002). Düşük kilolu ve fazla kilolu/obezler, normal kilolulara göre daha fazla yoğun bakım yatışı gerektirdi (sırasıyla p=0,003 ve p=0,001). Hastaların 116'sı (%93,5) sekelsiz iyileşti, 4'ü (%3,2) eksitus oldu.



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#### Öz

**Sonuç:** İnfluenza, çocuklarda solunum yolu enfeksiyonları arasında morbidite ve mortalite açısından önemli bir sorun olmasına rağmen, yüksek riskli gruplarda dahi aşılama oranlarımız yeterli değildir. İnfluenza özellikle <2 yaş çocuklarda önemli bir hastalıktır. Obez ve malnütre hastalar daha sık yoğun bakım ihtiyacı gerektirebilir.

Anahtar Kelimeler: İnfluenza, pediatri, grip aşısı

#### Introduction

The World Health Organization (WHO) reports that before the coronavirus disease-2019 (COVID-19) pandemic period, approximately 1 billion patients were infected annually worldwide due to the influenza virus, of which, approximately 3-5 million cases were in severe disease, and 300,000-500,000 cases resulted in death<sup>(1)</sup>. The influenza virus causes both the loss of workforce among parents and the attendance of school for children. It can also lead to economic losses caused by diagnostic and treatment cost due to the disease burden<sup>(2,3)</sup>. Although influenza symptoms are generally mild, they can cause severe complications and mortality, especially in patients with underlying chronic diseases and children aged 2 years of age<sup>(4,5)</sup>. Acute respiratory tract infections, which are among the most common epidemics, are characterized by serious clinical findings, especially in childhood, and are responsible for 1/5 of all deaths in children under 5 years of age<sup>(6)</sup>. It is known that approximately 20-60% of these diseases are caused by viruses; studies show that viral respiratory tract infections occur 5-6 times a year in the early stages of life. In general, influenza viruses are the most common agents are influenza viruses<sup>(7,8)</sup>.

#### **Materials and Methods**

The study was conducted at the Adnan Menderes University Faculty of Medicine, Department of Pediatrics, and Pediatric Intensive Care Unit between 01.01.2017 and 01.07.2020. In this study, we included pediatric inpatients who were admitted with influenza-like illness (ILI) symptoms for the last 10 days and were diagnosed with influenza virus according to the respiratory viral panel. Socio-demographic characteristics of patients (age, sex, body weight (underweight, normal, overweight/obese), breastfeeding status of those under 2 years of age, history of prematurity, chronic diseases, and medications they regularly use) were examined. Admission symptoms, length of stay, need for respiratory support, and intensive care, whether the patient received oseltamivir treatment or not, which day of infection, and whether the patient received antibiotic treatment or not, were examined. Complications associated with influenza, length of hospital stay, laboratory investigations, respiratory viral polymerase chain reaction (PCR) results, clinical course, morbidity, and mortality rates were evaluated retrospectively.

Cases were grouped as <2 years, 2-5 years and >5 years to evaluate risk status according to the age specified in the literature. The presence of at least one of these symptoms; cough, sore throat, and shortness of breath, which are also included in the Global Influenza Hospital Surveillance Network data collection forum, as respiratory symptoms for patients over 5 years of age, the onset of these symptoms, and the presence of tachypnea for patients under 5 years of age were examined. Patients were classified into underweight, normal weight, and overweight/obese according to the WHO body mass index (BMI) scoring by age and gender.

Patients with acute otitis media, laryngitis, sinusitis, bronchiolitis, bronchitis, pneumonia, or asthma attacks after influenza were evaluated as respiratory system complications. Seizures and changes in consciousness, encephalitis, Guillain-Barré syndrome, behavioral or personality disorders, and central or peripheral nervous system involvement were evaluated as neurological complications<sup>(9,10)</sup>. Patients with pericarditis, myocarditis and rhythm disturbances were evaluated as cardiac complications<sup>(11)</sup>. Hematological findings such as leukopenia, lymphopenia, and neutropenia are common after influenza and were evaluated as hematologic complications<sup>(12,13)</sup>.

Nasopharyngeal swab samples taken from patients who were sent to the Adnan Menderes University Faculty of Medicine Microbiology laboratory for the study of respiratory viral molecular panels. Nucleic acid extraction was performed using the Magnesia Viral DNA/RNA Extraction kit (Anatolia, Türkiye) in the Magnesia 16 (Anatolia, Türkiye) device, in line with the company's recommendations. Nineteen different viruses (influenza A, H1N1, influenza B) including nucleic acids belonging to influenza A (all types that cause infection in humans), influenza pandemic H1N1, and influenza seasonal H1N1 by multiplex real-time PCR using Bosphore Respiratory Pathogens Panel Kit (Anatolia, Türkiye), respiratory syncytial virus (RSV) A, RSV B, enterovirus, parechovirus, parainfluenza 1,2,3,4; metapneumovirus, adenovirus, bocavirus, rhinovirus, coronavirus 229E (OC43,NL63, HKU) nucleic acid presence were investigated.

#### **Statistical Analysis**

After all data were recorded on the computer, statistical evaluation was performed using the SPSS "Statistical Package for Social Sciences" (SPSS Inc. Chicago IL v 22.0. mean  $\pm$  standard deviation, median, minimum, and maximum values were given in descriptive statistics for continuous data, and percentage values were given in discrete data. P<0.05 was accepted as the threshold for statistical significance.

Prior to the study, permission was obtained from the Ethics Committee of Aydın Adnan Menderes University (number: 48843899-804.01, date: 24.07.2020).

#### Results

Nasopharyngeal swab samples from a total of 817 pediatric patients were obtained between the specified dates, and 124 patients with influenza A and/or B virus infection were included in the study. The mean age of the patients was  $4.85\pm3.94$  years, and the female/male ratio was 0.72. Of all the patients with influenza, 27 (21.8%) were <2 years old, 42 (33.9%) were 2-5 years old, and 55 (44.4%) were >5 years old. The highest number of patients was seen in 2020 (n=44, 35.2%), and the highest positivity rate in all years was observed in January (n=94, 75.8%).

Thirty-eight (30.6%) patients had family members with ILI symptoms at home, and no patient stayed in a nursing home. Fifty-four (43.5%) patients were going to school/nursery. Sixty-five patients (52.4%) had at least one concomitant chronic disease, with the most common being chronic lung disease (n=23, 18.5%). Neurological and hemato-oncological

diseases followed this group. Of the patients in our study, 25.8% were underweight and 9.7% were overweight or obese. Prematurity was present in 16.9% of patients in our study cohort (Table 1). Only 3 (2.4%) patients were known to have the influenza vaccine.

The most common complaints were fever (n=121, 97.6%) and cough (n=109, 87.9%) (Figure 1). The most common laboratory findings were elevated C-reactive protein (>5 mg/dL) (n=64, 51.6%) and lymphopenia (n=39, 31.5%). Influenza A PCR was positive in 84 (67.7%) and B PCR were positive in 40 (32.3%) patients. More than one virus was detected in 22 of the patients with influenza A and 11 with influenza B. The most common viral strain associated with influenza was RSV (n=11, 36.3%).

When analyzing the relationship between symptoms and viral agent, 10 (34.5%) of the patients with influenza B, 8 (12.9%) of the patients with influenza A, and only 1 (3%) of the patients who were found to have more than one virus. Myalgia was more common in patients with influenza B than in those with influenza A and more than one virus group (p=0.01 and p=0.002, respectively). Elevated creatine kinase (CK) (>200 U/L) was detected in 38.7% of patients in our study. However, no significant relationship was observed between influenza subtypes and high CK (p>0.05).

In our study, the probability of experiencing respiratory distress in patients <2 years of age was higher than those in the 2-5 age group and >5 age group (p=0.046 and p=0.002, respectively). In addition, the number of patients with more than one virus in the <2 age group (59.3%) was higher than those aged 2-5 (26.2%) and those aged >5 (10.9%) (p=0.004 and p<0.0001).

Oseltamivir was initiated in 79 (63.7%) patients, and antibiotics were initiated in 93 (74.4%) patients due to secondary bacterial infection [most frequently secondary

| Table 1. Risk factors of cases in terms of having influenza |                    |            |  |
|---|--------------------|------------|--|
|   | Number of patients | Percentage |  |
| Presence of people going to school/nursery at home          | 82                 | 66.1       |  |
| Presence of smoking individuals at home                     | 68                 | 54.8       |  |
| Presence of chronic disease                                 | 65                 | 52.4       |  |
| School/nursery attendance                                   | 54                 | 43.5       |  |
| Presence of individuals with similar symptoms at home       | 38                 | 30.6       |  |
| <2 years of age   | 27                 | 21.8       |  |
| Prematurity   | 21                 | 16.9       |  |
| Obesity   | 12                 | 9.7        |  |



Figure 1. Patient complaints on admission

bacterial pneumonia (52.0%)]. The most common antibiotic was ceftriaxone. The most common complication was respiratory system complications (n=97, 78.2%). Thirty-one (24.8%) patients required respiratory support, and 27 (21.6%) patients required intensive care at the time of hospitalization or during hospital stay. 10% of the patients with normal body weight, 40.6% of the underweight, and 50% of the overweight/obese patients were admitted to the intensive care unit. Underweight and overweight/obese patients were found to need more intensive care than those with normal body weight (p=0.003 and p=0.001, respectively). However, as a result of Spearman's correlation analysis, the correlation coefficient was found to be -0.118, which showed us that there was no significant correlation.

In our study, the median length of stay in pediatric services was 3 days (1-31), and the median length of stay in intensive care units was 5 days (2-90). In patients who were started on oseltamivir in the first 48 hours, the mean length of hospital stay in pediatric service was 5 days (2-90) and the intensive care unit length of stay was 3 days (1-20), whereas those started after 48 hours were 6 (2-17) and 3 (1-31), respectively. There was no significant relationship between the time of initiation of oseltamivir and the duration of hospitalization in the service-intensive care unit (p>0.05).

In our study, when factors such as sex, prematurity, breastfeeding under 2 years of age, exposure to passive cigarette smoke were compared to influenza complications and the need for intensive care admission, it was found that there was no statistically significant relationship (p>0.05). During follow-up, 116 (93.5%) patients recovered without sequelae, whereas 4 (3.2%) patients died (Table 2). All patients who died in our study were found to be influenza A (H1N1) positive. There was no significant relationship between viral agent type and morbidity and mortality. As a result of the Pearson chi-square test, the p-value was 1,182, and no statistically significant difference was found. According to these results, when the number of patients presenting with fever and respiratory complaints increases during a certain period, especially in the winter months, it should be considered that influenza positivity may be present, and appropriate treatments should be selected by conducting tests accordingly. Therefore, unnecessary antibiotic and antiviral use can be prevented.

#### Discussion

Although the whole world is currently under the influence of the COVID-19 pandemic, influenza, which has caused significant economic and social problems, sequelae, and deaths, remains one of the most important viral pathogens.

| Table 2. Clinical follow-up of patients                           |                    |            |  |
|---|--------------------|------------|--|
| Clinical follow-up of patients                                    | Number of patients | Percentage |  |
| Patients who started oseltamivir                                  | 79                 | 63.7       |  |
| Within 0-24 h of admission  | 28                 | 22.8       |  |
| Within 24-48 h of admission                                       | 13                 | 10.6       |  |
| >48 h of admission  | 38                 | 30.9       |  |
| Patients started on antibiotics                                   | 93                 | 74.4       |  |
| Complications developed in patients during follow-up              |                    |            |  |
| Respiratory system  | 97                 | 78.2       |  |
| LFT changes   | 16                 | 12.9       |  |
| Neurological  | 15                 | 12.1       |  |
| Myositis  | 13                 | 10.5       |  |
| Hematologic   | 8                  | 6.5        |  |
| Sepsis/MOD  | 7                  | 5.6        |  |
| Cardiological   | 2                  | 1.6        |  |
| Others  | 4                  | 3.2        |  |
| Patients in need of respiratory support                           | 31                 | 24.8       |  |
| Oxygen support  | 15                 | 12.1       |  |
| Mechanical ventilation  | 16                 | 12.9       |  |
| Patients who need intensive care during hospitalization/follow-up | 27                 | 21.6       |  |
| Neonatal intensive care   | 3                  | 2.4        |  |
| Pediatric intensive care  | 24                 | 19.2       |  |
| LET: Liver function tests MOD: Multiple organ dysfunction         |                    | •          |  |

Most influenza cases examined in this study were children <5 years. It has been reported by the centers for disease control and prevention (CDC) that children younger than 5 years, especially those under 2 years, are among the highest risk groups for influenza-related hospitalization and development of serious complications<sup>(3)</sup>. In our study, respiratory distress was more common in patients aged 2 years compared to other age groups. In a meta-analysis, it was estimated that 28,000-111,500 children under the age of five died in developing countries due to influenza-related acute lower respiratory tract infection<sup>(14)</sup>. In another metaanalysis, influenza-related hospitalizations under the age of 5 were estimated to be approximately 870,000 per year worldwide, and 10% of general hospitalizations under the age of 18 due to respiratory distress were related to influenza infection<sup>(15)</sup>. In the study of Çiftçi et al. <sup>(16)</sup> it was stated that respiratory distress is less in children older than five years, as in our study.

In our study, the probability of detecting more than one virus in patients aged 2 years was higher than that in other age groups. In a study conducted in Poland, including adult and pediatric patients, it was emphasized that influenza co-

infection was more common, especially in patients aged >65 years and in early childhood<sup>(17)</sup>. Similarly, in the study conducted by Kockuzu et al.,<sup>(18)</sup> the mean age of patients with only influenza was 41 (11-75) months, whereas the mean age in the group positive for non-influenza viruses was 10 (3.5-28) months. In our study, the higher incidence of respiratory distress in the group of children aged 2 years suggested that it may be related to the higher incidence of co-infection in this age group.

In our study, underweight and overweight/obese patients were found to need more intensive care than those with normal body weight. However, as a result of Spearman's correlation analysis, the correlation coefficient showed us that there was no significant correlation. Obesity (BMI >30) was first recognized by the WHO as a risk factor for serious illness in patients with influenza during the 2009 H1N1 pandemic<sup>(19)</sup>. In a study conducted in Mexico, in which children and adults were examined together, it was observed that both low-weight and morbidly obese patients had influenza more severely than those with normal body weight similar to our study<sup>(20)</sup>. It has been demonstrated that during an influenza pandemic in Türkiye, the need for intensive

care increased in the presence of obesity and malnutrition in children  $^{\mbox{\tiny (16)}}.$ 

When the relationship between the presenting symptom and viral agent of the patients in the study was examined, muscle pain was more common in patients with influenza B than in those with influenza A and more than one virus. In a systematic review, there was no significant difference between influenza A and B subtypes with other symptoms except myalgia; it has been reported that myalgia is more common in influenza B than in influenza A<sup>(21)</sup>. Similarly, in many studies evaluating pediatric influenza cases in the literature, children with influenza B infection were found to have higher CK value<sup>(22,23)</sup>. Although muscle pain was more common in patients with influenza B, no similar relationship was found in terms of CK elevation. Influenza-associated myositis in children is usually mild and regresses within 3-5 days with bed rest and anti-inflammatory drugs<sup>(2)</sup>.

The most common complication was pneumonia. One-fourth of these patients required respiratory support during followup. In a large series conducted in the United States, it was reported that the most common complication of influenza was respiratory complications, with pneumonia being the most common among them<sup>(21)</sup>. In our study, oseltamivir was initiated in 63.7% of patients, and antibiotic treatment was initiated in 74.4% of patients due to secondary bacterial infections [most commonly pneumonia (52%)].

The American Society for Infectious Diseasesrecommends initiating treatment for patients of all ages hospitalized for influenza and its complications and for patients at higher risk for influenza-related complications, regardless of the time of symptom onset<sup>(22)</sup>. It is known that the earlier oseltamivir treatment is initiated in influenza infection, the better the clinical outcomes<sup>(23)</sup>. In a Cochrane analysis, oral oseltamivir and inhaled zanamivir shortened the illness duration by 36 hours in 1255 laboratory-confirmed pediatric patients<sup>(5)</sup>. In our study, no statistically significant differences were found between the time of initiation of oseltamivir and the rates of complications, need for antibiotics, respiratory support, hospitalization in the service-intensive care unit, and mortality rates.

Influenza, on the other hand, is usually a self-limiting condition in healthy individuals. For this reason, only supportive treatment is applied to individuals without an underlying chronic disease and to those without complications. Antipyretic drugs, adequate fluid intake, and rest are recommended<sup>(1,5)</sup>. In a sentinel surveillance study

conducted jointly in France and Türkiye, it was emphasized that 26% of laboratory-confirmed influenza cases in France and 55% of cases in Türkiye were prescribed antibiotics, and the rate of unnecessary antibiotic use in influenza cases in both countries was high<sup>(24)</sup>. As a result of these findings, physicians should appropriately determine the indication and risk of complications when deciding on the initiation of oseltamivir and antibiotic treatment during influenza.

The American Academy of Pediatrics and the CDC recommend that all children aged 6 months and older without medical contraindications be vaccinated annually for influenza<sup>(25,26)</sup>. Although most patients in our study had risk factors for severe influenza infection, such as young age, underlying chronic disease, and obesity; vaccination rates were found to be insufficient. According to data from the Global Influenza Hospital Surveillance Network, the rate of influenza vaccination among children under the age of five in Türkiye was 2.1% in the 2015-2016 season and 1.3% in the 2016-2017 season<sup>(27)</sup>. It was noticed that the rate of 2.4% in our study was still above the country average. Since our study is a single-centered study, it cannot reflect general data in Türkiye. In addition, the retrospective nature of the study limited the accessibility of the whole data. Only hospitalized patients were included in the study. Therefore, outpatients with mild clinical courses were not included.

#### **Study Limitations**

The strength of this study is that it compares a large number of children admitted with microbiologically confirmed. Despite its strengths, our study has several limitations. First, it is a single-centre retrospective study. Its retrospective design and reliance on hospital data may limit generalizability. We only evaluated three influenza season so our findings may not generalizabl. In addition, we would like to follow upour patients todeterminewhetherthere have long-term impact of influenza.

#### Conclusion

Influenza is an important disease, especially in children under the age of two. The incidence of co-infection was also higher in this age group than in older children. Respiratory system complications were the most frequently detected complications in the study population; approximately onefourth of the patients received respiratory support, and onefifth received intensive care support. It has been observed that underweight and overweight/obese patients require more intensive care than those with normal body weight. There were no significant relationships between the time of initiation of oseltamivir treatment and the length of stay in the pediatric service-intensive care unit, antibiotic and respiratory support needs, complications, and mortality rates. In general, the vaccination rate of patients with several risk factors for influenza were very low in our study.

#### Ethics

**Ethics Committee Approval:** Prior to the study, permission was obtained from the Ethics Committee of Aydın Adnan Menderes University (number: 48843899-804.01, date: 24.07.2020).

**Informed Consent:** Retrospective study.

#### Footnotes

#### **Authorship Contributions**

Surgical and Medical Practices: G.S.Ö., S.S.K., G.S.Öz., Concept: G.S.Ö., S.S.K., G.S.Öz., Design: G.S.Ö., S.S.K., G.S.Öz., Data Collection or Processing: G.S.Ö., S.S.K., G.S.Öz., Analysis or Interpretation: G.S.Ö., S.S.K., G.S.Öz., Literature Search: G.S.Ö., S.S.K., G.S.Öz., Writing: G.S.Ö., S.S.K., G.S.Öz.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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# The Effect of Tissue Adhesive Coated Onlay Meshes on Wound Healing in Rabbits

Doku Yapıştırıcı ile Kaplanan Meşlerin Onlay Yerleştirilen Tavşanlarda Yara İyileşmesi Üzerine Etkisi

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#### Abstract

**Objective:** The aim of our study was to evaluate the histopathological effects of coating different types of meshes with tisseel<sup>®</sup> on wound healing in rabbits operated for incisional hernia (IH).

**Methods:** In this study, we used 35 New Zealand type rabbits. Midline defects were created in order to simulate IH and repaired with two different types of meshes [heavyweight (HW) vs. lightweight (LW)]. Each mesh group was further subdivided into two groups depending on the mesh fixation method (suture vs. tisseel®). The rabbits were re-operated on and full thickness samples were examined histopathologically 90 days postoperatively. American Society for Testing and Materials scales were used to score the inflammatory response to these meshes. Mean overall response (MOR) scores were calculated and statistically significant differences were examined.

**Results:** In the suture fixation group, histopathological examination of specimens revealed a significantly higher inflammatory response to HW meshes when compared to LW meshes. However, the inflammatory response and MOR values were not significantly higher when HW meshes were fixed with tisseel<sup>®</sup>. Surprisingly; LW meshes covered with tisseel<sup>®</sup> led to a significantly higher inflammatory response and MOR values when compared to tisseel<sup>®</sup> covered HW meshes, sutured LW meshes and sutured HW meshes.

**Conclusion:** In the routine surgical practice HW meshes create an elevated inflammatory response when fixed with suture materials. Tisseel<sup>®</sup> leads to a higher inflammatory response when used alone and when combined with LW meshes this response is even higher than HW meshes.

Keywords: Experimental, ventral hernia repair, polypropylene, tissue adhesive material

#### Öz

**Amaç:** Çalışmamızın amacı, tavşanlarda insizyonel herni tabanına serilen farklı yamaların doku yapıştırıcı ile kaplanması veya kaplanmamasının, yara iyileşmesi üzerine etkilerini histopatolojik olarak değerlendirmektir.

**Yöntem:** Çalışmada 35 adet Yeni Zelanda türü tavşan kullanılmıştır. Tavşanlarda orta hat defekti oluşturulmuş ve gruplara göre bu defektler onarılarak onarım alanının üzerine [ağır siklet (AS) ve hafif ağırlık (HA)] olmak üzere farklı iki meş konulmuştur. Her bir meşin bir grubu sütürle tespit edilip operasyon



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#### Öz

sonlandırılırken diğer grubun üzeri doku yapıştırıcı tisseel<sup>®</sup> ile kaplanarak işlem sonlandırılmıştır. Ameliyatın 90 gün sonrasında tavşanlar tekrar ameliyata alınarak meş ve altındaki dokudan tam kat örnek alınmış histopatolojik incelemeye tabi tutulmuştur. Histopatolojik inceleme Amerikan Test ve Malzeme Derneği değerlendirme skalasına göre yapılarak her bir denek için bir ortalama doku cevabı (ODC) sonucu alınmıştır. Gruplar istatistiksel olarak anlamlılık açısından birbiri ile kıyaslanmıştır.

**Bulgular:** Sonuç olarak tisseel<sup>®</sup> ile kaplanmayan AS ve HA meşler kıyaslandığında; AS meşin dokudaki enflamatuvar yanıtının anlamlı bir şekilde fazla olduğu görülmüştür. Bunun yanında HA meş tisseel<sup>®</sup> ile kaplandığında enflamatuvar yanıt ve ODC değerinde anlamlı artış olmamıştır. HA meşin kaplamasız kullanıldığında AS meşe göre ODC cevabı düşükken, HA meş tisseel<sup>®</sup> kaplandığında kaplamasız HA meşe, kaplamasız AS meşe ve kaplamalı HW meşe göre ODC skorunun anlamlı bir şekilde arttığı sonucuna ulaşılmıştır.

**Sonuç:** Rutin cerrahi pratikte kullanılırken; AS meşler sütür materyalleri ile tespit edildiğinde ileri derecede enflamatuvar yanıt oluştururlar. Tisseel® ise gerek tek başına gerekse HA meş ile kombine kullanıldığında AS meşin yarattığı enflamasyondan da yüksek bir yanıta sebep olmaktadır.

Anahtar Kelimeler: Deneysel, ventral herni tamiri, polipropilen, doku yapıştırıcı

#### Introduction

Abdominal wall hernia is one of the most frequent health problems encountered by general surgeons<sup>(1)</sup>. Incisional hernia (IH), is defined as bulging of abdominal organs from a defect on the abdominal fascia as a late complication of previous abdominal surgical procedures<sup>(2)</sup>. The risk of IH ranges from 10-20% after midline laparotomy<sup>(3)</sup>. Recurrence rates differ following IH repair with levels of 30-50% reported after repair without prosthetic material and 0-15% with mesh repairs. Because of the high recurrence rate, IH is related to significant loss of labor, important morbidity and mortality<sup>(2)</sup>.

Surgery is the only treatment for IH and involves primary repair, repairs performed with different types of materials or laparoscopic mesh repair. Mechanical failure, postoperative pain, mesh reaction, adhesion, seroma and erosion are the main reported complications from using prosthetic materials in IH repair. To reduce or avoid these complications; different types of meshes have been produced including meshes covered with various materials for the prevention of infection and excessive inflammation. These treatment options offer both advantages and disadvantages and there is currently no consensus about the ideal surgical choice<sup>(2,3)</sup>. Fibrin sealants are also alternative for fixation of meshes in hernia surgery. Tisseel<sup>®</sup> (fibrin sealant) is a two-component fibrin sealant made from pooled human plasma. When combined, the two components, Sealer Protein and Thrombin mimic the final stage of the blood coagulation cascade<sup>(4)</sup>.

The purpose of our study is to evaluate the histopathological effects of tisseel<sup>®</sup> (Baxter Healthcare Corporation, Westlake Village, CA, USA) coating of lightweight (LW) [DynaMesh<sup>®</sup> pancreatic polypeptide Light 36 g/m<sup>2</sup> 1.6x2.6 mm pore size

FEG Textiltechnik mbH Aachen, Germany] and heavyweight (HW) (paha<sup>®</sup> Polypropylene Mesh, 115 g/m<sup>2</sup> 0.75 mm. pore size. Altaylar Medical, Ankara, Türkiye) on wound healing in rabbits operated for IH.

#### **Materials and Methods**

The study was approved by the Ethics Committee of GATA Animal Experiments (date: 07/10/2011, no: 2011-10). Thirtyfive (n=35) female New Zealand rabbits were utilized. Guidelines of Helsinki Declaration on the animal care and use were carefully implemented during the study.

#### **Surgical Preparation**

After one-night fasting, anesthesia was administered with ketamine (ketalar<sup>®</sup>, Parke Davis and Co. Inc., 40 mg/kg) ve xylazine (rompun<sup>®</sup>, Bayer Ag, Leverkusen, Germany; 5 mg/kg) by intramuscular injection. Before incision, cefazolin (50 mg/kg) was intramuscularly administered. The hair of the rabbits was removed with a surgical clipper (3M<sup>®</sup>, St. Paul, MN, USA) and povidone iodine solution was used for skin preparation (Figure 1).

#### **Mesh Fixation**

The rabbits were divided into five groups. In all groups; 3 cm. midline incision was made, including skin, soft tissue fascia and peritoneum. The defect was reapproximated with 2/0 polypropylene (PP) (prolene®; Ethicon, Somerville, NJ/ USA) sutures, mimicking the wall closure in abdominal surgeries (Figure 2). Seven rabbits were signed as a control group and their skin defect was also sutured in the first surgical procedure. Four groups were mesh groups. Two types of meshes (DynaMesh<sup>®</sup> and paha<sup>®</sup>) 3x3 cm in size, were fixed on the sutured fascia defect with PP sutures in the first

two groups (Figure 3a-d). The same meshes were fixed to the fascia with tisseel<sup>®</sup> in the fourth and fifth groups (Figure 4a-d). Rabbits were assessed 12 hours postoperatively and started to eat normal feed.

#### Histopathological Evaluation

Ninety days after the first surgical procedure; rabbits were administered with the same preoperative management. The midline incision was repeated and the mesh region was dissected. For histologic assessment; a 1x1 cm sample was excised including mesh and fascial tissues. The samples were immersed in paraffin, 5 micron sections taken and



Figure 1. Preoperative preparation



Figure 2. Reapproximating fascia defect

stained with hematoxylin and eosin. Histopathological examination was performed with a light microscope (Nikon E 200 Tokyo/Japan) at 40x, 100x and 200x magnification by an experienced pathologist. The American Society for Testing and Materials (ASTM) scale was used for the histopathological assessment<sup>(5)</sup>. Inflammation score was calculated by the evaluation of polymorphonuclear leukocyte, lymphocytes, plasma cells, macrophages, giant cells and necrosis. For every sample, the inflammation subtotal was calculated by the sum of inflammatory cell scores multiplied by two (Table 1). Mean inflammation score (MI) was calculated by average of all inflammation subtotals. MI was calculated for each group. Mean overall response (MOR) was calculated by MI + fibrosis score (Table 2) + fatty infiltration score. Overall response was correlated with the extension of inflammation and fibrosis<sup>(6)</sup>.

#### **Statistical Analysis**

DATA were analyzed with Statistical Package for Social Sciences software (SPSS version 15.0, SPSS Inc., Chicago, IL, USA) using Mann-Whitney U test and a p-value of less than 0.05 was considered significant.

#### **Results**

At 90 days; no mortality and morbidity was seen in all subjects. Samples were assessed for MI and MOR scores. The control



**Figure 3.** Macroscopic structure and application of meshes, **a)** Hight weight (HW) mesh **b)** Onlay fixation of HW mesh with pancreatic polypeptide suture **c)** Low weight (LW) mesh **d)** Onlay fixation of LW mesh with PP suture

group and the other groups were comparable. MOR was higher in the HW and suture group hereditary neuropathy with liability to pressure palsies (HNPP) (p=0.011), lower in LW and suture group lipoprotein metabolism profile (LMPP) and higher in both HW with tisseel\* histone methyltransferases, (HMTS) and LW with tisseel\* laterally moving tactile stimuli (LMTS) (p=0.01 and 0.026), compared with the control group (Table 3). The inflammatory response was significantly lower in the LMPP group compared to HNPP (Figure 5a). The MOR score did not differ in the heavy mesh groups (p=0.383)



| Figure 4. a)          | Two cor  | nponent   | tiss | ue adhe  | sive m | aterial |
|-----------------------|----------|-----------|------|----------|--------|---------|
| tisseel®, <b>b,c)</b> | Applying | tisseel®, | d)   | tisseel® | coated | mesh    |
| material              |          |           |      |          |        |         |

(Figure 5b). Although the LMPP groups overall response was even lower than the control group; it showed excessive reaction when coated with tisseel<sup>®</sup>, compared to LMPP and HMTS groups (Figure 5c, d). 100x magnified microscopic photographs of histopathological examples for ASTM scales are shown in Figure 6.



**Figure 5.** Comparison of groups according to mean overall response (MOR) results. **a)** Hereditary neuropathy with liability to pressure palsies (HNPP) vs. lipoprotein metabolism profile (LMPP), **b)** HNPP vs. histone methyltransferases (HMTS), **c)** LMPP vs. laterally moving tactile stimuli (LMTS), **d)** HMTS vs. LMTS

| Table 1. ASTM inflammation scale   |       |         |          |         |          |
|--|-------|---------|----------|---------|----------|
| Inflammation   | 0     | 1       | 2        | 3       | 4        |
| PMNL   | 0/hpf | 1-5/hpf | 6-10/hpf | >10/hpf | Abundant |
| Lymphocytes  | 0/hpf | 1-5/hpf | 6-10/hpf | >10/hpf | Abundant |
| Plasma cells   | 0/hpf | 1-5/hpf | 6-10/hpf | >10/hpf | Abundant |
| Macrophages  | 0/hpf | 1-5/hpf | 6-10/hpf | >10/hpf | Sheets   |
| Giant cells  | 0/hpf | 1-2/hpf | 3-5/hpf  | >5/hpf  | Sheets   |
| Necrosis   | None  | Limited | Minimal  | Mild    | Moderate |
| ASTM: American Society for Testing and Materials. PMNI · Polymorphonuclear leukocyte |       |         |          |         |          |

| Table 2. ASTM fibrosis scale         |  |         |          |           |           |
|--------------------------------------|--|---------|----------|-----------|-----------|
|                                      | 0  | 1       | 2        | 3         | 4         |
| Fibrosis                             | None   | Minimal | Moderate | Extensive | Х         |
| Fatty infiltration                   | None   | Limited | Minimal  | Moderate  | Extensive |
| ASTM: American Society for Testing a | ASTM: American Society for Testing and Materials |         |          |           |           |

#### Discussion

Healing of surgical wounds includes an inflammation phase for the first 5 days, proliferation phase in 4-14 days, and a maturation phase at 11-16<sup>th</sup> days<sup>(7)</sup>. The maturation phase may extend in prosthetic hernia repairs. In recent years, low recurrence hernia repairs have been accomplished with the use of newly developed tension free meshes that provide high postoperative comfort. However, mesh-related complications have still been reported in one out of five patients<sup>(8,9)</sup>.

The repair of the hernia defect with support materials started with mid-18<sup>th</sup> century, although the pancreatic polypeptide mesh was used for the first time by Usher in 1958<sup>(9)</sup>. In later



Figure 6. Examples for American Society for Testing and Materials (ASTM) scaling haematoxylin & eosin 100x, a) fibrosis, b) inflammation around the mesh fibres (arrow), c) giant cell around the mesh fibre (arrow) (ASTM score 4), d) necrosis (ASTM score 4) years, different materials have been used for hernia repair. However, life-threatening complications including infection, migration and erosion of meshes, seroma, abscess, and fistula (entero-cutaneous, colo-cutaneous) have been reported in the short and long term, with materials applied using a tension-free technique<sup>(10-13)</sup>. There are an overwhelming number of different treatment options available including non-mesh repair for young people, wide-pore light mesh usage instead of conventional heavy meshes, coating the meshes with different materials like antibiotics, chitosan or silicone, usage of various methods of mesh fixation like progrip, tacker, suture or adhesive materials<sup>(14,15)</sup>. By covering the HW meshes with tisseel<sup>®</sup>, so reducing its direct contact with the tissue and using the tissue adhesive instead of excessive prosthetic material per unit area, we evaluated delaying the early inflammatory response and reducing complications. Weyhe et al.<sup>(16)</sup> reported in their study that; reduction of the amount of foreign materials used in ventral hernia repair were associated with postoperative comfort of the patients. In this study, we evaluated the complications and histopathologic/immunohistochemical evaluation of foreign body reactions in the tissue, when LW, large-pore mesh with lesser amounts of foreign body and HW, and small-pore mesh carrying larger amounts of foreign bodies were covered with tissue adhesive. Tissue evaluation was undertaken on the 90<sup>th</sup> postoperative day, when intensity of the immune response is complete. Junge et al.<sup>(17)</sup> analyzed the effects of the material weight, the filament structure, and the type of polymer on biocompatibility. As a result, they found that mesh biomaterial is of significant importance in causing foreign body reactions and also noted that all of these features contribute to the foreign body reaction, which is a main predictor of mesh biocompatibility, in our study, we have found that LW, large-pore mesh causes statistically (p=0.001) significantly less inflammatory tissue response

| Table 3. Comparison of control & mesh groups according to MOR values   |             |       |   |  |
|--|-------------|-------|---|--|
| Group  | MOR/SD      | р     | n |  |
| Control  | 21.57/0.487 | 0.011 | 7 |  |
| НМРР   | 22.57/0.899 | 0.011 | 7 |  |
| Control  | 21.57/0.487 | 0.01  | 7 |  |
| LMPP   | 17.42/1.214 |       | 7 |  |
| Control  | 21.57/0.487 | 0.026 | 7 |  |
| HMTS   | 23.42/1.864 | 0.020 | 7 |  |
| Control  | 21.57/0.487 | 0.01  | 7 |  |
| LMTS   | 23.71/0.487 | 0.01  | 7 |  |
| MOR: Mean overall response. SD: Standard deviation, n: Samples, LMTS: Laterally moving tactile stimuli, HMTS: Histone methyltransferases |             |       |   |  |

when compared to higher density prosthetic material including HW mesh. These results were similar to the study of Klosterhalfen et al.<sup>(18)</sup>, which reported low-weight meshes cause a lesser inflammatory response, because low-weight meshes contain lesser prosthetic material per unit. There was no significant difference in terms of inflammatory response between HW mesh covered with tissue adhesive and HW mesh without tissue adhesive (p=0.383). This was histopathologically confirmed and the authors assume this response was associated with delayed or diminished immune response secondary to covering. Additionally, when LMTS and long-term postoperative pneumonia groups were compared, a significant increase in the inflamatory response in the covered group was detected (p=0.01). In the case of comparing tissue adhesive-covered heavy and light meshes, although uncovered LW meshes initiate a reduced tissue response, covered LW meshes cause higher rates of tissue response (p=0.01). The ideal mesh for hernia repair is still unclear but should be tissue compatible, not alter abdominal wall compliance, support the defect entirely, not cause tissue tightness, be affordable, easily applicable, available, and resistant. Research about prosthetic materials are based on these principles. Melman et al.<sup>(6),</sup> compared LW and HW, PP mesh and large pore polytetrafluoroethylene mesh in a porcine model of ventral IH repair. They evaluated inflammation and tissue fibrosis at 1, 3, and 5 months in tissue samples and found no significant differences. On the other hand, they determined that the tissue response was decreased in the following months. In a randomised controlled study by Ladurner et al.<sup>(19),</sup> patient defects were prepared with HW and LW meshes and no differences were found in terms of life quality between the two patient groups. Bellon et al.<sup>(20)</sup> categorized the meshes into three categories, with a weight  $35 \text{ g/m}^2$  as LW, with a weight 35-80 $q/m^2$  as medium weight, and meshes with a weight >80 g/ m<sup>2</sup> as HW. In a review of mesh biocompatibility written by Weyhe et al.<sup>(21)</sup>, two studies conducted by Junge et al.<sup>(22)</sup> were evaluated and authors claimed that foreign body reactions were lesser in lighter meshes. On the other hand, in an experimental study by Weyhe et al.<sup>(16)</sup>, they reported that there was a greater inflammatory response in subjects with LW meshes when compared to subjects with HW meshes. In our study, there was a lesser inflammatory response in subjects with large-pore meshes. Carboxymethylcellulose coated PP mesh and pure mesh was compared in terms of developing fibrosis and inflammation in a study by Yelimlies et al.<sup>(23)</sup>, and the authors found coated mesh reduced adhesions but there was no significant differences in terms

of inflammation and fibrosis. Junge et al.<sup>(22)</sup> studied PP meshes modified by titanium coating and non-coated tissue samples taken from animals. Formation of granulomas and immunohistochemically detected macrophage counts were compared and no significant advantages of titanium coated PP meshes were found in terms of biocompatibility. Lehle et al.<sup>(24)</sup> presented results in contrast to this study in their in vitro study however an in vitro evaluation might not represent the real tissue response. Scheidbach et al.<sup>(25)</sup> compared conventional two different PP meshes with a titanium coated very low molecular weight mesh (16  $g/m^2$ ) in terms of inflammatory response and claimed that LW mesh showed a lesser response<sup>(25)</sup>. Although the response to the very LW mesh in this study is low and compatible with its weight, we found low levels of inflammation to the LW mesh and an increase in inflammatory response when the LW mesh was coated with tissue adhesive. This might be secondary to narrowing of mesh pores when coated with tisseel®.

Saygun et al.<sup>(26)</sup> compared gold, gold and palladium coated PP meshes and pure meshes in an infectious model of research, examining prevention of material infection. At first, the three different meshes used were washed with saline, following contamination with S. epidermidis washed with saline again and in the 3rd day implanted in the hernia areas of rats. After this procedure, culture samples were collected from the wounds at the 8<sup>th</sup> postoperative day and wound infection rates were 0% in the gold-palladium coated mesh implanted rats, 30% in the gold coated mesh group and 100% of infection rates in the PP used sample but further research is required to verify this theory. In another study; Cakmak et al.<sup>(11)</sup> used Chitosan, a polymer obtained by alkaline deacetylation of chitin to coat PP meshes in a model of hernia graft infection. There were no reported graft infections in the hernia repair with Chitosan coated meshes and no need for antibiotic prophylaxis. Sucullu et al.<sup>(27)</sup> conducted research into reusing the meshes after sterilizing them, and concluded that there were no significant differences between resterilized meshes and new meshes in tissue resilience, inflammatory response and development of an infection. Brandt et al.<sup>(28)</sup>, reported lower rates of inflammatory response in pure polyvinyl difluoride (PVDF) meshes compared with hydrocortisone and spironolactone coated PVDF meshes in an experimental study. We observed higher rates of inflammatory response in the samples from tisseel coated LW meshes than in the samples from non-coated LW meshes. Lobato et al.<sup>(29)</sup> conducted a randomised prospective study in IH patients. They found 20% postoperative complication rates including abscess, hematoma formation, and cellulitis in the group in which tisseel/tissucol was used with sutures for mesh fixation, and infection rates were 46.6% in the group without tisseel/tissucol. Mean hospitalization time was 7.1 days in the first group and 12.6 days in the second group. Eriksen et al.<sup>(30)</sup> compared tisseel/tissucol laparoscopic use with a titanium stapler for hernia repair. They reported significant differences in postoperative pain, time to returning to daily activity and hospitalization time in the tissue adhesive-used group. Stergios et al.<sup>(31)</sup> reported the results of their study on tisseel usage for colorectal anastomosis in diabetic rats. According to the study, tisseel was not only a positive factor for wound healing, but also a positive promoter for inflammatory response and fibroblast accumulation.

Research on tisseel<sup>®</sup> in the literature is commonly based on clinical symptoms and there have been no studies designed for gauging reactions against mesh. This topic is addressed in our study and according to the results, tisseel increases the inflammatory response, which is an important factor in wound healing around prosthetic material, but further studies are needed to determine appropriate coating of commercial meshes.

#### **Study Limitations**

Due to pre-study analyses, we used the smallest number of subjects possible statistically. For this reason, we believe that studies with more subjects or on humans for clinical use would be more meaningful. When the study was planned, MMP-2 antibody examination and sirrius red dye were planned for the pathological evaluation of wound healing. Due to problems during the supply phase, these materials could not be used and the evaluation was made with hematoxylene eosine dye and inflammation and fibrosis scoring. We believe that the pathological evaluation performed with the planned dye will yield more meaningful results.

#### Conclusion

The only treatment option for IH that develop as a complication after abdominal surgery is surgery. The most commonly used surgical treatment option is mesh repair. Many mesh materials have been developed that vary in terms of their weight, materials they contain, mesh structure and pore width. Although there are opposing views in the studies, it is argued that low-weight and large-pore meshes have less inflammatory response in the tissue and have a higher quality wound healing. In our study, we found that

the LW large-pore mesh we used showed less inflammatory response than the HW small-pore mesh. We concluded that tisseel® coating is not an effective repair method in mesh IH repair because tisseel® which is biocompatible when used in other surgical areas, did not suppress/increase the inflammatory response of the meshes we used in our study. Experimental studies are needed with new parameters, in larger numbers of subjects and for longer periods, using different mesh materials.

#### Ethics

**Ethics Committee Approval:** The study was approved by the Ethics Committee of GATA Animal Experiments (date: 07/10/2011, no: 2011-10). This study was conducted in Gülhane Military Medical Academy Command.

**Informed Consent:** Since it is an experimental animal study, patient consent information is not required.

#### Footnotes

#### **Authorship Contributions**

Concept: N.Z., N.E., Y.P., Design: N.Z., N.E., Data Collection or Processing: U.M.M., Analysis or Interpretation: U.M.M., N.E., A.F.Ç., Y.P., Literature Search: U.M.M., N.Z., Y.S.P., Writing: U.M.M., Y.S.P.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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# Early Respiratory Problems and Tobacco Use in the Region Affected by Kahramanmaraş Earthquakes

Kahramanmaraş Depremlerinden Etkilenen Bölgede Erken Solunum Sorunları ve Tütün Kullanımı

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#### Abstract

**Objective:** Many respiratory complications have been reported in post-earthquake conditions. We aimed to reveal respiratory medical requirements during the early post-earthquake period and possible changes in tobacco use.

**Methods:** Data on age, gender, symptom, diagnosis, medications used continuously, if any, earthquake-induced disruption in medications and medical devices, place of residence, prescribed medications, smoking status, and number of cigarettes consumed daily before and during the earthquake were collected.

**Results:** In 137 patients, the most frequently (29.9%) presentation was asthma, followed by chronic obstructive pulmonary disease (COPD)/chronic bronchitis. Twelve patients had chest trauma and nine had a costal fracture. Sixty-nine (50.4%) patients were admitted for chronic and 46 (33.6%) for acute respiratory diseases. Medication use was not interrupted in chronic respiratory diseases. The most common complaint was cough followed by shortness of breath. Bronchodilators and expectorants were frequently prescribed, and 15.3% of patients were treated/intervened in the emergency department. Interference in use of medical devices. The rate of smoking among patients was 28.5% compared with 24.1% before the earthquake. The number of daily cigarettes smoked by active smokers before and after the earthquake increased (p=0.048).

**Conclusion:** In the aftermath of the Kahramanmaraş earthquakes; exacerbation, medication, and device management for patients with asthma and COPD were the primary medical requirements in terms of respiratory diseases. Provision of medication support for chronic pulmonary diseases avoided interruption. Patients still living in crowded/dysadvantaged conditions need proper management of lower respiratory tract infections, pulmonary thromboembolism, asthma, and COPD exacerbations. The rate of smoking and the number of cigarettes smoked per day have increased among patients with respiratory problems.

Keywords: Kahramanmaraş earthquake, chronic obstructive pulmonary disease, asthma, tobacco use

#### Öz

**Amaç:** Deprem sonrası koşullarda birçok solunum komplikasyonu bildirilmiştir. Bu çalışmada, deprem sonrası erken dönemde solunumsal tıbbi gereksinimleri ve tütün kullanımı açısından meydana gelen olası değişiklikleri ortaya koymayı amaçladık.

**Yöntem:** Göğüs hastalıkları polikliniğine başvuranlarda yaş, cinsiyet, semptom, tanı, varsa sürekli kullanılan ilaçlar, ilaç ve tıbbi cihazlarda depreme bağlı bozulma, ikamet yeri, reçete edilen ilaçlar, sigara içme durumu, deprem öncesi ve deprem sırasında günlük tüketilen sigara sayısı toplandı.

**Bulgular:** Yüz otuz yedi hastada en sık (%29,9) astım, ardından kronik obstrüktif akciğer hastalığı (KOAH)/kronik bronşit başvurusu vardı. On ikisinde göğüs travması ve dokuzunda kosta kırığı vardı. Altmış dokuz hasta (%50,4) kronik, 46 hasta (%33,6) akut solunum yolu hastalığı nedeniyle başvurdu. Kronik solunum yolu hastalıklarında ilaç kullanımı kesintiye uğramamıştır. En sık görülen şikayet öksürük olup bunu nefes darlığı takip etmektedir. Bronkodilatörler ve ekspektoranlar sıklıkla reçete edilmiş ve %15,3'ü acil serviste tedavi/müdahale edilmiştir. Tıbbi cihaz kullanımında kesintiler vardı. Hastalar arasında



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#### Öz

sigara içme oranı depremden önce %24,1 iken depremden sonra %28,5 olmuştur. Depremden önce ve sonra aktif sigara içenlerin günlük içtikleri sigara sayısı artmıştır (p=0,048).

**Sonuç:** Kahramanmaraş depremleri sonrasında; astım ve KOAH'lı hastalarda alevlenme, ilaç ve cihaz yönetimi solunum yolu hastalıkları açısından öncelikli tıbbi gereksinimler olmuştur. Kronik akciğer hastalıklarına yönelik ilaç desteğinin sağlanması kesintiye uğramamıştır. Halen kalabalık/dezavantajlı koşullarda yaşayan hastaların alt solunum yolu enfeksiyonları, pulmoner tromboembolizm, astım ve KOAH alevlenmelerinin uygun şekilde yönetilmesi gerekmektedir. Solunum problemi olan hastalarda sigara içme oranı ve günlük içilen sigara sayısı artmıştır.

Anahtar Kelimeler: Kahramanmaraş depremi, kronik obstrüktif akciğer hastalığı, astım, tütün kullanımı

#### Introduction

An earthquake is a catastrophic natural disaster that not only kills and injures the people it affects but also displaces them and impacts healthcare delivery. There are many respiratory complications caused by both earthquake and post-earthquake exposure. These can be summarized as dust and particle inhalation, aspiration of water and waterborne pathogens, thoracic trauma, pulmonary thromboembolism (PTE), psychological effects of respiratory symptoms, and infectious respiratory diseases<sup>(1)</sup>.

Thoracic trauma is the most common cause of hospitalization within the first 24 hours after an earthquake. It accounts for 10% of hospital admissions at the first moment and has a high mortality risk. Dehydration, prolonged immobility, and earthquake-induced injuries effectively cause deep vein thrombosis in survivors<sup>(1-7)</sup>. In the 2004 Mid-Niigata Prefecture, Japan earthquake, the incidence of PTE was >5% in regions with a high rate of survivors<sup>(8)</sup>. Displacement of people, unsafe water and hygiene conditions, disabling health service provision, and weak or low immunity predispose individuals to post-earthquake lung infections<sup>(9)</sup>.

There is insufficient information on the effects of earthquakes on the development or attacks of chronic obstructive pulmonary disease (COPD) and asthma<sup>(10)</sup>. A large-scale disaster may cause exacerbation in patients with COPD. Lack of access to medication, medical devices, and medical resources<sup>(11)</sup>.

Considering the stress caused by a natural disaster, such as an earthquake, on living, working, and social conditions, it may be associated with changes in smoking habits. The September 11 terrorist attacks showed that up to 30% of New York City residents increased their use of cigarettes, alcohol, and addictive substances<sup>(12,13)</sup>. In the 2010 Canterbuty earthquake, approximately one-fourth of those who quit smoking started smoking again after the earthquakes, and more than one-third of those who increased their tobacco consumption cited earthquakes as the reason for the increase. Therefore, it is important to maintain public health services consistently in planning for disaster aftermaths<sup>(14)</sup>.

The aim of this study was to reveal the problems that emerged in terms of pulmonary diseases in the early period after the earthquakes that affected 10 provinces of our country and caused great destruction, the medication needs and the needs of patients with chronic respiratory system diseases, and to determine whether a change occurred in terms of tobacco use.

#### **Materials and Methods**

#### Workspace

The study was conducted at Samandağ near the Mediterranean coast, with a surface area of 446 km<sup>2</sup> and a population of 121,109. On February 6, 2023, two earthquakes with magnitudes of 7.8 Mw ( $\pm$ 0.1) and 7.5 Mw occurred nine hours apart, with epicenters in Pazarcık and Ekinözü districts of Kahramanmaraş, respectively. Then, on February 20, 2023, another earthquake with a magnitude of 6.4 occurred in Hatay's Defne district at 20.04, and three minutes later, at 20.07, another earthquake with a magnitude of 5.8 occurred in Hatay, Samandağ. According to official figures, the earthquakes killed at least 50,500 people in Türkiye and 8,476 people in Syria and injured more than 122,000 people in total. The earthquakes were followed by more than 24,000 aftershocks with magnitudes up to 6.7 Mw<sup>(15)</sup>.

The Chest Diseases Outpatient Clinic was first opened at the Samandağ State Hospital in Samandağ district on March 24, 2023. Data on patients were recorded between March 24, 2023 and 06.04.2023, when the outpatient clinic remained open. During this period, patients in the district were able to obtain their prescribed medicines from three open pharmacies, the Mamak Municipality Mobile Tent Pharmacy and the Bakırköy Municipality Mobile Container Pharmacy, which were set up in the hospital garden.

#### **Patient Selection and Measurement**

Age, gender, symptom, diagnosis, medications used continuously, if any, whether they experienced any earthquake-induced disruption in these medications, place of residence, continuous use of medical devices, medications prescribed in the outpatient clinic, smoking status, and number of cigarettes consumed daily before and during the earthquake were recorded for patients who applied to the chest diseases outpatient clinic and for whom consultation was requested from the emergency department.

The research was approved by the İzmir Bakırçay University Non-Interventional Clinical Research Ethics Committee (decision no: 1008, date: 26.04.2023).

#### **Statistical Analysis**

Parametric analyses were performed using the patient records. Patients who smoked before and after the earthquake were divided into two groups and compared using the independent samples t-test.

#### Results

A total of 137 patients, 58 women (42.3%) and 79 men (57.7%), were included in the study. The mean age was  $49.36\pm15.8$  years.

In the district, which was heavily affected by the earthquake, the most common (29.9%) presentation to the chest diseases outpatient clinic, which was opened for the first time after 48 days, was asthma, followed by COPD/chronic bronchitis (Table 1). Of the 12 patients with chest trauma, nine had a costal fracture and one had a lung contusion. Sixty-nine (50.4%) patients were admitted for chronic respiratory diseases, 46 (33.6%) for acute lung problems, and the remaining patients were admitted for control examinations and medical reports. When patients with chronic diseases and continuous medication use were questioned, it was learned that their medication use was not interrupted except for three days after the earthquake. After this date, two mobile pharmacies were established in the district by nongovernmental organizations, one in the form of a tent and one in the form of a container, and the three undamaged pharmacies were provided by their owners for urgent cases.

The most common complaint was cough (51.8%) followed by shortness of breath (35.8%) (Table 2). Four (2.9%), 52

(38%) and 54 (39.4%) patients were prescribed three, two and one medications, respectively. No prescription was made for 27 patients. The most common prescriptions were bronchodilators and expectorants, while 21 (15.3%) patients were treated and intervened in the emergency department (Table 3).

Of the patients, 129 (94.2%) lived in tents/containers, seven (5.1%) lived in slightly damaged structures, and one (0.7%) lived in a vehicle. When patients with continuous use of medical devices were questioned, four of the patients living in tents were still using oxygen concentrators, seven were using nebulizers, and one was using bi-level positive airway pressure for obstructive sleep apnea syndrome. The oxygen concentrators of two patients were trapped under the debris.

# Table 1. Diagnoses of patients affected by the earthquake at the chest diseases outpatient clinic

| Diagnosis   | n (%)     |  |  |
|---|-----------|--|--|
| Asthma  | 41 (29.9) |  |  |
| COPD/chronic bronchitis   | 27 (19.7) |  |  |
| Acute bronchitis  | 17 (12.4) |  |  |
| Upper airway infection  | 12 (8.8)  |  |  |
| Thoracic trauma   | 12 (8.8)  |  |  |
| Acute sinusitis   | 6 (4.4)   |  |  |
| Pneumonia   | 7 (5.1)   |  |  |
| Pulmonary thromboembolism   | 1 (0.7)   |  |  |
| OSAS  | 1 (0.7)   |  |  |
| Other   | 18 (13.1) |  |  |
| Normal  | 23 (16.8) |  |  |
| >100% for patients with multiple diagnoses, COPD: Chronic obstructive pulmonary disease. OSAS: Obstructive sleep apnea syndrome |           |  |  |

Table 2. Symptoms of patients affected by an earthquake

| and reported to the chest diseases outpatient clinic |           |  |  |
|--|-----------|--|--|
| Symptom  | n (%)     |  |  |
| Cough  | 71 (51.8) |  |  |
| Breathlessness                                       | 49 (35.8) |  |  |
| Chest pain   | 28 (20.4) |  |  |
| Sputum   | 21 (15.3) |  |  |
| Constituinal symptoms                                | 16 (11.7) |  |  |
| Rinitis  | 8 (5.8)   |  |  |
| Sore throat  | 6 (4.4)   |  |  |
| Fever  | 4 (2.9)   |  |  |
| Other  | 1 (0.7)   |  |  |
|  |           |  |  |

>100% for patients with multiple diagnoses

When the smoking status of patients was analyzed, the rate of smoking among patients admitted to the chest diseases outpatient clinic was 28.5% in the second month after the earthquake compared with 24.1% before the earthquake. The number of daily cigarettes smoked by active smokers before and after the earthquake increased statistically significantly (p=0.048) (Tables 4 and 5).

When the 24 consultations requested from the emergency department were analyzed; the diagnoses were COPD/ asthma exacerbation (n=21), trauma (three rib fracture, three general trauma, two pneumothorax an done hemothorax), carbon monoxide poisoning (n=5), pneumonia (n=3), gastrointestinal bleeding, cerebrovascular accident, acute bronchitis (n=2), food aspiration, myocardial infarction,

| Table 3. Treatment modalities applied in che outpatient clinic | st diseases |
|--|-------------|
| Treatment  | n (%)       |
| Bronchodilator   | 56 (40.9)   |
| Expectorant  | 47 (34.3)   |
| Leukotriene antagonist/antihystaminic                          | 16 (11.7)   |
| Analgesics   | 15 (10.9)   |
| Antibiotics  | 11 (8.0)    |
| Antipyretics   | 5 (3.6)     |
| Flu medicine   | 4 (2.9)     |
| Interventional thoracentesis                                   | 3 (2.2)     |
| Oral steroid   | 1 (0.7)     |
| Emergency service intervention                                 | 21 (15.3)   |
| Other  | 19 (13.9)   |
| None   | 27 (19.7)   |
| >100% for patients with multiple diagnoses                     |             |

| earthquake |                   |                  |  |
|------------|-------------------|------------------|--|
|            | Before earthquake | After earthquake |  |
| Smoking    | n (%)             | n (%)            |  |
| None       | 95 (69.3)         | 92 (67.2)        |  |
| Stop       | 9 (6.6)           | 6 (4.4)          |  |
| Active     | 33 (24.1)         | 39 (28.5)        |  |

Table 4 Concluing status

| Table 5. Amount of daily consumption of cigarette smokers before and after the earthquake |                          |                        |       |  |
|---|--------------------------|------------------------|-------|--|
|   | Before the<br>earthquake | After an<br>earthquake | р     |  |
| n of daily cigarette  | 14.45±9.89               | 20.62±15.02            | 0.048 |  |
| Independent samples t-test was applied  |                          |                        |       |  |

hypertension, respiratory failure, pulmonary edema, intraabdominal bleeding, and lumbar fracture (n=1).

#### Discussion

Post-earthquake lung diseases are an important cause of morbidity and mortality. Preventive and protective measures are effective. Disaster preparedness and response teams should implement these solutions<sup>(1)</sup>. Intervention with mobile healthcare services, such as field hospitals and infirmaries, for direct pulmonary complications during earthquakes is essential for early intervention. Again, organization is necessary for outpatient or inpatient treatment of conditions such as PTE and lung infections, etc. that are expected to occur after the earthquake. On the other hand, a critical requirement is the identification, treatment, and follow-up of the current health status of patients with chronic lung diseases who have survived the earthquake. As a matter of fact, the high number of risk factors in earthquakes -cold, rainy weather conditions, inhalation of dust and particles from buildings that collapsed during the earthquake or collapsed because they were heavily damaged after the earthquake, nutrition with a single type of food, reduced water intake, and change in hygiene conditions-led to more unfavorable conditions for these patients.

People who are forced to leave their homes are forced to make use of temporary sleeping places such as mattresses, tents, awnings, etc., and all kinds of life support (food, clean water, cleaning supplies) can be provided to these people to a limited extent. In crowded mass living environments where people are temporarily housed, children and the wounded are especially at risk of lung infections. This risk can only be eliminated by ensuring healthy airflow through clean, appropriate ventilation and preventing the inhalation of high concentrations of respiratory particles<sup>(16)</sup>. Infectious agents of the Wenchuan, China earthquake were reviewed. As a result of culture analysis of wound site, blood, and sputum samples, the most frequently growing bacteria were *Acinetobacter baumannii, Escherichia coli, Enteric bacilli, Klebsiella pneumoniae*, and *Psedudomonas aeruginosa*<sup>(17)</sup>.

In the second month after the earthquake in our country, the frequency of exacerbation of chronic lung diseases and acute upper and lower respiratory tract infections increased in applications to the chest diseases branch. Moreover, antibiotic use ranked first among the prescriptions issued. Life continues in crowded tents or containers, and the risk of lung infection persists. On the other hand, patient access to all types of medicines has been facilitated thanks to pharmacy areas that have been established and actively operated by public and non-governmental organizations.

In the 2011 Van earthquake, the most common types of injuries were extremity fractures and thoracic injuries. Numerous costal fractures, lung contusion, and hemopneumothorax require intervention<sup>(4)</sup>. In our analysis, 37.5% of the admissions to the emergency department were due to thoracic trauma, and radiologic presentations with high mortality, including pneumothorax and hemothorax, were encountered even in the second month after the earthquake. It was observed that some patients were not aware of costal fractures, and callus was observed on radiological images at outpatient clinic presentation.

The number of patients newly diagnosed with PTE increased significantly after the Niigata earthquake in Japan. Sedentary life in temporary shelters has been reported to be an important risk factor<sup>(18)</sup>. In addition, sympathetic nervous system activation caused by psychological and physical stress triggers excessive coagulation, resulting in increased platelet activity<sup>(19)</sup>.

The 2004 Chuetsu, Japan earthquake showed that people who stayed in vehicles for more than three nights were at great risk of deep vein thrombosis and PTE. Prolonged sitting, heat-related fluid loss, and decreased fluid intake are also risk factors<sup>(20)</sup>. PTE was diagnosed in one patient among 137 outpatient clinics and 24 emergency room visits included in our study. It was observed that only one patient stayed in an automobile, and the majority lived in tents. The region experienced cold weather in the first two months after the earthquake. When the situation in our country is considered from this point of view; it is thought that fluid losses will increase and PTE development will be seen more frequently with the warming of the weather in the regions affected by the earthquake and where people stay in temporary settlements.

After the 2011 Great East Japan earthquake, the prevalence of asthma was found to be 24.9% among individuals aged over 15 years who stayed in temporary mobile areas. Of these, 44.6% were diagnosed before the earthquake, 95% were in temporary accommodation, and 45.9% were diagnosed after moving to temporary housing. Attacks were reported in 71.4% of patients with asthma after moving to temporary homes. Allergic rhinitis or allergic conjunctivitis, family history of asthma, never smoking, and peripheral airway disease were risk factors. As a result, the earthquake increased mite allergen sensitization and attacks or caused asthma development in people over 15 years of age<sup>(10)</sup>. The COPD status of patients during the first six months of the same earthquake was analyzed. Patients who received long-term oxygen therapy at home were admitted to hospital within the first hour. The number of hospitalizations due to COPD exacerbation in the subacute period (between the first three and five weeks) increased significantly compared with the pre-earthquake period. Patients reported significantly less participation in activities of daily living upon admission. Six weeks after the earthquake, the COPD exacerbations returned to normal numbers<sup>(11)</sup>.

During the 2011 Tohoku earthquake, in addition to the anticipated problems and tasks, unforeseen ones were also encountered. For example, "tsunami lung" and thoracic trauma were the most important problems encountered at the earliest stage. On the other hand, because it coincided with cold spring days, influenza virus endemicity and pneumonia created an additional burden. Lack of energy supply leads to severe respiratory problems in patients requiring oxygen therapy for chronic respiratory failure and continuous positive pressure ventilation due to obstructive sleep apnea syndrome. Various problems have emerged in the diagnosis, treatment, and management of patients with asthma, COPD, and interstitial pneumonia in the subacute and chronic periods<sup>(21)</sup>. After the 2009 L'Aguila earthquake, the number of admissions for respiratory diseases increased. It has been reported that silent or subclinical chronic conditions, such as COPD, are triggered by earthquakes<sup>(22)</sup>.

In the 1999 Marmara earthquake, 34 people with chronic diseases were analyzed using the short form-(36) scale, and their scores related to the two basic elements of quality of life (physical and mental health) were found to be low. Individuals with chronic diseases that are among the risk groups in extraordinary situations, such as earthquakes, should be closely monitored and receive professional support. Quality of life can be improved by providing services to such individuals by a multidisciplinary professional team. In addition, it is recommended that units providing healthcare services after an earthquake structure their services for individuals with chronic diseases in a way to address their special and acute problems<sup>(23)</sup>. In the district where the study was conducted, health service provision was continued in the emergency department of the hospital belonging to the Ministry of Health in the early period, and a field hospital was established. Intense dust transport was observed from collapsed and heavily or moderately damaged buildings that began to be demolished during the earthquake. As a matter of fact, it is expected that asthma, COPD, and chronic bronchitis attacks will take the first place in the treatment of the chest diseases branch. The supply of medicines, consumables, and home treatment devices that these patients would need most could be managed through mobile pharmacies established in the district and hospital facilities.

#### **Study Limitations**

The limitations of this study include the fact that data were collected in a single center and in a limited time period, analysis was performed with a limited number of patients, and some diagnostic methods, especially the pulmonary function test, could not be applied due to the inadequate post-earthquake facilities of the institution where data were collected.

Thanks to the information, problems, and experiences gained after the devastating earthquake, it is possible to fully define and plan the ideal early and late period health service provision to be provided after the earthquake. The lessons learned will undoubtedly determine success in the next disaster.

#### Conclusion

In the aftermath of the Kahramanmaras earthquakes, exacerbation, medication, and device supply management were the primary early medical needs of patients with asthma and COPD. The provision of medication support, especially antibiotics and inhalers, by public institutions and non-governmental organizations in mobile settings ensured that the treatment and follow-up of chronic lung diseases were not interrupted in the early period. Patients are still living in crowded conditions, such as tents and containers, for an indefinite period and are exposed to adverse weather conditions. Therefore, they need to be managed properly in terms of lower respiratory tract infections, especially PTE, and asthma and COPD exacerbations. Compared with the pre-earthquake period, the rate of smoking and the number of cigarettes smoked per day have increased in patients with respiratory problems.

#### Footnote

**Ethics Committee Approval:** The research was approved by the İzmir Bakırçay University Non-Interventional Clinical Research Ethics Committee (decision no: 1008, date: 26.04.2023).

**Informed Consent:** The research that is the subject of our study was planned and carried out while I was working in

the region after the earthquake. All the data used in the research is the anamnesis information transferred to the hospital records of the patients. No prospective information specific to the research was collected and used.

#### **Authorship Contributions**

Surgical and Medical Practices: A.E.E., Concept: A.E.E, M.O.G., Design: A.E.E, M.O.G., Data Collection or Processing: A.E.E, Analysis or Interpretation: M.O.G., A.A., Literature Search: M.O.G., A.A., Writing: A.E.E, M.O.G., A.A.

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# Level of Knowledge and Awareness of Newly Diagnosed Cancer Patients About Cancer Diagnosis

Tıbbi Onkoloji Polikliniğine Başvuran Yeni Tanı Kanser Hastalarında, Hastalıkları Hakkındaki Bilgi ve Farkındalık Düzeyi

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#### Abstract

**Objective:** Cancer is a global health problem that threatens human lives worldwide. The awareness of cancer diagnosis varies over time. The level of knowledge and awareness of a cancer patient regarding his/her disease is one of the most important factors affecting the quality of life and psychology of the patient. This approach contributes to patient participation in treatment and decision-making. There have been very few studies on this subject in our country. Therefore, we aimed to measure the level of knowledge and awareness of newly diagnosed cancer patients admitted to our oncology unit.

**Methods:** Between January 1, 2018 and March 31, 2018, 159 newly diagnosed cancer patients admitted to the medical oncology outpatient clinic were included in the study. To evaluate the level of knowledge (sufficient or insufficient) and awareness of the patients and their relatives regarding their diseases, a questionnaire consisting of 21 questions was administered to them.

**Results:** Most patients (n=140, 88%) stated that they were informed about cancer diagnosis before being admitted to the oncology clinic. Eight patients (5%) reported that they did not receive any information. The relatives of 11 patients (7%) preferred not to reveal their cancer diagnosis. Relatives of elderly patients tended to conceal their diagnosis (p=0.023). Other demographic information and disease-related factors (organ, stage, etc.) did not influence awareness of the diagnosis. Although many patients with cancer and relatives were aware of their diagnosis, 25% of them defined their level of knowledge as insufficient. Older age, low income, diagnosis in non-surgical clinics, limited explanation time, and lack of clear language were associated with an insufficient level of knowledge. The most important expectations of patients from physicians were the prognosis of the disease, clear and understandable information about cancer, treatment options, and the side effect profile of the treatments.

**Conclusion:** The study revealed a high attitude toward providing information to patients with cancer at our hospital. The attitudes of patients' relatives should be improved to ensure that patients are better informed. Patient-physician communication is crucial for providing satisfactory patient information. Sufficient time should be allocated for explanations, and patients should be spoken to in a language they can understand. When providing explanations, patients' expectations should be considered.

Keywords: Neoplasm, communication, prognosis



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#### Öz

**Amaç:** Kanser, dünya çapında insan hayatını tehdit eden küresel bir sağlık sorunudur. Kanser tanısına ilişkin farkındalık zamanla değişim göstermiştir. Bir kanser hastasının hastalığı hakkındaki bilgi ve farkındalık düzeyi, hastanın yaşam kalitesini, psikolojisini etkileyen ve hastaların tedaviye ve karar alma sürecine katılımına katkıda bulunan en önemli faktörlerdendir. Ülkemizde bu konuda çok az çalışma yapılmıştır. Bu nedenle, onkoloji ünitemize başvuran yeni tanı almış kanser hastalarının bilgi ve farkındalık düzeyini ölçmeyi amaçladık.

**Yöntem:** Çalışmaya tıbbi onkoloji polikliniğine başvuran 159 yeni tanılı kanser hastası dahil edildi. Hastaların ve/veya hasta yakınlarının hastalıkları hakkındaki bilgi ve farkındalık düzeylerini değerlendirmek amacıyla 21 sorudan oluşan bir anket uygulandı.

**Bulgular:** Hastaların büyük çoğunluğu (n=140, %88), onkoloji kliniğine başvurmadan önce kanser tanısı hakkında bilgilendirildiğini belirtmiştir. Ancak sekiz hasta (%5) herhangi bir bilgi almadığını belirtti. On bir hastanın yakını (%7) hastalarından kanser tanısını gizlemeyi tercih etti. Yaşlı hastaların yakınları kanser tanılarını gizleme eğilimindeydi (p=0,023). Diğer demografik bilgiler ve hastalıkla ilişkili faktörler (organ, evre vb.) arasında tanı farkındalığı yönünden farklılık yoktu. Kanser hastası ve/veya yakınlarının çoğu tanılarını bilmesine rağmen, %25'i kendilerine verilen bilginin yeterli olmadığını düşünmektedir. Bunun ileri yaş, düşük gelir düzeyi, cerrahi olmayan kliniklerde tanı alma, açıklama için yeterli zaman ayrılmaması ve anlaşılır bir dil kullanılmaması ile ilişkili olduğu bulunmuştur. Hastaların hekimlerden en önemli beklentileri hastalığın prognozu, kanser hakkında açık ve anlaşılır bilgi, tedavi seçenekleri ve tedavilerin yan etki profili olmuştur.

**Sonuç:** Çalışma, ülkemizde kanser hastalarına bilgi sağlama konusundaki tutumların Batı ülkelerindeki tutumlara benzer olduğunu ve zamanla iyileştiğini göstermiştir. Hastaların daha iyi bilgilendirildiğinden emin olmak için hasta yakınlarının tutumu iyileştirilmelidir. Hastalara tatmin edici bilgi sağlamak için hasta-hekim iletişimi çok önemlidir. Açıklamalar için yeterli zaman ayrılmalı ve hastalarla anlayabilecekleri bir dilde konuşulmalıdır. Açıklama yaparken hastaların beklentilerini göz önünde bulundurmak önemlidir.

Anahtar Kelimeler: Neoplazi, iletişim, prognoz

#### Introduction

Cancer is a global health problem that threatens lives worldwide. The incidence of cancer is increasing worldwide and in our country. It is one of the most common causes of death worldwide<sup>(1)</sup>. According to 2022 Globocan data, the annual incidence of cancer in Türkiye was 240,013 new cases, and the 5-year prevalence was 679,335 patients<sup>(2)</sup>.

The increasing prevalence of cancer, encouragement for screening programs, and increased awareness in written and visual media increase the level of knowledge about cancer in patients and healthy individuals<sup>(3,4)</sup>. The majority of patients with cancer worldwide are eager to understand the factors contributing to their condition, prognosis, and available treatment options. Patients frequently seek valuable insights from healthcare professionals, family members, fellow patients, and from written materials and online resources.

In previous decades, the attitudes of physicians and patient relatives have often involved limiting the information given to patients to protect them and to present a more positive picture of their diagnosis, stage, and life expectancy. This approach, however, has been changing in recent decades toward greater transparency and information sharing<sup>(5)</sup>. The level of knowledge and awareness of a cancer patient regarding his/her disease is one of the most important factors affecting the quality of life and psychology of the patient. An increased level of awareness and knowledge contributes to patients'participation in treatment and decision-making, whereas insufficient information and miscommunication are associated with increased anxiety, non-compliance with treatment, and increased costs<sup>(6,7)</sup>. In this sense, oncology clinics, as well as all physicians and healthcare professionals involved in the diagnostic process of the disease, are responsible.

There have been very few studies on this subject in our country. A study conducted by Ateşci et al.<sup>(7)</sup> 20 years ago revealed that half of the patients were not informed about their cancer diagnosis, leading to an increase in psychiatric disorders. Therefore, we aimed to measure the level of knowledge and awareness of newly diagnosed patients with cancer admitted to the medical oncology outpatient clinic using a questionnaire prepared by us before their examination in medical oncology.

#### **Materials and Methods**

BetweenJanuary 1, 2018 and March 31, 2018, patients newly diagnosed with cancer admitted to the medical oncology outpatient clinic were included in the study. The study was approved by the Dokuz Eylül University Non-interventional Ethics Committee, İzmir (decision no: 2017/29-03, date: 21.12.2017). The demographic characteristics and disease information of the patients were obtained from the hospital records. Patients were evaluated in two groups (nonsurgical and surgical clinics. To asses patinets' knowledge and awareness regarding their diseases, a 21-guestion **Results** survey prepared in Turkish was administered to them. The questionnaires were administered face-to-face to literate patients after obtaining patient and family consent. In cases in which primary information was given to the patient's relatives at the time of diagnosis and the patient was not directly informed, a questionnaire was administered to the patient's relatives. The relevant literature was used in the preparation of the questionnaire. The questionnaire consisted of four parts. In the first part, demographic data (age, gender, marital status, educational status, income level, etc.) were collected from the patients. In the second part, the question was raised as to whether information about the diagnosis of cancer was given. If information was not provided, the questionnaire was terminated. Patients who were informed

about the diagnosis of cancer were asked questions about the disease (organ of origin, stage, etc.). In the third part, patients were asked to categorize their information level as sufficient or insufficient. In addition, questions measuring patient-physician communication and patient expectations from information sources were asked. In the last section, the sources of patient consultations other than physicians were guestioned. The guestionnaires were administered to 10 participants. The data obtained from these respondents were not included in the data to be obtained at the end of the study but were only used to identify problems that may be encountered during the application and to make some changes in the questionnaire form when necessary. The individuals included in the study were informed about the study in detail. After the informed consent form was obtained from the individuals who agreed to participate in the study, the guestionnaire, which included guestions to evaluate the intended information, was given to the participants, and the guestionnaires were taken back after they were completed under outpatient clinic conditions.

#### **Statistical Analysis**

The Statistical Package for Social Science 22. Oprogram (SPSS, Inc., Chicago, IL, USA) was used to evaluate the results. In the analyses, normally distributed continuous numerical variables were expressed as mean ± standard deviation and non-normally distributed variables were expressed as median and minimum-maximum values. Nominal data were expressed as ratios (%), and comparisons of numerical data were made by Kruskal-Wallis Htest, Mann-Whitney U-test, and chi-square test in dependent and independent samples.

In the intergroup comparisons, p<0.05 values were accepted as significant.

The study included 159 volunteers, with 148 patients and 11 patients' relatives participating in the questionnaire. The mean age of the participants was 59±14.5 years; 72 (45.3%) were female, and 87 (54.7%) were male. Furthermore, 67 (42.1%) patients were 65 years of age or older, and 43% had an income level of minimum wage or less. The patient characteristics are summarized in Table 1. Out of 159 volunteers, 126 (79.3%) were referred to the medical oncology department of surgical clinics, while 33 (20.7%) were referred from non-surgical clinics. The most common types of cancer diagnosed among the patients were colorectal cancer, breast cancer, and lung cancer, which represented 60% of all cases. Genito-urinary tract cancer and head-neckcancers comprised the majority of the remaining cases.

| Table 1. Patient characteristics             |                        |             |  |
|--|------------------------|-------------|--|
| Age (Mean ± SD)                              |                        | 59±14.54    |  |
| Candan                                       | Female                 | 72 (45.3%)  |  |
| Gender                                       | Male                   | 87 (54.7%)  |  |
|  | Literate               | 25 (15.7%)  |  |
| Education status                             | Primary education      | 67 (42.1%)  |  |
| EUUCALIOIT SLALUS                            | High school            | 33 (20.8%)  |  |
|  | University             | 34 (21.4%)  |  |
|  | Married                | 129 (81.1%) |  |
| Marital status                               | Singles                | 12 (7.5%)   |  |
|  | Divorced-widowed       | 18 (11.4%)  |  |
| lacomo status                                | Minimum wage and below | 69 (43.4%)  |  |
| Income status                                | Above minimum wage of  | 90 (56.6%)  |  |
| Diago of residence                           | Rural                  | 76 (47.8%)  |  |
| Place of residence                           | Urban                  | 83 (52.2%)  |  |
|  | Surgical               | 126 (79.3   |  |
| Referring clinic                             | Non-surgical group     | %)          |  |
|  |                        | 33 (20.7%)  |  |
|  | Colorectal             | 43 (27%)    |  |
|  | Lung                   | 31 (19.5%)  |  |
|  | Breast tissue          | 22 (13.8%)  |  |
| Tumor site                                   | Non-colorectal GI      | 21 (13.2%)  |  |
|  | Genito-urinary         | 16 (10%)    |  |
|  | Head & neck            | 7 (4.4%)    |  |
|  | Other                  | 19 (11.9%)  |  |
|  | Local                  | 94 (59.1%)  |  |
| Disease stage                                | Metastatic             | 65 (40.9%)  |  |
| SD: Standard deviation, GI: Gastrointestinal |                        |             |  |

Of the patients, 41% were in the metastatic stage, whereas 59% were referred for adjuvant treatment and follow-up due to non-metastatic cancer.

In the present study, 88% of patients (n=140) were clearly informed about their cancer diagnosis and were referred to a medical oncology clinic. Only 5% of patients (n=8) were not aware of their diagnosis and were not given any information about the cancer. However, 7% (n=11) of the patients' relatives chose not to disclose their cancer diagnosis. Instead, they provided limited information without using the word "cancer". Cancer diagnosis was concealed in 13% of older patients (≥65 years old), compared to only 3% of younger patients (p=0.023). Education level, income level, gender, and other demographic factors did not affect diagnostic awareness. It was also noted that 75% of the patients who were not informed about their cancer diagnosis were over 65 years old, and five were in the low-income group. However, this result did not reach statistical significance due to this group's small number of patients (p=0.89 and p=0.67, respectively).

After excluding eight patients who were unaware of their cancer diagnosis, the remaining 140 patients and 11 patients' relatives were questioned about whether the information given to them was sufficient and accurate. Almost all the volunteers who participated in the study knew the organ or tissue from which the cancer originated. Only five patients (3.3%) were not aware. However, 65% of patients were unaware of their disease stage, and 45% did not receive information about treatment options in medical oncology. Additionally, when guestioned regarding whether the information provided was sufficient, one in four participants stated that it was insufficient. Insufficient knowledge level was significantly higher among patients with advanced age, lowincome individuals, and those referred from non-surgical clinics (p<0.001, p=0.037, p=0.016, respectively). However, patient-related factors, such as gender, education level, rural or urban environment, and disease-related factors, such as organ of origin and disease stage, did not have any effect (seeTable 2).

In the information process, 74% of patients reported that they were given enough time, whereas 87% indicated that the information was presented in a clear and understandable language. A lack of sufficient time and the use of difficult language were linked to an insufficient level of patient knowledge (p<0.001 and p<0.001, respectively). Half of the participants reported an increase in their knowledge level using sources other than medical sources. Out of the 81 participants, 56 (70.3%) mentioned benefiting from the internet, while 24 (29.7%) stated that they received information from patients who were diagnosed with cancer. We asked one last question: what do patients and their relatives want to know about their diagnosis. This question covered six topics, and we requested patients to rank them from most to least preferred for learning. As shown in Graph 1, the volunteerswere most curious about the prognosis of the disease, general and understandable information about cancer, treatment options, and side effect profiles of the treatments.

| Table 2. Knowledge level and associated factors |                     |                      |         |
|---|---------------------|----------------------|---------|
| Knowledge level                                 | Sufficient<br>n (%) | lnsuffienct<br>n (%) | p-value |
| Age   |                     |                      | p<0.001 |
| 65 and above                                    | 41 (61.2%)          | 26 (38.8%)           |         |
| Under 65  | 78 (84.8%)          | 14 (15.2%)           |         |
| Gender  |                     |                      | p=0.438 |
| Woman   | 56 (77.8%)          | 16 (22.2%)           |         |
| Male  | 63 (72.4%)          | 24 (27.6%)           |         |
| Income status                                   |                     |                      | p=0.037 |
| Minimum wage                                    | 46 (66.7%)          | 23 (33.3%)           |         |
| Minimum wage                                    | 73 (81.1%)          | 17 (18.9%)           |         |
| Education status                                |                     |                      | p=0.492 |
| Primary education and                           | 67 (72.8%)          | 25 (27.2%)           |         |
| High school and above                           | 52 (77.6%)          | 15 (22,4%)           |         |
| Referring clinic                                |                     |                      | p=0.016 |
| Non-surgical                                    | 18 (58.1%)          | 13 (41.9%)           |         |
| Surgical  | 101 (78.9%)         | 27 (21.1%)           |         |
| Disease stage                                   |                     |                      | p=0.175 |
| Local   | 74 (78.7%)          | 20 (21.3%)           |         |
| Metastatic                                      | 45 (69.2%)          | 20 (30.8%)           |         |
| Allocation sufficient time                      |                     |                      | p<0.001 |
| Yes   | 99 (83.9%)          | 19 (16.1%)           |         |
| No  | 20 (48.8%)          | 21 (51.2%)           |         |
| Use of understandable language                  |                     |                      | p<0.001 |
| Yes   | 112 (81.2%)         | 26 (18.8%)           |         |
| No  | 7 (33.3%)           | 14 (66.7%)           |         |
| References to different sources of information  |                     |                      | p=0.002 |
| Yes   | 69 (85.2%)          | 12 (14.8%)           |         |
| No  | 50 (54.1%)          | 28 (35.9%)           |         |





#### Discussion

It has been observed that patients with insufficient knowledge and awareness struggle more when coping with cancer<sup>(8)</sup>. The level of knowledge they possess also affects their psychiatric well-being and active involvement in treatment<sup>(7-9)</sup>. However, delivering bad news is a challenging task that requires specific training. Regrettably, many physicians, including medical oncologists, do not receive sufficient training in effectively communicating bad news and discussing prognosis with their patients<sup>(10,11)</sup>.

As we survey the global landscape, we find that the level of awareness among patients with cancer regarding their diagnosis varies widely, with some regions reporting awareness rates as high as 90% and others as low as 50%. This disparity raises essential questions about access to information, healthcare systems, and cultural attitudes toward cancer. The rate of awareness regarding cancer diagnosis is reported to be 50-60% in Eastern and Middle-Eastern countries, whereas it is approximately 90% in Western Europe<sup>(12-14)</sup>. Upon reviewing the available literature, it has come to our attention that there is a scarcity of studies on this subject in our country. A study conducted by Atesci et al.<sup>(7)</sup> two decades ago indicated that awareness of cancer diagnosis among patients treated in the oncology unit was only at a 50% level. It is worth noting that this rate aligns with similar findings in our neighboring countries, as previously mentioned. In another study conducted with more than 3,500 patient relatives in Ankara, the capital and second largest city of Türkiye, in 2015, 70% of the patients were aware of their cancer diagnosis. In addition, only 65% of the volunteers preferred to be informed openly if they were diagnosed with cancer<sup>(15)</sup>. Our research conducted in İzmir,

Türkiye, indicates that the level of awareness among patients regarding cancer diagnosis is comparable to that in Western Europe. Considering that the studies were conducted at different times, the awareness rate can be interpreted as increasing over time. However, it was also observed that there was a 5% rate of patients who stated that they were not aware of this diagnosis; this is still an important ratio for our patients.

Another finding was that 7% of the relatives of the patients concealed the cancer diagnosis from them. In both developed and developing countries, most physicians tell the truth directly to patients. Still, in some geographical areas, the prevailing attitude is to convey the truth to relatives rather than to the patient<sup>(3,4,15)</sup>. In another study conducted 15 years ago in Türkiye, only half of the relatives of patients preferred to be informed about their patient's cancer diagnosis<sup>(16)</sup>. It has been shown that our country's perspective has changed over time. In previous studies, the rate of awareness regarding cancer diagnosis was found to be inversely associated with advanced age, low-income level, and low education level<sup>(7,8,12)</sup>. In our study, only being 65 years of age or older was associated with awareness of cancer diagnosis. Low income, educational status, and gender had no effect on diagnostic awareness. It is important to note that the attitudes of the patient's relatives can significantly influence the patient's willingness to participate in treatment. Additionally, these attitudes may impact the psychological well-being of the relatives themselves<sup>(17)</sup>. Telling the truth does not negatively impact cancer patients<sup>(18,19)</sup>. Informing patients' relatives about this fact can help change their attitude.

Another aspect we examined was the extent to which patients found the information sufficient after being informed of their cancer diagnosis. Although this was a subjective question, a notable finding was that 25% of the patients described the information provided as inadequate. Our result is valuable because we have not found any other study that assesses the adequacy of patient information. We mentioned that advanced age and low income are associated with awareness of diagnosis<sup>(8,9)</sup>. Similarly, it is anticipated that satisfaction with the level of information provided will be associated with this result. In contrast to the existing literature, no discernible effect of education level was observed. It is possible that this can be attributed to the varying expectations of individuals with different educational backgrounds.

Enhancing patient-physician communication within the context of severe and life-limiting diseases is a crucial ethical

obligation. Preparing clinicians for timely, high-quality conversations with patients with cancer requires addressing several barriers. These include inadequate training in communication skills for clinicians, time constraints, uncertainties about when to initiate specific conversations, ambiguity regarding the responsible clinician for initiating conversations, and inadequate healthcare systems to support clinicians<sup>(20,21)</sup>. The findings of the present study suggest that using understandable language and allowing sufficient time is crucial for adequately informing patients. Our findings showed that surgical department patients appeared to be better informed. Furthermore, existing evidence in the literature suggests that more practical information is available in surgical clinics<sup>(22)</sup>. Oncologic surgery and multidisciplinary tumor councils are actively performed in our hospital. These results confirmed our knowledge of surgical branches regarding oncologic treatmentsand our experiences with providing bad news.

Consistent with the literature, the most common sources of information for patients were the internet and other sources of cancer diagnosis<sup>(23,24)</sup>. Although this contributed positively to the level of knowledge in our study, it should be kept in mind that misinformation, especially from the internet, may negatively affect patient compliance.

The study makes a valuable contribution to the literature by shedding light on patient expectations from physicians. In addition to seeking general information about their condition, patients expressed interest in understanding the prognosis and available treatment options. This insight can help healthcare providers better meet the needs of their patients. This should be considered the most fundamental right of a patient diagnosed with cancer. Both ethically and medico-legally, patients should be informed in detail about their diagnosis, stage, prognosis, and treatment options. Due to the scarcity of studies on the level of knowledge and awareness of patients with cancer in our country, we believe that these results will make an important contribution to the literature and guide physicians.

#### **Study Limitations**

Our study was constrained by the 3-month time limit, which resulted in a limited sample size of 159 volunteers. An expanded patient population could facilitate more robust statistical analysis and potentially yield different findings. The study was conducted in a university hospital with regular multidisciplinary tumor councils. Results may vary among centers with less experience in cancer diagnosis and treatment. Given our country's large population, it is important to recognize that patient and family attitudes may differ across various geographical and cultural regions. The findings of this study may have limited generalizability across the country because of the constraints of the sample population.

#### Conclusion

The current study assessed the level of knowledge and awareness among patients with cancer. We found that patients were highly aware of their diagnosis. We observed that although a small number of patients were not initially aware of severe and vital conditions such as cancer at the time of diagnosis, this finding presents an opportunity for increased awareness and early detection initiatives. Although the results cannot be generalized nationwide, we have demonstrated an increasing awareness rate among patients with cancer in our country over time. The attitudes of patients' relatives should be improved to ensure that patients are better informed. Patient-physician communication is crucial for providing satisfactory patient information. Sufficient time should be allocated for explanations, and patients should be spoken to in a language they can understand. When providing explanations, it is important to consider patients' expectations. More study is needed on this topic in our country.

#### Ethics

**Ethics Committee Approval:** The study was approved by the Dokuz Eylul University Non-interventional Ethics Committee, İzmir (decision no: 2017/29-03, date: 21.12.2017).

**Informed Consent:** The demographic characteristics and disease information of the patients were obtained from the hospital records.

#### Footnotes

#### **Authorship Contributions**

Surgical and Medical Practices: S.Ö., Z.G.G., H.E., İ.Ö., Concept: S.Ö., Z.G.G., İ.Ö., Design: İ.Ö., Data Collection or Processing: S.Ö., H.E., Analysis or Interpretation: H.E., Literature Search: S.Ö., Z.G.G., İ.Ö., Writing: S.Ö., Z.G.G., H.E., İ.Ö.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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### Evaluation of the Correlation Between Preoperative Anterior Wall Myometrium Thickness and Uterine Closure Techniques in the Development of Uterine Scar Defect (Niche) After Previous Caesarean Section

#### Geçirilmiş Sezaryen Sonrası Uterin Skar Defekti (Niş) Gelişiminde Preoperatif Anterior Duvar Myometrium Kalınlığı ve Uterus Kapatma Teknikleri Arasındaki Korelasyonun Değerlendirilmesi

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#### Abstract

**Objective:** The objective was to evaluate the correlation between the development of uterine scar defect (niche) following cesarean section, preoperative thickness of the anterior wall myometrium, and uterine closure techniques.

**Methods:** In a prospective randomized study, the preoperative anterior myometrial thickness of 75 women scheduled for cesarean delivery was measured. Single and double-layer uterine closure techniques were employed during surgery. Patients were evaluated postoperatively in the 6<sup>th</sup> to 8<sup>th</sup> weeks using transvaginal ultrasonography for uterine niche.

**Results:** No statistically significant correlation was found between preoperative anterior wall myometrial thickness and the height, area, base, and width of the niche identified by transvaginal ultrasonography. In the group undergoing double-layer continuous unlocked suture technique, the niche area was significantly larger (p=0.023). No statistical differences were found between preoperative hemoglobin (HB) and hematocrit (HCT) values, but postoperative 6<sup>th</sup> and 24<sup>th</sup> hour HB and HCT levels were significantly lower in patients with double-layer uterine closure (p<0.05).

**Conclusion:** Selecting a continuous suturing technique without locking can significantly reduce the area of the developing uterine scar defect. Furthermore, postoperative declines in HB and HCT can be minimized. Although sufficient data has not yet been reached to clearly define an operation technique that reduces niche formation, further studies with larger series are needed.

Keywords: Cesarean scar defect, uterine niche, cesarean section



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#### Öz

**Amaç:** Sezaryen sonrası uterin skar defekti (niş) gelişiminde preoperatif anterior duvar myometrium kalınlığı ve uterus kapatma teknikleri arasındaki korelasyonun değerlendirmesi amaçlandı.

**Yöntem:** Prospektif randomize çalışmada sezaryenle doğum planlanan 75 gebenin preoperatif anterior myometriyum kalınlığı ölçüldü ve operasyonda tek kat ve çift kat uterin kapatma tekniği uygulandı. Hastalar postoperatif 6.-8. haftada uterin niş açısından transvajinal ultrasonografi ile değerlendirildi.

**Bulgular:** Preoperatif anterior duvar myometrium kalınlığının transvajinal ultrasonografi ile tespit edilen nişin yükseklik, alan, taban ve genişliği ile arasında istatistiksel olarak anlamlı fark bulunamadı. Geçirilmiş sezaryen endikasyonu ile sezaryen yapılan ve uterusu tek kat ve çift kat kapama uygulanan hastalar arasında, çift kat devamlı kilitsiz sütüre edilen grupta niş alanı anlamlı yüksek bulunmuştur (p=0,023). Preoperatif hemoglobin (HB) ve hemotokrit (HCT) değerleri arasında istatistiksel anlamda bir fark bulunmayan eski sezaryenli tek kat uterin kapatma ile çift kat uterin kapatma arasında postoperatif 6. ve 24. saat HB ve HCT değerleri çift kat uterin kapatma yapılan hastalarda istatistiksel olarak düşük bulundu (p<0,05).

**Sonuç:** Tek kat kilitlemeden devamlı sütür tekniği seçilerek gelişecek uterin skar defektinin alanı önemli ölçüde azaltılabilir. Ayrıca postoperatif HB ve HCT düşüşü azaltılabilir. Niş oluşumunu azaltan net bir operasyon tekniğinin tanımlanabilmesi için yeterli veriye ulaşamamakla birlikte daha geniş serili çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Sezaryen skar defekti, uterin niş, sezaryen

#### Introduction

The World Health Organization (WHO) recommends a cesarean section (CS) rate of 15% to optimize maternal and perinatal mortality outcomes. However, global CS rates have increased in recent years, and Türkiye has one of the highest rates in the world, at 48 percent, according to the Türkiye Demographic and Health Survey 2013. Cesarean delivery, particularly repeat cesarean delivery, is associated with increased risks of uterine rupture, abnormal placental implantation, placental abruption, and uterine scar dehiscence in subsequent pregnancies<sup>(1-3)</sup>. A uterine niche, identified via sonography, is characterized by a hypoechoic area within the myometrium of the lower uterine segment, indicating disruption of the myometrium at the site of a previous CS<sup>(4-6)</sup>.

A niche is an indentation within the myometrium that is at least 1 mm deep. Transvaginal ultrasonography (TVS) shows an anechoic area with a depth of  $\geq 1$  mm in the cesarean scar<sup>(4,7)</sup>. Incomplete healing of a cesarean scar is a long-term complication that can lead to gynecological disorders that adversely affect a patient's quality of life, including abnormal uterine bleeding, postmenstrual spotting, dysmenorrhea, dyspareunia, chronic pelvic pain, and secondary infertility<sup>(5,7-9)</sup>. Given the association between uterine niches and gynecological symptoms, obstetric complications, and potential subfertility, elucidating the etiology of niche development post-cesarean is crucial for developing preventive strategies<sup>(10)</sup>. This study aimed to evaluate the correlation between preoperative anterior wall myometrial thickness and uterine closure techniques in the development of uterine scar defects following cesarean surgery.

#### **Materials and Methods**

This prospective, randomized, double-blind, parallelgroup study was approved by the Ethics Committee of İzmir Katip Çelebi University Atatürk Training and Research Hospital (approval no: 44, date: 25.02.2016). Seventy-five consecutive singleton pregnant women requiring emergency or elective CS were enrolled at the Department of Obstetrics and Gynecology, İzmir Katip Celebi University Atatürk Training and Research Hospital between February 2016 and November 2016, in accordance with the Helsinki Declaration principles. The exclusion criteria were a history of previous CS or other uterine surgeries, active labor exceeding 5 hours, cervical dilation over 4 cm, history of pelvic radiation, bleeding diathesis, connective tissue disease, preeclampsia, eclampsia, HELLP (hemolysis, elevated liver enzmymes, low platelet) syndrome, gestational or pre-gestational diabetes, multiple pregnancies, preterm pregnancies (<37 weeks gestation), placental placement and invasion anomalies, and history of cervical cancer.

To ensure reliability and reproducibility, preoperative transabdominal sonography of anterior wall myometrial thickness and postoperative TVS screening for uterine niches at 6-8 weeks were conducted by the same researcher (R.T.). Anterior wall myometrial thickness and postpartum uterine niche dimensions were measured using 3-5 MHz transabdominal and 7.5-MHz transvaginal probes, respectively (Figure 1, 2). To minimize the effects of respiration and abdominal tension, participants were instructed to lie supine with a semi-full bladder and hold their breath during the measurements. Myometrial thickness was measured

approximately 4 cm above the internal cervical os, as demonstrated in the study by Uharček et al.<sup>(11)</sup>.

The Modified Misgav Ladach method was used for cesarean delivery<sup>(12)</sup>. Uterine closure techniques included continuous single-layer sutures without locking and continuous double-layer sutures without locking, incorporating full-thickness myometrial and endometrial tissues along the lower segment incision line. Participants who underwent their first CS were sutured using a continuous single-layer without locking (Group 1). Those with previous cesareans (1-3 prior) were randomly assigned to either a continuous single-layer without locking (Group 2) or a continuous double-layer without locking (Group 3). Hemograms assessing white blood cell (WBC) count, hemoglobin (HB), and hematocrit (HCT) were obtained at 6 and 24 hours postoperatively, and



**Figure 1.** Transabdominal ultrasound image of the measurement of preoperative anterior wall myometrial thickness



**Figure 2.** Transvaginal ultrasound image of the uterine niche in a patient undergoing cesarean for the first time

data were recorded. At 6-8 weeks postoperatively, all patients underwent TVS to assess uterine niches without knowledge of the surgical technique used, following the methodology of Pomorski et al.<sup>(13)</sup>.

The presence of a niche at the uterine incision line was evaluated in both the transverse and midsagittal longitudinal planes. The depth, length, and residual anterior wall myometrial thickness of the niche were also measured. Considering the uterine niche's resemblance to an isosceles triangle, its area was calculated using the formula: base × height/2<sup>(14)</sup>. Based on the calculated area, uterine niches were classified into three grades: Grade 1 (<15 mm<sup>2</sup>), Grade 2 (16-25 mm<sup>2</sup>), and Grade 3 (>25 mm<sup>2</sup>)<sup>(15)</sup>. A niche was considered large if the ratio of the niche height to the sum of the niche height and residual myometrial tissue was  $\geq$ 50%, as per Bij de Vaate et al.<sup>(16)</sup>.

Of the 117 patients who met the study criteria, 90 consented to participate. After excluding 15 dropouts, 75 patients were included in the final analysis. All participants underwent TVS 6-8 weeks post-cesarean section. No morbidity or mortality events were reported.

#### **Statistical Analysis**

The statistical analysis of the data was performed using the IBM SPSS statistics version 24 software package. The Pearson chi-square, Fisher's exact test, and chi-square test were used to compare categorical data between groups; the independent sample t-test and Mann-Whitney U statistical analyses were used for continuous data based on normal distribution properties. One-way ANOVA was used to test whether there was a statistically significant difference between the means of the independent groups that conformed to the normal distribution, and Kruskal-Wallis H analysis was used to compare the test scores of different groups. A p-value of <0.05 was considered statistically significant.

#### Results

This double-blind, parallel-group, prospective, randomized clinical study included 117 patients who met the study criteria, among whom 90 agreed to participate. After excluding 15 dropouts, 75 patients were included in the final analysis. The distribution of categorical and continuous variables was analyzed across three groups: Group 1 (first-time cesarean patients), Group 2 (patients with 1-3 previous cesareans sutured with a continuous single-layer non-locking stitch), and Group 3 (patients with 1-3 previous cesareans sutured with a continuous double-layer non-locking stitch) (Tables 1 and 2).

|                                  |                     | Group |       |       |       |         |      |       |
|----------------------------------|---------------------|-------|-------|-------|-------|---------|------|-------|
|                                  |                     | Group | 1     | Group | 2     | Group 3 |      | D     |
|                                  |                     | n     | %     | n     | %     | n       | %    |       |
|                                  | Anterior            | 3     | 12.0  | 11    | 44.0  | 8       | 32.0 |       |
| Placental localisation           | Fundal              | 15    | 60.0  | 6     | 24.0  | 2       | 8.0  | 0.001 |
|                                  | Posterior           | 7     | 28.0  | 8     | 32.0  | 15      | 60.0 |       |
|                                  | Male                | 13    | 52.0  | 10    | 40.0  | 14      | 56.0 | 0.500 |
| Gender of the baby               | Female              | 12    | 48.0  | 15    | 60.0  | 11      | 44.0 | 0.500 |
| <b>F</b> 00                      | Yes                 | 18    | 72.0  | 7     | 28.0  | 13      | 52.0 | 0.000 |
| Emergency CS                     | No                  | 7     | 28.0  | 18    | 72.0  | 12      | 48.0 | 0.008 |
| Dilatation (cm)                  | 0                   | 17    | 68.0  | 23    | 92.0  | 22      | 88.0 | 0.100 |
|                                  | ≤4                  | 8     | 32.0  | 2     | 8.0   | 3       | 12.0 | 0.100 |
| Fewer                            | Yes                 | -     | -     | 2     | 8.0   | 3       | 12.0 | 0.250 |
|                                  | None                | 25    | 100.0 | 23    | 92.0  | 22      | 88.0 | 0.359 |
|                                  | AF                  | 19    | 76.0  | 16    | 64.0  | 20      | 80.0 | 0.412 |
| oterine position                 | RF                  | 6     | 24.0  | 9     | 36.0  | 5       | 20.0 | 0.412 |
| Introutoring fluid               | Yes                 | 1     | 4.0   | 4     | 16.0  | 3       | 12.0 | 0 510 |
| inti duterine itulu              | None                | 24    | 96.0  | 21    | 84.0  | 22      | 88.0 | 0.518 |
|                                  | Grade 1             | 18    | 72.0  | 20    | 80.0  | 13      | 52.0 |       |
| Niche area grade                 | Grade 2             | 3     | 12.0  | 1     | 4.0   | 6       | 24.0 | 0.213 |
|                                  | Grade 3             | 4     | 16.0  | 4     | 16.0  | 6       | 24.0 |       |
| Nicho aroa (mm <sup>2</sup> )    | Grade 1             | 18    | 72.0  | 20    | 80.0  | 13      | 52.0 | 0.002 |
| NICHE died (IIIII <sup>2</sup> ) | Grade 2+3           | 7     | 28.0  | 5     | 20.0  | 12      | 48.0 | 0.092 |
| Nicho width                      | Non-wide            | 19    | 76.0  | 19    | 76.0  | 16      | 64.0 | 0.551 |
|                                  | Wide                | 6     | 24.0  | 6     | 24.0  | 9       | 36.0 | 0.551 |
| Tune of analothasia              | General anaesthesia | 1     | 4.0   | 2     | 8.0   | 2       | 8.0  | 1.000 |
| Type of alldestilesta            | Spinal anaesthesia  | 24    | 96.0  | 23    | 92.0  | 23      | 92.0 | 1.000 |
| Wound discharge in the first 6   | Yes                 | 3     | 12.0  | -     | -     | 2       | 8.0  | 0.261 |
| weeks postoperatively            | None                | 22    | 88.0  | 25    | 100.0 | 23      | 92.0 | 0.301 |

CS: Cesarean section, AF: Anteflex, RF: Retroflex

Among cases with previous CS (Groups 2 and 3), a statistically significant difference was found in the niche area, with Group 3 exhibiting a larger niche area ( $22.73\pm29.68 \text{ mm}^2$ ) compared with Group 2 ( $12.83\pm10.35 \text{ mm}^2$ , p=0.023). However, no significant differences were observed between the groups in terms of niche base (p=0.091) or preoperative anterior wall myometrial thickness (p=0.620) (Tables 3 and 4).

When examining the distribution of categorical variables based on niche width (wide and not wide), a statistically significant difference was found between groups in terms of uterine position (p<0.05). In contrast, 20.4% of the non-wide niche group had a retroflexed uterus, 42.9% of the wide niche group had a retroflexed uterus (Table 5).

#### Discussion

Incomplete healing of the cesarean scar is a long-term complication of cesarean delivery and is widely known to be associated with numerous gynecological symptoms<sup>(8)</sup>. Considering the relationship between uterine niche and gynecological symptoms, obstetric complications, and potential subfertility, it is crucial to clarify the etiology of niche development following cesarean delivery and develop preventative strategies<sup>(8)</sup>. Our study investigated whether the thickness of the lower segment has predictive value in postoperative niche formation to elucidate the etiology of this frequently occurring condition, which can cause various symptoms, and to develop a new predictive marker for predicting niche formation.

| Table 2. Average distribution of continuous variables by groups |                |                |                |       |  |  |
|---|----------------|----------------|----------------|-------|--|--|
|   | Group 1        | Group 2        | Group 3        | -     |  |  |
|   | Avg. ± SD      | Avg. ± SD      | Avg. ± SD      | p     |  |  |
| Age (year)  | 27.48±6.19     | 30.96±5.91     | 31.72±5.31     | 0.028 |  |  |
| Gestational week  | 38.92±1.47     | 38.32±0.69     | 38.20±0.71     | 0.168 |  |  |
| Gravida   | 1.96±1.31      | 2.88±0.78      | 3.44±1.42      | 0.001 |  |  |
| Parity  | 0.56±1.08      | 1.52±0.65      | 1.76±0.78      | 0.001 |  |  |
| Abortion  | 1.14±0.38      | 1.29±0.49      | 2.00±1.83      | 0.453 |  |  |
| Ectopic pregnancy   | 1.0            | -              | -              | -     |  |  |
| Evacuation curettage  | 1.00           | -              | 1.50±0.71      | 0.317 |  |  |
| Number of old CS  | 0              | 1.44±0.65      | 1.48±0.65      | 0.001 |  |  |
| Birth weight (gram)   | 3259.2±661.7   | 3368.8±314.05  | 3213.2±402.92  | 0.507 |  |  |
| BMI (kg/m <sup>2</sup> )  | 31.65±5.09     | 30.53±4.49     | 28.99±3.72     | 0.137 |  |  |
| Weight gain in pregnancy (kg)                                   | 14.18±5.87     | 12.36±5.82     | 10.2±7.85      | 0.108 |  |  |
| Preop WBC (mcL)   | 10387.2±2284.2 | 9521.6±1677.9  | 9689.6±2316.9  | 0.313 |  |  |
| Postop WBC 6h (mcL)   | 14630.4±3602.9 | 12515.6±3537.2 | 13367.2±2696.  | 0.042 |  |  |
| Postop WBC 24h (mcL)  | 12524.8±3153   | 11151.2±2318.3 | 11384.8±2483.7 | 0.029 |  |  |
| Preop Hb (gr/dL)  | 12.19±1.27     | 11.6±1.34      | 11.21±1.46     | 0.082 |  |  |
| Postop Hb 6h (gr/dL)  | 11.1±1.2       | 10.77±1.33     | 9.89±1.3       | 0.159 |  |  |
| Postop Hb 24h (gr/dL)   | 10.91±1.23     | 10.5±1.27      | 9.86±1.35      | 0.004 |  |  |
| preop HTC (%)   | 37.88±3.52     | 36.14±3.5      | 35.1±3.88      | 0.018 |  |  |
| Postop HTC 6h (%)   | 34.54±3.45     | 34.02±3.4      | 31.23±3.73     | 0.003 |  |  |
| Postop HTC 24h (%)  | 33.98±3.3      | 33.2±3.29      | 30.98±3.69     | 0.008 |  |  |
| Effacement (%)  | 16.4±27.5      | 4.4±15.3       | 2.8±9.8        | 0.053 |  |  |
| Preoperative anterior wall myometrium thickness (mm)            | 5.49±2.05      | 4.56±1.42      | 4.95±2.19      | 0.266 |  |  |
| Endometrial thickness (mm)                                      | 3.98±1.96      | 4.2±2.11       | 4.86±2.73      | 0.481 |  |  |
| Niche height (mm)   | 4.28±2.05      | 3.8±1.57       | 5.16±2.4       | 0.088 |  |  |
| Niche base (mm)   | 5.46±2.4       | 6.16±2.68      | 7.52±4.13      | 0.038 |  |  |
| Residual myometrium thickness (mm)                              | 6.06±2.5       | 5.08±1.86      | 5.8±2.19       | 0.382 |  |  |
| Niche area (mm²)  | 13.12±11.3     | 12.83±10.35    | 22.73±29.68    | 0.037 |  |  |
| Niche width (mm)  | 41.8±14.75     | 43.17±15.41    | 46.45±11.82    | 0.490 |  |  |

CS: Caesarean section, BMI: Body mass index, WBC: White blood cell, Hb: Hemoglobin, HTC: Hematocrit, SD: Standard deviation, Avg.: Average

Our findings indicated no correlation between preoperative anterior wall myometrial thickness and niche size assessed via TVS at 6-8 weeks postoperatively. Previous studies have suggested that incisions made close to the internal cervical os, potentially involving cervical tissue, may impair healing and contribute to scar defects<sup>(17)</sup>. Bij de Vaate et al.<sup>(16)</sup> identified low uterine incisions as an independent risk factor for niche development, and Zimmer et al.<sup>(18)</sup> reported higher niche occurrence following cesarean delivery when the cervix is effaced and incorporated into the uterine wall (17.9 $\pm$ 9.4 vs. 14.6 $\pm$ 9.1 mm; p=0.01). For this reason, patients with >5 hours of active labor and cervical dilatation exceeding 4 cm were not included in our study.

All participants in our study had anterior wall myometrial thickness measurements above 4 cm, with incisions consistently made at this location, thereby controlling for localization differences in niche development.

Various diagnostic methods have been used to identify the niche. A niche can be visualized through hysterosalpingography, transabdominal sonography, TVS, gel or saline infusion sonography, or hysteroscopy<sup>(5,7,19)</sup>.

| Table 3. Distribution of niche area and width ratios by groups for cases with previous CS |          |         |      |         |      |       |  |
|---|----------|---------|------|---------|------|-------|--|
|   |          | Group 2 |      | Group 3 |      |       |  |
|   |          | n       | %    | n       | %    | þ     |  |
| Niche area  | Grade 1  | 20      | 80.0 | 13      | 52.0 |       |  |
|   | Grade 2  | 1       | 4.0  | 6       | 24.0 | 0.118 |  |
|   | Grade 3  | 4       | 16.0 | 6       | 24.0 |       |  |
| Niche width   | Not wide | 19      | 76.0 | 16      | 64.0 | 0.255 |  |
|   | Wide     | 6       | 24.0 | 9       | 36.0 | 0.300 |  |
| CS: Cesarean section  | ÷        | ÷       | ·    |         |      |       |  |

Table 4. Average distribution of niche area, niche base, and preoperative anterior wall myometrium thickness by groups for cases with previous CS

|  | Group 2     | Group 3     | _     |  |  |
|--|-------------|-------------|-------|--|--|
|  | Mean ± SD   | Mean ± SD   | þ     |  |  |
| Niche area (mm²)                                     | 12.83±10.35 | 22.73±29.68 | 0.023 |  |  |
| Niche base (mm)                                      | 6.16±2.68   | 7.52±4.13   | 0.091 |  |  |
| Preoperative anterior wall myometrium thickness (mm) | 4.56±1.42   | 4.95±2.19   | 0.620 |  |  |
| SD: Standard deviation, CS: Cesarean section         |             |             |       |  |  |

There is no consensus on the gold standard method for detecting and measuring a niche<sup>(16)</sup>. TVS is a non-invasive approach for visualizing scar defects and is extremely sensitive in identifying defects. With the liberal use of TVS, the identification of cesarean scar defects has increased<sup>(20,21)</sup>. Due to its non-invasive nature, easy accessibility, and low cost, we preferred TVS for our study.

A study by Ofili-Yebovi et al.<sup>(20)</sup> attempted to assess cesarean scar integrity during pregnancy, but it was found that sonographic detection of uterine scars is easiest outside of pregnancy. Generally, wound healing assessment is performed via ultrasonography 6 weeks post-surgery<sup>(17,22)</sup>. All patients in our study were also evaluated in the 6-8 weeks postoperative period.

Another theory related to uterine closure involves the decision to lock or not to lock the sutures. Some studies have suggested that single-layer locking could increase tissue hypoxia and inadequate healing, potentially raising the risk of uterine rupture<sup>(23)</sup>. A study by Yasmin et al.<sup>(24)</sup> comparing locked and non-locked suturation showed that locking the first layer resulted in decreased myometrial thickness and increased blood loss. In light of these findings, we compared the outcomes of non-locked single- and double-layer uterine suturation in cesarean birth.

Another issue investigated in niche development is the incomplete closure of the uterine wall and the exclusion of

the endometrial layer, which leads to disrupted myometrium and niche formation. A prospective cohort study involving 78 patients by Yazicioglu et al.<sup>(25)</sup> compared single-layer uterine closure, including and excluding the endometrium, and reported less niche development in full-layer uterine closure, including the endometrium (44.7% versus 68.8%); (odds ratio: 2.718; confidence interval: 1.016-7.268). In our study, all patients were continuously sutured to full thickness without locking, including the endometrium. No significant difference was found between the single- and double-layer sutured old cesarean groups in terms of niche base, height, width, and residual myometrial thickness. The niche area was significantly larger in the group with doublelayer continuous non-locked suture in old cesarean cases (p=0.023).

#### **Study Limitations**

The limitations of our study include the relatively short postoperative period of 6-8 weeks for examining and the limited number of patients, which may have affected the ability to generate symptoms.

#### Conclusion

Once the decision to perform a cesarean is made, it is important to understand which factors may hinder proper

| Table 5. Distribution of categorical variables according to niche width |                     |    |      |      |       |         |  |
|---|---------------------|----|------|------|-------|---------|--|
| Niche width   |                     |    |      |      |       |         |  |
|   |                     |    | 2    | Wide |       | p       |  |
|   |                     | n  | %    | n    | %     |         |  |
|   | Anterior            | 14 | 25.9 | 8    | 38.1  | 0.410   |  |
| Placental localisation  | Fundal              | 16 | 29.6 | 7    | 33.3  |         |  |
|   | Posterior           | 24 | 44.4 | 6    | 28.6  |         |  |
| Gender of the baby  | Male                | 24 | 44.4 | 13   | 61.9  | 0.174   |  |
|   | Female              | 30 | 55.6 | 8    | 38.1  | 0.174   |  |
| Emergency CS  | Yes                 | 30 | 55.6 | 8    | 38.1  | 0.174   |  |
|   | None                | 24 | 44.4 | 13   | 61.9  |         |  |
|   | 0                   | 43 | 79.6 | 19   | 90.5  | 0.330   |  |
| Ditatation (Cm)   | ≤4                  | 11 | 20.4 | 2    | 9.5   |         |  |
| <b>F</b>  | Yes                 | 5  | 9.3  | -    | -     | 0.010   |  |
| Fewer   | None                | 49 | 90.7 | 21   | 100.0 | 0.313   |  |
| literine position   | AF                  | 43 | 79.6 | 12   | 57.1  | 0.040   |  |
| oterine position  | RF                  | 11 | 20.4 | 9    | 42.9  | 0.048   |  |
| Introdutoring fluid   | Yes                 | 6  | 11.1 | 2    | 9.5   | 1.000   |  |
|   | None                | 48 | 88.9 | 19   | 90.5  | 1.000   |  |
| Time of analothasia   | General anaesthesia | 4  | 7.4  | 1    | 4.8   | 1.000   |  |
| Type of anaestriesia  | Spinal anaesthesia  | 50 | 92.6 | 20   | 95.2  | 1.000   |  |
| Wound discharge in the first 6 weeks                                    | Yes                 | 3  | 5.6  | 2    | 9.5   | 0.015   |  |
| postoperatively   | None                | 51 | 94.4 | 19   | 90.5  | - 0.615 |  |
| CS: Cesarean section, AF: Anteflex, RF: Retroflex                       |                     |    |      |      |       |         |  |

wound healing to prevent niche formation. Only after proving the efficacy of specific cesarean techniques can we identify the most appropriate method for cesarean delivery and develop suitable training programs. To date, the optimal closure technique for preventing niches and associated symptoms has not been elucidated. Thus, further studies, including randomized controlled trials and long-term follow-ups with structural sonographic evaluations, are required.

#### Ethics

**Ethics Committee Approval:** The study was approved by the Ethics Committee of İzmir Katip Çelebi University Atatürk Training and Research Hospital (approval no: 44, date: 25.02.2016).

**Informed Consent:** This is a prospective, randomized, double-blind, parallel-group study.

#### Footnotes

#### **Authorship Contributions**

Surgical and Medical Practices: R.T., M.Ş., E.D., E.E., S.K., Concept: R.T., S.K., Design: R.T., S.K., Data Collection or Processing: R.T., Analysis or Interpretation: R.T., M.Ş., Literature Search: R.T., Writing: R.T., M.Ş.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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## **Evaluation of Bone Metabolism in Patients with Chronic Liver Disease due to Chronic Hepatitis B or C Infection**

Kronik Hepatit B veya C Enfeksiyonuna Bağlı Kronik Karaciğer Hastalığı Olan Hastalarda Kemik Metabolizmasının Değerlendirilmesi

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#### Abstract

**Objective:** Osteoporosis in chronic liver disease is couldn't be determined exactly. We aimed to investigate how the severity of liver function disorders affects bone mineral density (BMD) and the hormonal parameters associated with BMD in chronic hepatitis and cirrhosis patients.

**Methods:** A total of 32 patients (16 females) with chronic hepatitis associated with hepatitis B virus and hepatitis C virus and 32 patients (14 females) with liver cirrhosis were enrolled. Vitamin 25-hydroxy-D 3, calcium, parathyroid hormone (PTH), testosterone, estradiol, and dehydroepiandrosterone sulfate (DHEAS) levels evaluated. All patients underwent lumbar and femur neck BMD assessments.

**Results:** In patients with cirrhosis, the osteoporosis rate was 40.6 and the osteopenia rate was 28.1; in patients with hepatitis, the osteopenia rate was 43.8% and there were no osteoporotic patients. In the cirrhosis group, vitamin D levels were significantly lower than those in the hepatitis group (p<0.05). Calcium, PTH, testosterone, and estradiol levels were similar between the groups. DHEAS levels were lower in the cirrhosis group. In subgroup analyses; estradiol levels in cirrhotic women were lower than women with hepatitis. A positive correlation was observed between albumin levels and the femur T-score (p=0.002). There was no significant relationship between BMD and etiologic agent use, hepatic activity index, fibrosis and Child-Pugh score.

**Conclusion:** In cirrhotic patients, osteoporosis rates were significantly higher. The absence of a complete correlation between liver fibrosis and child stage and BMD signs that different factors play roles in osteoporosis development. In patients with cirrhosis, low vitamin D and DHEAS levels and in female patients with cirrhosis, impairment of estradiol were found to be important factors in osteoporosis.

Keywords: Chronic hepatitis, cirrhosis, bone mineral density, vitamin D, calcium

#### Öz

**Amaç:** Kronik karaciğer hastalığında görülen osteoporozun biyolojik mekanizması karmaşıktır ve nedeni kesin olarak belirlenememiştir. Kronik hepatit ve sirozlu hastalarda, karaciğer fonksiyon bozukluğunun derecesinin kemik mineral yoğunluğunu (KMY) ve onunla ilişkili bazı hormonal parametreleri nasıl etkilediğini araştırmayı amaçladık.



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#### Öz

Yöntem: Hepatit B virüs ve hepatit C virüs'e bağlı kronik hepatiti olan 32 hasta (16 kadın) ile sirozlu 32 hasta (14 kadın) çalışmaya alındı. Vitamin 25-hidroksi-D3, kalsiyum, parathormon (PTH), testosteron, östradiol, dehidroepiandrosteron sülfat (DHEAS) seviyeleri değerlendirildi. Tüm hastalarda, lomber ve femur boynu KMY değerlendirmeleri yapıldı.

**Bulgular:** Siroz hastalarında osteoporoz oranı %40,6 ve osteopeni oranı %28,1 idi; hepatit hastalarında osteopeni oranı %43,8 idi ve hiçbir osteoporotik hasta yoktu. Siroz grubunda, D vitamini düzeyleri hepatit grubundan anlamlı derecede daha düşüktü (p<0,05). Kalsiyum, PTH, testosteron ve östradiol düzeyleri gruplar arasında benzerdi. Ancak, DHEAS düzeyleri siroz grubunda düşüktü. Alt grup analizlerinde; sirozlu kadınlarda östradiol düzeyleri hepatitli kadınlara göre daha düşüktü. Albümin seviyesi ve femur T-skoru arasında pozitif bir korelasyon görüldü (p=0,002). KMY ve etken, hepatik aktivite indeksi, fibrozis ve Child-Pugh skoru arasında anlamlı bir ilişki saptanmadı.

**Sonuç:** Sirozlu hastalarda, osteoporoz oranları anlamlı derecede yüksek bulundu. Karaciğer fibrozis derecesi ve Child skoru ile KMY arasında tam bir korelasyon olmaması, osteoporoz gelişiminde farklı faktörlerin rol oynadığını göstermektedir. Sirozlularda D vitamini ve DHEAS düzeylerinin düşük olması ve kadın sirozlularda östradiol düşüklüğü osteoporozda önemli faktörler olarak bulundu.

Anahtar Kelimeler: Kronik hepatit, siroz, kemik mineral yoğunluğu, vitamin D, kalsiyum

#### Introduction

The biological mechanisms of osteoporosis in chronic liver disease are complicated and are yet to be clarified. Osteoporosis, a condition often experienced by patients with cirrhosis, is a serious condition that causes morbidity and immobility<sup>(1)</sup>. Recent studies that have focused on metabolic bone diseases in patients with cirrhosis have suggested that these patients, who are asymptomatic, need to be scanned in order to start therapy in the early phase<sup>(2,3)</sup>.

In this study, we evaluated the correlation between the severity of liver disease and bone mineral density (BMD), together with the nature of the biochemical and hormonal changes that may occur in patients with chronic hepatitis and cirrhosis with an etiology of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. We assessed how the severity of liver function disorders affected BMD.

#### **Materials and Methods**

The Ethics Committee of the University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital, İstanbul, Türkiye approved this study (decision no: 11290, date: 13.09.2007). Informed consent was obtained from each patient.

#### **Patient Selection**

A total of 64 patients aged 18-65 years were included. Of these, 32 patients (16 females) had liver cirrhosis secondary to HBV or HCV infections and 32 (14 females) were noncirrhotic. Patients were excluded if they had chronic renal failure, diabetes mellitus, any malignancy, chronic diseases that may cause secondary osteoporosis, or a history of alcohol abuse were excluded. Postmenopausal women who received hormone replacement therapy and those who had received any medications in the last six months that may have influenced BMD were also excluded from the study.

The diagnosis of cirrhosis was based on liver biopsy, imaging evidence of parenchymal changes, or portal hypertension. The hepatic activity index (HAI) and degree of fibrosis were determined according to the Child-Pugh score of patients with cirrhosis and the Knodell classification of liver biopsy results in chronic hepatitis patients<sup>(4)</sup>.

Both groups were assessed for osteoporotic risk factors: body mass index (BMI), smoking, coffee consumption, physical activity, exercise habits, exposure to the sun, and past medications. The number of pregnancies, lactation history, and duration of menopause were recorded for female patients.

Smoking behavior was described as either "smoker" or "non-smoker". Coffee consumption was categorized as none, rarely, or often (often: more than 2 cups/week, rarely: less than 2 cups/week). Physical activity was rated as light, moderate, or active (light physical activity: sedentary lifestyle; active: having a job that requires bodily exertion or a habit of physical activity, moderate: those between these two groups). Exposure to sunlight was defined as weak in those whose skin had no contact with sunlight (for example, veil or burqa wearers) and medium in those who had contact with sunlight only on the face and hand areas. Those with high exposure to sunlight were defined as normal.

#### **Biochemical Parameters**

The factors known to influence bone density were measured: 25-hydroxycholecalciferol [25(OH)D3], albumin-adjusted calcium, parathyroid hormone (PTH), testosterone, estradiol, and dehydroepiandrosterone sulfate (DHEAS). Total bilirubin and albumin levels and prothrombin time were determined to be used in the Child-Pugh scoring.

The 25(OH)D3 was measured using the high-performance liquid chromatography technique in the HPLC (Thermo-Finnigan, USA) device and with the help of the vitamin D3 ClinRep HPLC kit (Chemicals + Instruments GmbH, Munich, Germany). Calcium, albumin, and total bilirubin levels were measured using the Abbott C16000 device (65205, Wiesbaden, Germany), and the PTH level was determined using the Immulite 2500 autoanalyzer (LL554EL, UK). Testosterone, estradiol, and DHEAS levels were determined using the Abbott Architect Ci 2000 SR device (Wiesbaden, Germany). The Amax400 device (IDA Business Park, Bray, Co. Wicklow, Ireland) was used to establish prothrombin time.

#### Measurement of Bone Mineral Density

All patients underwent AP spine (lumbar, L1-4) and femur neck BMD measure ments using a Norland DEXA (dual energy X-ray absorption) Bone Densitometer (Norland Corp, Fort Atkinson, Wisconsin). Osteoporosis and osteopenia were defined according to the World Health Organization criteria [osteoporosis: T-score below -2.5 standard deviation (SD); osteopenia: T-score between -1.0 and -2.5 SD]<sup>(5)</sup>.

The BMI of the patients was calculated as weight/surface measurement=kg/m<sup>2</sup>. The BMI values of the patients were classified as follows: under 18 kg/m<sup>2</sup> = underweight, between 18-25 kg/m<sup>2</sup>=normal weight, between 25-30 kg/m<sup>2</sup>=overweight, between 30-40 kg/m<sup>2</sup>=obese, and those over 40 kg/m<sup>2</sup> = morbid obese.

#### **Statistical Analysis**

All statistical analyses were performed using SPSS-16. The results were calculated as means  $\pm$  SD. The Student's t-test was applied to differentiate between the averages of the two independent groups, and where the SD was greater than the average and/or the number of cases within the groups was small, the non-parametric Mann-Whitney U test was also applied. Analysis of variance was employed to compare the average values of more than two groups. For the comparison of the inter- group ratios, the non-parametric chi-square

test was applied, and the correlation studies between two variables were carried out using Pearson's correlation test, the Levene's test, the Spearman correlation analysis, and Kruskal-Wallis analysis methods. A multiple regression analysis was performed for the possible variables of BMD measurement: age, sex, BMI, pregnancy, lactation, physical activity, exposure to sunlight, Child-Pugh score, fibrosis all biochemical parameters; a value of p<0.05 was accepted as indicating statistical significance.

#### Results

#### **Demographic and Clinical Features**

The demographic features, except for age, were similar in both groups (Table 1). Both groups were similar in terms of the other generally accepted osteoporosis risk factors ie physical activity status, smoking habits, coffee consumption, exposure to sunlight, and sedentary lifestyle (p>0.05). When female patients with cirrhosis were compared with female patients with hepatitis, there was no significant difference between the number of pregnancies and the duration of lactation (p>0.05). However, when compared with the length of menopause, the duration was significantly longer in patients with cirrhosis than in those with hepatitis (p=0.013). In the cirrhosis group, the Child-Pugh score was between A5 and C11. There were 19 (59%) patients in child A, 7 (22%) in child B, and 6 (19%) in child C. The average score was 6.62±1.84. Twenty-five out of 32 patients in the hepatitis group underwent liver biopsy. The average HAI score was 5.64±3.16 (range 0-13) and the fibrosis grade was 1.36±1.22 (range 0-3).

| Table 1. Demographic features of the patients groups  |                        |                        |        |  |  |  |
|---|------------------------|------------------------|--------|--|--|--|
| Feature   | Cirrhosis<br>group     | Hepatitis<br>group     | р      |  |  |  |
|   | (n=32)                 | (n=32)                 |        |  |  |  |
| Sex (F/M)   | 16/16                  | 14/18                  | >0.050 |  |  |  |
| Age (years)   | 54.03±12.83<br>(18-65) | 39.46±14.00<br>(18-65) | <0.001 |  |  |  |
| Age / F   | 59.31±7.59             | 45.71±13.22            |        |  |  |  |
| Age / M   | 48.75±14.93            | 34.61±12.91            |        |  |  |  |
| HBV / HCV   | 19/13                  | 20/12                  | >0.050 |  |  |  |
| BMI (kg/m²)   | 28.15±4.87<br>(20-38)  | 28.59±6.62<br>(19-42)  | >0.050 |  |  |  |
| F: Female, M: Male, BMI: Body mass index, HBV: Hepatitis B virus, HCV:<br>Hepatitis C virus |                        |                        |        |  |  |  |

#### **Bone Density Measurements**

The femur T-score in patients with cirrhosis was measured as  $-2.14\pm1.38$  (-4.28/0.21), the Z-score as  $-0.94\pm0.95$  (-2.58/0.99); the lumbar T-score as  $-1.47\pm1.03$  (-3.42 /-0.61) and the Z-score as  $-1.19\pm0.91$  (-3.32/-0.36). In patients with hepatitis, the femur T-score was  $-0.72\pm1.09$  (-2.45/-2.30) with a Z-score of  $-0.24\pm1.06$  (-1.78/-2.62) and the lumbar T-score was  $-0.80\pm0.94$  (-2.08/-2.21) with a Z-score of  $-0.62\pm0.94$  (-1.95/-2.39). Although the femur T and Z-scores were lower in patients with cirrhosis than in those with hepatitis, no significant difference was observed between the lumbar T and Z-scores (Figure 1).

When BMD was evaluated for etiologic agent dependence, no significant difference was discovered (p>0.05).

In the cirrhosis group, BMD was normal in 10 patients (31.3%); 13 patients (40.6%) were osteoporotic and osteopenia was detected in 9 patients (28.1%). Among the hepatitis patients, 18 (56.2%) were normal, 14 (43.8%) were osteopenic, and none were osteoporotic. This situation was evaluated as highly significant (p<0.001) and it has been observed that there were more osteoporotic patients in the cirrhosis group than in the hepatitis group.

No relationship was found between BMD, HAI scores, and fibrosis grade in patients with hepatitis and between Child-Pugh score and BMD in the cirrhotic patients (p>0.05).

#### **Biochemical and Hormonal Parameters**

A positive correlation was observed between the femur T-score and albumin level in both groups (p=0.002). No significant correlation was found between femur Z and



**Figure 1.** Comparison of the hepatitis and cirrhosis groups in terms of bone mineral density

lumbar T-Z values (p>0.05) The bilirubin value had no significant relationship with the BMD in the cirrhotic patients (p>0.05).

When the hormonal parameters testosterone, estradiol, and DHEAS were examined, similar testosterone and estradiol levels were noted in both groups (p>0.05). DHEAS levels were significantly lower in the cirrhotic patients (p=0.001) (Table 2).

The average hormonal values of males and females in both groups were calculated. The resulting values indicated that the testosterone and estradiol levels of male patients with hepatitis and cirrhosis were similar, whereas the DHEAS levels in cirrhotic males were significantly lower than those in non-cirrhotic males. The testosterone levels in females were similar in both groups, but the estradiol and DHEAS levels were significantly lower in cirrhotic women than in non-cirrhotic women (Table 3). When the variables of PTH, vitamin D, and calcium, which indicate bone metabolism, were assessed, it was observed that the vitamin D-level was significantly lower in the cirrhosis group compared with the hepatitis group (p=0.045). The average calcium and PTH levels were similar between the groups (p>0.05) (Table 4).

#### Discussion

Studies conducted in the last 20 years have shown a prevalence of osteoporosis of 12–55% and a fracture incidence of 3–20% in patients with cirrhosis<sup>(6–18)</sup>. In accordance with these studies, we found an osteoporosis rate of 40.6% and osteopenia ratio of 28.1% in patients with cirrhosis, although none of our patients had experienced any fractures. Those with hepatitis also had an osteopenia ratio of 43.8%, but no osteoporotic patient was included in the group. The osteopenia ratio was approximately twice as high in the

| Table 2. Comparison of the testosterone, estradiol and DHEAS levels |                            |                           |            |  |  |  |
|---|----------------------------|---------------------------|------------|--|--|--|
|   | Hepatitis (n=31)           | Cirrhosis (n=30)          | р          |  |  |  |
|   | (MinMax.)                  | (MinMax.)                 |            |  |  |  |
| Testosterone*   | 3.90±4.20                  | 3.51±3.62                 | >0.050     |  |  |  |
|   | (0.20-20.80)               | (0.03-10.52)              |            |  |  |  |
| Fotradial**   | 46.69±6.10                 | 38.19±3.95                | >0.050     |  |  |  |
| ESITATION   | (8.81-307)                 | (10-161)                  |            |  |  |  |
| DHEAS***  | 213.09±147.60              | 96.19±123.50              | 0.001      |  |  |  |
|   | (4.64-475.30)              | (14.56-618.40)            |            |  |  |  |
| *Testosterone: ((M: 2.8-  | -8. F: 0.06-0.8 ng/mL). ** | Estradiol: (M: 25-107, F: | 18-427 pa/ |  |  |  |

\*Testosterone: ((M:2.8-8, F:0.06-0.8 ng/mL), \*\*Estradiol: (M:25-107, F:18-427 pg/mL), \*\*\*DHEAS: (F: 35-430, M: 80-560 ug/dL), DHEAS: Dehydroepiandrosterone sulfate, Min.: Minimum, Max.: Maximum

| Table 3. Comparison of the hormone levels of the males and females in both patient groups |                                       |                 |        |               |             |        |  |
|---|---------------------------------------|-----------------|--------|---------------|-------------|--------|--|
|   | Hepatitis M                           | Cirrhosis M     |        | Hepatitis F   | Cirrhosis F | n      |  |
|   | n=17                                  | n=14            | h      | n=14          | n=16        | h      |  |
| Testosterone  | 5 66,1 01                             | 6 90 . 2 22     | > 0.05 | 176,5 27      | 0 52 0 45   | > 0.05 |  |
| (ng/mL)   | 5.00±1.01                             | 0.09±2.32       | >0.05  | 1.70±5.27     | 0.52±0.45   | >0.05  |  |
| Estradiol   | 25.05.0.40                            | 20 10 20 26     | > 0.05 | 72.06,04.20   | 20.26,51.56 | 0.01   |  |
| (pg/mL)   | 25.05±9.49                            | 30.10±20.30     | >0.05  | 72.90±04.39   | 50.20±51.50 | 0.01   |  |
| DHEAS   | 275 27,120 F4                         | 140 10 . 165 14 | 0.01   | 12757.124.40  | F0 60 22 47 | 0.01   |  |
| (ug/dL)   |                                       | 148.18±103.14   | 0.01   | 137.37±134.48 | 50.08±33.47 | 0.01   |  |
| DHEAS: Dehydroepian   | DHEAS: Dehydroepiandrosterone sulfate |                 |        |               |             |        |  |

| Table 4. Comparison of the Vit-D, PTH and calcium levels   |                |                |        |  |  |  |
|--|----------------|----------------|--------|--|--|--|
|  | Hepatitis      | Cirrhosis      |        |  |  |  |
|  | n=32           | n=32           | þ      |  |  |  |
| \/#+ D*  | 24.75±1.29     | 18.84±9.82     | 0.045  |  |  |  |
| VIL-D  | (2.70-49.50)   | (2.50-38.90)   |        |  |  |  |
|  | 57.34±5.07     | 64.09±2.71     | >0.050 |  |  |  |
| rin  | (11.40-253.00) | (18.20-142.00) |        |  |  |  |
| Calaium***   | 9.21±0.48      | 9.06±0.40      | >0.050 |  |  |  |
| Calcium  | (8.4-10)       | (7.9-9.8)      |        |  |  |  |
| <sup>°</sup> Vit-D: (10-50 ng/mL), <sup>®</sup> PTH: (11-67 pg/mL), <sup>®</sup> Calcium: (8.6-10.2 mg/dL) |                |                |        |  |  |  |
| PTH: Parathyroid hormone, Vit-D: Vitamin D   |                |                |        |  |  |  |

hepatitis group than in the cirrhosis group. The interpretation of this finding may be that patients with hepatitis are further along the process of developing osteoporosis than those with cirrhosis.

Several studies exploring the state of osteoporosis in chronic liver diseases have suggested various etiopathogenic explanations. Ninkovic et al.<sup>(11)</sup> determined the risk factors for osteoporosis as low BMI and advanced age. Among our patients, the age of those with cirrhosis was greater than that of those with hepatitis, and the female patients with cirrhosis had a longer menopausal period. The BMI in both groups were similar. Giouleme defined the pathogenesis of osteoporosis as an "increased bone turnover" and although no relationship between the etiological agent and osteoporosis has been observed, a relationship between the grade of cirrhosis and the grade of osteoporosis has been determined<sup>(19)</sup>. In a study by Crawford et al.<sup>(16)</sup> involving patients with cirrhosis awaiting liver transplantation, a correlation was noted between BMD and vitamin D deficiency and the severity of the disease<sup>(20)</sup>. There are other studies that support this finding<sup>(9,16)</sup>. However, in our study, no significant correlation was observed between Child-Pugh score and BMD. Cijevschi et al.<sup>(21)</sup>, on the other hand, observed correlations between the nutritional status and chronic cholestasis and BMD in patients with cirrhosis.<sup>(21)</sup> The calcium-PTH-vitamin D axis plays a vital role in the pathogenesis of the osteometabolic diseases. The decrease in vitamin D levels goes hand in hand with an increase in PTH levels, and this probably contributes to the development of osteoporosis<sup>(22-24)</sup>. Studies focused on this point are also not in accordance with each other. Although vitamin D deficiency has been detected in many studies, its relationship with BMD has not been clarified<sup>(4,6)</sup>. There are studies emphasizing that increased PTH levels in patients with cirrhosis are observed parallel to degenerating liver function as well as studies that failed to observe any relationship between PTH levels and BMD<sup>(4,6)</sup>.

In our study, when the bone metabolism parameters PTH, 25(OH)D3 and calcium were assessed, the 25(OH)D3 vitamin level was significantly lower in the cirrhosis group than in the hepatitis group. There were no significant difference between the hepatitis and cirrhosis patients with albumin-adjusted calcium levels. The results were similar for the PTH values. It is hypothesized that the lower 25(OH)D3 vitamin levels in patients with cirrhosis with no difference in PTH levels is a consequence of the Child A status of most of these patients.

Although *in vitro* and animal studies have shown that free bilirubin inhibits osteoblastic activity and its functions, no relationship between the levels of conjugated, non-conjugated, and total bilirubin and BMD has been determined in patients awaiting liver transplantation<sup>(25-28)</sup>. Boone et al.<sup>(29)</sup> suggested that hyperbilirubinemia disrupts osteoblastic function and raises osteoclast levels. We also found that bilirubin levels were higher in patients with cirrhosis than in patients with hepatitis, but we did not observe a relationship between bilirubin and BMD.

Floreani pointed to the contribution of hypogonadism to the etiopathogenesis of osteodystrophy in patients with

cirrhosis<sup>(30,31)</sup>. A study by Kaymakoğlu et al.<sup>(32)</sup> suggested that hypogonadism and feminization are correlated with the grade of cirrhosis. In Grandi et al.<sup>(33)</sup> study, low testosterone levels were found to be a major determinant of bone loss, whereas in another study, the PTH, vitamin D3, testosterone, and estrogen levels in patients with cirrhosis were similar to healthy individuals, although BMD was significantly reduced<sup>(34)</sup>. We observed similar testosterone and estradiol levels in the hepatitis and cirrhosis groups, but the DHEAS levels were significantly lower in the cirrhotic patients. Additionally, low estradiol levels were detected in women with cirrhosis in the subgroup analysis, no correlation between testosterone or estradiol and BMD was detected, but there was a negative correlation between DHEAS and BMD. When Tsuneoka et al.<sup>(23)</sup> compared chronic viral hepatitis and cirrhosis patients, he found that BMD was significantly lower in the cirrhosis patients and indicated that vitamin D and albumin levels correlate with BMD. In our study, only a positive correlation between the femur T-score and albumin was observed.

In a study by Schiefke et al.<sup>(35)</sup>, no difference was observed between HBV and HCV as etiologic agents in terms of osteoporosis. We also note that BMD was not influenced by the etiologic agent. Schiefke et al.<sup>(35)</sup> detected a relationship between high PTH levels and histologic changes of the liver and emphasized that PTH pointed to a shift in metabolic balance toward bone resorption in chronic hepatitis patients. We did not find any significant relationship between HAI and fibrosis and BMD.

#### **Study Limitations**

The limitations of our study include its small sample size and cross-sectional design. Further research with larger patient cohorts is needed to achieve a better understanding of this topic.

#### Conclusion

In conclusion, the osteoporosis ratio in patients with cirrhosis was in accordance with the literature. However, there was no correlation between liver fibrosis or Child-Pugh score and BMD. This result suggests that other factors, such as low vitamin D and DHEAS levels, influence the development of osteoporosis in female patients with cirrhosis.

#### Ethics

**Ethics Committee Approval:** The Ethics Committee of the Turkish Health Sciences University, Istanbul Haseki Training

and Research Hospital, İstanbul, Türkiye approved this study (decision no: 11290, date: 13.09.2007).

**Informed Consent:** Informed consent was obtained from each patient.

#### Footnotes

#### **Authorship Contributions**

Surgical and Medical Practices: A.T.K., M.K., Y.S., M.Ko., Z.A., Ş.P., Concept: A.T.K., M.K., Y.S., M.Ko., Z.A., Ş.P., Design: A.T.K., M.K., Y.S., M.Ko., Z.A., Data Collection or Processing: A.T.K., Z.A., Analysis or Interpretation: A.T.K., Ş.P., Literature Search: A.T.K., Ş.P., Writing: A.T.K., M.K., Y.S., M.Ko., Z.A., Ş.P.

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## Determination of Symptom Frequency and Symptom Clusters in Cancer Patients in Palliative Care

## Palyatif Bakımdaki Kanser Hastalarında Semptom Sıklığı ve Semptom Kümelerinin Belirlenmesi

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#### Abstract

Objective: To determine the frequency of symptoms and symptom clusters experienced by patients with cancer receiving palliative care services.

**Methods:** This cross-sectional study included 187 patients with cancer who were hospitalized in the palliative care service between March 10, 2017 and October 30, 2018. The data were collected by the researcher face-to-face using the patient identification form, memorial symptom rating scale, and Karnofsky performance scale. The research data were analyzed using SPSS software.

**Results:** Cluster analysis identified 2 symptom clusters. The first symptom cluster included physical symptoms and psychogenic symptoms related to cancer diagnosis and treatment, while the second symptom cluster mainly included nutritional (gastrointesinal system related) and genitourinary system-related problems.

**Conclusion:** Further studies are recommended for effective symptom management according to the type of cancer and for developing detailed symptom clusters.

Keywords: Palliative care, symptom cluster, cancer

#### Öz

Amaç: Palyatif bakım hizmeti alan kanser hastalarının yaşadıkları semptomların sıklığını ve semptom kümelerini belirlemektir.

**Yöntem:** Araştırma kesitsel tipte olup 10 Mart 2017-30 Ekim 2018 tarihleri arasında palyatif bakım servisi'nde yatan 187 kanser hastası ile yapılmıştır. Veriler araştırmacı tarafından hasta tanılama formu, memorial semptom değerlendirme skalası ve Karnofsky performans skalası kullanılarak yüz yüze anket yönetimi ile toplanmıştır. Araştırma verileri SPSS programında analiz edilmiştir.

**Bulgular:** Kümeleme analizinde 2 semptom kümesi belirlenmiştir. Birinci semptom kümesinde kanser tanı ve tedavisiyle ilişkili fiziksel semptomların ve psikojenik semptomlar, ikinci semptom kümesinde ağırlıklı olarak beslenme (gastrointesinal sistem ilişkili), genitoüriner sistemle ilgili sorunların yer aldığı belirlenmiştir.



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#### Öz

Sonuç: Kanserin türüne göre etkin semptom yönetimi yapılabilmesi ve ayrıntılı semptom kümeleri çıkarılması için daha fazla çalışma yapılması önerilmektedir. Anahtar Kelimeler: Palyatif bakım, semptom kümelenmesi, kanser

#### Introduction

Patients with cancer, who constitute a significant proportion of palliative care patients, may experience many symptoms, such as pain, fatigue, nausea, vomiting, loss of appetite, constipation, anxiety, sleep disturbance, pruritus, and depression caused by the disease itself, the stage of cancer, or cancer treatment<sup>(1)</sup>. In symptom management, when only one symptom is evaluated or focused on, other symptoms may be overlooked, treatment may be incomplete, and the patient's quality of life may deteriorate<sup>(1,2)</sup>. At the same time, concurrent symptoms observed in patients with cancer can increase the severity of symptoms by increasing the effects of each other and causing the emergence of new symptoms<sup>(3)</sup>.

Distressing symptoms theory is an intermediate-level theory developed by Lenz et al.<sup>(4)</sup> in 1995 and revised in 1997. The theory of distressing symptoms is based on the integration of findings from symptom research. The model plays a key role in the creation of symptom clusters in terms of the synchronicity and interrelatedness of symptoms. This theory comprises three dimensions. The first dimension is defined as the factors affecting the symptoms (physical, psychological and situational), the second dimension is defined as the duration, intensity, quality, and distress of the symptoms, and the third dimension is considered the effect of these symptoms on the achievements of individuals, including cognitive and functional activities caused by these symptoms<sup>(5)</sup>.

The coexistence of three or more symptoms in patients with cancer was initially defined as a "symptom cluster", but today it is defined as the coexistence of two or more symptoms that are interrelated and continuously present in the patient continuously<sup>(6)</sup>. Although there is not yet a complete consensus on the definition of symptom clusters, symptom clusters have been created based on both definitions in studies<sup>(7)</sup>. It is necessary to increase evidence-based knowledge in the clinical management of symptom research, and more data on the symptoms experienced by patients with cancer are needed to generate evidence in this field. Symptom clustering is a concept that started to be used in the nursing literature about 15 years ago, and there are not enough studies in this field. It is emphasized that by

identifying symptom clusters, nurses will be better able to define symptoms more accurately and target interventions that will facilitate symptom management. Effective symptom identification is reflected in patient care and quality of life of patients undergoing effective symptom management<sup>(B)</sup>.

The aim of this study was to help caregivers improve the quality of care by reducing the symptom burden of patients with cancer, to determine patient care needs, and to assess the frequency of physical and psychological symptoms related to cancer diagnosis and treatment.

#### **Materials and Methods**

The type of study is cross-sectional. The study sample consisted of 187 patients with cancer who were hospitalized in the palliative care service of a hospital between March 10, 2017, and October 30, 2018, and who agreed to participate in the study.

#### **Statistical Analysis**

The data were entered into the statistical software program SPSS 25.0 (SPSS Inc., Chicago, IL, USA) and analyzed. The findings are presented as numbers, percentages, means, and standard deviations. The Kruskal-Wallis test was used to evaluate the significance of the difference between the means of the groups, and correlation analysis was used to compare the relationship between the groups. Cluster and factor analysis were used to determine the clusters. Statistical significance level p<0.05 was accepted. The patient introduction form, Karnovsky performance scale, and memorial symptom rating scale (MSRS) will be used as data collection tools in the study.

**I. Patient identification form:** This form consists of 10 questions regarding socio-demographic characteristics, such as age, gender, education and income status, and the duration of the individual's hospitalization in the clinic and current status<sup>(9)</sup>.

**II. Memorial symptom rating scale:** The MSRS is a comprehensive multidimensional cancer-related symptom assessment tool. The material safety data sheet (MSDS) format developed by Portenoy not only reveals the prevalence of symptoms but also the frequency and distress

analysis of 32 physical and psychological symptoms. In the scale. 24 symptoms were evaluated in terms of frequency. severity and distress; 8 symptoms are evaluated in terms of frequency and distress. The scale consists of the global distress index (GDI), physical symptom subscale score (MSDS-Physical), and psychological symptom subscale score (MSDS-Psychological). This validated multidimensional scale measures the prevalence, characteristics, and distress of common symptoms in serious illnesses. The Total MSDS 41 (TMSDS) score is the mean symptom score of the 32 symptoms in the MSDS scale<sup>(10)</sup> Turkish reliability analysis of the scale was conducted by Yildirim et al.<sup>(11)</sup>. In the validity and reliability analysis conducted by Yildirim et al.<sup>(11)</sup>, the item total score correlation was 0.03-0.64. The Cronbach's alpha values of the total MSDI and MSDI sub-dimensions were between 0.71 and 0.84.

**III. The Karnofsky performance scale (KPS):** Is a scale developed for patients with cancer and was introduced into the literature by Karnofsky et al.<sup>(12)</sup> in 1948. The Karnofsky performance scale was evaluated numerically on a scale of 0-100 with a 10-point incremental number. The scale provides information about the patient's functional capacity, such as the ability to perform normal activities and work, the need for caregivers, and the level of dependency on medical care.

Patients who agreed to participate were informed about the study and provided written informed consent. Participants were also informed that they could withdraw from the study at any time. Ethical approval for the current study was obtained from the Scientific Research Ethics Committee of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (approval number: 2018/8-9, date: 11.07.2018).

#### Results

A total of 187 patients receiving palliative care participated in the study. Of the study group, 73.3% (n=137) were male, and the mean age was  $63.7\pm12.124$  (min: 19; max: 109). 71.1% of the patients were not married and 51.3% (n=96) were not actively working. The percentage of those with high school education and above was 25.7% (n=48). It was found that 54% (n=101) of the patients had normal body weight and 76.5% (n=143) were anemic. It was learned that 61% (n=114) of the patients were diagnosed with lung cancer, 62% received the diagnosis 1 month ago, and 43.3% (n=81) had metastasis. The mean duration of hospitalization was 22.9±21.390 min: 1; max: 210) days, and the mean serum vitamin B12 level was 313.8±89.126 min: 129; max: 834) mg/dL. The socio-demographic characteristics of the study group are presented in Table 1.

The 3 most common symptoms according to the MSDS were fatigue [88.8% (n=166)], pain [81.3% (n=152)], feeling sad, and worrying [71.7% (n=134)], respectively. The frequency of symptoms according to MSDI is presented in Table 2.

| Table 1. Socio-demographic characteristics of palliative care patients socio-demographic |                                      |     |       |  |  |
|--|--------------------------------------|-----|-------|--|--|
| Socio-demograp   | hic characteristics                  | n   | %     |  |  |
| 0  | Woman                                | 50  | 26.7  |  |  |
| Gender   | Male                                 | 137 | 73.3  |  |  |
|  | ≤64                                  | 92  | 49.2  |  |  |
| Age group  | 65≥                                  | 95  | 50.8  |  |  |
|  | Married                              | 54  | 28.9  |  |  |
| Marital status   | Not married                          | 133 | 71.1  |  |  |
|  | Illiterate                           | 22  | 11.8  |  |  |
| Level of study   | Primary                              | 117 | 62.6  |  |  |
|  | High school and above                | 48  | 25.7  |  |  |
| Employment   | Actively working                     | 91  | 48.7  |  |  |
| status   | Not actively working                 | 96  | 51.3  |  |  |
|  | Slim                                 | 32  | 17.1  |  |  |
| Body mass  | Normal                               | 101 | 54.0  |  |  |
| muck   | Overweight/obese                     | 54  | 28.9  |  |  |
| Anomia   | There is                             | 143 | 76.5  |  |  |
| Anemia   | There isn't                          | 44  | 23.5  |  |  |
|  | Lung cancer                          | 114 | 61.0  |  |  |
|  | Breast cancer                        | 18  | 9.6   |  |  |
|  | Bowel cancer                         | 20  | 10.7  |  |  |
| Diagnosis of the   | Prostate cancer                      | 8   | 4.3   |  |  |
| disease  | Stomach cancer                       | 16  | 8.6   |  |  |
|  | Central nervous system<br>malignancy | 4   | 2.1   |  |  |
|  | Other                                | 7   | 3.7   |  |  |
|  | 1 month ago                          | 116 | 62.0  |  |  |
|  | 3 months ago                         | 26  | 13.9  |  |  |
| Time of<br>diagnosis   | 6 month ago                          | 16  | 8.6   |  |  |
| angriosis  | More than 1 year                     | 21  | 11.2  |  |  |
|  | More than 3 years                    | 8   | 4.3   |  |  |
| Metastasis   | Yes                                  | 81  | 43.3  |  |  |
| status   | No                                   | 106 | 56.7  |  |  |
| Total  |                                      | 187 | 100.0 |  |  |

As a result of the clustering analysis, 2 symptom clusters emerged in the palliative care patient sample. In the first symptom cluster, physical symptoms related to cancer diagnosis and treatment (shortness of breath, numbness and tingling in the hands and feet, changes in the skin, feeling irritable), pain, weakness/loss of energy, feeling sad, and worrying, which are included in the main cluster as a subcluster, are concentrated. The second cluster of symptoms is often characterized by gastrointestinal problems. These symptoms include changes in the taste of food, nausea, vomiting, bloating, itching, difficulty swallowing, and difficulty urinating. The second set of symptoms also includes psychosocial symptoms. The leading symptoms were self-dissatisfaction, sexual desire, and activity. The Dendogram obtained from the clustering analysis according to the frequency of symptoms is shown in Graph 1.

| Table 2. Symptom frequencies of the study group according to the MSDS |     |      |  |  |  |
|---|-----|------|--|--|--|
| MSDS substances   | n   | %    |  |  |  |
| Difficulty concentrating  | 63  | 33.7 |  |  |  |
| Pain  | 152 | 81.3 |  |  |  |
| Fatigue-loss of energy  | 166 | 88.8 |  |  |  |
| Cough   | 104 | 55.6 |  |  |  |
| Feel frustrated   | 118 | 63.1 |  |  |  |
| Dry mouth   | 120 | 64.2 |  |  |  |
| Nausea  | 75  | 40.1 |  |  |  |
| Feeling sleepy or light-headed  | 118 | 63.1 |  |  |  |
| Numbness/tingling in the hands and feet                               | 92  | 49.2 |  |  |  |
| Difficulty sleeping   | 91  | 48.7 |  |  |  |
| Feeling bloated   | 53  | 28.3 |  |  |  |
| Difficulty urinating  | 52  | 27.8 |  |  |  |
| Vomiting  | 46  | 24.6 |  |  |  |
| Dyspnea   | 102 | 54.5 |  |  |  |
| Diarrhea  | 25  | 13.4 |  |  |  |
| Feel sad  | 134 | 71.7 |  |  |  |
| Perspiration  | 98  | 52.4 |  |  |  |
| Be worry  | 134 | 71.7 |  |  |  |
| Problems with sexual desire and activity                              | 78  | 41.7 |  |  |  |
| ltch  | 48  | 25.7 |  |  |  |
| Loss of appetite  | 104 | 55.6 |  |  |  |
| Dizziness   | 99  | 52.9 |  |  |  |
| Dysphagia   | 59  | 31.6 |  |  |  |
| Feeling sensitive   | 98  | 52.4 |  |  |  |
| Mouth sores   | 30  | 16.0 |  |  |  |
| Change in the taste of food   | 71  | 38.0 |  |  |  |
| Weight loss   | 62  | 33.2 |  |  |  |
| Hair loss   | 103 | 55.1 |  |  |  |
| Constipation  | 115 | 61.5 |  |  |  |
| Swelling in the arms or legs  | 35  | 18.7 |  |  |  |
| Self-dissatisfaction  | 68  | 36.4 |  |  |  |
| Change in the skin  | 93  | 49.7 |  |  |  |
| MSDS: Material safety data sheet                                      |     |      |  |  |  |

In the comparison of the symptom clusters and sociodemographic data, males experienced more symptom clusters; single, anemic patients, patients diagnosed with lung cancer, patients diagnosed within one month, and patients without metastasis experienced more symptom clusters (Table 3). psychological subgroups, and scale global distress index (p<0.001). In addition, although a significant difference was identified between symptom clusters in terms of KPS scores (p=0.007), no significant relationship was found between length of hospitalization and B12 levels (Table 4).

In this study, a significant difference was found between the two symptom clusters of MSDS total score, physical and

| Table 3. Comparison of symptom clusters in terms of socio-demographic and diagnosis-related characteristics |                       |           |      |         |      |        |
|---|-----------------------|-----------|------|---------|------|--------|
|   |                       | Cluster 1 |      | Cluster | 2    | _      |
|   |                       | n         | %    | n       | %    | P      |
| Variables   |                       | 76        | 40.6 | 111     | 59.4 |        |
| Condon  | Woman                 | 15        | 19.7 | 35      | 31.5 | 0.072  |
| Gender  | Male                  | 61        | 80.3 | 76      | 55.5 | 0.073  |
|   | ≤64                   | 42        | 55.3 | 50      | 45   | 0.170  |
| Age group   | 65≥                   | 34        | 44.7 | 61      | 55   | 0.170  |
| Marital status  | Married               | 34        | 44.7 | 20      | 18   | -0.001 |
| Marilal Status  | Not married           | 42        | 55.3 | 91      | 82   | <0.001 |
|   | Illiterate            | 9         | 11.8 | 13      | 11.7 |        |
| Level of study  | Primary               | 44        | 57.9 | 73      | 65.8 | 0.472  |
|   | High school and above | 23        | 30.3 | 25      | 22.5 |        |
|   | Actively working      | 36        | 47.4 | 55      | 49.5 | 0.760  |
| Employment status   | Not actively working  | 40        | 52.6 | 56      | 50.5 | 0.769  |
|   | Slim                  | 13        | 17.1 | 19      | 17.1 |        |
| Body mass index   | Normal                | 42        | 55.3 | 59      | 53.2 | 0.948  |
|   | Overweight/obese      | 21        | 27.6 | 33      | 29.7 |        |
| Anomio  | There is              | 58        | 76.3 | 85      | 76.6 | 0.967  |
| Anernia   | No                    | 18        | 23.7 | 26      | 23.4 |        |
|   | Lung cancer           | 42        | 55.3 | 72      | 64.9 |        |
|   | Breast cancer         | 7         | 9.2  | 11      | 9.9  |        |
|   | Bowel cancer          | 11        | 14.5 | 9       | 8.1  |        |
| Diagnosis of the disease  | Prostate cancer       | 6         | 7.9  | 2       | 1.8  | 0.128  |
|   | Stomach cancer        | 6         | 7.9  | 10      | 9    |        |
|   | CNS malignancy        | 0         | 0    | 4       | 100  |        |
|   | Other                 | 4         | 5.3  | 3       | 2.7  |        |
|   | 1 month ago           | 44        | 57.9 | 72      | 64.9 |        |
|   | 3 months ago          | 8         | 10.5 | 18      | 16.2 |        |
| Time of diagnosis   | 6 month ago           | 9         | 11.8 | 7       | 6.3  | 0.137  |
|   | More than 1 year      | 9         | 11.8 | 12      | 10.8 |        |
|   | More than 3 years     | 6         | 7.9  | 2       | 1.8  |        |
| Matantania atatua   | Yes                   | 29        | 38.2 | 52      | 46.8 | 0.220  |
| metastasis status   | No                    | 47        | 61.8 | 59      | 53.2 | 0.239  |
| CNS: Central nervous system   |                       |           |      |         |      |        |

| performance scale          |           |     |         |         |        |         |        |
|----------------------------|-----------|-----|---------|---------|--------|---------|--------|
|                            |           | n   | Average | Max     | Min    | Z       | р      |
| MCDC total coord           | Cluster 1 | 76  | 44.15   | 3355,5  | 120 5  | -10 /21 | <0.001 |
|                            | Cluster 2 | 111 | 128,13  | 14222,5 | 429,5  | -10.421 |        |
| MCDC physical agore        | Cluster 1 | 76  | 47.27   | 3592,5  | 000 F  | -9.770  | <0.001 |
| MSDS-physical score        | Cluster 2 | 111 | 126     | 13985,5 | 000,5  |         |        |
|                            | Cluster 1 | 76  | 59.95   | 4556,5  | 1020 5 | -7.12   | <0.001 |
| MSDS-psychological score   | Cluster 2 | 111 | 117,31  | 13021,5 | 1030,5 |         |        |
|                            | Cluster 1 | 76  | 49.16   | 3736,5  | 010 5  | 0.205   | <0.001 |
| Scale global distress muex | Cluster 2 | 111 | 124,7   | 13841,5 | 810,5  | -9.585  |        |
| 1/DC                       | Cluster 1 | 76  | 100,0   | 8064,5  | 22075  | -2.674  | 0.007  |
| NP3                        | Cluster 2 | 111 | 85.71   | 9513,5  | 3297,3 |         |        |
| Length of star             | Cluster 1 | 76  | 89.45   | 6798    | 3872   | -0.952  | 0.341  |
| Length of stay             | Cluster 2 | 111 | 97.12   | 10780   |        |         |        |
| B12 level                  | Cluster 1 | 76  | 87.88   | 6679    | 2752   | -1.279  | 0.201  |
|                            | Cluster 2 | 111 | 98.19   | 10899   | 3/33   |         |        |

|   | Dendrogram using Ward Linkage<br>Rescaled Distance Cluster Combine |    |  |  |
|---|--|----|--|--|
|   | 0 5 10 15 20   | 25 |  |  |
| Perspiration                            |  |    |  |  |
| Feeling sensitive                       |  | 1  |  |  |
| Dizziness                               |  |    |  |  |
| Cough                                   |  |    |  |  |
| Loss of appetite                        |  |    |  |  |
| Hair loss                               |  | 1  |  |  |
| Dyspnea                                 |  |    |  |  |
| Numbness/tingling in the hands and feet |  | i  |  |  |
| Change in the skin                      |  |    |  |  |
| Difficulty sleeping                     |  |    |  |  |
| Pain                                    | PII  |    |  |  |
| Fatigue-loss of energy                  |  |    |  |  |
| Feel sad                                |  |    |  |  |
| Be worry                                |  |    |  |  |
| Feel frustrated                         |  |    |  |  |
| Feeling sleepy or light-headed          |  |    |  |  |
| Dry mouth                               |  |    |  |  |
| Constipation                            | H  |    |  |  |
| Difficulty concentrating                |  |    |  |  |
| Weight loss                             |  |    |  |  |
| Dysphagia                               |  |    |  |  |
| Change in the taste of food             |  |    |  |  |
| Self-dissatisfaction                    |  |    |  |  |
| Nausea                                  |  |    |  |  |
| Itch                                    |  |    |  |  |
| Diarrhea                                |  |    |  |  |
| Mouth sores                             | H  |    |  |  |
| Swelling in the arms or legs            | H  |    |  |  |
| _                                       | L  | 1  |  |  |

Graph 1. Symptom clustering of patients

#### Discussion

This study was conducted to determine the frequency of symptoms and symptom clusters experienced by patients with cancer receiving palliative care services. Two main symptom clusters were identified in this study. In the first symptom cluster, physical symptoms related to cancer diagnosis and treatment (dyspnea, numbness/tingling in hands and feet, skin changes, difficulty sleeping, pain, weakness-loss of energy, worrying and feeling irritable) were observed. The second set of symptoms consisted mainly of symptoms related to the gastrointesinal system, such as changes in the taste of food, difficulty swallowing, nausea, bloating, vomiting, itching, unpleasant feeling, difficulty urinating, and other symptoms. It has been reported that patients with cancer experience an average of 11-13 symptoms simultaneously<sup>(13,14)</sup>. Our study is consistent with the findings. As a result of our study, fatigue loss of energy was the most common symptom was fatigue-loss of energy (88.8%), followed by pain (81.3%). In the study conducted by Süren et al.<sup>(9)</sup>, the most common symptom was fatigue (98.2%), and similar results were observed in many studies<sup>(8,15,16)</sup>. Symptoms such as fatigue and malaise, the sub-pathologies of which are not well known and often overlooked, negatively affect the quality of life, participation in life, and emotional state of patients during the day, and increase exposure to conditions that complicate the disease process, such as physical immobility<sup>(17,18)</sup>.

Gastrointestinal symptoms such as nausea, vomiting, and anorexia are some of the symptoms that form a cluster due to conditions such as palliative care patients being in the terminal period and treatment side effects<sup>(19,20)</sup>. In addition to the negative effects of gastrointestinal symptoms on nutrition, it may lead to a poor response to the treatments applied due to the inability to meet the energy requirement<sup>(21)</sup>. In the management of gastrointestinal symptoms observed in patients, it is useful for nurses to know the importance of early planning of interventions that will prevent or stop the increase in severity starting from the emergence of the symptom in terms of symptom burden<sup>(22,23)</sup>. In patients with cancer, one symptom may trigger other symptoms, or symptoms may occur independently of each other through different mechanisms. Our symptom clusters include psychological and physical symptoms. This situation, which is also encountered in the literature as one of the conditions that make symptom management difficult, can cause difficulties in understanding symptom management and its etiology because of the mechanism of symptom occurrence, the multidimensionality of human beings as a being, and the fact that symptoms sometimes manifest themselves by causing a metabolic or endocrine disorder without causing a physical symptom finding<sup>(13)</sup>. In our study, males experienced symptom clusters more frequently. In some studies, it has been reported that women experience more symptom burden<sup>(13)</sup>, but there are also research findings with no difference between gender<sup>(24)</sup>.

In our study, the group with the most frequent symptom cluster was newly diagnosed patients. Here, as health professionals, it is important to recognize that patients are at higher risk than other groups because of the negative effects of cancer treatments, the hospital process, and the weakening of social relations<sup>(8)</sup>. Early initiation of effective symptom management, holistic treatment of the patient, and multidimensional follow-up of the patient by the primary care nurse and physician will reduce the risk.

#### **Study Limitations**

The fact that the research was conducted in a single center is one of the limitations of the study.

#### Conclusion

Palliative care patients are at high risk of experiencing more than one complex and unmanageable situation from diagnosis to bereavement. Patients' reactions to the diagnostic process, coping with rapid and severe bed-related effects, especially at the end of chemotherapy treatment, withdrawal from social life, and role changes increase the symptom burden and make symptom management difficult. It is recommended that health professionals, especially those working in the field of palliative care, recognize symptoms, understand the complex process caused by symptom coexistence, plan symptom-specific management to prevent the formation of symptom clusters, and carry the knowledge to the field by sharing the results of research with health professionals in clinical practice.

#### Ethics

**Ethics Committee Approval:** Ethical approval for the current study was obtained from the Scientific Research Ethics Committee of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (approval number: 2018/8-9, date: 11.07.2018).

**Informed Consent:** Patients who agreed to participate were informed about the study and provided written informed consent.

#### Footnotes

#### **Authorship Contributions**

G.D., Y.K.Ö, Y.Y., Design: F.Ş.A., G.D., Data Collection or Processing: G.D., Y.K.Ö., Analysis or Interpretation: F.Ş.A., G.D.,

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## The Quality of Life Among Pediatricians and Nurses Caring for Child Victims of the Kahramanmaraş Earthquake

Kahramanmaraş Depremi Sonrası Deprem Mağduru Çocukları Takip Eden Çocuk Hekimleri ve Hemşirelerin Yaşam Kalitesi

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#### Abstract

**Objective:** After the earthquakes in Kahramanmaraş in 2023, pediatric clinics played an important role in the treatment of physical and psychiatric treatment of child victims. In this study, it was aimed to evaluate the quality of life of pediatricians and nurses working in pediatric clinics after the earthquake by using the and to determine the reasons related to quality of life.

**Methods:** In this study, pediatricians and nurses were asked about age, gender, the service they worked in, following-up of earthquake victims, being a relative of earthquake victim family and then the professional quality of life scale was applied. The scale scores of the participants and the other parameters were evaluated.

**Results:** A total of 69 (73.4%) pediatricians and 25 (26.6%) nurses participated in the study. The mean age was 30.5±4.8 years and 77% were female. Burnout subscale of physician' was found to be significantly higher than nurses and burnout subscale of specialists' was found to be significantly higher than residents.

**Conclusion:** In conclusion, it should not be forgotten that health professionals, regardless of residents, specialists, and nurses, will be psychologically affected by major disaster processes such as earthquakes. In this process, the necessary support should be provided in the clinics where they serve, considering the characteristics of the person.

Keywords: Children, earthquake, nurse, pediatrician, quality of life

#### Öz

**Amaç:** 2023 yılında Kahramanmaraş'ta meydana gelen depremlerden sonra çocuk klinikleri, çocuk mağdurlarının fiziksel ve psikiyatrik tedavisinde önemli rol oynamıştır. Bu çalışmada, deprem sonrası çocuk kliniklerinde çalışan çocuk hekimleri ve hemşirelerin yaşam kalitelerini ve yaşam kalitesiyle ilişkili nedenleri belirlemek amaçlanmıştır.

**Yöntem:** Bu çalışmada çocuk hekimleri ve hemşirelere yaş, cinsiyet, çalıştıkları servis depremzede takip edip etmediği, depremzede yakını olma durumları sorulmuş ve çalışanlar için yaşam kalitesi ölçeği uygulanmıştır. Katılımcıların ölçek puanları ve diğer parametrelerle ilişkisi değerlendirilmiştir. Çocuk doktorlarının tükenmişlik alt ölçeği anlamlı derecede yüksek bulunmuştur.



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#### Öz

**Bulgular:** Çalışmaya toplam 69 (%73,4) çocuk hekimi ve 25 (%26,6) hemşire katıldı. Ortalama yaş 30,5±4,8 yıl olup, %77'si kadındı. Doktorlarının tükenmişlik alt ölçeği anlamlı derecede yüksek bulundu. Doktorlarını tükenmişlik alt ölçeği hemşirelerden, uzmanların tükenmişlik alt ölçeği ise asistanlardan anlamlı derecede yüksek bulundu.

**Sonuç:** Sonuç olarak, asistan, uzman ve hemşire fark etmeksizin sağlık çalışanlarının deprem gibi büyük afet süreçlerinden psikolojik olarak etkileneceği unutulmamalıdır. Bu süreçte, kişinin özellikleri göz önünde bulundurularak, hizmet verdikleri kliniklerde gerekli destek sağlanmalıdır.

Anahtar Kelimeler: Çocuklar, deprem, hemşire, çocuk doktoru, yaşam kalitesi

#### Introduction

Health professionals are one of the most important teams involved in the response to disasters and epidemics. They are involved both in the acute period and in the recovery period of long-term cases<sup>(1)</sup>. In recent years in the world, it has been observed that the psychological effects 60 of the Coronavirus pandemic on many physicians and nurses are significant and the quality of life is affected<sup>(2)</sup>. Earthquake is one of the most important natural disasters. After the earthquakes of 7.7 and 7.6 magnitudes centered in Kahramanmaras on 6 February 2023, which affected approximately 13.5 million people in 10 provinces in our country, more than 40000 lives died<sup>(3)</sup>. Physicians in various 65 hospitals in the country, especially in Ankara, İstanbul, and İzmir, voluntarily went to the regions and provided health services to the earthquake victims. In addition, many physicians received and treated earthquake victims in their hospitals. The nurses and physicians who provided health care services to the cases were interested in the mental and psychological effects of the patients as well as their physical effects.

Our hospital in İzmir province was selected as a pilot hospital among the provinces that were not affected by the earthquake in this process. Patients were referred to our hospital from the 3<sup>rd</sup> day after the earthquake, and the last patient admission with outpatient admissions and referrals was made on the 25<sup>th</sup> day of the earthquake. In our pediatric clinics, physical treatment of these children was carried out in consultation with orthopedics, pediatric surgery and neurosurgery. In addition, these cases were evaluated with social services and child psychiatry for psychological support for both the earthquake and post-earthquake losses (parents, friends, relatives, limbs, house, neighborhood, etc.). This process also caused psychological effects on 75 health professionals. For this reason, child psychiatry physicians provided information to pediatricians and nurses about approaching children and talking to them, and guided individuals on how to keep themselves psychologically healthy.

In this study, it was aimed to evaluate the quality of life of pediatricians and nurses working in pediatric clinics after the earthquake by using the professional quality of life revision IV (ProQOL R-IV) and to determine the reasons related to quality of life<sup>(4)</sup>.

#### **Materials and Methods**

In this cross-sectional descriptive study, the questionnaires prepared by the authors and the ProQOL R-IV were administered to pediatricians and nurses working in the pediatric clinics in May-June 2023. The study was started after obtaining permission from the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital's Ethics Committee (date: 05.04.2023, decision no: 2023/03-38). Verbal and written consent were obtained from volunteers before starting the survey. The survey was conducted with using a survey form. Pediatricians and nurses were asked about age, gender, marital status, presence of children, the service they worked in, occupation and years in the profession, following-up of earthquake victims, being a relative of earthquake victim family, death of a relative in an earthquake and then the ProQOL R-IV was 90 applied. The scale scores of the participants and the other parameters were evaluated. ProQOL R-IV was developed by B. Hudnall Stamm et et al.<sup>(5)</sup> in 2005, and validated of the Turkish version by Yesil et al.<sup>(4)</sup> in 2010. The scale is a self-report assessment tool consisting of three subscales (compassion satisfaction, burnout, and compassion fatigue) and 30 items. The compassion satisfaction subscale expresses the satisfaction that a person feels as a result 95 of helping an individual who needs help related to his/her profession or job. The burnout subscale expresses the hopelessness that occurs as a result of not being able to cope with the problems that develop in business life. The compassion fatigue subscale is used to measure the situations that occur as a result of encountering stressful events and needing support. The items in the scale are evaluated on a scale from "Never" (0) to "Very often" (4).

#### Statistical Analysis

Chi-square test, number, and percentage values were used in the analysis of data related to categorical (qualitative) variables. Pairwise comparisons in numerical data were performed with the Student's t-test and Mann-Whitney U test. Analyses of the available data were performed using IBM SPSS 24 software (Statistical Package for Social Sciences, Chicago, IL, USA). The significance level was accepted as p<0.05 in all statistical tests.

#### Results

A total of 69 (73.4%) pediatricians and 25 (26.6%) nurses participated in the study. The mean age was 30.5±4.8 years and 77% were female. Demographic data of the participants are shown in Table 1 with physician and nurse groups. The percentage of the participants who followed earthquakeaffected individuals in their department was 97.1% among pediatricians and 96% among nurses. 16% of the participants had children and 62.8% had relatives affected by the earthquake. Between the two groups, nurses had more relatives affected by the earthquake at a statistically significant level. All subscale scores of ProQOL R-IV were found to be higher in pediatricians, although the burnout subscale score was statistically significant (Table 1). When the pediatricians were grouped as resident and specialist pediatricians, having children and years in the profession were significantly higher in the specialist group. In the ProQOL R-IV score evaluation, burnout was significantly higher in specialists (Table 2).

When the scores of the ProQOL R-IV were evaluated according to gender, compassion fatigue was found significantly higher in women (p=0.011). In addition, according to the presence of earthquake survivor relatives, no difference was found between the groups. Also, the scale score of compassion fatigue was found to be significantly higher in those with children (p=0.047).

#### Discussion

In this study, the subgroup of burnout score was significantly higher in pediatricians than in nurses, and specialists than in residents. The subscale of compassion fatigue was found to be significantly higher in women. In the presence of earthquake survivor relatives, no difference was found between the groups in the ProQOL R-IV scores.

In the literature with victims of earthquake, it was showed that staying in a closed area in an earthquake, waiting helplessly

| Table 1. Comparison of data of physicians and nurses   |              |              |            |       |  |
|--|--------------|--------------|------------|-------|--|
|  | Physician    | Nurse        | Total      | _     |  |
|  | (n=69, 73.4) | (n=25, 26.6) | (n=94)     | p     |  |
| Gender   |              |              |            |       |  |
| Male   | 55 (79.7)    | 22 (88.0)    | 77 (81.9)  | 0.356 |  |
| Female   | 14 (20.3)    | 3 (12.0)     | 17 (18.1)  |       |  |
| Age  | 30.4±4.5     | 31.0±5.7     | 30.5±4.8   | 0.578 |  |
| Having children  | 11 (15.9)    | 4 (16.0)     | 15 (16.0)  | 0.995 |  |
| Service/outpatients clinic   |              |              |            |       |  |
| Pediatric emergency service  | 4 (5.8)      | 5 (20.0)     | 9 (9.6)    |       |  |
| Pediatric polyclinic   | 31 (44.9)    | 0            | 31 (33.0)  |       |  |
| Pediatric service  | 31 (44.9)    | 17 (68.0)    | 48 (51.1)  |       |  |
| Pediatric intensive care   | 3 (4.4)      | 3 (12.0)     | 6 (6.4)    |       |  |
| Years in the profession  | 6.07±4.55    | 8.04±5.29    | 6.58±4.80  | 0.084 |  |
| Follow-up of earthquake victims  | 67 (97.1)    | 24 (96.0)    | 91 (96.8)  | 0.788 |  |
| Being a relative of earthquake victim family   | 36 (52.8)    | 20 (80.0)    | 56 (62.8)  | 0.015 |  |
| Death of a relative in an earthquake   | 3 (4.3)      | 3 (12.0)     | 6 (6.4)    | 0.180 |  |
| ProQOL R-IV *  |              |              |            |       |  |
| Compassion satisfaction  | 35.28±6.75   | 33.36±6.87   | 34.77±6.80 | 0.230 |  |
| Burnout  | 21.75±7.12   | 17.68±7.06   | 20.67±7.30 | 0.016 |  |
| Compassion fatigue   | 20.75±7.60   | 17.08±8.92   | 19.77±8.09 | 0.051 |  |
| ProQOL R-IV *: Validity and reliability of the Turkish version of the professional quality of life ProQOL R-IV: Professional quality of life scale revision IV |              |              |            |       |  |

| Table 2. Comparison of data of residents and specialists   |              |              |        |  |
|--|--------------|--------------|--------|--|
|  | Resident     | Specialist   | р      |  |
|  | (n=52, 55.3) | (n=17, 18.1) |        |  |
| Gender   |              |              |        |  |
| Male   | 40 (76.9)    | 15 (88.2)    | 0.314  |  |
| Female   | 12 (23.1)    | 2 (11.8)     |        |  |
| Having children  | 4 (7.7)      | 7 (41.2)     | 0.001  |  |
| Service/outpatient clinic  |              |              |        |  |
| Pediatric emergency service  | 4 (7.7)      | 0            |        |  |
| Pediatric polyclinic   | 22 (42.3)    | 9 (52.9)     |        |  |
| Pediatric service  | 23 (44.2)    | 8 (47.1)     |        |  |
| Pediatric intensive care   | 3 (5.8)      | 0            |        |  |
| Years in the profession  | 3.8±2.7      | 12.7±0.9     | <0.001 |  |
| Follow-up of earthquake survivor patients  | 50 (96.2)    | 17 (100)     | 0.412  |  |
| Being a relative of earthquake victim famil  | 27 (51.9)    | 9 (52.9)     | 0.942  |  |
| Death of a relative in an earthquake   | 3 (5.8)      | 0            |        |  |
| ProQOL R-IV *  |              |              |        |  |
| Compassion satisfaction  | 35.44±7.74   | 34.76±1.52   | 0.553  |  |
| Burnout  | 20.48±6.82   | 25.64±6.78   | 0.008  |  |
| Compassion fatigue   | 19.76±7.60   | 23.76±6.95   | 0.059  |  |
| ProOOL P-IV *: Validity and reliability of the Turkish version of the professional quality of life scale |              |              |        |  |

| ProQOL R-IV \*: Validity and reliability of the Turkish version of the professional quality of life scale

for death is one of the most feared ways of death and they need the help of people they do not know at all, especially children who lose their caregivers during this period<sup>(5,6)</sup>. This situation leads to a difficult psychological process for both the earthquake survivors and the healthcare professionals caring for them<sup>(5)</sup>. During the February 2023 earthquake, our hospital took part in the follow-up of many child patients referred to our hospital from earthquake provinces and supported their treatment. While the trauma follow-up of the parents of the children continued, we became a partner in the psychological processes of these children and became a part of their families.

The most common psychiatric conditions in individuals affected by the earthquake have been evaluated as posttraumatic stress disorder and depression<sup>(7)</sup>. Thousands of people died and hundreds of thousands of people were injured in the 8.0-magnitude earthquake that occurred in China on 12 May 2008. Most of the adolescents who lost their families, homes, schools, and friends stated that they suffered psychological pain as well as physical pain. The studies, it was aimed to investigate the prevalence of post-traumatic stress disorder in adolescents after the Marmara earthquake in our country, and in a study conducted three years after the earthquake, it was observed that adolescents had difficulty sleeping, easy startle, and intense fear, helplessness and

concentration disorder in which the moment of the event was sadly remembered again<sup>(8-10)</sup>. While pediatricians and nurses are trying to establish this balance, their psychology is also affected by this process.

Although healthcare professionals are accustomed to stress due to their working environment and seeing a child sick, the fact that the event is a natural disaster, and the fact that their relatives and colleagues are affected by the event also affects the psychological state of healthcare professionals. Our hospital, which is not located in the region where the earthquake occurred and where there are no earthquake victims working, is in an easily accessible location in terms of social services and child psychiatry. In addition to the physical treatment of the patients, their psychiatric evaluations and needs were met through the social service, and the pediatricians and nurses involved in the followup of this process were able to receive adequate support from the child psychiatrist on how to approach children.

In this study, the subscale of burnout was found to be significantly higher in pediatricians than nurses and in specialists than residents. Burnout is a state of emotional, physical, and mental exhaustion resulting from long-term work in challenging working conditions<sup>(11)</sup>. In the literature, there are many studies evaluating burnout in healthcare

professionals. In these studies, there are many reasons for burnout such as gender, occupation in the health field, working time, working time at night, liking the job, and working years. For example, in a study conducted on pediatricians and nurses at Mersin University, the highest burnout level was found in pediatricians<sup>(12)</sup>. Again, in a study conducted at Dokuz Eylül University Faculty of Medicine in our country, depression, and anxiety levels of pediatricians were found to be higher<sup>(13)</sup>. Although some studies have reported that burnout is observed more frequently in young pediatricians because of future anxiety, studies advocating the idea that the longer the time in the profession, the higher the level of burnout is more intense<sup>(14)</sup>. In our study, residents had fewer years in the profession than specialists; therefore, it was thought that burnout was higher in specialists.

In many studies, the burnout status of females was found to be higher than males<sup>(15,16)</sup>. The reason for this is thought to be the combination of housework, the obligations of having children as a mother, and the problems of the work environment. In our study, no difference was observed in the burnout subscale. It was thought that a major disaster such as an earthquake affected all individuals, males, and females, and that feeling inadequate in the face of such a disaster caused a similar score in the sense of burnout. The compassion fatigue subscale is used to measure the situations that occur as a result of encountering stressful events and that require support and it is parallel with burnout<sup>(17)</sup>. It has been reported to be more common in young nurses and pediatricians due to less experience, and similar to burnout, it has been reported to be higher in healthcare professionals with children<sup>(17-19)</sup>. In our study, it was found to be significantly higher in females. Although there was no difference in burnout status, it was thought that additional situations such as home and child care outside the health unit in which females worked were accepted as stressful events. The high level of compassion fatigue in individuals with children also explains this situation.

#### **Study Limitations**

This study had several limitations. First, in order to disseminate the results to the general healthcare workers, the number of respondents in this study needed more pediatricians and nurses. Second, because health-related quality of life in healthcare workers was assessed using a self-reported questionnaire, it may not be adequate to explore actual quality-of-life patterns.

#### Conclusion

In conclusion, it should not be forgotten that health professionals, regardless of residents, specialists, and nurses, will be psychologically affected by major disaster processes such as earthquakes. In this process, the necessary support should be provided in the clinics where they serve, considering the characteristics of the person (resident/ nurse/specialist, having a child, the presence of earthquake survivor relatives).

#### Ethics

**Ethics Committee Approval:** The study was started after obtaining permission from the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital's Ethics Committee (date: 05.04.2023, decision no: 2023/03-38).

**Informed Consent:** Verbal and written consent were obtained from volunteers before starting the survey.

#### Footnotes

#### **Authorship Contributions**

Surgical and Medical Practices: Ö.Ü., G.T., G.Ö., Concept: Ö.Ü., G.T., G.Ö., Design: Ö.Ü., G.T., Data Collection or Processing: Ö.Ü., G.Ö., Analysis or Interpretation: Ö.Ü., Literature Search: Ö.Ü., G.Ö., Writing: Ö.Ü., G.T., G.Ö.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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## Comparison of the Outcomes of Open and Laparoscopic Radical Cystectomy

Açık ve Laparoskopik Radikal Sistektomi Uygulanan Hastaların Sonuçlarının Karşılaştırılması

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#### Abstract

**Objective:** Radical cystectomy (RC) can be performed using many methods. In this study, we compared the results of open RC and laparoscopic radical cystectomy (LRC) among patients with bladder cancer in our clinic.

**Methods:** Between 2019 and 2023, 64 patients who underwent ORC and 32 patients who underwent LRC were included in the study. Demographic, preoperative, intraoperative, and postoperative data of the patients were retrospectively reviewed and compared.

**Results:** There was no statistical difference between the two groups in terms of age, gender, and body mass index. In terms of total operation time and diversion time, the ORC group had significantly shorter operation times than the LRC group (p<0.001). Normal bowel function was observed in 1±0.2 days in LRC and 1.3±0.4 days in ORC, and this period was shorter in LRC (p<0.001). The duration of oral fluid intake was shorter in the LRC group (p=0.008). The length of hospital stay (LOS) was 16.7±9.9 days in the ORC group and 9.8±5 days in the LRC group and was significantly longer (p<0.001). There were no differences between the groups in terms of complications.

Conclusion: LRC is superior in terms of LOS, oral intake, and bowel function, whereas ORC is superior in terms of surgical duration.

**Keywords:** Radical cystectomy, bladder cancer, laporoscopic surgery, minimally invasive surgery

#### Öz

**Amaç:** Radikal sistektomi (RS) operasyonu birçok yöntemle yapılabilmektedir. Çalışmamızda kliniğimizde mesane kanseri hastalarında uyguladığımız açık RS ve laparoskopik radikal sistektomi (LRS) sonuçlarını karşılaştırdık.

**Yöntem:** 2019-2023 yılları arasında ARS uygulanan 64 ve LRS uygulanan 32 hasta çalışmada yer aldı. Hastaların demografik, preoperatif, intraoperatif ve postoperatif verileri retrospektif olarak tarandı ve verileri karşılaştırıldı.

**Bulgular**: İki grup arasında yaş, cinsiyet ve vücut kitle indeksi açısından istatistiksel bir fark yoktu. Toplam operasyon süresi ve diversiyon süresi açısından ARS grubu LRS grubuna göre istatistiksel olarak daha kısa sürelere sahipti (p<0,001). Normal bağırsak fonksiyonu LRS grubunda 1±0,2 gün, ARS grubunda ise 1,3±0,4 gün izlendi ve bu süre LRS grubunda daha kısaydı (p<0,001). Oral alıma geçiş süresi LRS grubunda daha kısaydı (p=0,008). Hastanede kalış süresi ARS grubunda 16,7±9,9 gün ve LRS grubunda 9,8±5 gün idi ve istatistiksel olarak daha uzundu (p<0,001). Komplikasyon açısından her iki grup arasında fark izlenmedi.

Sonuc: LRS, hastanede kalış süresi, orale geçiş ve bağırsak fonksiyonarının erken kazanılması açısından üstünken operasyon süresi açısından ARS üstündür.

Anahtar Kelimeler: Radikal sistektomi, mesane kanseri, laporoskopik cerrahi, minimal invaziv cerrahi

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#### Introduction

Radical cystectomy (RC), a common treatment for bladder cancer, is traditionally performed as an open surgery<sup>(1)</sup>. However, with advancements in surgical technology, laparoscopic methods have become increasingly common. This minimally invasive approach has been suggested to offer several advantages, including reduced blood loss and a shorter length of hospital stay (LOS)<sup>(2)</sup>. Nevertheless, the question remains whether the oncological and functional outcomes of laparoscopic radical cystectomy (LRC) can match or even surpass those of the conventional open method<sup>(3)</sup>. This article aimed to explore this issue by reviewing current research and comparing outcomes among patients undergoing both procedures.

#### **Materials and Methods**

Ethics committee approval was obtained from University of Health Sciences Türkiye, Ümraniye Training and Research Hospital (decision no: 173, date: 13.06.2024). The study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki. Written informed consent was obtained from patients who participated in this study.

Patients who underwent RC for bladder cancer between January 2019 and January 2023 were retrospectively reviewed. The exclusion criteria were patients with nodal and/or distant metastases, severe medical comorbidities contraindicated for major surgery, uncorrectable bleeding diathesis, and preoperative radiation therapy to the pelvis. After the exclusion criteria, the data of 32 patients who underwent LRC and 62 open RC patients were compared.

Preoperatively, all patients underwent investigations for distant metastases, including bone scintigraphy and computed tomography of the chest, abdomen, and pelvis. All cases were considered as MO. Preoperative bowel preparation consisted of a fiber-free diet for 5 days prior to surgery and the intake of 1.5 L of macrogol 3350 solution (Colopeg®) the day before surgery. Patients received lowmolecular-weight heparin injection and support stockings the day before surgery.

Preoperative parameters included age, body mass index (BMI), sex, American Society of Anesthesiologists (ASA) score, hemoglobin level, and serum creatinine. Intraoperative data included cystectomy time, diversion time, total operation time, estimated blood loss (EBL), number and type of intraoperative complications, and transfusion rate. Postoperative data included serum hemoglobin and creatinine levels, LOS,

major and minor complications, transfusion rate, time to return to normal bowel function, and resumption of liquid and solid food intake. T stage, N stage, and number of lymph nodes (LN) removed were also recorded. Postoperative ileus was defined as a period of >5 days before the return of normal bowel function. Early postoperative complications were defined as those occurring within 30 days after surgery, whereas late complications were defined as those occurring more than 30 days after surgery. Minor complications were defined as those requiring only medical treatment or observation, whereas major complications were defined as those requiring intensive care unit admission, reoperation, or fatal outcomes.

#### **Statistical Analysis**

Categorical data are presented as numbers and percentages. Normally distributed numerical data are presented as mean and standard deviation values. Kolmogorov-Smirnov test was used to assess normal distribution, and Student's t-test was used for comparison. Fisher's exact test was used to compare categorical variables. In our study, values below p<0.05 were considered statistically significant. Statistical analysis was performed using Statistical Package of Social Sciencesversion 21 (IBM SPSS Statistics; IBM Corp., Armonk, NY).

#### Results

There was no statistically significant difference between the two groups in terms of age, sex, and BMI. ASA 3 was higher in both groups in terms of ASA scores from preoperative evaluations, but no difference was observed between them. Among the preoperative T stages, 16.1% of the patients in the ORC group and 15.6% in the LRC group had T1 stage. The remaining patients were in the T2 stage on preoperative T staging. There was no statistical difference in postoperative T stages between both groups. Surgical margin positivity (PSM) was 21% in the ORC group and 18.8% in the LRC group, with no significant difference. The number of LN count in the ORC group was 15±5.9 and positive LN was 1.1±0.5, whereas the number of LNs removed in the LRC group was 15.6±4.2 and positive LN was 1±0.6. In terms of total operation time and diversion time, the ORC group had significantly shorter operation times than the LRC group (p<0.001). No differences were found between the groups in terms of EBL. There was no difference in preoperative hematocrit and creatinine levels among the laboratory tests, but postoperative hematocrit levels decreased more in the ORC group than in the LRS group (p<0.001). Normal bowel function was observed in  $1\pm0.2$  days in LRS and  $1.3\pm0.4$  days in ORS, and this period was shorter in LRC (p<0.001). Oral fluid intake time was shorter in the LRC group (p=0.008). The LOS was 16.7±9.9 days in the ORC group and 9.8±5 days in the LRC group, and it was significantly longer (p<0.001). In terms of complications, the most common Clavien 1 complication was observed more frequently in both groups, and no difference was found between the groups in terms of complications. The demographic, preoperative, and postoperative evaluations of the patients are shown in Table 1.

#### Discussion

RC with LN dissection is the main treatment for invasive or superficial high-grade bladder tumors that recur after conservative treatment<sup>(4)</sup>. Controlling cancer progression, rapid postoperative recovery, and satisfactory quality of life are the 3 goals of oncological surgery<sup>(5)</sup>. RC has a morbidity rate of 25-35% and mortality rate of up to 4%<sup>(6)</sup>. Surgeries performed to reduce morbidity and mortality tend to be more minimally invasive. Laparoscopic surgery has recently become one of the methods used in RC, but its advantages and disadvantages compared with open surgery are still a matter of debate<sup>(7)</sup>.

The patient's condition is an important consideration when deciding on the surgical method. Some of the parameters that evaluate the patient's condition are Eastern Cooperative Oncology Group (ECOG) and ASA<sup>(8,9)</sup>. More minimally invasive surgeries may be considered in patients with high ECOG performance score and high ASA score<sup>(10)</sup>. In our study, we did not find any difference between the ECOG and ASA scores of patients in the ORC and LRC groups.

Surgical quality measures for RC include PSM rates and LN counts, both of which have effects on oncological outcomes. PSM, which has an effect on local recurrence, may increase progression to metastasis<sup>(11)</sup>. In patients undergoing ORC, PSM was found to be 1.5% if the cancer was limited to the organ, whereas it was reported to increase by up to 39% in patients with extravesical disease<sup>(12)</sup>. In terms of LRC, although the general PSM rate was 6.8%, it was reported to increase to 8.3% in T3 patients and 39% in T4 patients<sup>(13)</sup>. In our study, PSM was found in 21% and 18% of patients undergoing ORC and LRC, respectively. The high rate of PSM may be attributed to the more advanced postoperative pathological stage. We believe that there was no difference between PSM rates in patients who underwent RC according to the surgical method.

LN dissection is a measure of staging and regional control in RC<sup>(14)</sup>. There are contradictions in the literature concerning which type of operation is better in terms of the number of LNs. While LRC was found superior in some studies<sup>(14,15)</sup>, ORC was found superior in some studies<sup>(16)</sup>. In some studies, LRC and ORC were not shown to be superior to each other<sup>(17)</sup>. In our study, the number of removed LN was 15 in patients who underwent ORC and 15.6 in patients who underwent LRC, and we did not find any significant difference. There was no difference in the positivity rates of the removed LNs between the two groups. We believe that there was no difference between the number of LNs removed and the surgical method in patients who underwent RC.

A short operation time is one of the factors indicating surgical success. In patients who underwent RC, the total operation time was longer in patients who underwent LRC compared with ORC<sup>(18)</sup>. In the study of Guillotreau et al.<sup>(18)</sup>, the total operation time was 382 min in the LRC group, whereas it was 354 min in the ORC group, and it was shorter in ORC patients. Fadlalla et al.<sup>(15)</sup> also reported that the operative time was significantly shorter in ORC patients. In our study, similar to studies in the literature, both the total operation time and diversion time were shorter in the ORC group. One of the drawbacks of the LRC is the long operation time.

Lower EBL during surgery was associated with lower postoperative morbidity<sup>(19)</sup>. Ha et al.<sup>(19)</sup> reported that EBL was much lower in patients with LRC in their study compared with those with ORC. Similarly, Porpiglia et al.<sup>(20)</sup> reported lower EBL and less need for blood transfusion in patients who underwent LRC. In our study, we did not detect any difference in terms of EBL between LRC and ORC patients, but the hematocrit level was found to be lower in ORC patients during postoperative follow-up.

In patients undergoing RC, early mobilization, normal bowel function, and a short time to return to oral feeding are desired. The later these factors are present, the higher is morbidity<sup>(21)</sup>. Basillote et al.<sup>(21)</sup> reported that all of these factors were shorter in patients undergoing LRC than in those undergoing ORC. Guillotreau et al.<sup>(18)</sup> reported that normal bowel function was restored in 3.9 days in patients with LRC and 7.2 days in patients with ORC, and oral intake started in 2.1 days in patients with LRC and 4.4 days in patients with ORC. These factors also affect LOS. In the study by Fadlalla et al.<sup>(15)</sup>, LOS in the LRC group was 9.8 days in patients with LRC and 13.8 days in patients with ORC. In our study, both

| Table 1. Comparison of demographic, preoperative, a | nd postoperative data | between the groups |             |        |
|---|-----------------------|--------------------|-------------|--------|
| Parameters  | Total                 | ORC                | LRC         | р      |
| Age (years)   | 65.4±9.3              | 65.6±9.7           | 64.9±8.6    | 0.708  |
| Gender  |                       |                    |             | 0.160  |
| Female  | 9 (9.6)               | 8 (12.9)           | 1 (3.1)     |        |
| Male  | 85 (90.4)             | 54 (87.1)          | 31 (96.9)   |        |
| BMI (kg/m²)   | 27.2±2.8              | 27.5±2.6           | 26.6±3      | 0.181  |
| Cigarettes (packet/year)                            | 38.2±16               | 38.2±18.2          | 38±10.9     | 0,952  |
| ASA (n, %)  |                       |                    |             | 0.167  |
| 1   | 1 (1.1)               | 0 (0)              | 1 (3.1)     |        |
| 2   | 28 (29.8)             | 16 (25.8)          | 12 (37.5)   |        |
| 3   | 65 (69.1)             | 46 (74.2)          | 19 (59.4)   |        |
| ECOG (n, %)   |                       |                    |             | 0.162  |
| 2   | 29 (30.9)             | 16 (25.8)          | 13 (40.6)   |        |
| 3   | 65 (69.1)             | 46 (74.2)          | 19 (59.4)   |        |
| Preoperative T stage (n, %)                         |                       |                    |             | 0.950  |
| 1   | 15 (16)               | 10 (16.1)          | 5 (15.6)    |        |
| 2   | 79 (84)               | 52 (83.9)          | 27 (84.4)   |        |
| Postop T stage (n, %)                               |                       |                    |             | 0.010  |
| 1   | 8 (8.5)               | 6 (9.7)            | 2 (6.3)     | 0.918  |
| 2   | 23 (24.5)             | 15 (24.2)          | 8 (25)      |        |
| 3   | 59 (62.8)             | 38 (61.3)          | 21 (65.6)   |        |
| 4   | 4 (4.3)               | 3 (4.8)            | 1 (3.1)     |        |
| PSM (n, %)  | 19 (20.2)             | 13 (21)            | 6 (18.8)    | 0.800  |
| Lymph node count                                    | 15.2±5.4              | 15±5.9             | 15.6±4.2    | 0.582  |
| + Lymph node count                                  | 1.1±0.4               | 1.1±0.5            | 1±0.6       | 0.871  |
| Diversion time (min)                                | 84.4±24.4             | 78.3±13.3          | 90.8±16.3   | <0.001 |
| Operation time (min)                                | 372.7±99.2            | 344.1±85.4         | 388.1±101.9 | <0.001 |
| EBL (cc)  | 247±124.7             | 247.4±146.4        | 246.4±66.8  | 0.970  |
| Preop hematocrit                                    | 37.3±6.2              | 36.6±6.5           | 38.5±5.4    | 0.172  |
| Preop creatine (mg/dL)                              | 1.3±0.6               | 1.4±0.7            | 1.3±0.8     | 0.630  |
| Postop hematocrit                                   | 30.7±5.3              | 29.1±4.9           | 33.8±4.8    | <0.001 |
| Postop creatine (mg/dL)                             | 1.1±0.4               | 1.2±0.4            | 1.2±0.6     | 0.57   |
| Oral fluid intake (days)                            | 1.6±0.6               | 1.7±0.6            | 1.4±0.4     | 0,008  |
| Bowel function activation (days)                    | 1.2±0.4               | 1.3±0.4            | 1±0.2       | 0.001  |
| LOS (days)  | 14.3±9.1              | 16.7±9.9           | 9.8±5       | <0.001 |
| Complication (n, %)                                 |                       |                    |             | 0.929  |
| Clavien 1   | 64 (68.1)             | 43 (69.4)          | 21 (65.6)   |        |
| Clavien 2   | 20 (21.3)             | 12 (19.4)          | 8 (25)      |        |
| Clavien 3   | 7 (7.4)               | 5 (8.1)            | 2 (6.3)     |        |
| Clavien   | 3 (32)                | 2 (3.2)            | 1 (3.1)     |        |

BMI: Body mass index, ASA: American Society of Anesthesiologist, ORC: Open radical cystectomy, LRC: Laparoscopic radical cystectomy, PSM: Surgical margin positivity, EBL: Estimated blood loss, LOS: Length of hospital stay, ECOG: Eastern Cooperative Oncology Group

oral intake and bowel function activation occurred earlier in the LRC group than in the ORC group. In addition, LOS was 9.8 days in the LRC group and 16.7 days in the ORC group. We believe that LRC is superior in terms of early oral return and bowel function activation and shortens LOS.

#### **Study Limitations**

Our study has some limitations. The first reason is that it is a single-center, the second is the small number of patients, and the third is the lack of long-term follow-up results.

#### Conclusion

Morbidity is an important condition in patients undergoing RC, and the factors affecting it are important. When LRC and ORC are compared, a lower LOS is observed in LRC, and oral intake is started earlier. In addition, bowel function was normalized in the earlier period. The shorter operation time in ORC is advantageous.

**Ethics Committee Approval:** Ethics committee approval was obtained from University of Health Sciences Türkiye, Ümraniye Training and Research Hospital (decision no: 173, date: 13.06.2024).

#### Footnotes

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

#### **Authorship Contributions**

Surgical and Medical Practices: F.Y.S., M.B., A.S.D., Ö.F.Ö., A.T., A.K., E.V.K., Concept: F.Y.S., E.V.K., Design: F.Y.S., M.B., A.S.D., A.K., Data Collection or Processing: Ö.F.Ö., A.T., E.V.K., Analysis or Interpretation: F.Y.S., A.T., E.V.K., Literature Search: F.Y.S., A.T., Writing: F.Y.S., A.T.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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# Evaluation of Immunohistochemical HIF-1 $\alpha$ Expression in Gastric Adenocarcinomas According to Clinicopathological Parameters

## Mide Adenokarsinomlarında İmmünohistokimyasal HIF-1α Ekspresyonunun Klinikopatolojik Parametrelerle İlişkisinin Değerlendirilmesi

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#### Abstract

**Objective:** The alpha subunit of hypoxia-inducible factor-1 (HIF-1 $\alpha$ ) activates glucose transport, glycolytic enzymes, and transcription of genes encoding vascular endothelial growth factor (VEGF). HIF-1 $\alpha$  expression is a mechanism by which tumor cells adapt to hypoxia. Gastric cancer is one of the most common cancers world-wide and has the highest mortality rate. Because patients are usually in their advanced stages at the time of diagnosis, the survival rates are low. The present study aimed to evaluate the prognostic significance of tissue expression of HIF-1 $\alpha$  in gastric adenocarcinomas.

Methods: In this study, immunohistochemical HIF-1 $\alpha$  expression was analyzed in gastrectomy materials from 114 gastric adenocarcinomas.

**Results:** HIF-1 $\alpha$  expression was detected in 24 cases (21.1%). One (p=0.02) and five-year (p=0.03) survival rates were higher in cases with HIF-1 $\alpha$  expression. In the regression analysis, the risk of death was 3.42 times higher in patients with advanced pathologic tumor stages (pT3 and pT4). Age, sex, tumor size, tumor location, lymphovascular and perineural invasion, human epidermal growth factor receptor 2 expression, and other clinicopathological parameters were not significantly correlated with HIF-1 $\alpha$  expression and survival.

**Conclusion:** It is important to identify specific prognostic markers and new targeted treatment options for gastric cancer. Despite conflicting findings, HIF-1 $\alpha$  expression is recognized as a negative prognostic factor in many malignancies, and therapeutic agents that may be effective, especially in the HIF-1 $\alpha$ /VEGF pathway, have been developed. However, the survival rate of patients with HIF-1 expression was higher in patients with HIF-1 $\alpha$  expression. A greater amount of data should be retrieved from further research studies on the prognostic significance of HIF-1 $\alpha$  expression in gastric carcinomas, especially after the standardization of immunohistochemical evaluation methods of its expression.

Keywords: Stomach, gastric carcinoma, HIF-1a, HER2



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## Öz

**Amaç:** Hipoksi ile indüklenen faktör-alfa alt ünitesinin (HIF-1α) aktivasyonuyla glukoz transportunu, glikolitik enzimleri ve vasküler endotelyal büyüme faktörü (VEGF) kodlayan genlerin transkripsiyonunu aktive eder. HIF-1α ekspresyonunun tümör hücrelerinin hipoksiye adaptasyon mekanizmalarından biri olduğu gösterilmiştir. Mide kanserleri dünyada en sık görülen ve mortalitesi en yüksek kanserler arasında yer almaktadır. Tanı anında genellikle ileri evrede olduğu için sağkalım oranı oldukça düşüktür. Bu çalışmada mide adenokarsinomlarında HIF-1α doku ekspresyonunun prognostik öneminin değerlendirilmesi amaçlanmıştır.

Yöntem: Bu çalışmada, 114 mide adenokarsinom olgusunun gastrektomi materyallerinde immünohistokimyasal HIF-1a ekspresyonu incelenmiştir.

**Bulgular:** Olguların 24'ünde (%21,1) HIF-1α ekspresyonu saptanmıştır. HIF-1α ekspresyonu saptanan olgularda bir (p=0,02) ve beş yıllık (p=0,03) sağkalım daha yüksek bulunmuştur. Regresyon analizinde patolojik tümör evresi ileri tümörlerde de (pT3 ve pT4) ölüm riski 3,42 kat daha yüksek bulunmuştur. Yaş, cinsiyet, tümör boyutu, tümör yerleşimi, lenfovasküler ve perinöral invazyon, insan epidermal büyüme faktörü reseptörü 2 ekspresyonu ve diğer klinikopatolojik parametreler ile HIF-1α ekspresyonu ve sağkalım açısından istatistiksel olarak anlamlı sonuç bulunmamıştır.

**Sonuç:** Mide kanserlerinde spesifik prognostik belirleyicilerin ve yeni hedefe yönelik tedavi seçeneklerinin belirlenmesi çok önemlidir. Çelişkili bulgular olsa da; HIF-1α ekspresyonu pek çok malignitede olumsuz bir prognostik faktör olarak değer görmektedir ve özellikle HIF-1α/VEGF yolağında etkili olabilecek tedavi ajanları geliştirilmiştir. Oysa çalışmamızda HIF-1α ekspresyonu saptanan olgularda sağkalım oranı daha yüksek bulunmuştur. Gastrik karsinomlarda HIF-1α ekspresyonunun prognostik önemiyle ilgili, özellikle immünohistokimyasal değerlendirmenin standardizasyonu sonrası yapılacak daha çok çalışma ve veriye ihtiyaç vardır.

Anahtar Kelimeler: Mide, gastrik karsinom, HIF-1a, HER2

## Introduction

Gastric cancer is the fifth most frequently occurring type of cancer world-wide. Despite its decreasing incidence, it still ranks fourth in terms of cancer-related mortality<sup>(1)</sup>. Gastric cancer is a multifactorial disease and is primarily caused by *Helicobacter pylori (H. pylori)* infection, diet, alcohol consumption, smoking, Ebstein-Barr virus infection, and genetic factors are effective in its development<sup>(2,3)</sup>. Human epidermal growth factor receptor 2 (HER2), also known as "erythroblastosis oncogene B2 (ERBB2)", is a proto-oncogene encoded by the *ERBB2* gene located on chromosome 17<sup>(4)</sup>. HER2 overexpression is a common molecular abnormality in gastric cancers. Although its prognostic significance for gastric cancers is debatable, the detection of its overexpression in tumors has gained importance with the development of targeted therapies<sup>(5)</sup>.

Tumor hypoxia plays a key role in the progression of malignancy, and hypoxia-inducible factor-1 (HIF-1) acts as a master regulatory molecule in the adaptation of cells to changing levels of oxygen. HIF-1 is composed of  $\alpha$  and  $\beta$  subunits of the basic helix-loop-helix transcription factor family. The  $\beta$  subunit is synthesized as a basic component, and its activity is controlled by an oxygen-independent mechanism. In contrast, the  $\alpha$  subunit (HIF-1 $\alpha$ ) is ubiquitinated and degraded under normoxic conditions and stabilized under hypoxia. Under hypoxic conditions, HIF-1 $\alpha$  activates many hypoxia-responsive elements, especially vascular endothelial growth factor, and stimulates pathways necessary for tumor progression<sup>(6,7)</sup>.

The aim of this study was to determine the possible prognostic significance of HIF-1 $\alpha$  in gastric cancer, to investigate its relationship with clinicopathologic parameters, and to contribute to the identification of HIF-1 $\alpha$  as a therapeutic target molecule.

## **Materials and Methods**

A total of 114 cases of gastric adenocarcinoma diagnosed in the medical pathology laboratory of a research hospital between 2011 and 2014 were included in the study. Data related to age, sex, tumor location, tumor diameter, presence of lymph node metastasis, and TNM stage were obtained from pathology records. The presence of distant metastasis and survival data were retrieved from the hospital's electronic patient file system. Hematoxylin&eosin stained slide preparations of all cases were re-examined for tumor type, grade, pathological stage, and lymphovascular and perineural invasion (PNI). Immunohistochemically stained slides to assess HER2 expression were re-evaluated. Patients whose clinical and follow-up data were not available and whose tumor tissue material was insufficient for analysis were excluded from the study. The study was approved by the Local Ethics Committee of the University of Health Sciences Türkiye, İzmir Tepecik Education and Training Hospital (approval number: 2017/14-37, date: 11.12.2017). Informed consent was obtained from all patients prior to surgery to allow the use of the surgical materials obtained for scientific purposes.

Paraffin block, which is most suitable for immunohistochemistry (IHC) evaluation and best reflects the

characteristics of tumor tissue, was selected for the analysis. Next, paraffinized cylindrical tissue samples with a diameter of 2 mm were taken from the donor blocks by marking them first on the slide and then on the block. Multiple blocks (microarray blocks) were prepared using mapping and addressing techniques. From the prepared blocks, 4-m thick sections were placed on lysine-coated. One section was stained with hematoxylin and eosin and the other was manually stained with polyclonal HIF-1 $\alpha$  primary antibody (ATLAS, 1/300 dilution, catalog number: HPA001275). After deparaffinisation in an oven at 60 °C for 12 h, the sections were boiled in citrate solution for 20 minutes at 65 °C in a PT LINK device. Slides were allowed to cool in buffer solution for 5 min. Sections incubated with antibody for 1 h were manually stained using biotin-avidin peroxidase method (Invitrogen, Camarillo, CA, USA). Inflammatory cells in the sections also showed positive nuclear staining and were used as a positive internal control. HIF-1 $\alpha$  expression was not observed in every tumor or field of view. Nuclear or nucleocytoplasmic staining was considered as evidence of HIF-1 $\alpha$  expression<sup>(8)</sup>. Since HIF-1 $\alpha$  expression was heterogeneously distributed, no quantitative grading was performed, and expression was only evaluated as "present" or "absent" (Figure 1).

## **Statistical Analysis**

Statistical analysis was performed using the IBM SPSS 22.0 statistical package program. P $\leq$ 0.05 was accepted as the level of significance. For the comparison of quantitative data, the chi-square test was used. In the comparison of

quantitative parametric data independent groups, the t-test and non-parametric data Mann-Whitney U test were used. The non-parametric Kruskal-Wallis test was utilized for the comparison of more than 2 groups. For survival analysis, survival probabilities were tested with the Kaplan-Meier method, and the log-rank test was performed to determine whether there was a difference between survival probabilities. Cox regression analysis was then performed to identify factors affecting survival.

## Results

The study population included 72 (63.2%) male and 42 (36.8%) female patients aged between 36 and 92 years, with a mean age at diagnosis of 63.8 years. Gastric adenocarcinomas were located in the cardia in 20 (17.5%), corpus in 54 (47.4%), and antrum/pylorus in 40 (35.1%) cases. The mean tumor size was 6.33 ±3.2 cm (range: 1-15 cm). According to the World Health Organization 2019 classification, the distribution of histological subtypes of tumors was as follows: poorly cohesive carcinoma (n=36; 31.6%), tubular (n=52; 45.6%), papillary (n=5; 4.4%), mucinous (n=12; 10.5%), and mixed (n=9; 7.9%) gastric adenocarcinomas. According to Lauren classification, the distribution of the histological types of the tumors was as follows: Diffuse type (n=36; 31.5%), intestinal type (n=69; 60.5%), and indeterminate type (n=9; 7%). According to pathologic TNM classification, adenocarcinomas were in stages pT4 (n=35; 30.7%), pT3 (n=66 cases; 57.9%), pT2 (n=6; 5.3%), and pT1b (n=7; 6.1%). Lymphovascular (n=74; 64.9%), perineural (n=68; 59.6%), and local lymph node metastasis



**Figure 1.** A) HIF-1 $\alpha$  expression in tubular adenocarcinoma and B) In a diffuse (poorly cohesive) carcinoma specimen (DAB,200x) *HIF-1: Hypoxia-inducible factor-1* 

(n=89; 78.1%) were detected in the indicated number of cases. The number of metastatic lymph nodes ranged from 1 to 44 (mean 7.5 $\pm$ 8.8, median 7 lymph nodes). The study population consisted of patients with stage NO (n=25; 21.9%), N1 (n=14; 12.3%), N2 (n=29; 25.4%), N3a (n=24; 21.1%), and N3b (n=22; 19.3%) gastric adenocarcinoma. Distant organ

metastases were observed in 35 (30.7%) patients, and they were localized in the lungs (n=11), liver (n=15), peritoneum (n=7), and ovaries (n=2). Immunohistochemical HIF-1 $\alpha$ expression was detected in 24 of 114 patients (21.1%). The relationship between clinicopathological findings and HIF-1 $\alpha$  expression in patients is presented in Table 1.

| HiF1-A expression     Absent M/SD     Present M/SD     p       Age (year)     64.1±12.7     63.1±9.8     0.740       Tumor diameter (cm)     6.6±3.3     5.3±2.75     0.830       Number of metastatic lymph nodes     9.5±8.4     9.4±9.3     0.380       Survival (months)     36.5±24.3     0.101     0.170       HIF1-A expression     Absent N/%     Present N/%     0.380       Gender     Male     55/61.1     17/70.8     0.380       Tumor type     Intestinal     52/57.7     17/70.8     0.380       Diffuse     32/35.6     4/16.8     0.170       Tumor type     Cardia     15/16.6     5/20.9     0.760       Tumor location     Cardia     15/16.6     12/50     0.760       HER2 positivity (with IHC)     Score 3 (++)     3/3.3     2/6.3     0.710       Score 2 (++)     6/6.6     1/4.1     0.710     0.710       Score 3 (++)     3/3.3     2/8.3     0.62     0.40       Lymphovascular invasion     Absent     3/37.7     6/25  | Table 1. Association between qualitative and quantitative findings of patients according to HIF-1A expression status |                   |             |              |       |  |
|---|--|-------------------|-------------|--------------|-------|--|
| Age (year)64.1±12.763.1±9.80.740Tumor diameter (cm)6.6±3.35.3±2.750.830Number of metastatic tymph nodes9.5±8.49.4±9.30.300Survival (months)23.6±22.13.6±24.30.101HIF1-A expressionPresent N/%Present N/%Present N/%GenderMate55/61.117/70.80.380Tumor typeIntestinal52/57.717/70.80.380Others6/6.7312.40.170Tumor locationCardia15/16.65/20.90.170Negative (- or +)81/9021/87.67/29.10.700Ketensive necrosisAbsent89/97.821/87.60.062Perint3/3.32/8.30.0620.062Lymphovascular invasionAbsent35/38.911/45.80.330Perint3/3.32/8.30.3300.330Distant metastasesAbsent35/38.911/45.80.330Present3/34.44/16.80.330Distant metastasesAbsent55/51.113/54.20.330Present59/65.52/8.30.330Distant metastasesAbsent59/65.52/8.30.330Present59/65.52/8.30.330Distant metastasesAbsent59/65.52/8.30.330Present59/65.52/8.30.330Distant metastasesAbsent59/65.52/8.30.330Present59/65.52/8.30.330  | HIF1-A expression  |                   | Absent M/SD | Present M/SD | р     |  |
| Tumor diameter (cm) 5.84.2.75 0.830   Number of metastatic lymph nodes 9.5±8.4 9.4±9.3 0.380   Survival (months) 23.6±22.1 36.5±24.3 0.101   HIF1-A expression Absent N/% Present N/% 0.380   Gender Male 55/61.1 17/70.8 0.380   Tumor type Intestinal 52/57.7 17/70.8 0.380   Diffuse 32/35.6 4/16.8 0.100   Tumor type Ofthers 6/6.7 3/12.4   Tumor location Cardia 15/16.6 5/20.9 0.760   Antrum/pylori 33/36.6 7/29.1 0.700   HER2 positivity (with IHC) Negative (- or +) 8/190 21/67.6   Score 2 (++) 6/6.6 1/4.1 0.710   Score 3 (+++) 3/3.3 2/8.3 0.62   Lymphovascular invasion Absent 8/197.8 21/87.6   Present 3/3.8.9 11/45.8 0.530   Juph node metastases Absent 3/3.8.9 11/45.8 0.530   Present 35/65.5 2/8.3 0.530   Lump honde metastases Present 5/56.1.1 13/54.2 0.530   Distant metastases Absent <td colspan="2">Age (year)</td> <td>64.1±12.7</td> <td>63.1±9.8</td> <td>0.740</td>   | Age (year)   |                   | 64.1±12.7   | 63.1±9.8     | 0.740 |  |
| Number of metastatic lymph nodes9.5±8.49.4±9.30.380Survival (months)3.6±22.13.6±24.30.101HIF1-A expressionAbsent N/%Present N/%1GenderMale5/50.1117/70.80.380Female5/36.97/29.10.380Tumor typeDiffuse3/35.64/16.80.170Others6/6.73/12.40.170Tumor locationCardia15/16.65/20.90.700Mater typeScore 2 (++)3/36.61/20.00.700Absent98/97.82/87.60.7010.701FerenceScore 2 (++)6/6.61/4.10.710Score 2 (++)6/6.61/4.10.7100.701Absent2/2.23/12.40.6220.623Persent2/2.23/3.32/8.30.623Lymph ovascular invasionAbsent3/38.911/45.80.300Persent3/38.911/45.80.5300.530Distant metastasesAbsent5/65.113/54.20.530Distant metastasesLiver10/11.11/4.11.411.41Present13/34.44/16.80.9180.918Lumor typeLung14/15.514/1.41.9181.918Lumor typeSize11/55.514/1.41.9181.918Lumor typeSize11/55.514/1.41.9181.918Lumor typeSize11/55.514/1.41.9181.918 </th <td>Tumor diameter (cm)</td> <td></td> <td>6.6±3.3</td> <td>5.3±2.75</td> <td>0.830</td>   | Tumor diameter (cm)  |                   | 6.6±3.3     | 5.3±2.75     | 0.830 |  |
| Survival (months)23.6±22.136.5±24.30.101HIF1-A expressionAbsent N%Present N%IGenderMale<br>Female55/61.117/0.80.380Tumor typeIntestinal52/57.717/70.80.170Tumor typeDiffuse32/35.64/16.80.170Cardia15/16.65/20.90.170Tumor locationCardia15/16.65/20.90.170Magative (- or +)8/39.67/29.10.170Megative (- or +)8/39.61/4.10.170Score 2 (++)<br>Score 3 (+++)8/36.61/4.10.170Extensive necrosisNegative (- or +)8/97.82/83.70.62Present3/3.32/8.30.620.170Lymphovascular invasionAbsent<br>Present3/37.76/25.10.330Perineural invasionAbsent<br>Present3/38.911/45.80.330Lymph node metastasesAbsent<br>Present3/37.44/1.80.330Distant metastasesAbsent<br>Present3/34.44/16.80.330Lucation of distant metastasesAbsent<br>Present3/34.44/16.80.330Lucation of distant metastasesAbsent<br>Present3/34.44/16.80.330Distant metastasesAbsent<br>Present3/34.44/16.80.330Distant metastasesAbsent<br>Present3/34.44/16.80.330Distant metastasesCardia<br>Present3/34.44/16.80.330 <t< th=""><td>Number of metastatic lymph nodes</td><td></td><td>9.5±8.4</td><td>9.4±9.3</td><td>0.380</td></t<>   | Number of metastatic lymph nodes   |                   | 9.5±8.4     | 9.4±9.3      | 0.380 |  |
| HIF1-A expressionAbsent N/%Present N/%0.380GenderMale<br>Female55/61.117/70.8<br>7/29.10.380Tumor typeIntestinal52/57.717/70.8<br>4/6.80.170Tumor typeDiffuse<br>Others2/35.64/6.80.170Tumor typeCardia<br>Corpus15/16.65/20.9<br>2/20.10.760Tumor locationCorpus<br>Antrum/pylori4/46.61/250<br>3/36.60.760HER2 positivity (with IHC)Negative (- or +)<br>Score 2 (++)8/90.821/87.6Extensive necrosisAbsent<br>Present8/97.821/87.6Lymphovascular invasionAbsent<br>Present3/33.21/41.3Perineural invasionAbsent<br>Present3/36.611/45.8Distant metastasesAbsent<br>Present3/36.911/45.8Lymph of distant metastasesAbsent<br>Present3/34.44/16.8Lumor full distant metastasesAbsent<br>Present3/34.41/41.1<br>4/1.1Luman full distant metastasesAbsent<br>Present3/34.41/41.1<br>4/1.1Luman full distant metastasesAbsent<br>Present3/34.41/41.1<br>4/1.1Luman full distant metastasesAbsent<br>Present3/34.41/41.1<br>4/1.1Luman full distant metastasesAbsent<br>Present3/34.41/41.1<br>4/1.1Luman full distant metastasesAbsent<br>Present3/34.41/41.1<br>4/1.1Luman full distant metastasesAbsent<br>Present3/34.41/41.1<br>4/1.1Luman fu  | Survival (months)  |                   | 23.6±22.1   | 36.5±24.3    | 0.101 |  |
| GenderMale<br>Fenale55/6.117/0.8 $$   | HIF1-A expression  |                   | Absent N/%  | Present N/%  |       |  |
| Female5/38.97/29.10.530Tumor typeIntestinal5/57.71/70.81/70.8Diffuse32/35.64/16.81/70Others6/6.73/12.41/70Tumor tocationCorpus4/46.61/250Matter to the total corpus4/46.61/2501/70Antrum/pylori3/36.67/29.11/70HER2 positivity (with IHC)Score 2 (++)6/6.61/4.11/70Score 2 (++)5/6.61/4.11/701/70Score 3 (++)3/3.32/8.31/701/70Extensive necrosisAbsent2/3.76/6.2.31/8/751/70Present2/2.23/12.40.0621/701/70Lymphovascular invasionAbsent3/3.9.91/45.83/301/45.8Perineural invasionAbsent18/207/29.13/303/30Distant metastasesAbsent1/201/70.83/303/30Present3/34.44/16.83/303/303/30Distant metastasesAbsent1/201/70.83/303/30Present1/111/41.81/41.81/411/411/41Lung1/41.51/41.81/411/411/411/41Lung1/41.51/41.81/41.81/411/411/41Lung1/41.51/41.81/41.81/411/411/41Lung1/41.551/41.81/41.81/411  | Condor   | Male              | 55/61.1     | 17/70.8      | 0.290 |  |
| Intestinal52/57.717/70.8ADiffuse32/35.64/16.80.170Others6/6.73/12.43/12.4Tumor LocationCardia15/16.65/20.90.700Magnice (- or +)3/36.67/29.17/29.1Megative (- or +)8/90.82/187.60.710Score 2 (++)3/3.32/8.37/29.1Score 3 (+++)3/3.32/8.37/29.1Extensive necrosisAbsent8/97.82/187.6Present2/2.23/12.40.710Perineural invasionAbsent8/97.82/187.6Persent5/61.113/54.20.63Umph node metastasesAbsent5/38.911/45.8Persent18/207/29.10.30Distant metastasesAbsent13/34.41/10.8Lucation of distant metastasesSofer 23/13.41/11Lung1/11.11/11.81/11Periton5/55.52/83.21/13.9Tumor stageErly8/69.72/10.8Tumor stageErly8/19.41/10.1Lucation of distant metastasesSofer 22/10.2Tumor stageErly8/19.41/11.11/11.1Lucation of distant metastasesSofer 22/10.2Tumor stageErly8/19.41/10.11/11.1Lucation of distant metastasesSofer 21/10.11/11.1Contor Distant metastaseErly1/10.11/11.11/11.1  | Gender   | Female            | 35/38.9     | 7/29.1       | 0.380 |  |
| Tumor typeDiffuse<br>Others32/35.64/16.80.170Others6/6.73/12.47/24.1Tumor locationCardia15/16.65/20.97/20.1Tumor locationCorpus<br>Antrum/ptori3/36.07/29.17/20.1HER2 positivity (with IHC)Negative (-or +)<br>Score 2 (++)8/90.02/87.67/20.1Bester 2 (++)<br>Score 3 (+++)3/3.32/8.37/20.17/20.1Extensive necrosisAbsent<br>Present8/97.82/87.67/20.1Imphovascular invasionAbsent<br>Present3/3.76/25.33/12.4Perineural invasionAbsent<br>Present5/38.911/45.83/20.0Imphonde metastasesAbsent<br>Present18/20.01/70.83/30Distant metastasesAbsent<br>Present13/34.44/16.83/30Imprineural invasionLiver<br>Present13/34.41/41.13/30Imprineural invasionAbsent<br>Present13/34.41/41.83/30Imprineural invasionLiver<br>Present13/34.41/41.83/30Imprineural invasionLiver<br>Present13/34.41/41.83/30Imprineural invasionAbsent<br>Present13/34.41/41.83/30Imprineural invasionLiver<br>Present1/31.41/41.83/30Imprineural invasionAbsent<br>Present1/32.41/31.43/30Imprineural invasionAbsent<br>Present1/32.41/31.43/30Imprineural i  |  | Intestinal        | 52/57.7     | 17/70.8      |       |  |
| IdentifyOthers6/6.73/12.4IdentifyTumor locationCardia15/16.65/20.9Approximate of the second | Tumor type   | Diffuse           | 32/35.6     | 4/16.8       | 0.170 |  |
| Tumor locationCardia<br>Corpus15/16.65/20.9Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<br>12/50Apple<   |  | Others            | 6/6.7       | 3/12.4       |       |  |
| Tumor locationCorpus42/46.612/500.760Antrum/pylori3/36.67/29.17/29.1HER2 positivity (with IHC)Negative (- or +)81/9021/87.67.40Score 2 (++)6/6.61/4.10.710Score 3 (+++)3/3.32/8.37.40Extensive necrosisAbsent88/97.821/87.67.40Present2/2.23/12.47.407.40Lymphovascular invasionAbsent3/37.76/257.40Perineural invasionAbsent3/38.911/45.87.40Present55/61.113/54.27.307.30Lymph node metastasesAbsent51/61.113/54.27.30Distant metastasesEvery51/65.520/83.27.30Lung10/11.11/4.11/4.11.411.41Periton5/5.52/8.37.307.30Tumor stageEarly<br>Periton6/5.52/8.37.30Tumor stageEarly<br>Periton6/9.97.20.97.00  |  | Cardia            | 15/16.6     | 5/20.9       |       |  |
| IndexAntrum/pylori33/36.67/29.1HER2 positivity (with IHC)Negative (- or +)<br>Score 2 (++)6/6.61/4.1Score 2 (++)6/6.61/4.1Score 3 (+++)3/3.32/8.3Extensive necrosisAbsent8/97.821/87.6Present2/2.23/12.4Lymphovascular invasionAbsent3/37.76/25Perineural invasionAbsent3/38.911/45.8Present5/61.113/54.2Lymph node metastasesAbsent1/207/29.1Present7/801/70.8Distant metastasesLiver1/11.11/4.1Lung1/15.52/8.3Periton5/55.02/8.3Tumor stageEarly8/20NoneColuble2/2.2Distant metastagesLiver0.11.11/4.1Lung2/2.22/2.2Coluble2/2.22/2.2Distant metastasesLiver0.11.11/4.1Coluble2/2.2<  | Tumor location   | Corpus            | 42/46.6     | 12/50        | 0.760 |  |
| HER2 positivity (with IHC)Negative (- or +)<br>Score 2 (++)<br>Score 3 (+++)81/9021/87.6<br>(   |  | Antrum/pylori     | 33/36.6     | 7/29.1       |       |  |
| HER2 positivity (with IHC)Score 2 (++)<br>Score 3 (+++)6/6.61/4.10.710Score 3 (+++)3/3.32/8.32/8.32/8.3Extensive necrosisAbsent<br>Present89/97.821/87.60.062Lymphovascular invasionAbsent<br>Present3/3.76/250.062Perineural invasionAbsent<br>Present35/38.911/45.80.210Perineural invasionAbsent<br>Present55/61.113/54.20.300Lymph node metastasesAbsent<br>Present18/207/29.10.300Distant metastasesAbsent<br>Present59/65.520/83.20.300Distant metastasesLiver<br>Present10/11.11/4.10.130Lung<br>Perinon<br>Oray1/41.51/41.10.918Lung<br>Perinon<br>Ovary2/2.22/2.02/2.90.9018Tumor stageEarly<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>Para<br>P  | HER2 positivity (with IHC)   | Negative (- or +) | 81/90       | 21/87.6      |       |  |
| Score 3 (+++)3/3.32/8.3Extensive necrosisAbsent<br>Present88/97.821/87.60.062Lymphovascular invasionAbsent<br>Present3/3.76/250.240Perineural invasionAbsent<br>Present35/38.911/45.80.530Perineural invasionAbsent<br>Present55/61.113/54.20.530Lymph node metastasesAbsent<br>Present18/207/29.10.330Distant metastasesAbsent<br>Present59/65.520/83.20.330Distant metastasesLiver10/11.11/4.114.1Lung<br>Periton14/15.51/4.10.918Tumor stageEarly<br>Loca6/8.95/20.90.100  |  | Score 2 (++)      | 6/6.6       | 1/4.1        | 0.710 |  |
| Extensive necrosisAbsent88/97.821/87.6 $\partial_{0.02}$ Present2/2.23/12.4 $\partial_{0.02}$ Lymphovascular invasionAbsent34/37.76/25 $\partial_{1.02}$ Perineural invasionAbsent56/62.318/75 $\partial_{1.02}$ Lymph node metastasesAbsent55/61.113/54.2 $\partial_{1.02}$ Distant metastasesAbsent18/207/29.1 $\partial_{1.02}$ Distant metastasesAbsent59/65.520/83.2 $\partial_{1.02}$ Lung10/11.11/4.14/16.8 $\partial_{1.02}$ Peritorio of distant metastasesLiver10/11.11/4.1 $A_{1.02}$ Tumor stageEarly88.95/20.9 $\partial_{1.00}$   |  | Score 3 (+++)     | 3/3.3       | 2/8.3        |       |  |
| Present     2/2.2     3/12.4     5002       Lymphovascular invasion     Absent<br>Present     34/37.7     6/25     0.240       Perineural invasion     Absent<br>Present     35/38.9     11/45.8     0.530       Lymph node metastases     Absent<br>Present     55/61.1     13/54.2     0.530       Lymph node metastases     Absent<br>Present     18/20     7/29.1     0.330       Distant metastases     Absent<br>Present     59/65.5     20/83.2     0.130       Lung     14/15.5     1/4.1     1/4.1     1/4.1       Lung     14/15.5     1/4.1     0.918       Tumor stage     Early     8/8.9     5/20.9     0.100   | Extensive necrosis   | Absent            | 88/97.8     | 21/87.6      | 0.062 |  |
| Lymphovascular invasion     Absent<br>Present     34/37.7     6/25     3.240       Persent     56/62.3     18/75     18/75     3.240       Perineural invasion     Absent<br>Present     35/38.9     11/45.8     3.300       Lymph node metastases     Absent<br>Present     18/20     7/29.1     3.300       Distant metastases     Absent<br>Present     17/08     3.300     3.300       Liver     13/34.4     4/16.8     3.130       Lung<br>Present     10/11.1     1/4.1     4.16.8     3.130       Location of distant metastases     Liver     10/11.1     1/4.1     3.130       Lung<br>Periton<br>Ovary     2/2.2     -     -     0.130       Tumor stage     Early<br>Late     8/8.9     5/20.9     0.100   |  | Present           | 2/2.2       | 3/12.4       |       |  |
| Present     56/62.3     18/75     0.10       Perineural invasion     Absent<br>Present     35/38.9     11/45.8     0.530       Lymph node metastases     Absent<br>Present     18/20     7/29.1     0.330       Lymph node metastases     Absent<br>Present     72/80     17/70.8     0.330       Distant metastases     Absent<br>Present     59/65.5     20/83.2     0.130       Location of distant metastases     Liver<br>Lung     10/11.1     1/4.1   | lymphovascular invasion  | Absent            | 34/37.7     | 6/25         | 0.240 |  |
| Perineural invasion     Absent<br>Present     35/38.9     11/45.8     0.530       Lymph node metastases     Absent<br>Present     18/20     7/29.1     0.330       Distant metastases     Present     72/80     17/70.8     0.330       Distant metastases     Absent     59/65.5     20/83.2     0.130       Lung     31/34.4     4/16.8     0.130       Periton     5/5.5     2/8.3     0.130       Lung     14/15.5     1/4.1     1/4.1       Periton     5/5.5     2/8.3     0.918       Tumor stage     Early     8/8.9     5/20.9     0.100   | -2b  | Present           | 56/62.3     | 18/75        |       |  |
| Present     55/61.1     13/54.2     0.000       Lymph node metastases     Absent<br>Present     18/20     7/29.1     0.330       Distant metastases     Absent<br>Present     59/65.5     20/83.2     0.130       Liver<br>Lung<br>Periton     10/11.1     1/4.1     0.130       Periton     5/5.5     2/8.3     0.130       Tumor stage     Early<br>Late     8/8.9     5/20.9     0.100   | Perineural invasion  | Absent            | 35/38.9     | 11/45.8      | 0.530 |  |
| Lymph node metastases     Absent<br>Present     18/20     7/29.1     3.30       Distant metastases     Absent<br>Present     59/65.5     20/83.2     3.30       Liver     31/34.4     4/16.8     3.30       Location of distant metastases     Liver     10/11.1     1/4.1     ,41       Veritoria     5/5.5     2/8.3     ,31       Tumor stage     Early     8/8.9     5/20.9     ,30   |  | Present           | 55/61.1     | 13/54.2      |       |  |
| Present     72/80     17/70.8     0.000       Distant metastases     Absent<br>Present     59/65.5     20/83.2     0.130       Location of distant metastases     Liver     10/11.1     1/4.1     0.130       Periton     5/5.5     2/8.3     0.130       Tumor stage     Early     8/8.9     5/20.9     0.100  | Lymph node metastases  | Absent            | 18/20       | 7/29.1       | 0.330 |  |
| Absent     59/65.5     20/83.2        Present     31/34.4     4/16.8  | -yp.i iloue illeustuses  | Present           | 72/80       | 17/70.8      |       |  |
| Present     31/34.4     4/16.8     0.100       Liver     10/11.1     1/4.1  | Distant metastases   | Absent            | 59/65.5     | 20/83.2      | 0.130 |  |
| Liver     10/11     1/4.1       Lung     14/15.5     1/4.1     0.918       Periton     5/5.5     2/8.3     0.918       Ovary     2/2.2     -     0.918       Tumor stage     Early     8/8.9     5/20.9     0.100   |  | Present           | 31/34.4     | 4/16.8       | 0.100 |  |
| Lung     14/15.5     1/4.1     0.918       Periton     5/5.5     2/8.3     0.918       Ovary     2/2.2     -     -       Tumor stage     Early     8/8.9     5/20.9     0.100   | Location of distant metastases   | Liver             | 10/11.1     | 1/4.1        |       |  |
| Periton     5/5.5     2/8.3     0000       Ovary     2/2.2     -     -     -       Early     8/8.9     5/20.9     0.100       Integen     02/01 I     10/70 I     0.100   |  | Lung              | 14/15.5     | 1/4.1        | 0.918 |  |
| Ovary     2/2.2     -     -       Early     8/8.9     5/20.9     0.100  |  | Periton           | 5/5.5       | 2/8.3        |       |  |
| Early     8/8.9     5/20.9     0.100  |  | Ovary             | 2/2.2       | -            |       |  |
|   | Tumor stage  | Early             | 8/8.9       | 5/20.9       | 0.100 |  |
| Late 82/91.1 19/79.1  |  | Late              | 82/91.1     | 19/79.1      |       |  |
| Survival status     Deceased     67/74.4     13/54.2     0.054  | Survival status  | Deceased          | 67/74.4     | 13/54.2      | 0.054 |  |
| Survived 23/25.6 11/45.8  |  | Survived          | 23/25.6     | 11/45.8      |       |  |

HER2 IHC scores were 0 or 1+ in 102 (89.5%) cases, and both groups were considered HER2-negative. IHC scores of 2+ and 3+ were detected in 6.1% (n=7) and 4.4% (n=5) of the cases, respectively. While HIF-1 $\alpha$  expression was observed in 3 (25%) HER2- positive, but in 21 (20.58%) HER2- negative cases. There was no statistically significant correlation between HER2- negative and positive groups and HIF-1 $\alpha$  expression (p=0.71).Similarly, there were no statistically significant differences in HIF-1 $\alpha$  expression according to most clinicopathological features, such as sex (p=0.38), age (p=0.74), tumor location (p=0.76), histological type of tumors (p=0.17), presence of lymph node metastasis (p=0.33), pathological tumor stage (p=0.10), tumor size (p=0.83), lymphovascular invasion (LVI) (p=0.24), PNI (p=0.53), presence of extensive tumor necrosis (p=0.062), and presence of distant metastases (p=0.13). Although there was no statistical relationship between the presence of HIF-1 expression and the mean survival time and survival status, the difference was significant when compared with the median survival time. The reason for this can be explained by the fact that the survival times of the patients were in a very wide range, and the standard deviation was large. On the other hand, the median survival times were 41.4 and 15.4 months in HIF-1 $\alpha$  positive, and negative cases, respectively, and a statistically significant (p=0.03) difference was detected between both groups in terms of HIF-1 $\alpha$ staining status. Contrary to most studies in the literature, the survival time was longer in our patients with HIF-1 $\alpha$ expressing tumors (Figure 2). In terms of HIF-1 $\alpha$  staining status, the 1- and 5-year survival rates in HIF-1 $\alpha$  positive, and negative groups were 45.8% vs. 36.9% and 25.6% vs. 22.3%, respectively, with statistically significant intergroup differences (p=0.02 vs. 0.03).

## Discussion

The incidence of gastric cancer significantly increases with age. Most patients are diagnosed between the ages of 60 and 80 years. Gastric cancers are rarely diagnosed in patients aged 45 years and are defined as "early-onset gastric cancer". It is believed that early-onset cases have different clinicopathological characteristics and develop in different models of carcinogenesis<sup>(9)</sup>. The mean age at diagnosis in our study population was 63.89 years, which is consistent with the literature findings. Only 7% of our patients were under 45 years of age at the time of diagnosis.

Gastric cancer is twice as common in men as in women. In addition, they are the fourth and fifth most common causes of cancer-related deaths in men and women, respectively<sup>(1-3)</sup>. The gender distribution of the study population was consistent with the literature findings. The process of gastric carcinogenesis is multifactorial, and both environmental and genetic factors play a role in the development of gastric cancers<sup>(9)</sup>. Approximately 89% of all gastric tumors are associated with *H. pylori* infection<sup>(2)</sup>.

Although gastric tumors seem to represent a single disease state, they can be considered as two entities "cardia" and "non-cardia" gastric cancers based especially on their widely different etiopathogenesis. Although HP infection, low socio-economic status, and dietary factors are blamed for the development of non-cardia gastric cancers, obesity and gastroesophageal reflux disease are believed to play a role in the etiology of gastric cardia cancers. Age, male sex, family history, smoking, and radiation exposure are common risk factors for tumors located in both regions<sup>(2,5,10-12)</sup>. Gastric cancer localization frequently varies according to the geographic region in which the patient lives. Although distally localized tumors i.e., in the corpus, antrum, and pylorus) constitute the majority of cases in the geographic regions where gastric cancer is endemic, tumors localized in the cardia and fundus are slightly more common in other geographic regions<sup>(12)</sup>. It is known that the prognosis of gastric cardia cancer is worse than that of distal gastric tumors because they are usually diagnosed at an advanced stage<sup>(9)</sup>. Although 20 (17.5%) cases of gastric carcinomas included





in our study were located in the cardia/fundus, 94 (82.5%) were located in the distal stomach. A statistically significant difference was not detected in survival times between patients with gastric tumors of different localizations. More than 90% of gastric cancers have adenocarcinoma morphology, and the most common histologic type is tubular adenocarcinoma according to the World Health Organization classification. When the Lauren classification is taken into consideration, intestinal-type gastric carcinoma was more common in the past, whereas in recent years, especially in some countries, the incidence rates of diffuse and intestinal carcinoma seem to be close to each other<sup>(2)</sup>. Similarly, 45.6% of our cases had tubular adenocarcinoma morphology, followed by poorly cohesive carcinomas with a frequency of 31.6%. According to Lauren classification, most of the cases were intestinal type carcinomas (60.5%).

TNM staging alone is the most important prognostic factor of gastric cancer. Although 5-year survival is >90% in patients with pT1 tumors without lymph node metastasis, this rate decreases to 30% in those with pT3 tumors<sup>(2)</sup>. Our patients had pT1 and pT2 (n=13; 11.4%), pT3 (n=66; 57.9%), and pT4 (n=35; 30.7%) adenocarcinomas. When pT1 and pT2 cases were included in the early-stage gastric adenocarcinoma group and pT3 and pT4 cases in the late-stage gastric adenocarcinoma group, the median survival was 55 months in patients with pT1 and pT2 tumors, whereas it was 27.9 months in those with pT3 and pT4 tumors, with a statistically significant difference between groups (p=0.006).

The lymph node status is not only important in determining the stage of gastric cancer but also in indicating the need for adjuvant treatment. Recent studies have shown that "metastatic lymph node ratio", defined as the ratio of metastatic lymph nodes to total resected lymph nodes, may be an independent prognostic factor for gastric cancers<sup>(13)</sup>. Our study population of 114 patients were included in stages N0 (n=25; 21.9%), N1 (n=14; 12.3%), N2 (n=29; 25.4%), N3a (n=26; 21.1%), and N3b (n=22; 19.3%) based on the number of metastatic lymph nodes. Although the median survival time of patients without lymph node metastasis was significantly longer, the intergroup difference was not statistically significant.

Despite the fact that LVI is one of the most important factors in the development of lymph node metastasis in gastric carcinomas, data on its effect on survival as an independent factor remain controversial<sup>(14)</sup>. LVI was observed in 52 (31.9%) of 114 patients. In terms of survival, the median survival time was slightly longer in patients without LVI (20.1 months) than in those with LVI (18 months). However, the difference between the two groups was not statistically significant. Although PNI can predict recurrence in gastric cancers, there is not enough data on its prognostic value. Deng et al.<sup>(15)</sup> reported that PNI can be considered an independent prognostic factor in a meta-analysis of 24 studies including 30,590 patients who underwent curative gastrectomy. In the present study, PNI was found in 43 patients (25.9%). The median survival time was 17.9 months in patients with PNI and 24.7 months in those without. The difference between the two groups was not statistically significant in terms of median survival time.

Approximately 40% of gastric cancers are metastatic at the time of diagnosis, and the median survival for untreated metastatic gastric cancers is 4 months, whereas the 5-year survival is 3-6%<sup>(16)</sup>. Metastases commonly spread to the lungs and liver via hematogenous routes. Distant metastasis was found in 35 (30.7%) patients. In parallel with the literature, these metastases were most commonly observed in the liver, lungs, peritoneum, and ovaries. The median survival times were 24.2 months in patients without distant metastases and 14.7 months in patients without. Although this intergroup difference was remarkable and consistent with the literature, it was not statistically significant.

One of the most important molecules for targeted gastric cancer treatment is HER2. HER2 participates in cell growth and differentiation. The association between HER2 positivity and poor prognosis, especially in breast cancer, has paved the way for the study of HER2 overexpression in gastric cancer. Overexpression of HER2 is found in approximately 10-30% of gastric cancers<sup>(2,5)</sup>. HER2 was found to be associated with male sex, intestinal type cancer, and moderate/good cell differentiation in gastric cancers<sup>(5)</sup>. The total gene expression analysis study conducted by targeting HER2 revealed that trastuzumab, a HER2 monoclonal antibody, may contribute favorably to survival in the treatment of gastric cancer<sup>(14)</sup>. The relationship between HER2 positivity and prognosis remains controversial<sup>(2,5)</sup>. HER2 was evaluated immunohistochemically in all specimens from the 114 patients included in our study. In 102 (89.5%) patients, the HER2 IHC scores were 0 and 1+, indicating HER2-negativity. HER2 IHC scores of 2 (n=7; 6.1%) and 3 (n=5; 4.4%) were designated for the indicated number of patients. We were able to access the data of 99 patients whose HER2/neu gene expression status was evaluated using the fluorescence in situ hybridization (FISH) method. HER2 overexpression was observed in 10 of 99 cases (10.1%). The findings obtained using both methods were consistent with the literature. The median survival time was 3.6 months in patients with HER2 overexpression (score 3), 18 months in patients with HER2 IHC scores of 2, and 22.1 months in HER2-negative patients. Similarly, median survival times were 11.4 and 22.9 months in patients with and without HER2 overexpression when the FISH method was used. The results obtained by both methods were guite similar. The median survival of patients with HER2 overexpression was markedly shorter, but no statistically significant difference was observed between both groups. Studies examining the relationship between HER2 and HIF-1 $\alpha$  have shown that HER2 overexpression stimulates HIF-1 $\alpha$ -dependent gene transcription not directly but in combination with other tumor-specific genetic and physiological changes<sup>(6)</sup>. It should be kept in mind that the fact that all HER2-positive patients in our study received targeted therapy may have led to the lack of a statistically significant difference in survival between groups with and without HER2 overexpression.

In mammalian cells, it is essential to maintain oxygen homeostasis to meet energy needs and sustain aerobic metabolism. In rapidly proliferating cancer cells, increased oxygen consumption and decreased oxygen transport and diffusion lead to hypoxia. Inadequate and chaotic vascularization also leads to severe deterioration of the oxygen balance in tumor cells<sup>(6,7)</sup>. It has been shown that HIF-1 $\alpha$  plays an important role in the adaptation of tumor cells to these changes in oxygen concentrations and thus in tumor progression. HIF-1 $\alpha$  realizes this adaptation by regulating many genes involved in the angiogenesis, glucose metabolism, cell proliferation, invasion, and metastasis pathways<sup>(17,18)</sup>. In the literature, HIF-1 $\alpha$  overexpression has been reported in many organ cancers, including colorectal, breast, lung, ovarian, and pancreatic cancers. In most of these malignancies, HIF-1 $\alpha$  is generally associated with poor prognosis<sup>(19)</sup>. Since gastric cancers still rank high in cancer mortality and are usually diagnosed at an advanced stage, the search for new treatment modalities and agents that will contribute to survival continues. HIF-1 $\alpha$ is becoming one of the popular targets in the approach to gastric cancers<sup>(20,21)</sup>.

Despite the advocacy of opposing views, in many studies, HIF-1 $\alpha$  expression in a wide range of malignant tumor tissues, including gastric adenocarcinomas, has been associated with low survival and adverse clinicopathological factors<sup>(20-23)</sup>. In our study, the 1-year survival rates were

45.8% in HIF-1 $\alpha$  positive, and 25.6% in the HIF-1 $\alpha$  negative group with a statistically significant intergroup difference (p=0.02). Contrary to most studies cited in the literature, the 5-year survival rates were 36.9% and 22.3% in the HIF-1 $\alpha$ positive, and negative groups with a statistically significant difference between groups. The existence of contradictory and sometimes conflicting results in the literature may be related to the fact that HIF-1 $\alpha$  is a complex molecule that may have both apoptosis-inducing and inhibitory effects in cell metabolism, as well as stimulating or inhibiting cell proliferation<sup>(6,7)</sup>. In addition, pathways involved in tumor progression and induced pathways may be differentially stimulated by HIF-1 $\alpha$ . It is thought that the level of hypoxia, presence of an oncogene, or homologs such as HIF-2 $\alpha$ and HIF-3 $\alpha$  may also be effective in the regulation of these pathways, which may affect HIF-1 $\alpha$  expression levels in tumors<sup>(11)</sup>. In addition, interobserver differences in the evaluation of HIF-1 $\alpha$  immunohistochemistry should be considered when analyzing different results. All of these data support the argument that further studies are needed to accept HIF-1 $\alpha$  as a target molecule for determining prognosis and targeted therapies<sup>(24)</sup>.

While HIF-1 $\alpha$  expression was detected in 60% of the cases with extensive tumor necrosis, whereas 19.3% of the cases without necrosis were HIF-1 $\alpha$  positive. Considering the role of HIF-1 $\alpha$  in hypoxic conditions, this finding was considered to be compatible with the nature of the molecule, and the fact that this finding was not statistically significant may be related to the small number of cases with necrosis included in our study. In the regression analysis, the risk of death was 3.42 times higher in advanced tumors than in early-stage tumors.

## **Study Limitations**

Our study has several limitations. The most important of these limitations is that the tissues used for immunohistochemical staining were obtained by the tissue microarray method, which suggests that our results may be affected by tumor heterogeneity. Second, there is no specific standardization for the immunohistochemical evaluation of HIF-1 $\alpha$  expression. For example, Rohwer et al.<sup>(®)</sup> not only performed a quantitative evaluation of HIF-1 $\alpha$  expression in tumor cells but also divided them into groups to perform a qualitative evaluation, perhaps to eliminate the handicaps of heterogeneous staining. Because very small tumor areas were evaluated in our study, it was not possible to create ordinal groups. In addition, nuclear or nucleocytoplasmic staining was used as the basis in the studies we referenced in our study. There is no consensus on any cut-off value for HIF- $1\alpha$  expression level. Under these conditions, comparing data obtained from different sources will not yield optimal results. Finally, the fact that patients who received neoadjuvant treatment were not allocated into different groups during patient selection may be a factor that may affect both HIF- $1\alpha$ expression and survival.

## Conclusion

As a result,  $HIF-1\alpha$  and cancer-related studies have shown that  $HIF-1\alpha$  expression can have positive effects on cancer treatment and prognosis.  $HIF-1\alpha$  can also be used to improve survival in patients with gastric cancer, which is one of the most frequently seen and aggressive cancers. Therefore, new and comprehensive studies are needed in this regard.

## Ethics

**Ethics Committee Approval:** The study was approved by the Local Ethics Committee of the University of Health Sciences Türkiye, İzmir Tepecik Education and Training Hospital (approval number: 2017/14-37, date: 11.12.2017).

**Informed Consent:** Informed consent was obtained from all patients prior to surgery to allow the use of the surgical materials obtained for scientific purposes.

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\*The English translation and editing of the article were done by Gökhan Kazancı.

## Footnotes

## **Authorship Contributions**

Surgical and Medical Practices: T.A., G.D., P.Ö., Y.K., S.A., Concept: T.A., G.D., Design: T.A., G.D., Data Collection or Processing: T.A., G.D., P.Ö., Y.K., Analysis or Interpretation: T.A., G.D., P.Ö., Y.K., S.A., Literature Search: T.A., G.D., P.Ö., Y.K., Writing: T.A., G.D., P.Ö., S.A.

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## Retrospective Examination of the Clinical and Demographic Characteristics of Patients with Geriatric Forensic Trauma Admitted to the Emergency Department: A Single-center Experience

Acil Servise Başvuran Geriatrik Adli Olguların Klinik ve Demografik Özelliklerinin Retrospektif İncelenmesi: Tek Merkez Deneyimi

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## Abstract

**Objective:** To determine the demographic and epidemiological characteristics of geriatric patients with forensic trauma admitted to the emergency department of our hospital and to examine factors associated with forensic events in our country.

**Methods:** The data of individuals aged 65 years and older who were admitted to the emergency department of our hospital due to forensic events between 2013 and 2023 were retrospectively analyzed. The patients' demographic characteristics, date and nature of the forensic incident, injury zones, final diagnoses of the forensic patient, and nature and content of the forensic report were examined from the forensic records.

**Results:** Of 173,080 geriatric patients admitted to the emergency department during the study period, 679 were forensic cases. Most patients were men (n=481, 70.8%). The most common type of forensic incident was falls (37.4%), followed by assault (18.1%). Half of the intoxication cases were caused by carbon monoxide. The most frequently injured body areas were the head and neck (39.8%), followed by the upper limbs (27.4%) and lower limbs (19%). Forensic admissions were most common during the summer months (August, July, and June).

**Conclusion:** In this study, falls were the most common cause of geriatric forensic trauma. Therefore, potential fall-related complications can be prevented by carefully evaluating older adults at high risk of falls and taking necessary precautions.

Keywords: Geriatrics, trauma, forensic case, emergency, elderly



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## Öz

**Amaç:** Hastanemiz acil servisine başvuran geriatrik adli travma hastalarının demografik ve epidemiyolojik özelliklerinin saptanması, adli olaylarla ilişkili faktörlerin irdelenerek ülkemizdeki literatüre katkıda bulunulması amaçlandı.

Yöntem: Hastanemiz acil servisine 2013-2023 yılları arasında adli olaylar nedeniyle başvurusu yapılmış 65 yaş ve üzeri bireylerin verileri retrospektif olarak incelendi. Hastaların demografik özellikleri, adli olay tarihi, niteliği, yaralanma bölgeleri, adli olgu sonuç tanıları, düzenlenen adli raporun niteliği ve içeriği adli rapor kayıtlarından incelendi.

**Bulgular:** Araştırma süresince acil servise başvuran geriatrik hasta sayısı 173.080 olup, bu kişilerin 679'u adli olgu olarak değerlendirilmiştir. Hastaların 481'i (%70,8) erkekti. Adli olguya konu olan en sık olay türü %37,4 ile düşme idi, ikinci sırada %18,1 ile darp yer aldı. İntoksikasyonların ise %50'sinin karbonmonoksit nedeniyle gerçekleştiği görüldü. En sık yaralanan vücut bölgesi %39,8 ile baş-boyun iken, sonrasında %27,4 oranında üst ve %19 oranında alt ekstremite yer aldı. Adli olay başvurularının en sık yaz ayları olan Ağustos, Temmuz ve Haziran aylarında olduğu görüldü.

**Sonuç:** Çalışmamızda düşmenin geriatrik adli travmaların en sık nedeni olduğu saptanmıştır. Bu nedenle düşme riski yüksek olan yaşlılar ayrıntılı değerlendirilerek gerekli önlemlerin alınması ile düşme sonrası gelişebilecek komplikasyonların önüne geçilebilir.

Anahtar Kelimeler: Geriatri, travma, adli olgu, acil, yaşlı

## Introduction

The older population is growing in Türkiye and worldwide. The geriatric population in Türkiye was 7,186,204 in 2018 and increased by 21.4% over the last 5 years to 8,722,806 in 2023. The proportion of older adults in the population rose from 8.8% in 2018 to 10.2% in 2023. According to population projections, this rate is expected to increase further to 12.9% in 2030, 16.3% in 2040, 22.6% in 2060, and 25.6% in 2080<sup>(1)</sup>.

With this growth of the older population, increased participation in active lifestyles<sup>(2,3)</sup> and age-related physiological changes, such as decreases in perception and attention, visual acuity, and mental and motor activity, as well as postural changes, can increase rates of trauma and injury in older adults<sup>(4)</sup>. Epidemiological studies have shown that 23% of all trauma admission involve geriatric patients<sup>(2)</sup>.

Trauma is the fourth most common cause of death after heart disease, cancer, and stroke in all age groups<sup>(5)</sup> and the fifth most common cause of death in the geriatric population<sup>(2,6)</sup>. Geriatric traumas are mostly caused by falls (from a height or at the same level) or motor vehicle accidents (driver, occupant, pedestrian, or cyclist)<sup>(7,8)</sup>. Trauma is associated with high morbidity and mortality and has more severe consequences in older adults than in other populations because of the presence of concomitant diseases and limited physiological reserves<sup>(8,9)</sup>.

Our aim in this study was to determine the demographic and epidemiological characteristics of geriatric forensic trauma patients admitted to the emergency department of our hospital and to contribute to the literature by examining the factors associated with forensic incidents in our country.

## **Materials and Methods**

In this retrospective cross-sectional study, we examined the records of individuals aged 65 years who presented to the emergency department of the Atatürk University Faculty of Medicine Hospital due to forensic incidents between 2013 and 2023. The patients' demographic characteristics (age, gender, occupation, education level, cohabitation, marital status, place of residence), chronic diseases, and drugs used were obtained from the hospital information system and patient files. The date, nature, and setting of the forensic incident, injury zones, related outcomes (hospitalization, mortality), diagnosis of the forensic patient, and the nature and content of the forensic report were examined from the forensic records. In addition, we recorded the mode of admission to the emergency department, the consultations requested in the emergency department, the mode of discharge, and the length of stay in the emergency department and hospital if admitted.

#### **Statistical Analysis**

The data were analyzed using SPSS version 21.0 (IBM, USA). Categorical descriptive data were expressed as frequency distribution and percentage; continuous variables were expressed as mean, standard deviation, median, and range. The independent samples t-test, Fisher's exact test, and Pearson's chi-square test were used for intergroup comparisons of categorical data, and p $\leq$ 0.05 was considered statistically significant.

Permission to conduct the study was obtained from the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (date: 07.09.2023, approval no: 6/11).

## Results

Of the 173.080 older adults admitted to the emergency department during the study period, 679 were forensic cases. The median age of the patients was 71 years (range, 65-107 years), and 481 (70.8%) were male. The demographic characteristics and chronic diseases of the participants are presented in Table 1. The most common chronic comorbidities were hypertension (n=306; 45.1%) and diabetes mellitus (n=117; 17.2%). The median number of diseases was 2 (range, 0-12) and the median number of drugs used was 1 (range, 0-6).

The distribution of the mode and time of admission and incident type of geriatric forensic cases evaluated in the emergency department is presented in Table 2. We observed that 51.3% of the patients were transported by ambulance, whereas the rest were transported by personal means. The most common type of forensic incident was falls (n=254; 37.4%), followed by assault (n=123; 18.1%). Of 20 trafficrelated incidents, 8 (40.0%) were drivers/occupants, and the rest were pedestrian/cyclist (n=12; 60.0%). Of the 10 intoxications, 6 (50.0%) occurred as a result of carbon

Table 1. Demographic characteristics and chronic diseases

|            | n   | %  |
|------------|---|--|
| 65-74      | 466   | 68.6   |
| 75-84      | 165   | 24.3   |
| ≥85        | 48  | 7.1  |
| Male       | 481   | 70.8   |
| Female     | 198   | 29.2   |
| HT         | 306   | 45.1   |
| DM         | 117   | 17.2   |
| CHF        | 34  | 5.0  |
| CAD        | 95  | 14.0   |
| CVD        | 13  | 1.9  |
| COPD       | 58  | 8.5  |
| Asthma     | 11  | 1.6  |
| AF         | 28  | 4.1  |
| Depression | 40  | 5.9  |
| Dementia   | 19  | 2.8  |
| CRF        | 9   | 1.3  |
| Arthritis  | 3   | 0.4  |
| Parkinson  | 16  | 2.4  |
|            | 65-74<br>75-84<br>≥85<br>Male<br>Female<br>HT<br>DM<br>CHF<br>CAD<br>CVD<br>COPD<br>Asthma<br>AF<br>Depression<br>Dementia<br>CRF<br>Arthritis<br>Parkinson | n       65-74     466       75-84     165       ≥85     48       Male     481       Female     198       HT     306       DM     117       CHF     34       CAD     95       CVD     13       COPD     58       Asthma     11       AF     28       Depression     40       Dementia     19       CRF     9       Arthritis     3       Parkinson     16 |

pertension, DM: Diabetes mellitus, CHF: Congestive hi CAD: Coronary artery disease, CVD: Cerebrovascular disease, COPD: Chronic obstructive pulmonary disease, AF: Atrial fibrillation, CRF: Chronic renal failure

monoxide (CO), 3 (25.0%) as a result of chemical inhalation, and 1 (8.3%) as a result of fungus, food, or drug exposure.

The distribution of forensic case presentations by months is presented in Figure 1. These cases occurred most commonly in the summer months of August (13.7%), July (12.4%), and June (11.9%). The injury zone distribution according to incident type is shown in Table 3. The most common injury site was the head and neck (n=270; 39.8%), followed by the upper limbs (n=186; 27.4%) and lower limbs (n=129; 19.0%). The most common sites of injury according to incident type were as follows: Head and neck in traffic accidents (n=10: 50.0%), lower limbs in firearm injuries (n=8; 61.5%), upper limbs in sharp trauma (n=8; 61.5%), head and neck in assault (n=82; 66.7%), head and neck in falls (n=106; 41.7%), upper limbs in occupational accidents (n=14; 48.3%), upper limbs in dog attacks (n=9; 62.2%), and the thorax in other animal attacks/kicks (n=27; 37.0%). The limbs of two patients with burns and electric shock were affected.

The injury type by incident type distribution is presented in Table 4. The most common types of injury were soft tissue trauma (n=251; 36.9%), bone fracture (n=170; 25.0%), and skin/mucosa laceration (n=163; 24.1%). The most common

| emergency department |                                 |     |      |  |  |
|----------------------|---------------------------------|-----|------|--|--|
|                      |                                 | n   | %    |  |  |
| Mode of              | Walk-in/personal transportation | 331 | 48.7 |  |  |
| admission            | Ambulance service               | 348 | 51.3 |  |  |
|                      | Traffic accident                | 20  | 2.9  |  |  |
|                      | Intoxication                    | 12  | 1.8  |  |  |
|                      | Firearm injury                  | 13  | 1.9  |  |  |
|                      | Sharp trauma                    | 50  | 7.4  |  |  |
|                      | Blunt trauma                    | 123 | 18.1 |  |  |
| Incident<br>type     | Fall                            | 254 | 37.4 |  |  |
|                      | Electrocution                   | 2   | 0.3  |  |  |
|                      | Occupational accident           | 29  | 4.3  |  |  |
|                      | Burn                            | 2   | 0.3  |  |  |
|                      | Suspicious death                | 4   | 0.6  |  |  |
|                      | Dog attack                      | 13  | 1.9  |  |  |
|                      | Other animal attacks            | 73  | 10.8 |  |  |
|                      | Other                           | 84  | 12.4 |  |  |
| Admission<br>time    | 00:00-08:00                     | 61  | 9.0  |  |  |
|                      | 08:00-16:00                     | 316 | 46.5 |  |  |
|                      | 16:00-00:00                     | 302 | 44.5 |  |  |

Table 2. Distribution of mode and time of admission and incident type of older forensic patients evaluated in the injury types according to incident type were as follows: Bone fracture in traffic accidents (n=9; 45.0%), soft tissue trauma in firearm injuries (n=7; 53.8%), skin/mucosa laceration in sharp trauma (n=30; 60.0%), soft tissue trauma in assault (n=50; 40.7%), bone fracture in falls (n=96; 37.8%), skin/mucosa laceration in occupational accidents (n=14; 48.3%), skin/mucosa laceration in dog attacks (n=13; 100%), and soft tissue trauma in other animal attacks/kicks (n=27; 37.0%).

The length of stay in the emergency department, treatments/consultations, and outcomes of the forensic



Figure 1. Distribution of geriatric forensic cases by months

cases are presented in Table 5. Only 13 patients (1.9%) had life-threatening injuries upon admission, and almost half had injuries that could be treated with simple medical interventions (n=329; 48.5%). The three most frequently consulted clinics were orthopedic, neurosurgery, and thoracic surgery. In total, 409 (60.2%) were discharged as outpatients, 212 patients (31.2%) were hospitalized.

## Discussion

A total of 173,080 geriatric patients presented to the emergency department of our hospital during the study period, of which 679 were forensic trauma patients. The majority of patients were male (70.8%). The most common types of forensic incidents were falls (37.4%), assault (18.1%), and sharp trauma (7.4%). The rate of traffic accidents was 2.9%, and the majority were drivers/occupants. The most common cause of intoxication (50.0%) was CO poisoning.

With the aging of the global population, the number of older people with active lifestyles has increased. This is associated with an increase in older patients admitted to hospitals because of trauma<sup>(10-13)</sup>. A study by Chang et al.<sup>(14)</sup> showed that extreme efforts are needed to diagnose and treat older adults. Therefore, traumatic injuries are less frequently overlooked.

In addition, population aging also brings about an increase in individuals with cardiovascular, pulmonary, neurological, and cognitive disorders, malnutrition,

| Table 3. Distribution of injury zones according to incident type |            |            |                    |             |             |          |
|--|------------|------------|--------------------|-------------|-------------|----------|
|  | Head/neck  | Thorax     | Abdomen/<br>pelvis | Upper limbs | Lower limbs | Spine    |
| Traffic accident   | 10 (50.0)  | 4 (20.0)   | 4 (20.0)           | 6 (30.0)    | 1 (5.0)     | 2 (10.0) |
| Intoxication   | -          | -          | -                  | -           | -           | -        |
| Firearm injury   | 1 (7.70)   | -          | 2 (15.4)           | 3 (23.1)    | 8 (61.5)    | -        |
| Sharp trauma   | 5 (10.0)   | 3 (6.00)   | 2 (4.0)            | 37 (74.0)   | 9 (18.0)    | -        |
| Blunt trauma   | 82 (66.7)  | 10 (8.10)  | 10 (8.10)          | 22 (17.9)   | 11 (8.9)    | 3 (2.4)  |
| Fall   | 106 (41.7) | 57 (22.4)  | 40 (15.7)          | 56 (22.0)   | 59 (23.2)   | 14 (5.5) |
| Electrocution  | -          | -          | -                  | 1 (50.0)    | 1 (50.0)    | -        |
| Occupational accident  | 10 (34.5)  | 3 (10.3)   | -                  | 14 (48.3)   | 6 (20.7)    | -        |
| Burn   | -          | -          | -                  | 2 (100)     | -           | -        |
| Suspicious death   | -          | -          | -                  | -           | -           | -        |
| Dog attack   | 1 (7.70)   | 1 (7.70)   | -                  | 9 (69.2)    | 3 (23.1)    | -        |
| Other animal attacks/kicks                                       | 23 (31.5)  | 27 (37.0)  | 9 (12.3)           | 9 (12.3)    | 21 (28.8)   | 1 (1.4)  |
| Other  | 32 (38.1)  | 9 (10.7)   | 2 (2.40)           | 27 (32.1)   | 10 (11.9)   | -        |
| Total  | 270 (39.8) | 114 (16.8) | 69 (10.2)          | 186 (27.4)  | 129 (19.0)  | 20 (2.9) |
| Row percentages are presented as n (%)                           |            |            |                    |             |             |          |

| Table 4. Distribution of injury type by incident type |                       |                  |                      |                               |  |  |
|---|-----------------------|------------------|----------------------|-------------------------------|--|--|
|   | Soft tissue<br>trauma | Bone<br>fracture | Tendon<br>laceration | Skin/<br>mucosa<br>laceration | Intracranial<br>hemorrhage/<br>contusion | Internal<br>organ/large<br>vessel damage |
| Traffic accident                                      | 4 (20.0)              | 9 (45.0)         | 1 (5.0)              | 2 (10.0)                      | 2 (10.0)                                 | -  |
| Intoxication  | -                     | -                | -                    | -                             | -  | -  |
| Firearm injury  | 7 (53.8)              | 2 (15.4)         | -                    | 2 (15.4)                      | -  | 2 (15.4)                                 |
| Sharp trauma  | 14 (28.0)             | 9 (18.0)         | 7 (14.0)             | 30 (60.0)                     | 1 (2.0)                                  | 1 (2.0)                                  |
| Blunt trauma  | 50 (40.7)             | 22 (17.9)        | -                    | 28 (22.8)                     | 1 (0.8)                                  | 1 (0.8)                                  |
| Fall  | 90 (35.4)             | 96 (37.8)        | -                    | 47 (18.5)                     | 2 (0.8)                                  | 8 (3.1)                                  |
| Electrocution   | 2 (10.0)              |                  | -                    | -                             | -  | -  |
| Occupational accident                                 | 11 (37.9)             | 6 (20.7)         | 1 (3.4)              | 12 (41.4)                     | -  | 4 (13.8)                                 |
| Burn  | 2 (100)               | -                | -                    | -                             | -  | -  |
| Suspicious death                                      | -                     | -                | -                    | -                             | -  | -  |
| Dog attack  | -                     | 1 (7.70)         | -                    | 13 (100)                      | -  | -  |
| Other   | 42 (50.0)             | 7 (8.30)         | 1 (1.2)              | 18 (21.4)                     | 1 (1.2)                                  | 1 (1.2)                                  |
| Other animal attacks/kicks                            | 27 (37.0)             | 18 (24.7)        | 2 (2.7)              | 14 (19.2)                     | 1 (1.4)                                  | 2 (2.7)                                  |
| Total   | 251 (36.9)            | 170 (25.0)       | 12 (1.8)             | 163 (24.1)                    | 8 (1.2)                                  | 19 (2.8)                                 |
| Pow percentages are presented as n (%)                |                       |                  |                      |                               |  |  |

Row percentages are presented as n (%)

| Table 5. Duration of hospital stay, treatment/consultations, and outcomes of forensic cases |                                     |     |      |  |  |
|---|-------------------------------------|-----|------|--|--|
|   |                                     | n   | %    |  |  |
|   | Yes                                 | 13  | 1.9  |  |  |
| Life-threatening  | No                                  | 475 | 70.0 |  |  |
|   | Unspecified                         | 191 | 28.1 |  |  |
|   | Yes                                 | 329 | 48.5 |  |  |
| Treatable through simple medical interventions  | No                                  | 142 | 20.9 |  |  |
|   | Unspecified                         | 208 | 30.6 |  |  |
|   | 0-1 hours                           | 81  | 11.9 |  |  |
| Length of stay in FD  | 1-4 hours                           | 329 | 48.5 |  |  |
| Length of stay in ED  | 4-8 hours                           | 105 | 15.5 |  |  |
|   | >8 hours                            | 164 | 24.2 |  |  |
|   | Orthopedics                         | 163 | 24   |  |  |
|   | Neurosurgery                        | 88  | 13   |  |  |
|   | Thoracic surgery                    | 87  | 12.8 |  |  |
|   | Plastic surgery                     | 29  | 4.3  |  |  |
| Consultations requested   | General surgery                     | 24  | 3.5  |  |  |
|   | Neurology                           | 11  | 1.6  |  |  |
|   | Internal medicine                   | 6   | 0.9  |  |  |
|   | Intensive care                      | 3   | 0.4  |  |  |
|   | Infectious diseases                 | 1   | 0.1  |  |  |
|   | Referral to another hospital        | 4   | 0.6  |  |  |
| Outcomes after ED treatment   | Mortality                           | 4   | 0.6  |  |  |
|   | Discharged after refusing treatment | 50  | 7.4  |  |  |
|   | Hospitalization                     | 212 | 31.2 |  |  |
|   | Discharge                           | 409 | 60.2 |  |  |
| ED: Emergency department  |                                     |     |      |  |  |

osteoporosis, electrolyte imbalance, and polypharmacy<sup>(15)</sup>. For these reasons, posttraumatic complications also increase. Delirium and infections are among the most common posttraumatic complications<sup>(15)</sup>. Low cardiac output, perioperative hypotension, postoperative hypoxia, time spent in surgery, excessive postoperative analgesia, immune suppression, and the presence of chronic comorbid diseases are factors that increase the risk of posttraumatic delirium and infection<sup>(16,17)</sup>. All of these factors necessitate close observation and multidisciplinary management of this population. In our study, we observed that consultation was frequently requested from the orthopedic, neurosurgery, and thoracic surgery departments after trauma.

Falls are among the most common causes of trauma in the elderly population. Approximately one-third of older adults die annually<sup>(18,19)</sup>. Risk factors contributing to falls include physical and mental disorders, such as osteoarthrosis, osteoporosis, visual impairments, polypharmacy, balance and gait disturbances, depression, vertigo, cognitive impairment, diabetes, and sarcopenia<sup>(20)</sup>. The frequency of osteoporosis and sarcopenia is higher in the geriatric population, thereby increasing the risk of traumatic fractures. Moreover, this procedure leads to a protracted hospitalization and rehabilitation process after injury<sup>(21)</sup>. In studies conducted in the early 2000s, the most common cause of injury in seriously injured geriatric patients was falls (50-60%), followed by motor vehicle accidents (pedestrian or driver/occupant) (9-20%)<sup>(22,23)</sup>. However, recent epidemiological studies on trauma in geriatric patients have shown a decline in the rate of injuries due to vehicle accidents and an increase in fall-related injuries<sup>(11,24)</sup>. Our study is similar to the recent literature, with falls being the most common cause of trauma (37.4%) and traffic accidents being relatively less prevalent (8%). This decline in traffic accidents as an etiology of trauma worldwide and in our country may be related to more careful urban planning and road construction and better implementation of traffic rules. In contrast, the increasing rates of assault are related to social and moral factors and are thus more difficult to regulate. Similar to our study, traffic accidents are decreasing but assault rates are increasing in countries such as South Africa<sup>(25)</sup>. In addition, because livestock farming is common in our country and especially in the region where this study was conducted, most blunt traumas in relation to animals occur in rural areas. In countries where animal husbandry is common, there is also a high rate of animal-related trauma, which is similar to the results of our study<sup>(26)</sup>.

The most commonly injured parts of the body in patients with geriatric trauma are the head and neck, upper limbs, and lower limbs<sup>(27-29)</sup>. Head and neck trauma is important for older adults because of the risk of traumatic brain injury. An increase in the frequency of falls is associated with an increase in brain injuries. The subgroup of older adults aged 75 years and older constitutes the highest risk of hospitalization and mortality<sup>(30-32)</sup>. Older adults with head trauma may present with mild symptoms. These patients can develop intracranial hematomas without any neurological deficits<sup>(33)</sup>. This may cause diagnostic delays and poor outcomes<sup>(30)</sup> and can be even more complicated in individuals using anticoagulants, such as vitamin K antagonists<sup>(34)</sup>.

Geriatric patients are usually exposed to blunt rather than penetrating trauma<sup>(35)</sup>. Animals such as cattle or horses that can kick, crush, and cause head and facial injuries are characteristically the most common causes of blunt trauma. Agricultural workers in particular face a risk of fatal injuries involving the head and body<sup>(36)</sup>. Cattle cause a significant number of trauma-related deaths worldwide. Behavior can be unpredictable even among domesticated animals, and attacks by individuals or herds are possible. Trauma due to kicking, trampling, goring, or crushing can often cause head or chest injuries. The risk of trauma and trauma-related death is higher among men living in rural areas<sup>(37)</sup>. In our study, the most frequently injured body areas were the head and neck at a rate of 39.8%, consistent with other studies, followed by the upper limbs at a rate of 27.4% and the lower limbs at a rate of 19%. We found that the head and neck region and upper limbs were most frequently affected by blunt trauma, sharp trauma, falls, dog attacks, and traffic accidents. In attacks and kicks, the thoracic region was the most frequently affected area.

In our study, 12 patients presented with intoxication, and most of these cases were CO poisoning. CO is an odorless, colorless, tasteless, non-irritant gas that is also a highly reactive and flammable molecule that mixes with air. Gas can be produced from natural or anthropogenic sources, especially as a result of incomplete fossil fuel combustion or biomass combustion. It is extremely poisonous<sup>(38)</sup>. CO exposure and poisoning can occur in environmental, occupational, and domestic settings. The causes of home exposure include fires, malfunctioning heating systems, and suicide attempts. CO poisoning and related deaths should be considered in workplaces with machines in closed and poorly ventilated areas<sup>(39)</sup>. Although there is no genderbased difference in the incidence of CO poisoning, mortality

rates are twice as high in men. The prevalence showed two distinct peaks between the ages of 0-14 and 20-39 years. The mortality rate among these patients also increases with age, peaking in those 80 years and older<sup>(40)</sup>. The geriatric status is an independent factor associated with increased mortality in CO poisoning cases. With aging, individuals become frail, and adaptive responses to stressors decrease because of increased rates of comorbid diseases and decline in physiological reserves<sup>(41)</sup>. Cardiorespiratory capacity decreases and the half-life of CO elimination increases in the elderly because of increased cardiovascular and respiratory system diseases<sup>(42)</sup>. For these reasons, older adults are more severely affected by CO poisoning and often cannot be saved due to late diagnosis. Unfortunately, sufficient studies on this topic have not been conducted in the geriatric population. Factors that may explain the high frequency of CO intoxication include the long, severe winter season and the living conditions associated with the socioeconomic level in our region.

Although women outnumber men in older populations, trauma cases are more common in men<sup>(23,24,43-46)</sup>. In our study, the majority of individuals who presented with forensic cases were men. Similar rates have also been reported in the literature. This pattern of older men being disproportionately affected by trauma may be related to their more active work and social lives.

When the seasonal distribution of the forensic cases was evaluated, we observed that most cases occurred in summer (August, July, and June). Another study showed that accident rates peaked between June and September, the hottest period of the year, and decreased in the winter months<sup>(47)</sup>. We attribute this decrease in our study to the severe winter in our region and the limited social activity during this season.

Nearly one-third of the forensic patients in our study were hospitalized after trauma (31.2%). This rate was found to be 58.4% and 57.4% in other studies conducted in our country by Yildiz et al.<sup>(48)</sup> and Akköse Aydin et al.<sup>(49)</sup>, respectively. Our findings may have differed from those of the other studies because most patients were followed up and treated in the emergency department observation room of our hospital.

## **Study Limitations**

The main strengths of our study are that it covers a long period (10 years) and includes a large number of patients. The limitations of the study are that it was retrospective and-conducted in a single center; the etiology of falls in the patients was not determined; and the medications used by the patients were not examined.

## Conclusion

The geriatric population is more affected by trauma than other age groups, and trauma-related morbidity and mortality are high among older adults. Older patients presenting with trauma should be closely followed. In our study, falls were the most common cause of geriatric trauma. Potential postfall complications can be prevented by carefully evaluating older adults at high risk of falls and taking the necessary precautions.

## Ethics

**Ethics Committee Approval:** Permission to conduct the study was obtained from the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (date: 07.09.2023, approval no: 6/11).

**Informed Consent:** Retrospective study.

## Footnotes

## **Authorship Contributions**

Surgical and Medical Practices: A.L.T., S.T.A.G., Concept: M.K., S.T.A.G., P.T.T., Design: M.E.Ş., M.K., P.T.T., Data Collection or Processing: M.E.Ş., A.L.T., S.T.A.G., Analysis or Interpretation: Ö.K., Literature Search: M.E.Ş., M.K., Ö.A., Ö.K., P.T.T., Writing: M.E.Ş., M.K., Ö.A., Ö.K., P.T.T.

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## Evaluating the Success Rate of the Online Chat-based Artificial Intelligence Program ChatGPT in Answering Basic Questions Related to Thyroid Cancer

Çevrimiçi Sohbet Tabanlı Yapay Zeka Programı ChatGPT'nin Tiroid Kanseri ile İlgili Temel Soruları Yanıtlamadaki Başarı Oranının Değerlendirilmesi

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## Abstract

**Objective:** ChatGPT, an advanced conversational bot based on artificial intelligence (AI) and a large language model, is designed to understand and generate responses to inputs. This study aims to assess the accuracy of responses provided by ChatGPT to questions that might be asked by patients concerning thyroid cancer.

**Methods:** A total of 27 questions in Turkish, relevant to thyroid cancer and likely to be asked by non-healthcare professionals, were prepared under four categories (general information, diagnosis, treatment, follow-up). These questions were posed to the free public version of ChatGPT, version 3.5. Three experts in endocrine surgery (A.C.D., S.T., Ö.M.) were asked to evaluate the responses. The answers were classified into three categories: appropriate, inappropriate, and insufficient/incomplete.

**Results:** Upon evaluating the responses given by ChatGPT to the prepared questions across the four categories, 9 responses (33.3%) were considered "appropriate" by two of the three experts and "insufficient/incomplete" by one expert. Six responses (22.2%) were deemed "appropriate" by two experts and "inappropriate" by one. Overall, a total of 16 responses (59.25%) were considered "appropriate" by at least two experts.

**Conclusion:** At this stage, AI-based conversational programs like ChatGPT are not seen as capable of replacing a specialist from whom patients receive medical advice.

Keywords: ChatGPT, thyroid cancer, artifical intelligence

in Antalya between April 24-28.



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## Öz

**Amaç:** Yapay zeka (YZ) tabanlı bir büyük dil modeli olan ChatGPT, girdileri anlayabilen ve üretebilen bir program olan gelişmiş bir sohbet botudur. Bu çalışmada tiroid kanseri ile ilgili hastaların sorabileceği sorulara ChatGPT'nin verdiği yanıtların doğruluğunu değerlendirmeyi amaçladık.

**Yöntem:** Tiroid kanseri ile ilgili sağlık profesyoneli olmayanların sorabileceği toplam dört başlıkta (genel bilgiler, tanı, tedavi, takip) 27 Türkçe soru hazırlandı. Bu sorular ücretsiz halka açık versiyon olan ChatGPT sürüm 3.5'e soruldu. Endokrin cerrahisi alanında uzman üç akademisyenden (A.C.D., S.T., Ö.M.) yanıtları değerlendirmesi istendi. Cevaplar uygun/uygun değil/ yeterli değil-eksik, şeklinde üç ayrı grupta sınıflandırdı.

**Bulgular:** ChatGPT'nin hazırlanan dört gruptaki sorulara verdiği yanıtlar genel olarak değerlendirildiğinde 27 soruya verilen 9 yanıt (%33,3), üç uzmandan ikisi tarafından "uygun", bir uzman tarafından "yeterli değil/eksik" olarak değerlendirildi. Altı (%22,2) yanıt ise iki uzman tarafından "uygun", bir

**Sonuç:** ChatGPT gibi YZ tabanlı sohbet programları hastaların medikal tavsiyeler aldığı bir uzmanın yerini alması şu aşamada mümkün görülmemektedir. **Anahtar Kelimeler:** ChatGPT, tiroid kanseri, yapay zeka

## Introduction

Large language models (LLMs) are AI products that use deep learning techniques, such as artificial neural networks, to replicate human language processing capabilities<sup>(1)</sup>. They are capable of learning and processing vast amounts of language data from various sources. ChatGPT, developed by OpenAI (OpenAI, L.L.C., San Francisco, CA, USA) as a non-profit initiative and released on November 30, 2022, is an advanced chatbot that uses a text interface to understand and generate responses<sup>(2)</sup>. The accessibility of this application at no cost has encouraged people to use it as a tool for acquiring information on various topics, including health.

The operating principle of the application involves scanning all data on the internet using keywords from the queried questions. While the internet contains much accurate information, it also hosts incorrect or misleading data. Thus, the application can present erroneous information alongside accurate data. In sensitive topics such as health, especially concerning diseases like cancer, if the application provides incorrect information, it could cause medical and psychological distress to a patient<sup>(3,4)</sup>. Consequently, it is necessary for the responses given by the application to be evaluated by expert clinicians.

According to data from the World Health Organization, thyroid cancer is the second most common cancer among women in our country, a region endemic for goitre. It follows breast cancer, with approximately 13,500 cases annually (representing 5.9% of all cancers)<sup>(5)</sup>. Given this prevalence, there is a clear need for the public to access information in Turkish about thyroid cancer, both from the internet and through the ChatGPT application. Our study aims to evaluate the appropriateness of the ChatGPT application in

answering basic questions about thyroid cancer posed by non-healthcare professionals in Turkish.

## **Materials and Methods**

A total of 27 Turkish questions were prepared in four different sections (general information, diagnosis, treatment and follow-up), which non-healthcare professionals could ask about thyroid cancer (Table 1). These questions were prompted twice in the free public version of ChatGPT 3.5 for consistency. The responses obtained were compiled using a survey via Google Forms. Three expert academicians in endocrine surgery, each holding a European Board of Endocrine Surgery certification and having a Web of Science H-index above 10, were asked to evaluate the responses provided by ChatGPT to the prepared Turkish questions on thyroid cancer.

Ethical approval was obtained for the study from the Ege University Medical Research Ethics Committee (decision no: 23-12T/32, date: 14.12.2023). An informed consent form was presented online to the three academicians, who provided their consent.

#### **Statistical Analysis**

The academicians categorized ChatGPT's responses into three groups: Appropriate, Inappropriate, and Insufficient/ Incomplete. The responses were recorded using Microsoft 365 Excel. Descriptive datasets were compiled from an excel spreadsheet for the ChatGPT answers to each question.

## Results

When evaluating the responses provided by ChatGPT to the prepared questions across four groups, of 27 responses: 9 (33.3%) were considered "appropriate" by two of the three experts and "insufficient/incomplete" by one expert. Six

responses (22.2%) were deemed "appropriate" by two experts and "inappropriate" by one expert. There were six responses (22.2%) categorized as "Insufficient/Incomplete" by two experts and "appropriate" by one. One response was judged as "appropriate" by all three experts, while another received a rating of 3 for "insufficient-incomplete". One response was assessed differently by each of the three experts (Table 2).

The number of responses found "appropriate" by at least two experts was 16 (59.2%), while the responses considered "inappropriate" by at least two experts were only 2 (7.4%). Responses labelled as "insufficient/incomplete" by at least two experts totalled 8 (29.6%).

The response to the question "My ultrasound results mention "EU-TIRADS 4". What does this mean?" under the Diagnosis section was evaluated as "appropriate" by all three experts (Figure 1). The response to "Who performs thyroid cancer surgery?" under the Treatment section was assessed differently by each expert (Figure 2). The response to "How is thyroid cancer surgery performed?" also under the Treatment section was rated as "insufficient/incomplete" by all three experts (Figure 3).

## Discussion

When existing questions were asked to traditional search engines, advertisements were typically encountered within the first one or two links. Subsequently, it was observed that the information obtained by clicking on links other than these was often hosted on health-related websites that generally lacked proper citations of sources. Accessing accurate information through traditional search engines was found to be significantly more challenging and time-consuming compared to ChatGPT. While ChatGPT is a highly effective and efficient artificial intelligence chat program, especially in scientific research and healthcare professional training due to its ability to guickly access vast information in various languages, there are still ethical issues associated with its use at the community level in addressing health problems. These include biases in data and concerns over the privacy and security of personal data<sup>(6)</sup>.

| Table 1. The question's asked to ChatGPT in the four groups                |   |   |   |  |  |
|--|---|---|---|--|--|
| General information  | Diagnosis   | Treatment   | Follow-up   |  |  |
| 1- What is thyroid cancer?   | 1- What are the symptoms of thyroid cancer?                                   | 1- How is thyroid cancer treated?   | 1- How is follow-up done after thyroid cancer surgery?                        |  |  |
| 2- How common is thyroid cancer?   | 2- How can I understand if I have thyroid cancer?                             | 2- Who performs thyroid cancer surgery?   | 2- Does thyroid cancer recur after surgery?                                   |  |  |
| 3- What factors increase the risk of thyroid cancer?                       | 3- How is thyroid cancer diagnosed?   | 3- Does thyroid cancer heal with surgery?   | 3- When I will recover and<br>return to work after thyroid<br>cancer surgery? |  |  |
| 4- Is thyroid cancer genetic?  | 4- I have a lump in my neck, do I<br>have thyroid cancer?                     | 4- How is thyroid cancer surgery performed?                                       | What happens if I don't take my thyroid medications?                          |  |  |
| 5- Is thyroid cancer fatal?  | 5- My ultrasound result reported<br>as "EU-TIRADS 4". What does this<br>mean? | 5- What are the risks of thyroid cancer surgery?                                  |   |  |  |
| 6- How can I prevent thyroid cancer?                                       | 6- Why do some thyroid cancer patients have hoarseness?                       | 6- Do all thyroid cancer patients receive radiation therapy?                      |   |  |  |
| 7- Should I undergo<br>screening for early detection<br>of thyroid cancer? |   | 7- How is radiation therapy performed in thyroid cancer?                          |   |  |  |
|  |   | 8- How is treatment done for<br>thyroid cancer that has spread to<br>lymph nodes? |   |  |  |
|  |   | 9- Why does hoarseness occur after thyroid surgery?                               |   |  |  |
|  |   | 10- Is there any treatment for thyroid cancer other than surgery?                 |   |  |  |

| Table 2. The appropriateness of the responses provided by ChatGPT to the prepared questions |               |                         |                                      |  |  |
|---|---------------|-------------------------|--------------------------------------|--|--|
| The number of experts evaluating the responses  |               |                         | The responses provided by ChatGPT to |  |  |
| Appropriate   | Inappropriate | Insufficient/incomplete | the questions                        |  |  |
| 3   | -             | -                       | 1                                    |  |  |
| -   | 3             | -                       | -                                    |  |  |
| -   | -             | 3                       | 1                                    |  |  |
| 2   | 1             | -                       | 6                                    |  |  |
| 2   | -             | 1                       | 9                                    |  |  |
| 1   | 2             | -                       | 1                                    |  |  |
| 1   | -             | 2                       | 1                                    |  |  |
| 1   | 1             | 1                       | 1                                    |  |  |
| -   | 2             | 1                       | 1                                    |  |  |
| -   | 1             | 2                       | 6                                    |  |  |
| Total   |               |                         | 27                                   |  |  |

5- The ultrasound report mentions the term 'EU-TIRADS 4'. What does this mean?

ChatGPT 3.5 Answer: "EU-TIRADS 4" refers to the *European Thyroid Imaging Reporting and Data System* (EU-TIRADS), which is a classification system used in the European Thyroid Imaging Reporting and Data System. This system is used to evaluate thyroid nodules and to determine their risk levels. It is designed to assist in determining the likelihood of malignancy in thyroid nodules and to guide clinical management accordingly.

The EU-TIRADS classification generally includes 5 categories, from 1 to 5. Here are the meanings of each category:

- 1. EU-TIRADS 1: Definitely benign nodule (non-cancerous).
- 2. EU-TIRADS 2: Probably benign nodule.
- 3. EU-TIRADS 3: Indeterminate nodule, with a higher probability of being benign.
- 4. EU-TIRADS 4: Suspicious nodule, likely benign but follow-up and possibly biopsy may be needed.
- 5. EU-TIRADS 5: Probably malignant nodule (high cancer risk), biopsy is recommended.

Therefore, a nodule classified as EU-TIRADS 4 is likely benign, but due to certain suspicious features, further evaluation and possibly a biopsy may be necessary. In this case, your doctor will likely recommend further evaluation, including fine needle aspiration biopsy and other tests. These tests help to determine whether the nodule is benign or malignant and assess the potential risk of cancer.

**Figure 1.** The question was evaluated as "Appropriate" by all three experts (the question asked of ChatGPT in Turkish is translated into English in this figure)

In the increasingly consumer-focused model of healthcare services, the unprecedented access to information could extend to patients using ChatGPT to form opinions on medical questions. A recent study revealed that 89% of people in the United States consult Google for health symptoms before visiting a doctor<sup>(7)</sup>. The popularity of the LLM-based AI chat

program ChatGPT has grown significantly over the past two years, demonstrating its potential use by patients as an access tool for health information. However, although the AI chat program ChatGPT can simplify our lives in many ways, its responses to Turkish questions about thyroid cancer, which requires specific expertise, were found to be 2- Who performs thyroid cancer surgery?

ChatGPT 3.5 Answer: Thyroid cancer surgery is usually performed by a surgeon, typically a head and neck surgeon or an endocrine surgeon. These types of surgeons are specialized professionals with expertise and experience in the thyroid gland and surrounding tissues.

Thyroid surgery can range from simple procedures such as removing thyroid nodules, to more complex operations such as the complete removal of the thyroid gland in patients with thyroid cancer. These procedures may include lobectomy (removal of one lobe), total thyroidectomy (removal of the entire thyroid gland), and if necessary, removal of nearby lymph nodes (neck dissection).

The extent of the surgery depends on several factors including the type of thyroid cancer, the size of the tumor, its spread, and the general health status of the patient. Surgery is generally part of the treatment for thyroid cancer and aims to remove the cancerous cells from the body.

Thyroid cancer surgeries are typically performed by experienced surgeons. After surgery, it is important to monitor the patient's recovery and hormone levels. Treatment may also include radioactive iodine therapy, hormone replacement therapy, or other methods. Patients are followed up and their treatment plans are adjusted as necessary by specialists such as endocrinologists (hormone doctors) or oncologists (cancer doctors).

**Figure 2.** The question was assessed differently by each expert (the question asked of ChatGPT in Turkish is translated into English in this figure)

appropriate by at least two experts in about 60% of the cases. On the other hand, a study by Zalzal et al.<sup>(8)</sup> reported that responses provided by ChatGPT to patient questions about ENT diseases were quite satisfactory. Furthermore, a study examining responses by ChatGPT to general questions found that approximately 87% of responses to 38 questions about colon cancer management were deemed appropriate and consistent by at least two independent experts<sup>(9)</sup>. Another study evaluating the appropriateness of cardiovascular disease prevention recommendations provided by ChatGPT found that 84% of the recommendations were consistent and appropriate<sup>(10)</sup>.

Köroğlu et al.<sup>(11)</sup> found the responses given by ChatGPT on the management of thyroid nodules to be mostly accurate and reliable when evaluated by two expert endocrinologists. However, they did not consider it appropriate as a primary source for physicians, suggesting it could guide patients. The lower appropriateness rates in our study compared to others might be due to our use of the Turkish language. The primary mechanism of the ChatGPT program is to analyze data sources on the internet to generate answers. The lesser availability of Turkish sources compared to sources in more frequently used languages like English could also be a factor in the inadequacy of responses<sup>(12)</sup>. Deiana et al.<sup>(13)</sup> study on myths about vaccination asked questions of both ChatGPT 3.5 and ChatGPT 4.0, finding a 17% difference in clarity between the versions, which could be a factor contributing to the unsuitability of responses in our study. The paid 4.0 version, containing improvements and updates, is likely to provide more detailed and acceptable responses than the free version used in our study.

Some studies have shown that ChatGPT has similar accuracy rates in different languages<sup>(14)</sup>, but no literature reviews have encountered a study comparing Turkish with other languages. Future studies should consider this and design their studies to include comparisons between Turkish and other languages to achieve more effective results. A study on thyroid nodules by Campbell et al.<sup>(15)</sup> found the accuracy rate of responses given by the ChatGPT application to be 69.2%, which aligns with our study, suggesting that lower accuracy rates in two studies could be topic-dependent. The appropriateness of responses given by ChatGPT on thyroid nodules and treatment may be lower than other health topics. This deficiency could be addressed over time by making more databases available to applications like ChatGPT. The readability level of responses provided by ChatGPT for community use has been indicated by international standards<sup>(16)</sup> to be higher than middle school

4- How is thyroid cancer surgery performed?

ChatGPT 3.5 Answer: Thyroid cancer surgery involves the complete or partial removal of the thyroid gland and is usually performed by head and neck surgeons or endocrine surgeons. The surgical procedure may vary depending on the type, size, and stage of the thyroid cancer. Below are the general steps involved in thyroid cancer surgery:

1. Preparation and Anesthesia:

-The patient's overall health status is evaluated before the operation. -The anesthesiologist administers general anesthesia to ensure the patient sleeps through the surgery and feels no pain.

2. Determining the Incision Site:

-The surgeon makes an incision, usually in the neck area, to access the thyroid gland. -The location of the incision may vary depending on the type of surgery to be performed (e.g., thyroid lobectomy or total thyroidectomy), the surgeon's preferences, and the patient's condition.

3. Removal of the Thyroid Gland:

-The surgeon accesses the thyroid gland through the incision. -Depending on the extent of the disease, type of cancer, and tumor size, the operation may involve removal of one lobe (lobectomy), the entire thyroid (total thyroidectomy), or part of the thyroid.

-If needed, surrounding tissues or lymph nodes may also be removed.

4. Closure:

-After removing the thyroid gland, the incision site is closed with sutures. -A surgical drain may be placed if needed.

5. Postoperative Monitoring and Care:

-The patient is monitored after surgery, and their recovery is assessed.

-Thyroid hormone levels are checked and managed accordingly.

-Radioactive iodine therapy or other treatments may be required, depending on the pathology results.

In some cases, patients may be discharged the same day, while others may need to stay in the hospital for a short period. After discharge, regular follow-up visits are scheduled to monitor hormone levels, ensure healing, and determine if further treatment is needed.

**Figure 3.** The question was assessed as "insufficient/incomplete" by all three experts (the question asked of ChatGPT in Turkish is translated into English in this figure)

level, which shows a gap in reaching the public effectively in health education. No study evaluating the language level of responses in Turkish has been found, although language level assessments have been researched in English. Future study designs are advised to consider this issue. ChatGPT, a 24/7 accessible application, has become an increasingly popular AI-based chat program for medical advice, yet it must be remembered that ChatGPT is not a medical application. If used without proper oversight in the health sector, it is expected to lead to medical and paramedical problems.

#### **Study Limitations**

This study has limitations such as the limited access to accurate data of ChatGPT due to the fact that the questions are in Turkish but most of the resources accessible on the internet are in English, the small number of academics who check the questions and meet the selection criteria, and the inability to evaluate the access to ChatGPT 4.0 (paid version).

## Conclusion

Although technological advancements are increasingly integrating artificial intelligence into our daily lives, and its usage by the public is growing, it is currently not deemed appropriate for AI-based chat programs like ChatGPT to replace medical professionals. Such programs should not provide advice on specific issues requiring professional health services, such as thyroid cancer. Certainly, as this AI program continues to evolve, it is expected to greatly benefit the health sector by providing doctors with the opportunity to save time in clinics, thereby reaching more patients effectively and offering patients 24/7 access to information. However, patients should obtain the most reliable and accurate information about their conditions through specialists in the field.

#### Ethics

**Ethics Committee Approval:** Ethical approval was obtained for the study from the Ege University Medical Research Ethics Committee (decision no: 23-12T/32, date: 14.12.2023).

**Informed Consent:** An informed consent form was presented online to the three academicians, who provided their consent.

#### Footnotes

#### **Authorship Contributions**

Surgical and Medical Practices: Y.T., B.E.B., Concept: R.G.İ., Design: Y.T., Data Collection or Processing: B.E.B., Analysis or Interpretation: B.E.B., A.C.D., S.T., Ö.M., Literature Search: B.E.B., M.Ö., Writing: Y.T., B.E.B.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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# **Rare Clinical Case: Polyorchidism**

## Nadir Klinik Olgu: Poliorşidizm

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#### Abstract

Polyorchidism is a rare embryological anomaly that encompasses various forms, such as triorchidism, and involves at least one supernumerary testis, which may reside within or outside the scrotum. Approximately 65% of cases are reported on the left side, with the majority located in the scrotal area (75%). According to the literature, no specific abnormality has been consistently associated with polyorchidism. Patients are generally asymptomatic, but they may more commonly encounter conditions, such as cryptorchidism, inguinal hernia, testicular torsion, hydrocele, varicocele, or testicular cancer. However, although polyorchidism has been recognized as an anomaly for many years, there is no consensus on its management.

Keywords: Polyorchidism, supernumerary testis, triorchidism

## Öz

Poliorşidizm, triorşidizm gibi çeşitli formları kapsayan ve skrotumun içinde veya dışında bulunabilen en az bir fazla sayıda testis içeren nadir bir embriyolojik anomalidir. Olguların yaklaşık %65'i sol tarafta bildirilmektedir ve çoğunluğu skrotal bölgede (%75) yer almaktadır. Literatüre göre poliorşidizm ile tutarlı bir şekilde ilişkilendirilen spesifik bir anormallik bulunmamaktadır. Hastalar genellikle semptomsuzdur ancak daha sık olarak kriptorşidizm, kasık fitiğı, testis torsiyonu, hidrosel, varikosel veya testis kanseri gibi durumlarla karşılaşabilirler. Ancak poliorşidizmin uzun yıllardan beri bilinen bir anomali olmasına rağmen tedavisi konusunda hala bir fikir birliği yoktur.

Anahtar Kelimeler: Poliorşidizm, fazladan testis, triorşidizm

## Introduction

Polyorchidism is a rare embryological anomaly ,which has many forms, such as triorchidism, characterized by at least one supernumerary testis (SNT) and placement in the scrotum or ectopically. Approximately 65% of cases were reported on the left side and mostly scrotal (75%)<sup>(1)</sup>.

According to the literature, no specific abnormality has been found to be associated with polyorchidism in terms of etiology. The first case in the literature was reported by Blasius in 1670 during routine autopsy. Subsequently, first described an extra testes with histological confirmation in 1895. The most commonly used classification system is the Leung classification. Patients with polyorchidism are usually asymptomatic and commonly present with cryptorchidism, inguinal hernia, testicular torsion, hydrocele, varicocele or testicular malignancy more commonly<sup>(2)</sup>. Although poliorchidism is a very well-known abnormality for decades, there is still no consensus in disease management. Written informed consent was obtained from patient.



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## **Case Report**

A 23-year-old man presented to the urology clinic with a palpable mass in the right hemiscrotum. In patient history, no comorbid disease, family history, or medication received was found.

In the scrotal examination, both the right and left testes were palpated in the scrotum. Additionally, a scrotal mass in the right hemiscrotum was detected with a similar size and was adjacent to the right testis. Subsequent to physical examination, blood tests, scrotal ultrasonography (USG), and magnetic resonance imaging (MRI) were performed to identify the mass. Blood tests showed normal serum levels of testicular tumor markers (hCG <0.20 IU/L; lactate dehydrogenase, 169 U/L, alpha fetoprotein/(AFP) 1.37  $\mu$ g/L. Scrotal USG demonstrated normal-sized right and left testises with 48x30x25 mm and 30x22x17 mm diameters, respectively, and additional SNTs with 32x29x20 mm and separated epididymis for each one (Figure 1 and 2). There



Figure 1. Ultrasounds image showed two right testes



Figure 2. Ultrasounds image showed left testis

was no evidence of hydrocele, varicocele, or inguinal hernia. MRI showed similar findings to USG (Figure 3).

After a meticulous evaluation, the patient was informed about the abnormality and potential long-term outcomes, including fertility, and the recommended conservative management. Subsequent to this consultation, follow-up with USG and examination via clinical visits (in every 6-12 months), and self-scrotal examination were planned.

## Discussion

Polyorchidism is a rare congenital genitourinary anomaly, which is defined by the presence of three or more testicles. The precise etiology of this condition remains unclear. There are many theories about the potential causes of polyorchidism, including abnormalities during division and union of the urogenital ridge and mesonephric ducts.

Triorchidism is the most common type of polyorchidism, besides case studies reported four or five testicles have also been published in the literature<sup>(3)</sup>. A recent metaanalysis concluded that the median age for diagnosis was 17 years, and the majority of cases were left-sided (65%). In addition, the most common anomalies associated with polyorchidism were inguinal hernia (30%), undescended testis (15-30%), testicular torsion (13%), hydrocele (9%), and malignancy (<1%)<sup>(1)</sup>.According to the Leung classification, there are 4 types of polyorchidism which are described as follows<sup>(4)</sup>:



Figure 3. Twice testes in the MRI image MRI: Magnetic resonance imaging

Type 1- SNT lacking epididymis or vas and no attachment to the usual testis.

Type 2- Supernumerary testes drain into the epididymis of the usual testes and share a common vas.

Type 3- SNT has its own epididymis, and both epididymis of the ipsilateral testis drain into the common vas.

Type 4- Complete duplication of the testes, epididymis and vas.

Type 2- Is considered the most common type.

The most common locations of extra testes were the sctorum (66%), inguinal canal (23%) and abdomen (9%) respectively<sup>(5)</sup>. The vast majority of the patients were asymptomatic and incidentally detected. USG is the most commonly used imaging modality, and MRI is very helpful in determining whether the diagnosis remains unclear with USG.

In the literature, no consensus has been established regarding the management of polyorchidism. However, conservative management, including clinical visits and self-examination, is recommended if scrotal placement, the absence of a concomitant disorder, and testicular tumor signs are detected<sup>(6)</sup>.

## Conclusion

Polyorchidism is a rare urogenital anomaly. USG or MRI are used in diagnosis most commonly. In decision making for treatment strategies, the location of SNT, concomitant disorders, and the existence of a potential testis neoplasm must be evaluated.

## Ethics

**Informed Consent:** Written informed consent was obtained from patient.

#### Footnotes

#### **Authorship Contributions**

Surgical and Medical Practices: A.E.C., M.U., Concept: O.Ö., A.E.C., Design: M.U., Data Collection or Processing: O.Ö., M.U., Literature Search: A.E.C., M.U., Writing: O.Ö., M.U.

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## Intestinal Lipomatosis of the Ileum: A Rare Cause of Small Bowel Perforation

İleumun İntestinal Lipomatozisi: İnce Bağırsak Perforasyonunun Nadir Bir Nedeni

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#### Abstract

Intestinal lipomatosis is characterized by submucosal infiltration of mature adipose tissue, which is usually asymptomatic and can be detected incidentally. However, it may cause complications, such as intussusception, bleeding, and perforation. We describe a 12-year-old female patient who underwent surgery after the detection of intestinal perforation on abdominal computed tomography. Histopathologic examination of segmentary small bowel resection revealed a lesion predominantly located in the submucosa, occasionally causing atrophy in the muscle tissue and extending to the serosa. The lesion consisting of mature lipocytes was completely unencapsulated. Based on these findings, the patient was diagnosed with intestinal lipomatosis. Intestinal lipomatosis is usually asymptomatic and can be detected incidentally. However, it can lead to complications, such as intussusception, bleeding, and perforation, and these clinical conditions may be the first signs of the lesion, as in our case.

Keywords: Intestinal lipomatosis, ileum, intestinal perforation, intussusception

#### Öz

İntestinal lipomatozis, genellikle asemptomatik olan ve insidental olarak saptanan, tümör oluşumu olmaksızın matür adipöz dokunun submukozal infiltrasyonu ile karakterize lezyonlardır. Ancak invajinasyon, kanama ve perforasyon gibi komplikasyonlara neden olabilir. Bu olgu sunumunda, batın bilgisayarlı tomografisinde bağırsak perforasyonu saptanması üzerine opere edilen 12 yaşında kız hasta sunulmaktadır. Segmenter ince bağırsak rezeksiyonunun histopatolojik incelemesinde ağırlıklı olarak submukoza yerleşimli, yer yer kas dokuda atrofiye neden olan ve serozaya uzanım gösteren lezyon gözlenmiştir. Matür lipositlerden oluşan lezyon bütünüyle kapsülsüz görünümdedir. Bu bulgularla olguya intestinal lipomatozis tanısı konulmuştur. İntestinal lipomatozis genellikle asemptomatiktir ve rastlantısal olarak tespit edilir. Ancak invajinasyon, kanama, perforasyon gibi komplikasyonlara yol açabilmekte ve bu klinik durumlar bizim olgumuzda olduğu gibi lezyonun ilk belirtisi olabilmektedir.

Anahtar Kelimeler: İntestinal lipomatozis, ileum, intestinal perforasyon, intussusepsiyon

## Introduction

Intestinal lipomatosis refers to lesions characterized by submucosal infiltration of mature adipose tissue without the formation of a tumor<sup>(1)</sup>. Unlike lipoma, intestinal lipomatosis is not encapsulated lesions<sup>(2)</sup>. Adipose tissue proliferation

and deposition are usually limited to the submucosa but may also extend to the serosa and mesenteric adipose tissue<sup>(3)</sup>. The cause of fat deposition is unclear<sup>(4)</sup>. Intestinal lipomatosis does not show sex predominance and usually occurs after the fourth decade of life<sup>(5)</sup>. The most common



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location of lipoma is the colon (65-75%), while the ileum is the second most common location<sup>(6)</sup>. In the literature, no predilection site for lipomatosis has been described<sup>(1)</sup>. Intestinal lipomatosis is usually asymptomatic and can be detected incidentally. However, it may cause complications, such as intussusception, bleeding, and perforation, and these clinical manifestations may be the first signs of the lesion<sup>(7)</sup>. Lipomatosis of the gastrointestinal tract is rare, and only few cases have been reported<sup>(1)</sup>. Because it is a rare entity and, as in our case, complications, such as perforation, may be the first presentation finding, we herein report a case of intestinal lipomatosis.

## **Case Report**

A 12-year-old girl presented to the emergency department with complaints of vomiting and abdominal pain that persisted for 2 days. It was explained that the patient had previously been followed up for chronic constipation. The examination revealed no findings except minimal tenderness in the umbilical region. The patient was operated upon the detection of intestinal perforation on abdominal computed tomography. Segmentary small bowel resection was performed because of the large perforation area in the middle part of the ileum and stool in the abdomen during the operation. In the gross examination of the small bowel resection, a perforation area of 7.5 cm in diameter was observed, and the segment adjacent to the perforation was found to have a dilated appearance. The mucosa of the dilated segment was hyperemic in places, with an area of approximately 3 cm in diameter, paler color, and flattening

of the mucosa. In the cross-section of this area, the intestinal wall was yellow under the mucosa (Figure 1). Microscopic examination revealed mucosal ischemic changes in the dilated segment. In areas adjacent to the perforation, where the mucosa was flattened and pale in appearance, a lesion was observed predominantly located in the submucosa, occasionally causing atrophy in the muscle tissue and extending to the serosa. The lesion, consisting of mature lipocytes, including congested vessels and connective tissue areas, was completely unencapsulated (Figure 2).



**Figure 1.** Perforation area with a diameter of 7.5 cm (A), hyperemic mucosa in the dilated segment and the adjacent pale-looking area (B), and cross-section of the pale-looking area (C, D)



**Figure 2.** A lesion consisting of mature lipocytes in the submucosa (A, B; x20), unencapsulated lesion, and ischemic changes in the superficial mucosa (C, D; x20, x40), areas where the lesion causes muscle tissue atrophy and extends to the serosa (E, F; x40)

In many samples of the material, submucosal adipose tissue was observed only in this segment. Based on these findings, the patient was diagnosed with intestinal lipomatosis. Informed consent was obtained.

## Discussion

Abnormal deposition of mature adipose tissue in the intestine occurs in four different ways. The first category includes single and well-circumscribed lipomas, while the second category includes cases that present as multiple well-circumscribed lipomas. The third type of abnormal adipose tissue deposition is diffuse nodular lipomatosis, which is characterized by numerous nodules growing into the lumen leading to an increase in the irregular intestinal wall thickness. The fourth form, called intestinal lipomatosis, refers to lesions characterized by submucosal infiltration of mature adipose tissue without tumor formation<sup>(8)</sup>. Although intestinal lipomatosis is usually asymptomatic and can be detected incidentally, it can lead to complications, such as intussusception, bleeding, and perforation, and these clinical conditions may be the first signs of the lesion<sup>(7)</sup>. The most common symptoms in symptomatic patients are non-specific abdominal pain, constipation, diarrhea, and bleeding<sup>(2)</sup>. Although our case was followed up with a complaint of chronic constipation, surgical treatment was applied because of ileum perforation, which was only diagnosed in this way. Due to its rarity, there are no current guidelines for the selection of imaging modalities for intestinal lipomatosis. Surgical treatment may be required in patients who present with complications and do not respond to conservative measures<sup>(9)</sup>.

The term "intestinal lipomatosis" is used by some authors to describe cases of multiple lipomas<sup>(6,10,11)</sup>. However, in some publications, this refers to unencapsulated lesions characterized by submucosal infiltration of mature adipose tissue without tumor formation, unlike lipomas<sup>(2)</sup>. We propose that these two distinct morphological appearances may represent separate entities with different pathogenesis: a neoplastic process and a developmental abnormality. This terminological confusion could be clarified through the reporting of new cases and a better understanding of the pathological and molecular features distinguishing the two groups.

## Ethics

Informed Consent: Informed consent was obtained.

#### Footnotes

#### **Authorship Contributions**

Surgical and Medical Practices: H.İ.T., Concept: Ö.A., S.A., Design: Ö.A., S.A., Data Collection or Processing: Ö.A., S.A., P.T., H.S.M., Analysis or Interpretation: Ö.A., S.A., P.T., Literature Search: Ö.A., P.T., H.S.M., Writing: Ö.A., S.A., P.T.

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