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**RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ**

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EDITORIAL

EDİTÖRYAL

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# Lipid lowering and additional pleiotropic effects of statins.

## Lipid düşürücü ve pleiotropik etkileriyle statinler.

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**ABSTRACT**

Statins are among the most commonly prescribed drugs worldwide today. They are primarily effective in primary and secondary prevention of cardiovascular diseases with their cholesterol-lowering properties. Recent studies have reported that statin derivatives have positive outcomes in different clinical conditions with different mechanisms, in addition to their lipid-lowering effects. In this paper, we aimed to discuss the pleiotropic effects of statins in addition to their protective effects in cardiovascular practice.

Key Words: Pleiotropic effects, statins, antihyperlipidemic

**ÖZ**

Dünya çapında statinler günümüzde en sık reçetelenen ilaçlar arasında yer almaktadırlar. Temel olarak kardiyovasküler hastalıklardan birincil ve ikincil korunmada kolesterol düşürücü özellikleriyle etki göstermektedirler. Son zamanlarda yapılan çalışmalarda statinler türevi ilaçlarla mevcut olan lipid düşürücü etkilerinin yanında farklı klinik durumlarda farklı mekanizmalarla olumlu sonlanımlar elde edildiği bildirilmiştir. Bu yazımızda statinlerin kardiyovasküler hastalıklardaki koruyucu etkileri dışında pleiotropic etkilerinden de bahsetmeyi amaçladık.

Anahtar Kelimeler: Pleiotropik etki, statinler, antihiperlipidemik

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Serum cholesterol levels, particularly LDL cholesterol, are closely related to the development of atherosclerotic cardiovascular disease. Many randomized clinical trials investigating lipid-lowering treatments have found that lowering LDL cholesterol reduces the incidence of atherosclerotic cardiovascular disease. Statins (3-hydroxy-3methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) decrease serum cholesterol levels, primarily LDL cholesterol. The role of statins in primary and secondary prevention of cardiovascular diseases has long been proven in clinical studies. Some of these beneficial effects are independent of LDL cholesterol decrement and have been described as pleiotropic effects. Pleiotropy associated with statins has been investigated not only in the cardiovascular system but also in non-cardiovascular conditions. Through cellular and molecular mechanisms that have not yet been fully elucidated, statins have shown beneficial effects in renal function, infectious diseases including sepsis, rheumatic diseases, gastrointestinal diseases, neurological disorders, periodontal diseases, bone fractures, and malignancies [1]. In this mini-review, we aimed to summarize the cardiovascular and non-cardiovascular pleiotropic effects of statins, in addition to the cardiac protection they provide through their LDL cholesterol lowering effects.

Statin dosage of patients with a very high risk profile should be adjusted depending on the presence of atherosclerotic heart disease. According to 2021 European Society of Cardiology (ESC) Guidelines about Cardiovascular Disease Prevention, the target LDL cholesterol level should be <55 mg/dL (<1.4 mmol/L) in patients with established aterosclerotic heart disease or in type 2 diabetes mellitus patients with a very high risk profile [2]. Potent statins such as atorvastatin (40-80 mg/day) or rosuvastatin (20-40 mg/day) should be chosen to prevent adverse coronary events in patients with a very high risk. Beside LDL cholesterol lowering effect, potent statins stabilize unstable coronary plaques in acute coronary syndrome patients [3].

Statins reduce the incidence of perioperative cardiac events in high-risk cardiovascular surgery patients. However, there is limited data on the perioperative role of statins in intermediate-risk noncardiac, nonvascular surgery patients. Raju MG et al. reported in their retrospective study involving 752 patients, statin usage was associated with a lower composite endpoint of in-hospital nonfatal myocardial infarctus, new onset atrial fibrillation, and 30-day all-cause mortality [4]. Despite the widespread use of statins in patients undergoing surgery, the results of randomized controlled trials on the effects of starting statins in the perioperative period are not clear. Therefore, routine initiation of statins in the perioperative period is not recommended. However, in patients undergoing high-risk surgery, such as vascular surgery, initiation of statins in the perioperative period is recommended [5].

The blood-brain barrier is the most centrally located point of the neurovascular structure and plays a key role in the maintenance of internal continuity of the central nervous system and the regulation of homeostasis. The role of the blood-brain barrier in the development and progression of ischemic stroke has been demonstrated. Various neuroprotective drugs have been researched to provide neuroprotective effects and improve prognosis in ischemic stroke patients. It has been shown that statins improve neurological functions, reduce inflammation, and increase angiogenic and synaptic connections in ischemic stroke patients. It has also been determined that statins have protective and reparative effects on the blood-brain barrier via components of the neurovascular unit [6].

Some specific types of cancer that use the mevalonate pathway associated with the HMG-CoA reductase enzyme have been shown to benefit from statin therapy. It has been suggested that these beneficial effects may be independent of cholesterol reduction [7]. In another study involving breast cancer patients, statin use after breast surgery was found to be associated with less metastasis onset, fewer metastatic foci, less death, longer metastasis-free survival, and greater overall survival percentage [8]. In the subgroup analysis according to type of statin used, rosuvastatin, a relatively hydrophilic statin, was observed to have more positive clinical outcomes than the others.

Although current treatment approaches such as immobilization, surgery, and bone grafting are effective in bone fractures, they have disadvantages such as long recovery periods and high costs. The biological agents, pharmacological treatments, and physical stimulation techniques that are being studied have also high costs, possible side effects, and practical difficulties. Low-cost, safe, and easy-to-apply alternative treatment options are needed in this context. Recent studies have reported that statins accelerate bone healing through increase in bone formation and reduction in bone resorption via various biochemical pathways [9]. Another issue concerning bone tissue is the osteonecrosis of femoral head. Patients who use steroid for a long period are particularly at risk for this. Adipogenesis and mitochondrial cardiolipin metabolism disruption can play role in the development of osteonecrosis of the femoral head [10]. In vitro and animal studies have shown that statin use may have a positive effect in preventing the development of osteonecrosis of the femoral head due to steroid use [11]. Prospective, long-term clinical studies are needed to examine this protective effect of statins [12].

We believe that the role of statin derivatives, which have been used in our clinical practice so far due to their lipid lowering effects in primary and secondary prevention of cardiovascular diseases, will increase with further studies on their pleiotropic effects in cardiovascular and non-cardiac conditions.

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RESEARCH ARTICLE

ARAŞTIRMA MAKALESİ

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# Efficacy of Unilateral Greater Occipital Nerve Block in Migraine Management: A Focused Approach for Targeted Relief

## Migren Yönetiminde Unilateral Büyük Oksipital Sinir Blokajının Etkinliği: Hedefe Yönelik Yaklaşım

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## ABSTRACT

**Aim:** Migraine is one of the most common and disabling neurological disorders, causing a great deal of suffering both from an individual perspective and a public health point of view. Patients often suffer from either lack of efficacy or adverse reactions of oral treatments. The Greater occipital nerve (GON) block has recently come forward as a potentially useful choice for migraines. This study, therefore, assessed unilateral GON block to treat migraine.

**Methods:** A total of 35 patients with migraine were included in this prospective study. The frequency, duration, pain severity and analgesic consumption of headaches were evaluated at baseline and 1 week, 1 month and 3 months post-treatment in GON block. The primary outcome measures included changes in the number of migraine attacks, duration, and the severity of pain using a visual analogue scale (VAS).

**Results:** A substantial decrease was shown in the median number of migraine attacks, from 12 at baseline to 3 at month 3 ($p=0.007$). The mean duration of migraine attacks reduced from 12 hours at baseline to 3 hours at month 3 ($p < 0.0001$), and the mean VAS score was improved from 10 at baseline to 4 at month 3 ($p < 0.0001$). There was also a significant reduction in analgesic use from 12 at baseline to 2 doses per month ($p=0.005$).

**Conclusion:** Our results show that unilateral GON block is an efficient and well-tolerated intervention for migraine patients, significantly decreasing headache frequency, intensity and duration.

Keywords: Migraine, Greater occipital nerve block (GON), Visual analogue scale (VAS)

## ÖZ

**Amaç:** Migren hem bireysel açıdan hem de halk sağlığı perspektifinden büyük acılara neden olan en yaygın ve engelleyici nörolojik bozukluklardan biridir. Hastalar, genellikle ağızdan alınan tedavilerin ya etkinlik eksikliği ya da yan etkileri nedeniyle sıkıntı yaşamaktadır. Son zamanlarda, Büyük oksipital sinir (greater occipital nerve-GON) blokajı migren tedavisinde potansiyel bir seçenek olarak öne çıkmıştır. Bu çalışma, bu nedenle, migren tedavisinde tek taraflı GON blokajını değerlendirmiştir.

**Yöntem:** Bu prospektif çalışmaya toplam 35 migren hastası dahil edilmiştir. Başlangıçta ve GON blokajı tedavisinden sonra 1 hafta, 1 ay ve 3 ayda baş ağrılarının sıklığı, süresi, ağrı şiddeti ve analjezik kullanımını değerlendirilmiştir. Birincil sonuç ölçütleri, migren ataklarının sayısındaki, süresindeki ve görsel analog skala (visual analogue scale- VAS) kullanılarak ölçülen ağrı şiddetindeki değişiklikleri içermektedir.

**Bulgular:** Migren ataklarının ortanca sayısının başlangıçta 12'den 3. aya kadar üçe düştüğü görülmüş ve anlamlı bir azalma gösterilmiştir ($p=0.007$). Migren ataklarının başlangıçtaki ortalama süresi 12 saatten 3. ayda 3 saate düşmüş ($p < 0.0001$) ve başlangıçtaki ortalama VAS skoru 10'dan 3. ayda 4'e iyileşmiştir ($p < 0.0001$). Ayrıca, alınan analjezik ilaç sayısı da başlangıçtaki 12 iken, 3. ayda 2'ye gerilemiştir ($p=0.005$).

**Sonuç:** Sonuçlarımız, migren hastaları için tek taraflı GON blokajının, baş ağrısı sıklığını, şiddetini ve süresini önemli ölçüde azaltan etkili ve iyi tolere edilen bir müdahale olduğunu göstermektedir.

Anahtar Kelimeler: Migren, Büyük oksipital sinir blokajı (GON), Vizüel analog skala (VAS)

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## Introduction

Migraine is a common neurological disorder characterized by recurrent attacks of headaches, nausea, vomiting, and photophobia [1]. Despite being less prevalent than chronic migraine, episodic migraine has a major impact on the quality of life and impairs productivity [2]. Migraine has traditionally been treated with medications such as triptans and prophylactic agents, as well as lifestyle changes and behavioral interventions [3]. However, with these choices, many patients continue to suffer from inadequate responses and side effects of medications, such as medication overuse, also known as rebound headache, which is a secondary headache disorder caused by the frequent or excessive use of acute headache medications. [4].

A potentially promising alternative in the treatment of migraine is the greater occipital nerve (GON) block, consisting of an anesthetic injection around a target area near the GON [5]. This helps to block the painful signals developed by the nerve, which further helps to treat migraine headaches [6]. However, most studies have reported bilateral GON blocks (i.e., both sides are treated). Although unilateral GON blockade directed at one side has been introduced and investigated in previous studies [7], its effectiveness has not been well established.

The purpose of this study was to determine the effectiveness of unilateral GON block in patients with episodic migraine. This approach may better delineate potential efficacy and adverse effects, offering important guidance to clinicians in the search for efficacious and patient-friendly migraine therapies. This study seeks to contribute to the growing body of evidence supporting GON block as a viable intervention for migraine management.

## Materials and Methods

The demographics of patients who were treated in the outpatient headache clinic of Haydarpaşa Educational and Research Hospital with a diagnosis of episodic migraine were reviewed prospectively after approval by the Ethics Committee (approval number: 2019/151) in accordance with the Declaration of Helsinki. The study period was October 2020 to October 2023. Eligible patients comprised those over 18 and under 65 years diagnosed with migraine according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) who had received unilateral GON block [8]. The exclusion criteria were prior allergic reactions, craniocervical surgery before or in this study, hemorrhagic diathesis (anticoagulant treatment), superficial infection of the area where GON blockade would be performed, not giving consent to the study, and incomplete medical records. Forty patients who met all inclusion criteria were included in the study. Patients who did not complete the 3-month follow-up period or those with missing medical data were excluded from the study. Eventually, the study included 35 patients. (Fig.1)

The study was followed by a patient-maintained headache diary, which noted the duration and days of occurrence (frequency rate) as well as severity on the visual analog scale (VAS) before and after treatment. The visual analog scale (VAS) assesses pain on a scale of 0 to 10, where 0 = no pain and 10 = the worst imaginable for both acute and chronic pain patients. Outcome measures were collected at three time points: baseline (pre-first GON block) and 1st and 3rd months post-treatment. The main outcomes were mean differences in headache frequency, duration, severity, and analgesic consumption. The outcomes were assessed at baselining and 1st month and 3rd month post-treatment, respectively.

The GON block protocol was used to mirror the process prior to each experimental session. The external occipital protuberance was palpated to identify the point of the injection. After disinfection of the antiseptic solution at the site of interest. Two milliliters of 2% lidocaine was injected suboccipitally to the area 2 cm lateral and inferior from the occipital protuberance (long-axis view) using a final common needle gauge for all patients along with a puncture point located at the occipital protuberance. Patients were monitored for 30 minutes after the procedure to record any immediate adverse effects. The GON block was repeated on a weekly basis for the first month and then once monthly for two additional months [9, 10].

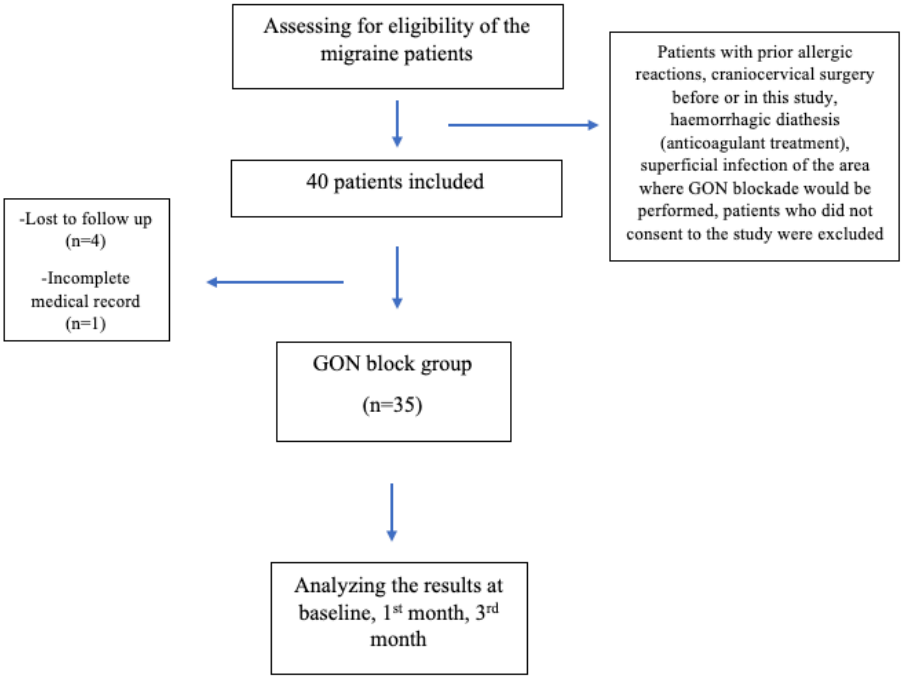


Figure 1. Flowchart of migraine patients

### Statistical Analysis

Quantitative data were analyzed using IBM SPSS Statistics version 21. All data were summarized using descriptive statistics, with categorical variables displayed as frequency (n and %) and continuous variables as mean (SD) and median (interquartile range [IQR]; 25th-75th percentiles). Data distribution normality was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. As the data were not normally distributed, the Wilcoxon signed-rank test within-group comparisons were performed. Differences were considered statistically significant at a p-value of $< 0.05$.

## Results

A total of 35 patients were included in the study, with 32 (91.4%) females and 3 (8.6%) males in the unilateral GON blockade group. The prevalence of medication overuse was 45.7% (n=16). Prophylactic treatment was used by 51.4% (n=18) of patients in the unilateral group. Patient characteristics are detailed in Table 1.

The median number of migraine attacks also decreased significantly. At baseline, migraine attacks were 12 (6-15) per month, which decreased to 1, 3, and 3 at weeks 1, 1, and 3, respectively. In contrast, the patients showed a significant reduction in the median number of analgesics. The mean analgesic use (12 at baseline) decreased to 1, 4, and 2 at weeks 1, 1, and 3, respectively.

Moreover, the duration of migraine attacks significantly decreased from a median of 12 (6-15) hours at baseline to 1 (1-3) hours at Week 1 ($p<0.0001$) to 3 (2-8) hours at Month 1 ($p<0.0001$) and to 3 (2-4) hours at Month 3 ($p<0.0001$). The median VAS scores in the patients decreased from 10 (8-10) at baseline to 6 (2-7) at weeks 1 to 5 (4-8) at months 1 and 4 (3-6) at month 3. The results are presented in Tables 2 and 3.

In comparison with baseline, at week 1, month 1, and month 3 of the monthly follow-up, unilateral GON blockade showed a statistically significant improvement in attack number, analgesic usage, and attack duration ($p <0.0001$ for all). No side effects were observed in any of the patients.

## Discussion

This study aimed to provide a comprehensive evaluation of unilateral GON block in the management of patients with episodic migraine. The results validate the supposition that one

Table 1. The patients demographic and clinical features: Gender, Mean of patients age, medication overuse, prophylactic treatment given.

| | Unilateral GON Block n (%) |
|---|---|
| **Gender** | |
| Female | 32 (91,4) |
| Male | 3 (8,6) |
| **Medication overuse** | |
| Yes | 16 (45,7) |
| No | 19 (54,3) |
| **Prophylactic treatment** | |
| Yes | 18 (51,4) |
| No | 17 (48,6) |
| **Mean of patients age** | |
| Female | 40,97 |
| Male | 34.25 |

Unilateral GON: Great Occcipital Nerve Blok performed in one side

Table 2. Statistical evaluation of initial values and values at months 1, and 3 for VAS, attack duration, and monthly number of attacks and analgesics.

| | Initial- Week 1 ($p^{**}$) | Week 1- Month 1 ($p^{**}$) | Month 1-Month 3 ($p^{**}$) |
|---|---|---|---|
| Number of attacks | <0,001 | <0,001 | 0,006 |
| Number of analgesics | <0,001 | <0,001 | 0,003 |
| Attack duration | <0,001 | <0,001 | 0,006 |
| VAS | <0,001 | 0,29 | 0,006 |

VAS (Visual analogue scale) *: Wilcoxon test

Table 3. Median values of initial, values at months 1, and month 3 for VAS, attack duration, and monthly number of attacks and analgesics.

| | Initial Median Value (Median (25p-75p) | p* | Median Value Week 1 (Median 25p-75p) | p* | Median Value Month 1 (Median 25p-75p) | p* | Median Value Month 3 (Median 25p-75p) | p* |
|---|---|---|---|---|---|---|---|---|
| Number Of Attacks | 12 (6-15) | 0,45 | 1 (1-3) | 0,25 | 3 (2-8) | 0,27 | 3 (2-4) | 0,007 |
| Number Of Analgesics | 12 (8-30) | 0,91 | 0 (0-2) | 0,18 | 4 (2-8) | 0,21 | 2 (1-5) | 0,005 |
| Attack Duration | 12 (6-15) | 0,001 | 1 (1-3) | <0,001 | 3 (2-8) | <0,001 | 3 (2-4) | <0,001 |
| VAS | 10 (8-10) | 0,33 | 6 (2-7) | 0,45 | 5 (4-8) | 0,72 | 4 (3-6) | 0,04 |

VAS (Visual analogue scale) * Mann Whitney-u Test

side of the GON block has the ability to improve headache as well as decrease its frequency of attack duration and intensity; therefore, it seems to be a beneficial treatment in patients with episodic migraine.

This reduction in headache frequency was consistent with prior work on bilateral GON blocks, which consistently demonstrated significant decreases in headache days per month following the treatment. Of note, our study extends these findings by showing that even a unilateral approach can produce equivalent improvements and may therefore offer a less invasive intervention for the management of migraines. An estimated 4 million patients with headache have chronic daily headaches, the most disabling form of migraine [11].

An improvement in the number of headache days is important when considering overall patient health and well-being. Fewer days of headache not only diminishes the immediate load of pain but also reduces many comorbidities such as anxiety, depression, and medication overuse [12]. We observed a significant decrease in analgesic drug use in our patients.

The choice to use a unilateral model in this study was a decision that must be mindful of. Although widely practiced using the traditional method, bilateral GON blocks are associated with headache

or soreness on both sides as a common side effect. The rationale for utilizing a less invasive treatment approach, such as unilateral GON, included the expectation of at least equivalent effectiveness with respect to robust pain reduction and inconsequential rates of adverse events that are characteristic of bilateral interventions.

This was confirmed by our results in that the side effects were minimal and tolerable if GON blockade was performed unilaterally. It is in contrast to some literature on bilateral GON block that showed effectiveness; however, complications like bilateral soreness, discomfort, etc. can result in discomfort and less patient satisfaction [13, 14]. The lower risk profile associated with unilateral GON may render it a more appropriate choice for patients who are acutely sensitive to side effects or have contraindications to, and cannot tolerate, more aggressive treatments.

Whereas the bilateral GON block refers to bringing treatment to both sides, the unilateral GON block is situated only on one side. The approach was chosen because it would allow sufficient pain control with a low incidence of side effects [15]. Bilateral GON block may result in bilateral pain or collateral pain and discomfort (pain related to interscalene brachial plexus nerve block), which could be distressing for patients. The single GON block was found to be associated with no statistically significant adverse effects in our study, and we believe that this makes it a safer alternative for patients.

A major effect of our study was the decrease in analgesic intake after the unilateral GON block. This is an important consideration in the management of migraine, which is common and where medication overuse occurs. It occurs when a person uses acute or symptomatic medications too frequently, leading to worsening of symptoms rather than relief. Analgesic overutilization not only predisposes patients to medication-overuse headache, but also places a patient with serious medical difficulty with regard to overall headache management, usually associated with a vicious cycle of chronic pain and medication dependability [16].

Our data suggest that the GON block unilaterally is beneficial in reducing frequent requirements of analgesics, which breaks this cycle and helps prevent the development of medication-overuse headaches. The decrease in the consumption of analgesics underlines the increase in patient comfort after treatment. We showed that mean analgesic use decreased from 12 at baseline to 1 at week 1, 4 at month 1, and 2 at month 3. This finding suggests that GON blockade is not only effective in pain control but may also form part of the effort toward reducing analgesic dependence. The decrease in analgesic requirement could be due to the longer duration of action of nerve block, which lowers the acute need for pain medication. These findings have important implications by demonstrating that in addition to the acute effect of reducing migraine pain, unilateral GON block could contribute to long-term treatment stability and lower healthcare utilization.

The noteworthy reduction in headache duration and intensity also confirms the effectiveness of unilateral GON block. This led to shorter and milder migraine attacks. One of the key determinants for increasing functionality and subsequently relieving not only daily functioning, but also decreasing the overall burden of migraine in patients. In our study, we showed that treatment likewise significantly shortened the duration of migraine attacks from a median of 12 hours (6-15) at baseline to 1 hour (1-3) at week 1, 3 hours (2-8) at month 1, and 3 hours (2-4) at month 3. Moreover, there was a marked improvement in the VAS scores, with median values decreasing from 10 (8-10) at baseline to 6 (2-7) at week 1, 5 (4-8) at month 1, and 4 (3-6) at month 3. These findings indicate a robust effect on the reduction in attack severity over time. The more disabled the patients, the greater their severity and duration. A unilateral GON block can reduce headache frequency and severity and could therefore be used as a more general treatment modality, especially if patients do not respond to or cannot tolerate pharmacological therapies [17, 18].

### Future Directions

Although this study provides new insights into the concept of unilateral GON block in patients with migraine, further studies are needed to explore its long-term benefits and modes of action. Although the exact physiological basis for symptomatic

relief following a GON block remains to be fully understood, speculations include effects on nociceptive pathways or central pain processing. It is also of interest to research the use of unilateral GON blocks in other headache disorders. Future research should also compare the effect of unilateral versus bilateral GON block in larger and more heterogeneous patient populations and guide practitioners toward more personalized treatments for patients with migraine.

## Conclusion

In conclusion, unilateral GON is an effective and well-tolerated treatment intervention for patients with migraine headache. This convincingly adds to the clinical trial evidence that it works and leads to a large drop in headache frequency, duration, and severity, as well as a reduced need for acute analgesics. The results highlight that unilateral GON block is a safe and effective therapeutic intervention that may serve as an alternative to other more invasive or systemic treatments owing to its favorable safety profile. Subsequent prospective studies on unilateral GON block might be directed towards investigating the long-term benefits, mechanisms of action, and its use in other types of headache disorders.

## Limitations

An episodic/chronic migraine subgroup analysis could not be performed because of the small sample size. The absence of a control group is a limitation of this study as it prevents direct comparisons and may affect the generalizability of the findings. The presence of auras was not mentioned because patients interpreted prodromes as auras, and the duration of the condition was not mentioned because the patients reported a wide window.

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# External Fixator Applications in Phalanx and Metacarpal Bone Fractures

## Falanks ve Metakarpal Kemik Kırıklarında Eksternal Fiksatör Uygulamaları

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## ABSTRACT

**Objective:** Hand injuries can be a great source of stress and a cause of disconnection from life by negatively impacting the work that patients do in their daily lives. This study aimed to evaluate the presence of fracture union and deformity in patients operated on with a mini external fixator for metacarpal and phalanx fractures in our institution.
**Method:** A total of 148 patients who underwent external fixation due to phalanx and metacarpal bone fractures were retrospectively evaluated. The patients' radiographic examinations were performed, and fracture union and deformity were evaluated. The results were clinically assessed by applying joint movements and scoring the Total Active Joint Range of Motion (Strickland-Glogovac finger function scale).
**Results:** The patients were operated on within the first three days after their trauma; 17 (15.3%) of the patients had metacarpal fractures, 94 (84.7%) had phalanx fractures, 8 (47%) of the metacarpal fractures were 2nd metacarpal fractures, and 26 (27.6%) of the 94 patients with phalanx fractures had 5th finger fractures. According to the Strickland–Glogovac finger function scale, the number of patients with active joint range of motion >150 (excellent) was 45, the number of patients with 125–149 (good) was 36, the number of patients with 90–124 (moderate) was 20, and the number of patients with <90 (poor) was 10. In total, excellent and good results were found in 81 patients.
**Conclusion:** Mini external fixators should be preferred more frequently among surgical options for tubular bone fractures of the hand because they are easy to apply, have satisfactory stability, are safe, allow for painless early mobilization, and provide versatility in treatment options.

Keywords: external fixation, mini external fixator, phalanx fracture, metacarpal fractures, K–wire

## ÖZ

**Amaç:** El yaralanmaları, hastaların günlük yaşamlarında yaptıkları işleri olumsuz etkileyerek büyük bir stres kaynağı ve yaşamdan kopma nedeni olabilir. Bu çalışma, kurumumuzda metakarpal ve falanks kırıkları için mini harici fiksatörle ameliyat edilen hastalarda kırık kaynaması ve deformitenin varlığını değerlendirmeyi amaçlamıştır.
**Yöntem:** Falanks ve metakarpal kemik kırıkları nedeniyle harici fiksasyon uygulanan toplam 148 hasta retrospektif olarak değerlendirildi. Hastaların radyografik muayeneleri yapıldı ve kırık kaynaması ve deformite değerlendirildi. Sonuçlar, eklem hareketleri uygulanarak ve Toplam Aktif Eklem Hareket Aralığı (Strickland-Glogovac parmak fonksiyon ölçeği) puanlanarak klinik olarak değerlendirildi.
**Bulgular:** Hastalar travmalarından sonraki ilk üç gün içinde ameliyat edildi; Hastaların 17'sinde (%15.3) metakarpal kırık, 94'ünde (%84.7) falanks kırığı, metakarpal kırıkların 8'inde (%47) ikinci metakarpal kırık ve falanks kırığı olan 94 hastanın 26'sında (%27.6) beşinci parmak kırığı vardı. Strickland-Glogovac parmak fonksiyon skalasına göre aktif eklem hareket açıklığı >150 (mükemmel) olan hasta sayısı 45, 125–149 (iyi) olan hasta sayısı 36, 90–124 (orta) olan hasta sayısı 20 ve <90 (kötü) olan hasta sayısı 10 idi. Toplamda 81 hastada mükemmel ve iyi sonuçlar bulundu.
**Sonuç:** Mini eksternal fiksatörler, elin tübüler kemik kırıkları için cerrahi seçenekler arasında daha sık tercih edilmelidir çünkü uygulanması kolaydır, tatmin edici stabiliteye sahiptir, güvenlidir, ağrısız erken mobilizasyona izin verir ve tedavi seçeneklerinde çok yönlülük sağlar.

Anahtar kelimeler: eksternal fiksasyon, mini eksternal fiksatör, falanks kırığı, metakarpal kırıklar, K-teli

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## Introduction

Hand injuries are frequently encountered orthopedic issues, particularly in industrialized environments. They can occur due to accidents, disasters, floods, wars, and fights. 14% of all emergencies are hand fractures and dislocations [1]. Accordingly, hand fractures constitute 12% of all fractures and 23% of upper extremity fractures. Although hand injuries are not life-threatening, they cause functional losses and disability in daily life activities. Since most hand injuries occur in workplaces, dirty environments, with heavy machinery and cutting tools, the wounds are infected and dirty. Therefore, the evaluation and treatment of hand injuries are critical. Careless intervention or inappropriate rehabilitation programs can cause permanent damage to patients in terms of sensation, movement, and skills [2, 3].

Upper extremity injuries cause various personal, psychological, and social consequences. These consequences are accompanied by psychological problems that occur with patients returning to their daily activities later, delayed return to work, the appearance of the extremity, and restrictions in social and occupational activities [4]. It has been reported that factors such as the severity of the injury, its type, and the characteristics of the injured structures are different elements that affect the long-term results of rehabilitation and return to work. Hand injuries can be a great source of stress and a cause of disconnection from life by negatively impacting the work that patients do in their daily lives. Since the human hand is the main instrument in maintaining a sense of independence and participation in activities in life, hand injuries can change a person's goals in life, economic level, and role in the family [5]. Using valid and reliable methods to reveal the injury's functional, social, and occupational consequences is also important from a clinical perspective. With the definition of the International Classification of Functioning, Disability and Health (ICF), the concepts of body structure and functions, activity, and participation were used to determine the effect of the disease on health. In recent years, outcome measures used in evaluating upper extremity injuries have also been implemented within the framework of these concepts [6].

Swanson's statements, "If hand fractures are not treated at all, they result in deformity, if over-treated, they result in stiffness, and if treated poorly, they result in both deformity and stiffness," emphasized how sensitive and experienced the treatment of hand fractures should be [7].

Within the scope of this research, the presence of fracture union and deformity were evaluated in patients who were operated on with a mini external fixator for metacarpal and phalanx fractures in our institution.

## Method

A total of 148 patients who underwent external fixation due to phalanx and metacarpal bone fractures were retrospectively evaluated. Thirty-seven patients were excluded from the analysis as they did not come for postoperative check-ups. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution with protocol number 2017-17/37, and informed consent has been obtained from all participants.

Posterior-anterior (PA), oblique, and lateral radiographs were taken, and surgical treatment was applied after acute conservative treatment of metacarpal and phalanx fractures. Mini external fixator technique was preferred among surgical treatment techniques as it is easy, fast to use, cost-effective, has a short operation and hospitalization time, is easy to follow up the high number of patients in industrial zones, and allows early mobilization. The study group consisted of open metacarpal and phalanx fractures, unstable metacarpal and phalanx fractures, intra-articular or extra-articular metacarpal and phalanx fractures, patients who could not undergo general anesthesia due to medical problems, metacarpal and phalanx fractures with segmental bone loss, and multiple metacarpal and phalanx fractures due to external fixation.

The patients' radiographic examinations were performed, and fracture union and deformity were evaluated. The results were clinically assessed by applying joint movements and scoring the Total

Active Joint Range of Motion (Strickland-Glogovac finger function scale).

The inclusion criteria could be elaborated as open metacarpal and phalanx fractures, unstable metacarpal and phalanx fractures, intra-articular or extra-articular metacarpal and phalanx fractures, patients who cannot undergo general anesthesia due to medical problems, metacarpal and phalanx fractures with segmental bone loss, and all patients were between the ages of 9 and 79. Additionally, I suggest expanding on the surgical techniques and postoperative care instructions, including any specific safety measures taken.

**Surgical Procedure**

First-generation cephalosporin treatment (1 g) was administered before the surgery for prophylactic purposes. A hand table was set up on the side of the extremity to be operated on in the patient lying in the supine position. After the patients were cleaned with chlorhexidine gluconate solution, they were disinfected using povidone-iodine. No tourniquet was used. Monolateral mini external fixators (a simple system established between half-chanz pins with the help of bars and clamps) were applied to the patients under local anesthesia (Figure 1).

Considering the safe areas, the application was performed from the hand dorsomedial or dorsolateral. While applying the chanz under scopy, the muscle was kept at the maximum possible length/stretched. It was anticipated that muscle functions would be allowed in the postoperative period thanks to this maneuver. The chanz pins were first advanced in the soft tissue and reached on the bone. The safe corridor was caught after gently ensuring the bone was in contact (up-down/forward-back). After the appropriate angle was given, the pins were applied.

During this application, the pins must be sent at the appropriate depth and should not protrude from the opposite cortex. After clamps were placed on the transmission pins, the fractures were reduced with the help of 1 carbon rod, which had the effect of ligamantotaxis and was fixed. In applying the preoperative external fixator, attention was paid to the cortex's continuity and the pins' parallel placement to avoid rotation. A resting splint was applied to the patient for the first three days to support postoperative stabilization and patient compliance. The patients were informed about what to do in postoperative care during discharge. Postoperative care includes recommendations such as keeping the operated hand of the patient elevated, pin site dressing for wound care, antibiotic therapy, and analgesia. The splint applied to the patients was removed on the 3rd postoperative day. The patients were called for outpatient clinic control 3 weeks later.

After the scopic control (Figure 1), a resting splint was applied to the patient, and the patient's operation was terminated and discharged on the same postoperative day.

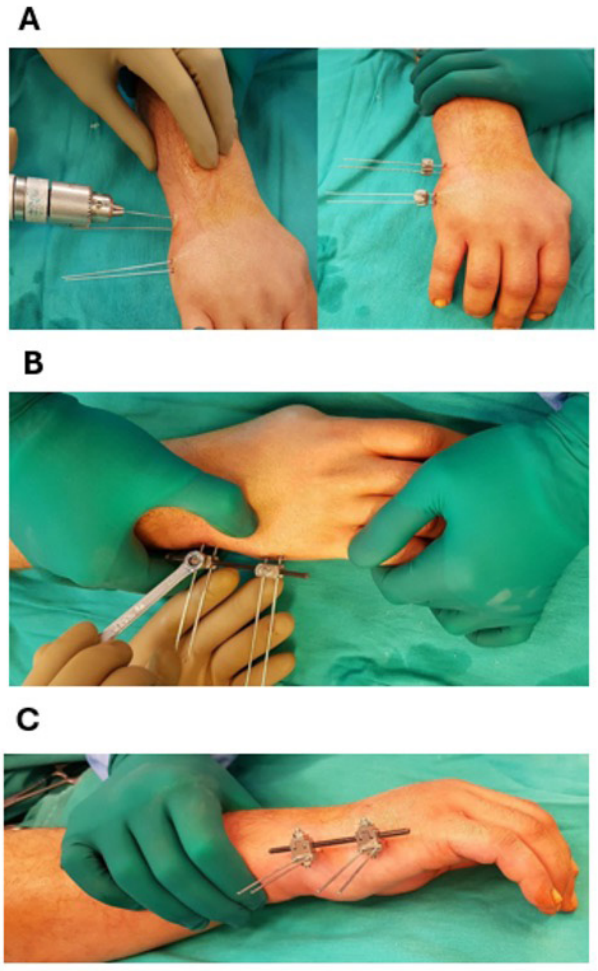


Figure 1: External fixator application procedure

The patients were informed about what to do in postoperative care during discharge. Postoperative care includes suggestions such as keeping the patient's operated hand elevated, pin site dressing for wound care, and providing analgesia. In the

postoperative period, the patients were called for a 3rd-day outpatient clinic check, and the resting splint applied to the patients was terminated at this check. The patients were told to continue with pin-site dressing for wound care. From the moment the resting splint was terminated (postoperative day 3), joint movements were started in the patients. The patients were called for an outpatient clinic check-up three weeks later; a joint range of motion and imaging were examined.

Radiological imaging of the patients was performed on the 3rd week. After radiological healing/union (formation of a trabecular bridge on the fracture line in the obtained X-ray images, absence of radiolucent image on the fracture line, and absence of tenderness on the fracture line clinically) was observed, local anesthesia was applied under outpatient clinic conditions and mini external fixators were removed. It was observed that the number of patients whose mini external fixators were removed in the third week was 55 (Figure 2).

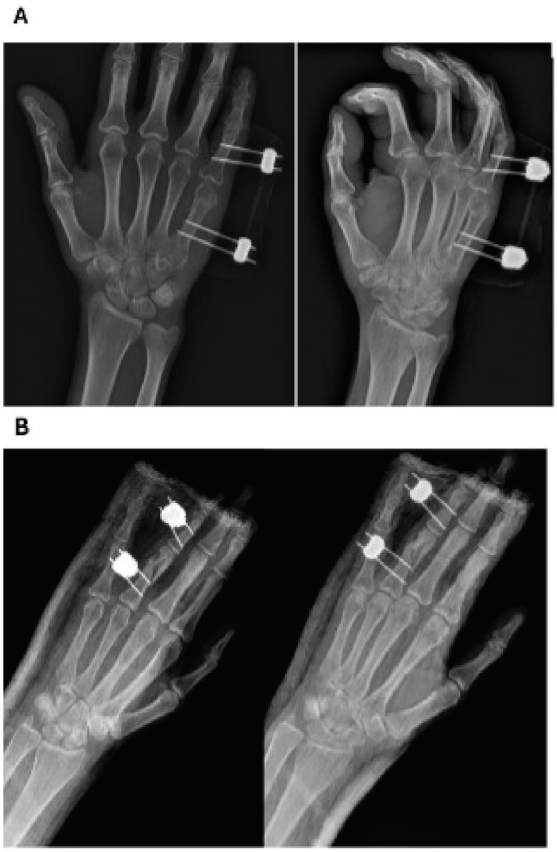


Figure 2: (A): Fifth metacarpal boxer's fracture postoperative 4th week control radiographs showed union.(B): Fourth finger proximal phalanx fracture postoperative 1st day radiographs

Patients with incomplete union were called for weekly check-ups for imaging. Of the remaining 56 patients, 33 had their mini external fixators removed on the 4th week, 11 on the 5th week, and 12 on the 6th week. Hand ROM exercises were started on the patients whose fixators were removed. After removing the mini external fixator, patients were called for check-ups at regular intervals, and their joint movements at their last check-up and Total Active Joint Range of Motion (Strickland-Glogovac finger function scale) scoring were evaluated at their follow-up.

### Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 26.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data were given as descriptive values. For comparisons between groups, the “Independent Sample T-test” was used for two groups, and the “Pearson Chi-Square Test” was used to compare categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

## Results

This retrospective analysis evaluated 111 patients who underwent external fixation for phalanx and metacarpal bone fractures. Regarding gender distribution, 95 were male, and 16 were female. The mean age was 34.3 years (range 8–78 years). Fractures occurred in 78 patients due to work accidents, 19 patients due to home accidents, 5 patients due to traffic accidents, and nine due to falls (Table - 6). The average follow-up period of the patients was 23.1 months (range 8–40 months) (Table 1). The patients were operated on in the first three days after their trauma. Fifty-one patients had right-hand injuries, and 60 had left-hand injuries. Seventeen (15.3%) of the patients had metacarpal fractures, and 94 (84.7%) had phalanx fractures. Of the 47%, metacarpal fractures were 2nd metacarpal fractures. Twenty-six (27.6%) of the 94 patients with phalanx fractures had 5th finger fractures. When the patients were evaluated according to their ages, one patient was between 0-9 years old, 24 patients were between 10-19

years old, 23 patients were between 20-29 years old, 25 patients were between 30-39 years old, 20 patients were between 40-49 years old, eight patients were between 50-59 years old, eight patients were between 60-69 years old, and two patients were between 70-79 years old (Table 2).

Table 1: Demographic characteristics of the patients participating in the study

| | |
|---|---|
| **Mean Age** | 34.3 ( 8 – 78) |
| **Gender** | 95 M / 16 F |
| **Involvement (Right/Left)** | 51 / 60 |
| **Injury Mechanism** | Work Accident 78 |
| | Domestic Accident 19 |
| | Traffic Injury 5 |
| | Fall 9 |
| **Fracture localization** | Phalanx Fracture 94 |
| | Metacarpal Fracture 17 |
| **Median Follow-up** | 23.1 months (8–40) |

Table 2: Distribution of the patients according to age according to the 15.3-Glogovac finger function scale

| Age | Very Good | Good | Moderate | Low |
|---|---|---|---|---|
| 0-9 | | | 1 | |
| 10-19 | 20 | 3 | 1 | |
| 20-29 | 13 | 4 | 4 | 2 |
| 30-39 | 9 | 10 | 4 | 2 |
| 40-49 | 3 | 9 | 6 | 2 |
| 50-59 | | 6 | 2 | |
| 60-69 | | 3 | 2 | 3 |
| 70-79 | | 1 | | 1 |

In 54 patients (57.4%) with phalanx fractures, there were proximal phalanx fractures in 21 (22.3%) and distal phalanx fractures in 19 (20.2%). In 9 of 111 patients (8.1%), there was a Gustilo Anderson type 1 open fracture. The fracture was at the middle phalanx level in 5 patients with open fractures (55.5%). The patients were followed up radiologically for a mean of 3.8 weeks (range 3–6 weeks). In cases where the union was assessed, the patients were called for a control visit one month after removing the mini external fixator, and the patients were evaluated radiologically and clinically. Nonunion was detected in 11 patients. Of the patients with nonunion, 2 had open fractures, and 1 had a comminuted fracture. Patients with nonunion were subsequently treated with graft and plate-screw osteosynthesis. The joint range of motion was assessed using the Strickland-Glogovac finger function scale, which evaluates the total active joint range of motion (Table 3).

Table 3: Distribution of the number of patients participating in the study according to the Strickland-Glogovac finger function scale

| Strickland-Glogovac finger function scale | n |
|---|---|
| **Excellent** | 45 |
| **Good** | 36 |
| **Moderate** | 20 |
| **Poor** | 10 |

According to the Strickland–Glogovac finger function scale, the number of patients with active joint range of motion >150 (excellent) was 45, the number of patients with 125–149 (good) was 36, the number of patients with 90–124 (moderate) was 20, and the number of patients with <90 (poor) was 10. Overall, excellent and good results were found in 81 patients (Table 3 & Table 4).

Table 4: Distribution of the Strickland-Glogovac finger function scale according to the fracture location and the number of patients participating in the study

| | Excellent | Good | Moderate | Poor | Total |
|---|---|---|---|---|---|
| **Intraarticular** | 19 | 7 | 2 | 3 | 31 |
| **Extraarticular** | 26 | 29 | 18 | 7 | 80 |

When the patients were classified according to their ages and the Strickland-Glogovac finger function scales were compared, it was found that one patient between the ages of 0–9 had good results, 20 of 24 patients between the ages of 10–19 had excellent results, 3 had good results, and 1 had fair results, 1 of 23 patients between the ages of 20–29 had excellent results, 4 had good results, 4 had fair results, and 2 had poor results, 9 of 25 patients between the ages of 30–39 had excellent results, 10 had good results, 4 had fair results, and 2 had poor results, 2 of 20 patients between the ages of 40–49 had excellent results, 9 had good results, 6 had fair results, and 2 had poor results, eight patients between the ages of 50–59 had good results, 2 had fair results, 3 of 8 patients between the ages of 60–69 had good results, It was determined that two patients had moderate results, 3 had poor results, two patients between the ages of 70–79 had one good result, and 1 had poor results.

Thirty-one patients (27.9%) had intraarticular fractures, and 80 patients (72.1%) had extraarticular fractures. In 19 patients (61.2%)

with intraarticular fractures, excellent results were found; 7 patients (22.5%) had good results, two patients (6.4%) had fair results, and three patients (9.6%) had poor results. In 26 patients (32.5%) with extraarticular fractures, excellent results were found; 29 patients (36.2%) had good results, 18 patients (22.5%) had fair results, and seven patients (8.7%) had poor results. Post-traumatic arthritis was observed in 5 patients (16.1%) with intraarticular fractures.

The Strickland-Glogovac finger function scale was evaluated using external fixator removal times. It was determined that 38 of 55 patients whose external fixator removal time was 3 weeks had excellent results, 6 had good results, 11 had fair results; 7 of 33 patients whose external fixator removal time was 4 weeks had excellent results, 18 had good results, 5 had fair results, and 3 had poor results; 6 of 11 patients whose 5-week follow-up time was 5 weeks had good results, 5 had fair results; 1 of 12 patients whose 6-week follow-up time was 6 weeks had good results, 4 had fair results, and 7 had poor results.

The number of patients working in the preoperative period was 86, the mean age was 29.1, the mean follow-up time was 26.4 months, the number of patients who returned to work was 71, and the mean return to work time was 2.2 months (range 1–10 months). No union was found in 11 patients; 2 patients with nonunion had open fractures, and one had comminuted fractures. Apart from these three patients, five patients with nonunion were found to be over 60 years of age. No factor affecting nonunion was found in the other three patients.

Three of the patients had comminuted fractures, and despite being under 50 years of age, two had union, and one had no union. According to the Strickland—Glogovac finger function scale, the patients with no union had poor range of motion, while those with union had good results. During the follow-up period, three patients were reoperated due to implant insufficiency. It was determined that the implant insufficiency of these patients was patient-related (implants could not be removed at their request). Therefore, the patients were reoperated. There were no problems in union and range of motion in the three reoperated patients. Apart from implant failure and union, no complications such as pin tract infection, osteomyelitis, or neurological and vascular damage were observed in the patients.

## Discussion

The most common fractures in our body are fractures of the metacarpals and phalanges. This frequency is 10% of all fractures or 1/3 of all hand injuries. 14% of all emergencies are hand fractures and dislocations [1–3]. Most metacarpal and phalangeal fractures can be treated conservatively. However, surgical treatment is the preferred option for some unstable fractures. Two types of fixation options exist for hand region fractures: internal fixation according to AO standards and external fixation in fractures with open, unstable fractures and severe soft tissue injuries [8].

Although plate-screw fixation used for open reduction internal fixation provides good stability, it can cause soft tissue damage and progressive devascularization of bone fragments [9, 10]. The least invasive intervention in the surgical treatment of hand region fractures is fixation with k-wires. After closed reduction, fixation with K wires minimizes soft tissue damage and does not disrupt bone blood flow. In the early 1900s, Parkhill in the USA and Lambotte in Belgium performed the first external fixator applications in the hand region without knowing each other. The external fixator applied in the hand region has undergone many changes and developments until today. Today, sophisticated miniature devices have replaced hand-made external fixators [11]. Mini external fixators do not require open reduction and can be applied from safe areas, so they do not cause soft tissue damage, are easy to use, and allow sufficient reduction to provide standard bone length in multi-part fractures. Despite all these advantages, some studies have not achieved satisfactory results. The inadequacy in these studies is thought to be due to the inadequacy of the mini external fixator system. The small diameter of the fixator pins is also effective in insufficient rigidity [11, 12].

A comparative biomechanical study conducted by Tun et al. [13] using mini external fixators found no loosening in the pins compared to similar devices. They stated that mini external fixators

were found to be less rigid than comparable devices. However, the pins were not loosened. The same study noted that using mini external fixators in hand fractures provides versatility in surgical treatment. Our analysis indicated that the mini external fixator technique should be preferred more among surgical treatment techniques because it is easy, fast to apply, cheap, and allows early mobilization. In our study, it was seen that there were 72.9% successful results. When the literature was reviewed, it was determined that our study was compatible with the literature.

In many studies, mini external fixators have been used in open complicated fractures, fractures with serious soft tissue damage, severely contaminated fractures, intra-articular fractures, and fractures with significant bone loss. Some authors have advocated that mini external fixators should also be used in closed simple fractures. Schuind and colleagues applied standard mini external fixators to uncomplicated hand region fractures, especially closed metacarpal fractures [14]. Our study used external fixators to close simple fractures, leaving fracture characteristics in the background. Of 111 patients, 45 (40.5%) had excellent functional results, and 36 (32.4%) had good functional results.

Clinically satisfactory results are obtained with the use of mini external fixators in all types of hand region fractures, including those with severe soft tissue injuries and open, complicated, contaminated, intra-articular multi-fragmented fractures. The biggest problem in external fixator applications is that they cause soft tissue contractures. For this reason, it is a surgical method preferred as a secondary option by surgeons. It has been demonstrated that mini external fixator applications have good results by rendering acute fractures painless quickly and allowing early mobilization. In one study, mini external fixator results were successful in fracture-dislocations of the neglected PIP joint [15].

A study by Yaseen et al. determined that 66.07% of 56 patients had excellent functional results, 16.07% had good functional results, 10.71% had moderate functional results, and 7.14% had poor functional results. In this study, union was observed in 51 (91.07%) patients, and nonunion was detected in 5 (8.93%) patients [16]. Our analysis detected nonunion in 11 (9.99%) of 111 patients. In a study conducted by Thakur et al., it was determined that 98% of patients had a union, 68% had excellent functional results, 22% had good functional results, 8% had moderate functional results, and 2% had poor functional results [17]. Li et al. [18] reported that (n=26) with intra-articular fractures, eight patients (30.9%) had excellent functional results, 13 patients (50%) had good functional results, and three patients (11.5%) had moderate functional results. Two patients (7.6%) had poor functional results.

A study by Dailiana et al. [19] with 33 patients found that the results were sufficiently good. It was determined that none of the patients in the study group had any changes in their activities or occupations at the end of treatment. Dailiana et al. [20] found high efficacy and good functional results in patients who underwent mini external fixation for intra-articular and complicated fractures. Margic [21] found 25% nonunion and 62.5% moderate and poor functional results. It was thought that the poor results in this study may be due to the small number of patients, the selection of patients with open fractures and segmental bone tissue loss with severe soft tissue injuries, and the properties of the materials used being inadequate compared to the mini external fixators used today. A study by Ahmad et al. [22] determined that 66.07% of 56 patients had excellent functional results, 16.07% had good functional results, 10.71% had moderate functional results, and 7.14% had poor functional results. In this study, union was observed in 51 (91.07%) patients, and nonunion was detected in 5 (8.93%) patients. Our analysis detected nonunion in 11 (9.99%) of 111 patients. In a study by Gupta et al. [23], 6 out of 20 patients had excellent, and 4 had good results. Although satisfactory results were obtained in 50% of the patients, the results were found to be unsatisfactory in the rest. In this study, it is thought that the results were not good enough because ten patients had open fractures, and seven patients had intra-articular fractures. In a study by Gupta et al., 45.1% of the patients had excellent results, 41.9% had good results, 9.6% had moderate results, and 3.2% had poor results. In this study, 6.4% of the patients had nonunion [23]. In a study conducted by El-Shaer et al. [24], excellent results were determined in 6 out of 20

patients and good results in 4. Although satisfactory results were obtained in 50% of the patients, the results were found to be unsatisfactory in the rest. In this study, it is thought that the results were not good enough because ten patients had open fractures, and seven patients had intra-articular fractures. Tank and Patel [25] had done a similar study with a spinal needle cap as a uniplanar unilateral fixator for phalangeal fractures; they had stated that “at 3 months follow-up of range of motion and TAM score ion 27 patients 19 had an excellent result, five cases had good range, and three had a fair result.

Our study included a higher number of patients compared to the existing literature. It was observed that most of the patients participating in our research had injuries due to work accidents. The reason for the high number of patients and the fact that the mechanism of injury in most of these patients was work accidents was thought to be related to the fact that our province is one of the few industrial provinces in our country. The number of male workers in our study was high due to the high number of male workers in industrial zones. Treatment of hand injuries occurring in industrial zones should be fast, easy to apply, cheap, and allow early mobilization to shorten the time needed to return to work. Therefore, the mini external fixator technique is suitable for patients undergoing surgery. Distal phalanx fractures are the most common fractures among hand region fractures. However, the majority of these fractures heal with conservative treatment. Fractures requiring surgical treatment are usually fractures at the proximal phalanx level. As in our study, the number of proximal phalanx fractures was high, consistent with the literature.

The extended follow-up period between patients due to patient density made it difficult to follow up on patient recovery. Although it is thought that external fixator applications in simple fractures, not only complicated fractures, may positively affect the study results, we think that external fixator applications frequently cause soft tissue contractures, and this positivity is balanced. Monolateral external fixator use may cause implant failure due to insufficiency instability. In our study, reoperation was required due to implant failure in 3 patients during the follow-up period. The large number of patients and the good results will be a good data quality for comparing other treatment options in future studies.

## Conclusion

The mini external fixator technique can be easily applied under local anesthesia and is fast and safer than internal fixation techniques. It can help shorten the treatment of hand injuries and the time to return to work, especially in industrial areas where patient circulation is fast. II. To apply a mini external fixator, the operator must have sufficient knowledge. Given all this information, we believe that the mini external fixator technique, applied with the right indication, the right patient selection, and the right technique, should be used more frequently in tubular bone fractures of the hand region.

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# Evaluation Of The Effect Of Autologous Dermis Graft On Rat Achilles Tendon Healing

## Otolog Dermis Greftinin Rat Aşil Tendonu İyileşmesi Üzerindeki Etkisinin Değerledirilmesi

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## ABSTRACT

**Aim:** The Achilles tendon is one of the most frequently injured tendons. It is more common in young and middle-aged individuals who are particularly active in sports. Re-surgery or permanent disabilities may occur as a result of tendon rupture after tendon repair. Various methods to enhance Achilles tendon healing have been described in the literature. However, there is limited data on the use of dermis grafts for tendon augmentation. Dermis grafts; Since they are core tissue, they have less foreign body reaction, can be obtained in a short time, and can be an alternative due to less donor area morbidity. The aim of our study is to reduce the risk of re-rupture by strengthening tendon healing in Achilles tendon injuries and to determine the effectiveness of autologous dermis grafts on healing for strong healing.

**Methods:** In our study, 20 male rats were randomly divided into two groups as Control and Experimental groups. All rats underwent tendon repair after an atraumatic, full-thickness, straight incision was applied to the right Achilles tendon. After tendon repair in the rats in the experimental group; dermis grafts taken from the back were wrapped around the tendon repair area and sutured. The other rats constituted the control group. Rats were sacrificed at week 4 and their Achilles tendons were removed and examined histopathologically, immunohistochemically and biomechanically.

**Results:** Tendons were intact and no rupture was observed in all samples. Positive results were observed in favor of the experimental group in type I collagen and type I/type III collagen density and biomechanical examinations in rats repaired with dermis grafts.

**Conclusion:** As a result of our study; it was shown that dermis grafts can positively contribute to tendon healing. Tendon repair with dermis grafts can be a good alternative to other methods for tendon augmentation or strengthening.

Keywords: Achilles tendon, Tendon healing, Dermis graft

## ÖZ

**Amaç:** Aşil tendon sık yaralanan tendonlardan, özellikle aktif spor uğraşı olan genç-orta yaşta bireylerde daha sık görülmektedir. Tendon tamiri sonrası tendonun tekrar kopması sonucunda tekrar ameliyat veya kalıcı sakatlıklar gelişebilmektedir. Literatürde aşil tendon iyileşmesini artırıcı çeşitli yöntemler tarif edilmiştir. Ancak, dermis greftin tendon augmentasyonu amacıyla kullanımına dair kısıtlı veri mevcuttur. Dermis greftleri; öz doku olduğundan yabancı cisim reaksiyonu az, kısa zamanda alınabilen ve daha az donör alan morbiditesi nedeniyle alternatif olabilecek niteliktedir. Çalışmamızdaki amaç, aşil tendon yaralanmalarında tendon iyileştirmesini güçlendirirerek tekrar kopma riskini azaltmak ve güçlü iyileşme için otolog dermis greftinin iyileşme üzerinde etkinliğini belirlemektir.

**Yöntem:** Çalışmamızda 20 erkek rat Kontrol ve Deney grubu olarak rastgele iki gruba ayrıldı. Tüm ratların sağ aşil tendonuna atravmatik, tam kat, düz kesi uygulandıktan tendon onarımı yapıldı. Deney grubundaki ratlara tendon onarımı sonrasında; sırttan alınan dermis grefti tendon onarım bölgesine sarılarak sütüre edildi. Diğer ratlar kontrol grubunu oluşturdu. Ratlar 4. haftada sakrifiye edilerek aşil tendonları cikartılarak histopatolojik, immünohistokimyasal ve biyomekanik olarak incelendi.

**Bulgular:** Bütün numunelerde tendon intakt ve rüptür gözlenmedi. Dermis grefti ile onarım yapılan ratlarda tip I kollajen ve tip I/tip III kollajen yoğunluğunda ve biyomekanik incelemelerde deney grubu lehine olumlu sonuçlar izlendi.

**Sonuç:** Çalışmamız sonucunda; dermis greftinin tendon iyileşmesine olumlu katkı sağlayabileceğini gösterdi. Dermis grefti ile tendon onarımı; tendon augmentasyonu veya güçlendirmesi için diğer yöntemlere göre iyi bir alternatif olabilir.

Anahtar Kelimeler: Aşil tendon, Tendon iyileşmesi, Dermis grefti

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## Introduction

Tendon injuries are an important reason for emergency room visits in daily life. Achilles tendon is one of the most frequently injured tendons, and most commonly occurs in the form of injuries with sharp objects, firearms, crushing, and closed injuries. It is especially seen in young-middle-aged men, and its annual incidence in the society is reported as 7-40/100,000 [1].

Degeneration and inadequate perfusion in the Achilles tendon over time pose a risk for rupture. Although conservative and surgical options are available in treatment options, surgical repair of the tendon has become more popular in recent years [2]. While the immobilization period is found to be shorter in patients who undergo surgery compared to conservative treatment, the risks of re-rupture are found to be lower in open technique tendon repair. Especially in athletes, the return to work times in Achilles ruptures seriously affect the athlete's career.

Complications such as re-rupture are frequently encountered in patient follow-ups after tendon repair is performed surgically. This situation may cause negative situations such as partial or complete disability of limb function in patients, in addition to repeated surgeries.

Various methods have been tried in the literature to strengthen the Achilles tendon, which has a problematic healing due to insufficient perfusion. Various biological materials such as pantaris tendon graft, fascial flaps, synthetic grafts and acellular dermal matrix have been used for tendon strengthening [2-4]. In addition, various injections such as stem cells, PRP, autologous serum, growth factors, hydrogels have been made to the repair area to strengthen tendon healing [3,4]. Some studies have shown that the re-rupture rate of repair with skin-equivalent biological material is lower [5]. In this field, where many different materials are investigated, a complete solution for reinforced tendon repair has not been produced.

In our study, in order to prevent these complications that we frequently encounter after tendon repair; We planned to use the dermis graft, which is a subunit of the skin tissue that is currently used in many operations such as dorsum in rhinoplasty [6] and philtral column augmentation in cleft lip surgery and scar revision. When the skin and tendon are examined histologically, they have common cellular content in terms of type 1 collagen and fibroblasts. Therefore, the dermal layer of the skin can be used to strengthen the repair after tendon repair. Although there are experimental studies on dermis grafts in rats in the literature [7], no study on dermis grafts on tendon healing was found. In our study, it was aimed to use dermis grafts for tendon strengthening following the repair after atraumatic full-thickness Achilles tendon transection.

## Materials and Methods

Our study was conducted with the approval of the Local Animal Experiments Ethics Committee using 20 male Sprague Dawley rats aged 2-3 months and weighing between 300-350 g. The rats were randomly divided into 2 groups, each consisting of 10 rats in the control and experimental groups. The right Achilles tendons of all rats were cut in full thickness approximately 0.5 cm proximal to the calcaneus attachment and repaired with the modified Kessler method in the same session. Dermis grafts taken from the backs of 10 rats were placed in the tendon repair area in the same session and this group constituted the experimental group, while the other 10 rats remained as the control group. All rats were sacrificed at the end of the 28th day and Achilles tendon samples were taken. All surgical procedures were performed under aseptic conditions and general anesthesia with 50 mg/kg ketamine hydrochloride and 5 mg/kg xylazine hydrochloride administered intramuscularly. After anesthesia was provided, the right hind legs of all rats were shaved, in addition to the back region of the rats in the experimental group. The surgical areas were painted with povidone-iodine solution. The skin was passed through the Achilles tendon with a 2 cm incision using the classic posteromedial longitudinal approach. The incision was made sharply up to the tendon sheath. The Achilles tendon and plantaris tendon were explored. The Achilles tendon was thoroughly stripped from the nearby soft tissues with the help of a clamp. The Achilles tendons of all rats were cut in full thickness with a scalpel blade number 11 approximately 5 mm proximal to the attachment point to the calcaneus (Figure

1). The cut tendon ends were repaired end-to-end with the modified Kessler method using 4/0 Propylene suture (Figure 2).

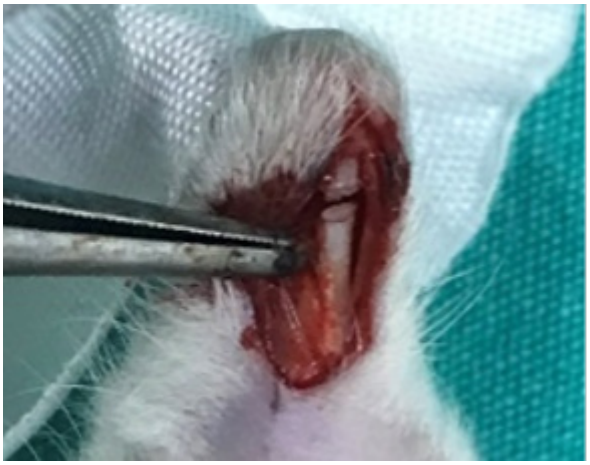

Figure 1. Incised tendon

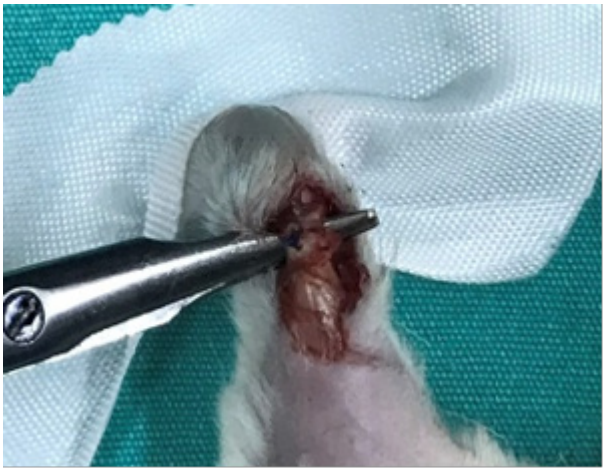

Figure 2. End-to-end repair using the modified Kessler method

The skin sutures of the rats in the control group were closed with 3/0 silk sutures without any additional surgical procedures. In the experimental group, a 1x2 cm elliptical skin island was marked on the back with a surgical pen after tendon repairs. The epidermis in the uppermost layer was de-epithelialized using a scalpel No. 10 on the marked skin island. Then, the incisions were completed and the dermis graft was taken (Figure 3). After the graft was taken, it was placed in a container containing physiological serum so that it would not retract and shrink. Then, the donor area where the graft was taken was closed by primary suturing without tension with 3/0 sharp silk suture. The dermis graft taken was placed so that it would completely surround the tendon repair area (Figure 4). Then, the ends of the dermis graft that surrounded the tendon and became a tube were sewn end-to-end with 6/0 Tekmon sutures. Skin sutures were placed. All surgical areas were dressed with povidone-iodine solution. Immobilization was not applied to all rats. Tramadol at a dose of 5 mg/kg was administered intraperitoneally for postoperative pain control.

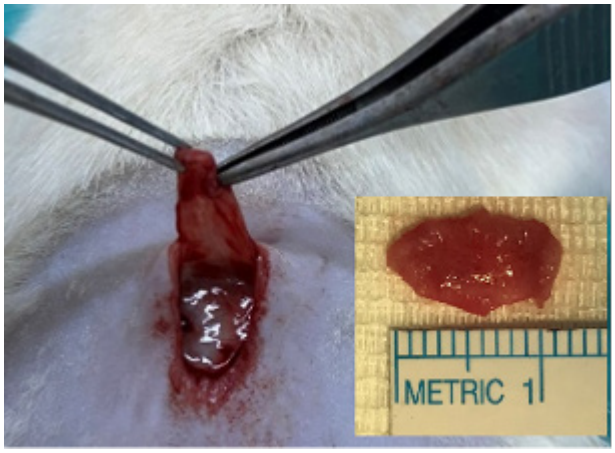


Figure 3. De-epithelialization and dermis graft

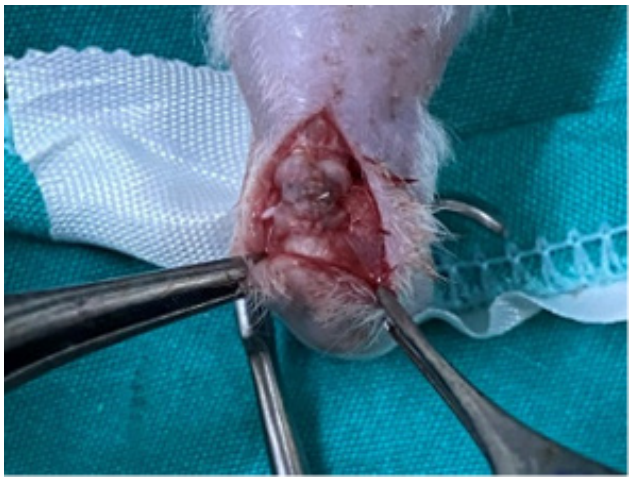

Figure 4. Tendon reconstruction with dermis graft

No loss of rats was observed in any group during the follow-up period. At the end of the 28th day, all rats were sacrificed with high-dose anesthesia. Achilles tendon samples of every 10 rats in the control and experimental groups were randomly divided into two groups of 5. 5 from each group were separated for histopathological and immunohistochemical examinations, and 5 were separated for biomechanical examinations. Samples taken for histopathological and immunohistochemical examinations were taken from the muscle-tendon junction proximally, and from the calcaneus attachment point distally below the repair site (Figure 5). For biomechanical

examinations, the muscle tissue above the muscle-tendon junction was included proximally, and the entire foot was included distally (Figure 6).

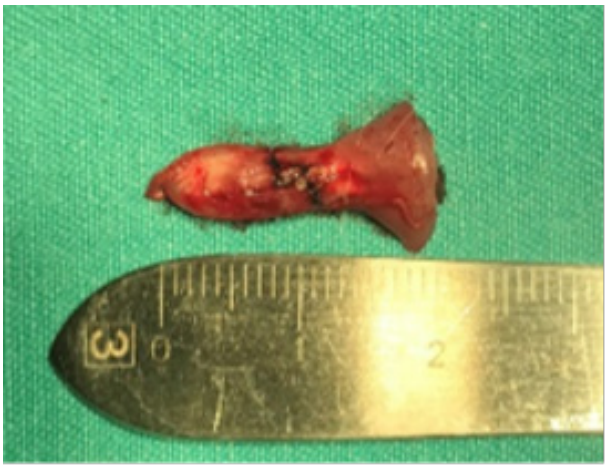

Figure 5. Histopathological sample

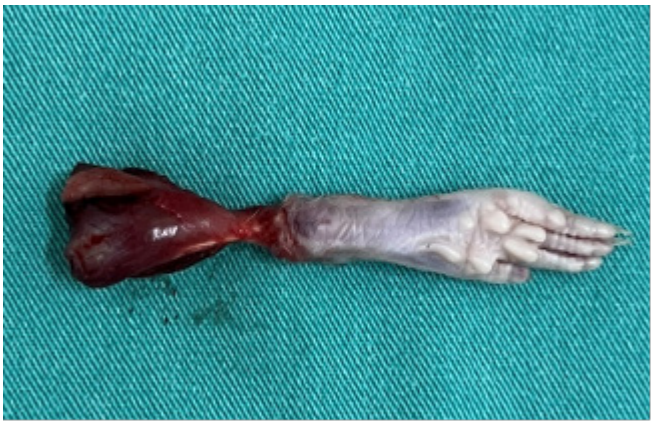

Figure 6. Biomechanical examination sample

The samples taken for histopathological and immunohistochemical examination were placed in containers containing formaldehyde and delivered to the Pathology and Biophysics Department Laboratories for examination. After routine histological follow-up procedures, 4 µm thick sections were taken from the obtained paraffin blocks with a microtome (Minux S700A Rotary Microtome) for histochemical and immunohistochemical methods. Movin scoring is based on 8 histological parameters and scores each parameter between 0-3 and then a total score is obtained [8]. A high score here indicates histopathological abnormality. On the other hand, in the Bonar design; Stage 0-3 is scored in 4 histological parameters and a total score is obtained [9]. Here, high scores indicate histopathological abnormality. Then, the samples were stained with Hematoxylin-Eosin (HE), Alcian Blue (AB), Masson Trichrome (MT) dyes and examined with Bonar and Movin semiquantitative scores [8, 9] (Figure 7, Figure 8).

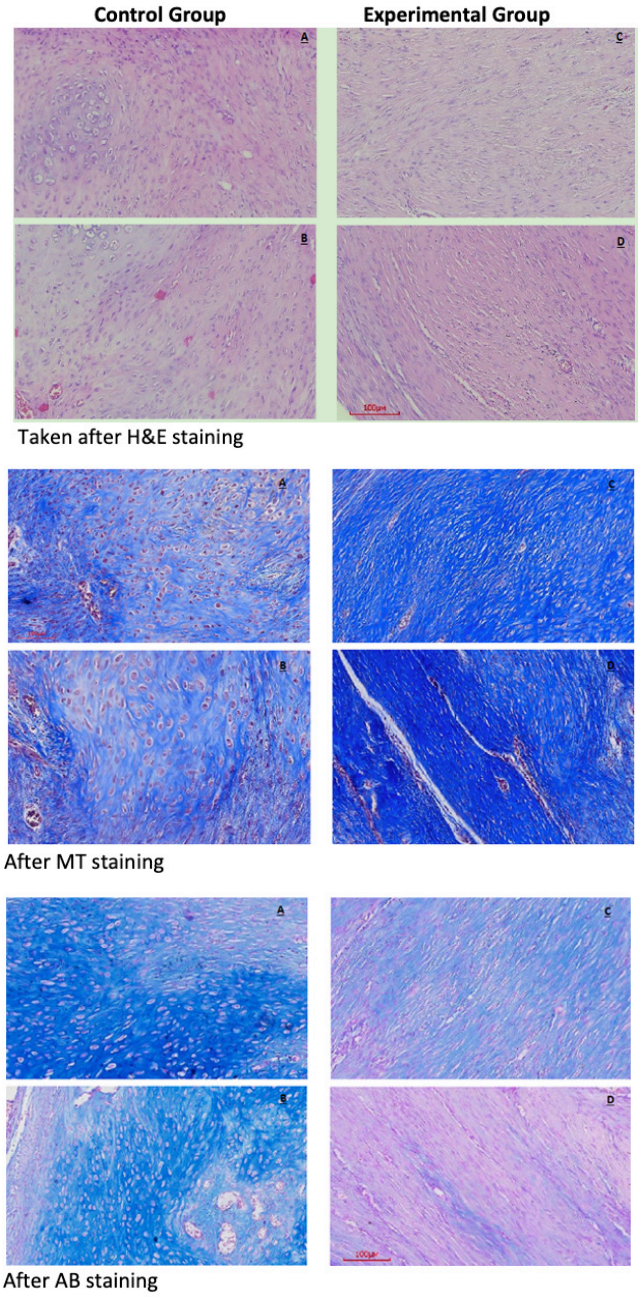


Figure 7. Histological sections

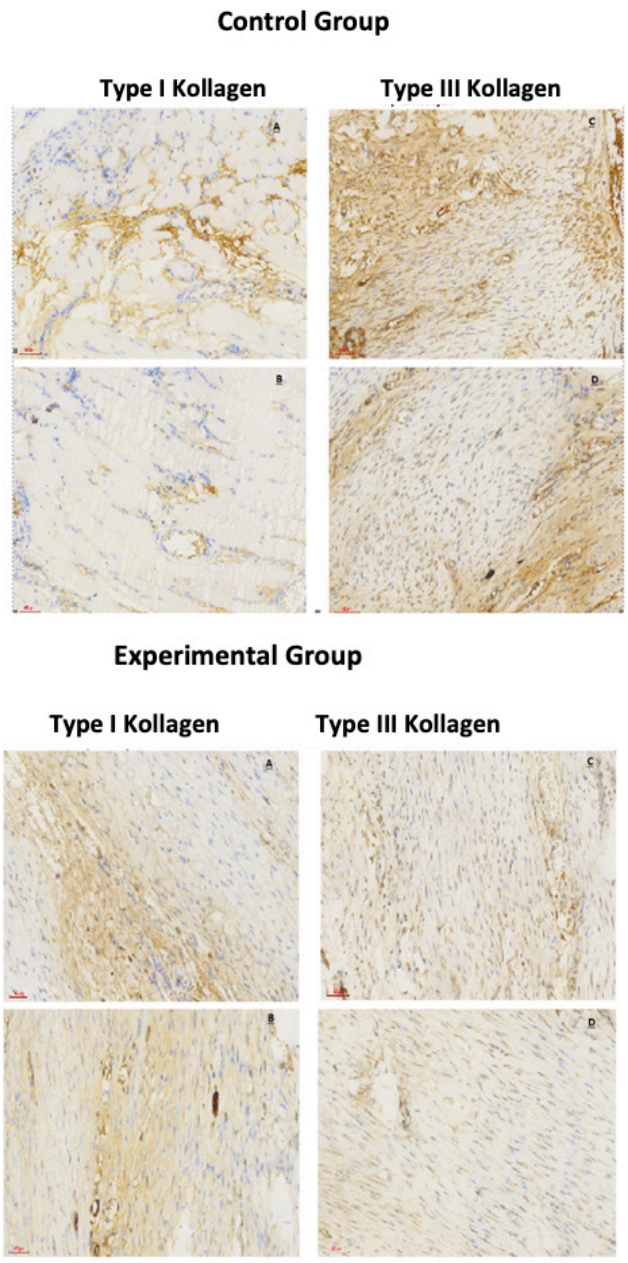


Figure 8. Collagen densities in histological sections after collagen staining.

At the end of routine immunohistochemical procedures, the preparations were examined with a light microscope. Type I and Type III collagen immunoreactivity density in tendon sections was evaluated using the Image J program. The Achilles tendons isolated for biomechanical measurement were performed with the Tension Test Device (İlfa Elektronik San. Tic. Ltd. Şti) located in the Biophysics Department Laboratory, which has a tension speed of 0-250 mm/min and a load cell capable of measuring up to a maximum of 1000 N. Before starting the biomechanical test, the initial lengths of the tendons were measured (L~8-9 mm). Width (D; mm), thickness (T; mm) and initial lengths (L; mm) were measured with a digital caliper. Then, aluminum powder was sprinkled on both ends of the tendon in order to ensure that the tendon adheres more tightly to the clamps and to prevent it from stretching. The tendons were placed in the Tension Test device with the gastrocnemius muscle tip on the lower clamps and the calcaneus tip (attached to the clamps with the foot and bones) on the upper clamps. Then, based on the literature, the distance between the clamps was set to be equal and 17±3 mm, and the tension speed was set to be 25 mm/min [10]. At the end of the tensile test, the Load-Deformation data recorded on the device were transferred to the LoggerPro software (V 3.8.3, Vernier Software & Technology, Orlando, FL, USA) and evaluated. At the end of the test, the load-deformation curve was drawn and the maximum force (FU; N), maximum deformation (dU; mm), energy stored until rupture (U; mj) and hardness (S; N/mm) parameters were obtained directly. In addition, the maximum breaking strength (σU; MPa), maximum strain (εU; mm/mm), maximum stress (maximum tensile strength, σU; MPa), elasticity modulus (E; MPa) and durability (u; MPa) parameters were calculated by obtaining the Stress-Strain curve [11].

## Results

No rats were lost in the 28th day of follow-up after tendon repair performed on rats. The analyses of the study were performed using the SPSS 25.0 package program. Continuous numerical variables were summarized with mean ± standard deviation, median (minimum - maximum) values. The conformity of continuous numerical variables to normal distribution was checked with the Shapiro Wilk test. It was determined that the numerical data between the groups were not normally distributed. The Mann Whitney U test was used to compare continuous numerical variables between the groups. A p value of less than 0.05 was accepted as the statistical significance limit.

The comparison of biomechanical measurement values and results of the groups is shown in Table 1. When the biomechanical measurement values were compared according to the groups; it was found that the stored energy, hardness, breaking

force, maximum deformation, Young's modulus, durability, maximum stress and maximum strain values were statistically significantly higher in the Experimental group than in the Control group ($p<0.05$).

Comparison of Bonar scoring results of the groups is shown in Table 2. When Bonar scoring results were compared according to the groups; collagen, vascularity and Bonar score were found to be statistically significantly lower in the experimental group than in the control group ($p<0.05$), while there was no statistically significant difference between the groups in terms of tenocyte and ground substance values ($p>0.05$).

The comparison of Movin scoring results of the groups is shown in Table 3. When Movin scoring results were compared according to the groups; fibril structure, fibril level, nucleus roundness, increased vascularity, GAG content and Movin score were found to be statistically significantly lower in the experimental group compared to the control group ($p<0.05$), while there was no statistically significant difference between the groups in terms of cellular change, decrease in collagen staining and hyalinization values ($p>0.05$).

Comparison of collagen densities between groups is shown in Table 4. When collagen densities were

Table 1. Comparison of biomechanical results between groups

| Parameter | Control (n = 5) | | Experiment (n = 5) | | p* |
|---|---|---|---|---|---|
| | Ort± SS | Med (Min-Maks) | Ort± SS | Med (Min-Maks) | |
| Stored energy (mj) | 75,53±12,77 | 69,02(64,88-90,98) | 132,5±38,39 | 116,1(104,6-198,5) | 0,008 |
| Hardness (N/mm) | 19,61±4,34 | 20,51(14,52-25,38) | 30,87±4,95 | 30,64(25,74-38,6) | 0,008 |
| Break force (N) | 41,89±9,61 | 37,74(33,1-52,75) | 60,82±7,72 | 65,17(49,65-67,24) | 0,032 |
| Max. deformation (mm) | 4,11±0,78 | 3,7(3,4-5,19) | 6,41±2,03 | 5,59(4,79-9,89) | 0,016 |
| Young modulus (MPa) | 1,92±0,57 | 1,72(1,37-2,58) | 3,27±0,67 | 3,32(2,59-4,24) | 0,008 |
| Toughness (MPa) | 8,5±1,05 | 8,85(6,79-9,33) | 13,39±1,98 | 13,24(11,2-16,53) | 0,008 |
| Max. stress (MPa) | 4,95±1,01 | 5,32(3,8-5,88) | 7,85±0,42 | 7,98(7,29-8,33) | 0,008 |
| Max. strain (mm/mm) | 3,98±1,1 | 3,67(3,11-5,78) | 7,36±1,19 | 7,89(5,43-8,33) | 0,016 |

* Mann-Whitney U test, p<0.05 statistically significant

Table 2. Comparison of Bonar scoring results between groups

| Parameter | Control (n = 5) | | Experiment (n = 5) | | p* |
|---|---|---|---|---|---|
| | Ort± SS | Med (Min-Maks) | Ort± SS | Med (Min-Maks) | |
| Tenocyte | 2,2±0,84 | 2(1-3) | 0,8±0,84 | 1(0-2) | 0,056 |
| Ground material | 1,8±0,84 | 2(1-3) | 0,8±0,45 | 1(0-1) | 0,095 |
| Collagen | 2,6±0,55 | 3(2-3) | 1±0 | 1(1-1) | 0,008 |
| Vascularity | 2,8±0,45 | 3(2-3) | 1,4±0,55 | 1(1-2) | 0,016 |
| Bonar score | 9,4±0,89 | 10(8-10) | 4±1 | 4(3-5) | 0,008 |

* Mann-Whitney U test, p<0.05 statistically significant

Table 3. Comparison of Movin scoring results

| Parameter | Control (n = 5) | | Experiment (n = 5) | | p* |
|---|---|---|---|---|---|
| | Ort± SS | Med (Min-Maks) | Ort± SS | Med (Min-Maks) | |
| Fibril structure | 2,2 ± 0,45 | 2 (2 - 3) | 1 ± 0 | 1 (1 - 1) | 0,008 |
| Fibril arrangement | 2,4 ± 0,55 | 2 (2 - 3) | 1 ± 0,71 | 1 (0 - 2) | 0,016 |
| Nucleus roundness | 2 ± 0,71 | 2 (1 - 3) | 1 ± 0 | 1 (1 - 1) | 0,032 |
| Cellular change | 2,2 ± 0,84 | 2 (1 - 3) | 1 ± 0,71 | 1 (0 - 2) | 0,056 |
| Increased vascularity | 2,8 ± 0,45 | 3 (2 - 3) | 1,4 ± 0,55 | 1 (1 - 2) | 0,016 |
| Decreased collagen staining | 1,8 ± 0,84 | 2 (1 - 3) | 0,8 ± 0,45 | 1 (0 - 1) | 0,095 |
| Hyalinization | 1,8 ± 0,84 | 2 (1 - 3) | 0,6 ± 0,55 | 1 (0 - 1) | 0,056 |
| Movin GAG content | 2 ± 0,71 | 2 (1 - 3) | 0,6 ± 0,55 | 1 (0 - 1) | 0,016 |
| Movin score | 17,2 ± 2,39 | 16 (15 - 21) | 7,4 ± 1,82 | 8 (5 - 9) | 0,008 |

Table 4. Comparison of collagen densities between groups

| Parameter | Control (n = 5) | | Experiment (n = 5) | | p* |
|---|---|---|---|---|---|
| | Ort± SS | Med (Min-Maks) | Ort± SS | Med (Min-Maks) | |
| Tip I | 8,5±2,74 | 7,1(6,1-12,1) | 18,9±5,95 | 19,6(11,6-24,7) | 0,016 |
| Tip III | 21,7±6,71 | 23,1(13,6-2876) | 15,7±5,25 | 13,2(10,8-21,5) | 0,095 |
| Tip I / Tip III | 0,4±0,05 | 0,4(0,31-0,45) | 1,3±0,7 | 0,98(0,67-2,29) | 0,008 |

* Mann-Whitney U test, p<0.05 statistically significant

compared according to groups; type I collagen density and type I collagen/type III collagen ratio were found to be statistically significantly higher in the experimental group than in the control group (p<0.05), while no statistically significant difference was found between the groups in terms of type III collagen density (p>0.05).

## Discussion

In this study, where the effect of autologous dermis graft on tendon healing in a rat Achilles tendon injury model was examined; histopathological, immunohistochemical and biomechanical positive results were obtained and the working hypothesis was confirmed. Since there was no study examining the effects of autologous dermis graft on tendon healing in Achilles tendon repair in detailed literature searches, this study is an original study.

Tendons are intermediate structures in the musculoskeletal system that transfer the energy received from the muscle to the bones. The Achilles tendon, which is the strongest and thickest tendon in the body, is the main plantar flexor of the foot. Achilles tendon, one of the most frequently injured tendons in the body, has acute and chronic injury types. Chronic degeneration theory is one of the basic mechanisms accused in ruptures in Achilles tendon, where ruptures are observed mostly in areas with poor vascularization [12].

Tendon healing consists of 3 phases that are not separated by sharp boundaries; inflammation, proliferation and remodeling phase. While Type III collagen is dominant at the beginning of the healing process, Type I collagen continues to dominate collagen in later periods, especially in the remodeling phase. Type III collagen, which is mostly in the healing phase, has a larger cross-sectional area compared to the healthy tendon and tends to elongate. Therefore, it cannot fulfill its functional properties biomechanically [13]. Therefore, tendons tend to rupture again in the pre-remodeling period and their tensile strength may remain lower than in the healthy tendon. Conservative and surgical treatment options are available among treatment methods. There are discussions about which treatment to use. Khan et al. [12] reported in their study that while surgical treatment had a significantly lower recurrence rate, conservative treatment had a lower complication rate. Holm et al. [14] reported that there was no significant difference in terms of complication and recurrence rates between the two treatment types. These studies show that surgical treatment is the preferred option, but alternative techniques are needed to further reduce both recurrence and complication rates.

Augmentation has been used in tendon repair to strengthen the repair site and reduce the risk of re-rupture. Although augmentation has been used in tendon repair types, particularly rotator cuff repair [15], fewer studies have been reported on its use, including randomized controlled trials in Achilles tendon treatment [16]. Different types of tendon augmentation materials are available, including autografts, xenografts, and allografts. While autografts do not carry the risk of cellular rejection, these grafts potentially increase the duration of surgery and may also cause morbidity and pain at the donor site. Although xenografts have no donor morbidity, the foreign material can cause hypersensitivity reactions in human patients, and poor clinical results have led some researchers to abandon their use for tendon augmentation [17]. Dermis grafts, a subunit of skin tissue used in many operations such as dorsum augmentation in rhinoplasty surgeries [6], philtral column augmentation in cleft lip surgeries, and scar revision, have been used successfully. There are two main problems with the use of dermis grafts; resorption and cyst formation [18,19]. Thompson reported that he obtained very good results with dermal grafts in facial reconstruction,

but a resorption rate of more than 20%. In addition, he stated that small epidermoid cysts developed from hair follicles and sebaceous glands, but these were phagocytosed over time and replaced by fibrous tissue [20]. Peer and Paddock [21] showed in their study that epidermal components remained in dermis grafts, small cavitations formed in the early period due to these, but these disappeared over time. They also reported that the epidermis, hair follicles and sebaceous glands disappeared within ten weeks; sweat glands persisted but did not show activity and there was no cyst formation. In our study, no cyst cases were encountered, similar to the literature [21].

Philip et al. [22] examined the effect of amniotic-derived multipotent progenitor cells on tendon healing in a study conducted on 126 rat Achilles tendons. The group administered amniotic-derived multipotent progenitor cells and the control group of 48 were statistically compared in terms of maximum load, but no significant difference was observed between the two groups.

Genç et al. [4] found no significant difference in maximum force comparisons between the control and PRP groups on the 15th and 30th days in their study. It was found that the values on the 15th day were lower in the control group than on the 30th day. No significant difference was found in the PRP group between the 15th and 30th days. Kim et al. [5] compared the biomechanical data between the saline and hydrogel groups on the 2nd, 4th and 8th weeks in their experimental study. In light of the data, no significant results were found in the data other than the maximum load obtained on the 4th week.

Barber et al. [23] found that the repair strength and stiffness of Achilles tendons augmented using GraftJacket matrix (Acellular dermal matrix) were statistically significant in the experimental group in their biomechanical study. Preliminary studies support the idea that these biomaterials have the ability to provide an alternative for tendon augmentation. However, there is a lack of available data that would allow definitive conclusions regarding the use of biomaterials for tendon augmentation [15]. The difficult accessibility and high costs of biomaterials, on which there is no clear consensus, should be considered regarding their use in tendon augmentation. When we look at the biomechanical results of our study, statistically significant results were obtained in all parameters, including maximum load, in the light of the data obtained at the end of the 4th week. These results suggest that in rats subjected to equal stress under standardized conditions, the dermis graft may have a positive effect on the tendon healing process with statistically significant high maximum force values in the experimental group.

Devana et al. [24] showed that stem cell injection improved the biomechanical properties of early Achilles tendon healing after transection of the tendon using stem cells, not the histological properties. The reason why the histological properties did not change may be that the tendon injury model was performed with transection. In our study, we performed our tendon injury model by incision of the tendon. In our study, histopathological examination was performed separately according to semiquantitative Movin and semiquantitative Bonar scores. In the Movin score, fibrillar arrangement, fibrillar structure, nucleus roundness, neovascularization and GAG content were found to be statistically significantly lower in the experimental group. In the Bonar score, collagen and vascularity increase were found to be statistically significantly lower in the experimental group. Also, In our study, we investigated the effect on healing by evaluating type 1 and type 3 collagen densities with immunohistochemical evaluation using a computer program. At the beginning of the healing period, type 3 collagen synthesis is more intense in the proliferation period. Collagen densities may vary during the proliferation and remodeling period. While both type 1 and type 3 collagen synthesis increases at the beginning of the healing period, type 3 collagen synthesis is more intense. In the late healing period along with the healing process, type 1 collagen density increases in the remodeling phase, type 3 collagen density decreases, and the type 1/type 3 collagen density ratio increases [13]. In our study, we found that type I collagen density and type I/type III collagen density ratio were significantly higher in the experimental group compared to the control group. In light of the data, it can be said that the dermis graft transitioned from the proliferation phase to the remodeling phase earlier at the end of the 4-week follow-up.

Limitation

There are some limitations in our study. The limitations such as the small number of animals, the follow-up period being limited to only 4 weeks, and the lack of genetic/molecular evaluations may create some limitations on the generalizability of the study. However, due to ethical concerns, the local ethics committee recommended that the number of animals should not be too high, and on the other hand, the difficulties such as the inability to conduct genetic/molecular studies due to budget constraints were some of the possible reasons for the limitations. The limited number of animals may have affected some results. The study could have been made stronger by evaluating the tendon section diameter, adhesion and genetic studies. The follow-up period of the animals could have been longer in order to see the long-term effect. Since it was an experimental study, clinical results could not be evaluated. Further experimental studies are needed for clinical use. Future studies can be designed with greater scope in terms of sample size and follow-up duration. Furthermore, genetic and molecular studies can be added to these comprehensive designs.

## Conclusion

The results of this study show that dermis grafts can contribute positively to tendon healing. Tendon repair with dermis grafts may be a good alternative to other methods for tendon augmentation or strengthening. Because of There is no standardized protocol yet for tendon augmentation after Achilles tendon injuries. The biomaterials, drugs and other methods used for augmentation are not easily accessible and their high costs limit their use. Donor site morbidity and surgical extraction can be considered disadvantages in autologous grafts. The experience of the surgeon and studies in the literature are important in terms of the materials and techniques to be used. According to the data we obtained in this study, dermis grafts can be used for tendon augmentation. However, further experimental studies are needed for clinical use.

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

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**Ethics Committee Approval:** Permission for this study was obtained by the Dicle University Animal Experiments Local Ethics Committee (DÜHADEK) with the protocol number 2022/41 dated 30.06.2022.

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**Peer-review:** Externally peer reviewed

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# Single-Center Outcomes of Autologous Hematopoietic Stem Cell Transplantation Accompanied by High-Dose Chemotherapy in Patients with Solid Organ Tumors

## Solid Organ Tümörlü Hastalarda Yüksek Doz Kemoterapi Eşliğinde Otolog Hematopoietik Kök Hücre Naklinin Tek Merkez Sonuçları

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## ABSTRACT

**Aim:** In contrast to hematologic diseases, the use of hematopoietic stem cell transplantation (HCT) for solid organ tumors is limited, with recommendations available only for certain selected diagnoses and cases.
**Methods:** Data from 16 adult patients who underwent HCT with a diagnosis of solid organ tumor between 2006-2023 were analyzed.
**Results:** The median age of the patients was 36.5 years (21–46), and 13 (81.2%) were male. Seven patients (43.7%) had testicular germ cell tumors (GCT), four (25%) had Ewing sarcoma, and five (31.3%) had other solid organ tumors. Autologous HCT was performed in 14 patients (87.5%) due to relapsed/refractory disease, and only five patients (31.3%) achieved a complete response to salvage therapy prior to transplantation. Post-transplant relapse occurred in 92.8% of patients, with a median progression-free survival (PFS) of 6.5 (2-32) months. Fourteen patients (87.5%) died, including two during transplantation, with a median overall survival (OS) of 53.0 (9–213) months. Although the median PFS for testicular GCT patients after autologous HCT was longer than that of other patients (12.0 vs. 4.5 months; p=0.04), the median OS was similar (90.0 vs. 46.0 months; p=0.52).
**Conclusion:** The literature regarding the role of HCT in solid organ tumors is generally based on retrospective data and periods when older treatment approaches are employed. With the current use of immunotherapy and targeted therapies, both the necessity and stage at which HCT should be performed should be further investigated, and new studies are needed to address this issue.

Keywords: Solid organ tumors, Germ cell tumors, Ewing sarcoma, Autologous hematopoietic stem cell transplantation

## ÖZ

**Amaç:** Hematopoetik kök hücre naklinin (HCT), hematolojik hastalıkların aksine, solid organ tümörlerinde kullanımı sınırlı olup, öneriler bazı seçilmiş tanılarda ve seçilmiş olgularda mevcuttur.
**Yöntem:** Solid organ tümörü tanısıyla, 2006-2023 yılları arasında HCT yapılan 16 erişkin hastanın verisi analiz edildi.
**Bulgular:** Hastaların ortanca yaşı 36.5 (21-46) olup, 13'ü (%81.2) erkekti. Hastaların 7'sinde (%43.7) testis kaynaklı germ hücreli tümör (GCT), 4'ünde (%25) Ewing sarkomu ve 5'inde ise diğer (%31.3) solid organ tümörü tanısı vardı. Otolog HCT, 14 (%87,5) hastaya relaps/refrakter hastalık nedeni ile uygulandı ve sadece 5 (%31.3) hasta nakil öncesi kurtarma tedavisine tam yanıtlıydı. Nakil sonrası relaps %92.8 hastada görülürken, ortanca progresyonsuz sağkalım süresi (PFS) süresi 6.5 (2-32) aydı. Hastalardan, 2'si nakilde olmak üzere, 14'ü (%87.5) öldü ve hastaların ortanca genel sağkalım süresi (OS) süresi 53.0 (9–213) aydı. Testis GCT hastalarının otolog HCT sonrası ortanca PFS'si diğerlerine göre daha uzun olsa da (12.0 ve 4.5 ay; p=0.04), ortanca OS'si benzerdi (90.0 ve 46.0 ay; p=0.52).
**Sonuç:** Solid organ tümörlerinde HCT'nin yerine dair literatür bilgileri genellikle eski tedavi yaklaşımların uygulandığı döneme ve retrospektif verilere dayanmaktadır. Günümüzde kullanımları ön plana çıkan immunoterapi ve hedefe yönelik tedavilerle birlikte, HCT'nin hem gerekliliği hem de hangi aşamada yapılmasının daha fazla sorgulanmalıdır ve bu yönde yeni çalışmalar gerekmektedir.

Keywords: Solid organ tümörleri, Germ hücreli tümör, Ewing sarkomu, Otolog hematopoietik kök hücre nakli

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## Introduction

Hematopoietic stem cell transplantation (HCT) is a process in which hematopoietic stem cells of any donor type and from any source are administered to a recipient to replace (autologous) or change (allogeneic) the hematopoietic system after intensive chemotherapy, which is also considered beneficial for the disease. Hematologic malignancies such as bone marrow-derived cancers and lymphoproliferative diseases, some hematologic and non-hematologic benign diseases, and some solid organ malignancies benefit from this treatment method at different stages of the treatment process, depending on the disease [1]. In the 1990s, with some successful outcomes obtained from the use of high-dose chemotherapy combined with autologous HCT (auto-HCT) in certain solid organ tumors, interest in this approach increased [2]. However, in the early 2000s, in addition to the possible exception of breast carcinoma, the benefit of this treatment approach for solid tumors remains uncertain, and many oncologists believe that it should be discontinued [3]. Failure to successfully complete prospective randomized trials in this direction and HCT-related toxicity have led to a decline in interest in this approach, although there is evidence suggesting that it may improve tumor response rates and/or possibly progression-free survival (PFS), especially in some selected patient subgroups. [4]. During the same period, HCT administered in combination with high-dose chemotherapy in adult patients was reported to have largely equivocal results in solid tumors other than breast carcinoma and germ cell tumors (GCTs) [5]. Based on current knowledge, the use of HCT in solid organ tumors is limited, and recommendations are available for selected diagnoses and cases [1,6].

In the 2015 guidelines, HCT was generally not recommended, except for solid tumors such as GCTs, neuroblastoma, medulloblastoma, selected breast cancer, and sarcoma, which were generally reiterated in the 2022 recommendations with very few changes. Although the primary diagnoses for HCT in the pediatric age group (neuroblastoma, medulloblastoma, and Ewing's sarcoma) and the adult age group (primarily GCTs and, to a lesser extent, Ewing's sarcoma and breast and ovarian cancers in selected cases) vary, there are recommendations for only auto-HCT in adult patients and allogeneic HCT (allo-HCT) in addition to auto-HCT in pediatric patients at the selected case level [1,6].

Based on the current knowledge, the use of HCT in solid organ tumors is limited, with recommendations available only for certain selected diagnoses and specific cases. In this retrospective study, we aimed to evaluate patients with solid organ tumors who underwent HCT with high-dose chemotherapy in light of the literature.

## Materials and Methods

Patients over the age of 18 years who were diagnosed with solid organ tumors and underwent HCT between 2006 and 2023 in the adult HCT unit of Akdeniz University Faculty of Medicine Hospital were included in the study. Data were collected from written patient files, an electronic hospital database, clinical records from the hematology and oncology departments, hospital central laboratory records, and the national death notification system. Information on sex, age, Eastern Cooperative Oncology Group (ECOG) performance score, comorbidities, date of diagnosis, initial treatment and response to this treatment, mobilization methods, transplant dates, preparation regimens, number of stem cells administered, engraftment status, post-transplant infectious processes, tandem transplantation status, relapsed disease and subsequent treatments, last visit dates, and survival status were recorded.

The post-transplant PFS status of the patients was evaluated. Post-transplant PFS was defined as the time from the date of transplantation to the date of disease progression, the date of the last follow-up if the patient was alive, or the date of death due to any cause. Overall survival (OS) was defined as the time from the date of diagnosis to the date of death from any cause or the date of the last follow-up.

### Statistical analysis

IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Descriptive statistics were used to analyze the data. Categorical data were

presented as numbers and ratios, and numerical data were presented as medians, minima, and maxima. Comparisons between independent groups were conducted using the Mann-Whitney U test, which is appropriate for non-normally distributed continuous variables. Kaplan-Meier survival analysis was applied for OS and PFS, and log-rank tests were used to examine the factors affecting survival.

## Results

Between 2006 and 2023, 19 patients with solid organ tumors who underwent HCT were identified, but 3 were excluded from the study because of insufficient data. The analysis included 16 patients with a median age of 36.5 years (21–46), 13 (81.2%) of whom were male. All the patients had an ECOG performance score of 0–1. Regarding additional comorbidities, one patient each had chronic renal failure, hypertension, and asthma. Seven patients had testicular GCT, four had Ewing sarcoma, two had gestational trophoblastic tumors (one choriocarcinoma), two had soft tissue sarcomas (one rhabdomyosarcoma and one synovial sarcoma), and one had osteosarcoma. In the first-line treatment after diagnosis, six patients received BEP (bleomycin, etoposide, cisplatin), three received IMA (ifosfamide, mesna, and adriamycin), two received IMA+HD-MTX (high-dose methotrexate), and one each received VAC-IE (vincristine, adriamycin, cyclophosphamide-ifosfamide, etoposide) and MTX. The treatment protocols for the 3 patients were not accessible. Patients received a median of three cycles (2–4) as first-line therapy. Fourteen out of 16 patients had relapsed/refractory disease prior to transplantation, including seven patients with primary refractoriness, and received a median of four (2–8) additional cycles of chemotherapy. Five of 11 patients achieved a complete response (CR), 3 had a partial response (PR), 2 had stable disease (SD), and 1 had progressive disease. All transplants were auto-HCTs; 10 patients were mobilized with chemotherapy+granulocyte colony-stimulating factor (G-CSF) and the others were mobilized with G-CSF alone. The time from diagnosis to transplantation was 6 months in 2 patients who underwent consolidative auto-HCT as first-line treatment, whereas the median time from diagnosis to transplantation was 29.5 (6–187) months in 14 patients who experienced relapse/refractory disease. Eleven patients received carboplatin+etoposide, four patients received high-dose (HD)-ICE (ifosfamide, carboplatin, etoposide), and one patient received busulfan+melphalan. After the preparation regimen, patients received a median of 4.7x106 (3.4–8.7) CD34+ stem cell infusions per kilogram. Two patients died in the first month post-transplant, one from neurological and cardiac complications, and the other from Klebsiella-induced sepsis, while still in the neutropenic period. The median neutrophil engraftment time for the other 14 patients was 10 (8–12) days, and the median platelet engraftment duration was 13 (11–27) days. The most common post-transplant complications were diarrhea and mucositis, which developed in all the patients.

A second auto-HCT (non-tandem) was performed in three patients (two with testicular GCT and one with gestational trophoblastic tumor). Prior to the second transplant, all three patients had progressive disease and received carboplatin+etoposide as the conditioning regimen. None of the patients experienced engraftment issues and no mortality related to the second transplant was observed. Among the three patients who underwent a second transplant, 13 of the 14 patients (92.8%) developed disease relapse after auto-HCT. The posttransplant PFS of these patients is a median of 6.5 (2–32 months). Due to relapsed/refractory disease, all patients received additional chemotherapy, with a median of three cycles (2–4) of different chemotherapy protocols. The OS for two patients (one with osteosarcoma who remained in remission after auto-HCT and another with testicular GCT who received chemotherapy following relapse after auto-HCT) was 46 and 39 months, respectively. All the other patients died. Two of the deaths occurred due to causes other than an active malignancy. During follow-up, only one patient developed secondary myelodysplastic syndrome (MDS). The median number of treatment lines administered to all patients, including transplant patients, was six (3–14) months, with a median OS of 53.0 (9–213) months. The demographic characteristics, treatments, response status, and survival outcomes of the patients are presented in Table 1.

Table 1. Demographic characteristics, treatments, response, and survival status of the patients.

| Parameters | | Patients (n=16) |
|---|---|---|
| Age (Median, years) | | 36.5 (21–46) |
| Gender | Male | 13 (81.2%) |
| | Woman | 3 (18.8%) |
| Comorbidity | Hypertension | 1 (6.2%) |
| | Asthma | 1 (6.2%) |
| ECOG | 0–1 | 16 (100%) |
| Solid Organ Tumor | Testicular GCT | 7 (43.7%) |
| | Ewing sarcoma | 4 (25%) |
| | Gestational trophoblastic tumor | 2 (12.5%) |
| | Soft tissue sarcoma | 2 (12.5%) |
| | Osteosarcoma | 1 (6.2%) |
| RR disease before auto-HCT | | 14 (87.5%) |
| Mobilization | Chemotherapy+G-CSF | 10 (62.5%) |
| | G-CSF | 6 (37.5%) |
| Time from diagnosis to auto-HCT (Median, months) | | 29.5 (6-187) |
| Response prior to auto-HCT | Complete response | 5 (31.3%) |
| | Partial response | 3 (18.8%) |
| | Stable disease | 2 (12.5%) |
| | Progressive disease | 1 (6.2%) |
| | Uncertain | 5 (31.2%) |
| Conditioning regimen | Carboplatin+Etoposide | 11 (68.7%) |
| | HD-ICE | 4 (25%) |
| | Busulfan+Melphalan | 1 (6.2%) |
| Given CD34+ cells (Median, cells/kg) | | 4.7x10^6 (3.4–8.7) |
| Engraftment time (Median, days) | Neutrophil | 10 (8–12) |
| | Thrombocyte | 13 (11–27) |
| Insufficient engraftment | | 2 (12.5%) |
| Auto-HCT related mortality | | 2 (12.5%) |
| Relapse after auto-HCT | Exist | 13 (81.2%) |
| | None | 1 (6.2%) |
| Latest status | Alive | 2 (12.5%) |
| | Death | 14 (87.5) |

Auto-HCT; Autologous hematopoietic stem cell transplantation, ECOG; Eastern Cooperative Oncology Group (ECOG) performance score, GCT; Germ cell tumor, G-CSF; Granulocyte colony stimulating factor, HD-ICE; High-dose ifosfamide, carboplatin, etoposide,RR; relapsed and refractory

Patients with testicular GCT were compared with other patients (Table 2). There was no difference between the two groups in terms of median age, time from diagnosis to auto-HCT, or the total number of treatment lines, including auto-HCT. While PFS was significantly longer after auto-HCT in testicular GCT patients than in patients with other solid tumors, the OS in both groups was similar.

Table 2. Comparison of testicular germ cell tumor and other solid organ tumors.

| | Testicular GCT (n=7) | Other solid tumors (n=8) | P value |
|---|---|---|---|
| Age (Median, years) | 41 | 36.5 | 0.71 |
| Time from diagnosis to auto-HCT (Median, months) | 86.2 | 69.6 | 0.42 |
| Total number of treatment lines (Median) | 5.5 | 6 | 0.17 |
| PFS after auto-HCT (Median, months) | 12 | 4.5 | 0.04 |
| OS (Median, months) | 90 | 46 | 0.52 |

Auto-HCT; Autologous hematopoietic stem cell transplantation, GCT; Germ cell tumor, OS; Overall survival, PFS; Progression-free survival

## Discussion

We present the outcomes of 16 adult patients who underwent auto-HCT, 43.7% of whom were diagnosed with GCT, 25% with Ewing sarcoma, and 31.3% with other solid organ tumors. Relapse occurred in 92.8% of patients post-transplant, with a median PFS of 6.5 (2-32) months. A total of 14 patients (87.5%) died, including 2 at the time of transplantation, and the median OS duration for these patients was 53.0 (9–213) months.

Randomized controlled studies are infrequent, and information on the role of HCT in solid organ tumors is generally based on retrospective data. The most comprehensive data and information are available from the European Society for Blood and Marrow Transplantation (EBMT) registry, which reported that by the end of 2022, 65,586 transplants (97% auto-HCT and 3% allo-HCT) were performed in 47,221 patients with solid organ tumors, 52% of whom were women and 58% of whom were in the adult age group (≥18 years). One of the striking points here is that, while auto-HCT was primarily performed in the adult age group before the 2000s, it has been preferred in the pediatric age group at a similar

or higher rate since then. The primary reason for this shift appears to be the documented success of auto-HCT in treating different diagnoses across age groups over time [7]. Currently, auto-HCT is predominantly used in pediatric cases of diseases such as neuroblastoma, medulloblastoma, and Ewing sarcoma [8,9]. In adults, it is primarily applied in GCT, with less frequent use in Ewing sarcoma, other sarcomas, breast cancer, and ovarian cancer [7].

Although HCT emerged as a potential option for adult solid organ tumors after the 1990s, the lack of randomized trials designed to either validate or refute its efficacy has resulted in most of the current knowledge being based on nearly 30 years of retrospective experience [7]. In recent years, particular focus has been placed on its effectiveness in high-risk advanced-stage breast cancer in adults. Studies have demonstrated that auto-HCT, when used as an adjuvant treatment, prolongs PFS and improves OS in certain subgroups [10,11]. However, according to the results of 15 randomized controlled trials conducted until 2011, auto-HCT significantly improved PFS and was reported to have no impact on OS [12]. In a 2020 study presenting updated data with 20 years of follow-up, compared with standard adjuvant chemotherapy, auto-HCT significantly improved OS only in very high-risk patients (with involvement of ≥10 axillary lymph nodes) [13]. However, considering that the patients in this study were also treated with the same treatment strategies and agents for breast cancer 20 years ago, and the significant increase in OS and PFS provided by targeted therapies in current approaches (trastuzumab, humoral therapies, drug-antibody conjugates, and immune checkpoint inhibitors) [14], auto-HCT no longer seems to be a treatment strategy in this patient group. Since breast cancer patients are now treated with current oncological approaches, no patients have been diagnosed with breast cancer who underwent auto-HCT in our clinic.

Unlike other solid organ tumors treated with chemotherapy alone, GCT is a curable cancer, even in advanced stages, with a 5-year OS rate of over 95%, especially with cisplatin-based treatment. However, an estimated 20–30% of patients either have refractory disease or experience disease recurrence [15]. Unlike the non-standardized and less effective salvage treatments before 1990, over the past 20–25 years, high-dose chemotherapy combined with auto-HCT has shown longer PFS and OS advantages in relapsed/refractory patients than classical salvage chemotherapy [16]. Studies have highlighted that conditioning regimens with carboplatin and etoposide are particularly effective in this patient group, with 5-year PFS and OS rates reported to be approximately 50% with auto-HSCT [17]. Experience has been obtained primarily from male and testicular cancer patients with GCTs. The number of female patients with relapsed/refractory GCT, mostly of ovarian origin, who underwent auto-HCT with intensive chemotherapy was very low. Nevertheless, the recommendations for GCT in female patients are similar [18]. Previous studies have shown that age ≥ 40 years, which is an unfavorable prognostic indicator in addition to metastatic disease and histological subtype, is not an unfavorable prognostic factor when auto-HCT is combined with intensive chemotherapy. In addition, it has been reported that this treatment approach has similar toxicity and safety in patients aged ≥ 40 years and those aged < 40 years; therefore, it can be applied to patients aged ≥ 40 years who are suitable for treatment [19]. In contrast to gonadal GCTs, non-gonadal GCTs, which are rarer, have worse responses to both first-line and salvage therapies. These patients have OS rates of 40–50%, whereas the OS rate in relapsed patients is approximately 10% [20,21]. In summary, auto-HCT with high-dose chemotherapy (carboplatin+etoposide) is recommended as a standard approach for patients with GCTs, primarily those refractory to platinum-based chemotherapy or those who have relapsed, rather than first-line treatment [6,17,22]. In our study, 3 out of 5 patients ≥ 40 years of age (40–46) were GCTs patients, and all GCTs occurred in men, originated from the testis, and were of non-seminoma histological subtype. The carboplatin+etoposide regimen was used as the conditioning regimen in all our GCTs patients, except for one who received the HD-ICE regimen. Compared with other solid organ tumors, auto-HCT in testicular GCT patients provided a PFS advantage, but no OS advantage.

However, studies on other solid organ malignancies are limited. Although data on different histological

subtypes are limited, there is no strong evidence supporting the efficacy of auto-HCT in soft tissue sarcomas [22]. In a study conducted on patients with advanced-stage ovarian cancer and those with limited or extensive small cell lung cancer, high-dose chemotherapy as first-line treatment did not provide any additional advantage in terms of PFS or OS [3]. Data on auto-HCT in adult patients with other chemosensitive cancers, including Ewing/PNET (primitive neuroectodermal tumors) and certain CNS tumors, are limited, and this approach cannot be recommended as a standard [6]. However, based on studies in pediatric age groups with solid tumors such as Ewing sarcoma and medulloblastoma, high-dose chemotherapy and auto-HCT may be potential clinical options in selected adult and adult young adolescent (AYA) patients [23,24]. In our study, the most common patient group to receive auto-HCT after GCTs was the AYA (adolescent and young adult) group with Ewing sarcoma (26% of patients).

Although interest in tandem transplantation is increasing due to the advantageous results provided by HCT in some pediatric and adult patient groups, studies in adult patients with adult breast cancer have not shown any additional benefits compared to single HCT. In pediatric patients, no additional benefit has been shown, except for the potential benefit in selected neuroblastoma and Ewing sarcoma patients with a poor prognosis [7,11,13]. The information and experience regarding allo-HCT is much weaker than that regarding auto-HCT. Checkpoint inhibitors, such as nivolumab/pembrolizumab (PD-1/PD-L1) and ipilimumab (CTLA-4), which have achieved successful results through T-cell cytotoxicity in cancer immunotherapy [25], led to the idea that similar outcomes could be obtained with donor-derived healthy T cells following allo-HCT. However, contrary to expectations, allo-HCT has been nearly abandoned, particularly in the adult patient group, owing to both transplant-related toxicity and the success achieved with molecularly targeted therapies. Therefore, allo-HCT is now recommended only within the scope of clinical trials [7,26]. In our clinic, no patients with solid organ tumors underwent allo-HCT.

One of the most critical aspects of this treatment option is treatment-related mortality (TRM), as we unfortunately lost two patients due to sepsis caused by engraftment failure/delay. In fact, the exclusion of total body irradiation (TBI), which does not provide a treatment advantage and leads to late complications, along with the use of peripheral stem cells, has significantly reduced the TRM over time to approximately 1%. Another important point is the HCT recommendations according to the response status or relapse time of patients. In selecting patients and diseases in which auto-HCT is planned in the first-line setting (primarily pediatric patients), HCT is recommended for patients with CR, very good partial response (VGPR), and PR to induction therapy, whereas auto-HCT is recommended for patients with SD or minimal response (MR) (<50%) in early phase studies. HCT is not recommended for this patient group because the life expectancy of unresponsive/refractory and progressive patients is very short, even after transplantation. The recommendation for HCT in patients with relapsed disease is limited to those who have not previously received HCT, respond to previous treatment, and experience relapse 12 months after diagnosis [7]. In our study, 14 patients (87.5%) underwent auto-HCT for relapsed/refractory disease, and only five (31.2%) achieved CR.

## Conclusion

The literature recommendations are primarily based on retrospective data, usually from past treatment algorithm periods. In the era of immunotherapy and targeted therapies, which has become prominent in current treatment algorithms, there is a need for updated randomized controlled trials or well-designed registry studies to provide information on the necessity of HCT and the optimal timing for its administration.

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# Effectiveness of Intrauterine Levonorgesterel-Releasing Device in the Treatment of Endometrial Hyperplasia in Obese Patients

## Endometrial Hiperplazi Tedavisinde İntrauterin Levo-Norgestrel Salgılayan Cihazların Obez Hastalarda Etkinliğinin Araştırılması

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## ABSTRACT

**Aim:** Endometrial hyperplasia (EH) is a precursor lesion of endometrial adenocarcinoma, the most common gynecological malignancy in women. Endometrial hyperplasias divided in two groups: non-atypical hyperplasia and atypical hyperplasia. The most commonly used treatment approach is progestin therapy for non-atypical hyperplasias. In this study, we aimed to compare the regression outcomes in control biopsies between obese and non obese patients diagnosed with non-atypical endometrial hyperplasia who were treated with an LNG-IUD and followed up in our clinic.

**Methods:** This study conducted was patients were diagnosed with non-atypical endometrial hyperplasia via endometrial biopsy and treated with intrauterine levonorgestrel. Patient data were reviewed retrospectively. Patients were divided into two groups based on BMI: obese and non-obese. İn regression and treatment success were assessed between control endometrial biopsies taken at 6 and 12 months in the obese and non-obese groups.

**Results:** A total of 110 patients were included in the study who were categorized into two groups according to BMI as obese and non-obese. Data of 32 patients in the obese patient group and 78 patients in the non-obese patient group were examined. In obese patients, the regression rate at the 6th month was 62.5%, and the regression rate at the 12th month was 90.6%. In non-obese patients, the regression rate at the 6th month was 96%, and the regression rate at the 12th month was 97.4%. In the obese patient group, both the 6th-month regression rate and the 12th-month regression rate were statistically significantly lower compared to the non-obese patient group. ($p < 0.05$).

**Conclusions:** Obesity negatively affects the response to progesterone treatment and that regression rates decrease as BMI increases.

Keywords: Endometrial hyperplasia, Obesity, Progestin, Levo-norgestrel

## ÖZ

**Amaç:** Endometrial hiperplazi; en sık görülen jinekolojik kanser olan endometrium adenokarsinomunun öncül lezyonudur. Bu çalışmada kliniğimizde atipisiz endometrial hiperplazi tanıyla levo-norgestrel salgılayan intrauterine cihaz ile tedavi edilen obez ve obez olmayan hastaların kontrol biyopsileri ile regresyon oranlarını karşılaştırmayı amaçladık.

**Yöntemler:** Çalışma endometrial biyopsi ile atipisiz endometrial hiperplazi tanısı alan ve intrauterine levonorgestrel ile tedavi edilen hastalar üzerinde yapıldı. Hastalara ait veriler retrospektif olarak incelendi.Hastalar vücut kitle indeksine göre obez ve obez olmayan olarak iki gruba ayrıldı.Obez ve obez olmayan hasta gruplarında 6. ve 12. ayda alınan kontrol endometrial biyopsileri incelenerek regresyon oranı ve tedavi başarısı araştırıldı.

**Bulgular:** Vücut kitle indeksine göre obez ve obez olmayan olarak iki grubu ayrılan toplam 110 hasta çalışmaya dahil edildi. Obez hasta grubunda 32 hasta, obez olmayan hasta grubunda 78 hasta verileri incelendi. Obez hasta grubunda 6. ayda regresyon oranı %62.5 ve 12. ayda regresyon oranı %90.6 olarak saptandı. Obez olmayan hasta grubunda 6. ayda regresyon oranı %96 ve 12. ayda regresyon oranı %97.4 olarak saptandı. Obez hasta grubunda hem 6. hem 12. ay regresyon oranı normal kilolu hasta grubuna göre istatistiksel olarak anlamlı düzeyde düşük saptandı. ($p < 0.05$).

**Sonuç:** Obezite progesteron tedavisine cevabı olumsuz etkiler ve vücut kitle indeksi arttıkça regresyon oranı azalır.

Anahtar kelimeler: Endometrial hiperplazi, Obezite, Progestin, Levo-norgestrel

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## Introduction

Endometrial hyperplasia (EH) occurs due to the abnormal proliferation of glandular epithelial cells and stromal cells within the endometrial tissue lining the uterine cavity [1]. It is considered a precursor lesion of endometrial adenocarcinoma, the most common gynecological malignancy in women. Endometrial cancer ranks as the sixth most frequent cancer among women, with its incidence reportedly increasing worldwide [2]. In women of reproductive age, estrogen and progesterone are secreted in a specific sequence each month from developing follicles in the ovarian tissue. During the follicular phase, estrogen is secreted, and the follicle completes its development, culminating in ovulation at mid-cycle. Progesterone release into the bloodstream begins with ovulation. Progesterone serves to protect the endometrial tissue from the proliferative effects of estrogen, acting as a safeguard against uncontrolled proliferation [3].

The most significant risk factor for EH is anovulation and other pathologies causing unopposed estrogen exposure, such as polycystic ovary syndrome (PCOS), hyperprolactinemia, hypo/hyperthyroidism, early menarche, late menopause, and nulliparity. During anovulation, elevated estrogen levels persist in the bloodstream, lacking the balancing effect of progesterone, leading to uncontrolled proliferation of endometrial epithelial cells. Another critical risk factor is obesity. Obesity contributes to anovulation and increases estrogen production through heightened aromatization in adipose tissue, further stimulating endometrial proliferation. Other less common risk factors include estrogen-secreting tumors, hormonal therapies with exogenous estrogen exposure, and certain genetic disorders and syndromes [4].

The most common clinical presentation of EH is abnormal uterine bleeding in premenopausal women and vaginal bleeding in postmenopausal women [5]. By performing endometrial sampling, pathologists classify EH according to the 2014 WHO classification into two groups: non-atypical hyperplasia (benign hyperplasia) and atypical hyperplasia/endometrial intraepithelial neoplasia [6]. For non-atypical hyperplasias, hysterectomy is not the primary treatment choice. The most commonly used treatment approach is progestin therapy. Exogenously administered progestins induce endometrial decidualization, inhibiting the progression of hyperplasia to malignancy. Various progestin administration methods are available, with the most widely used being oral, vaginal, and intramuscular formulations, as well as the levonorgestrel-releasing intrauterine device (LNG-IUD) [7].

In this study, we aimed to compare the regression outcomes in control biopsies between obese and normal-weight patients diagnosed with non-atypical endometrial hyperplasia who were treated with an LNG-IUD and followed up in our clinic.

## Materials and Methods

This study was conducted on patients who presented to the Obstetrics and Gynecology Clinic at Alanya Training and Research Hospital between 2021 and 2024. The patients were diagnosed with non-atypical endometrial hyperplasia via endometrial biopsy and treated with intrauterine levonorgestrel. Patient data were reviewed retrospectively. Age, height, weight, body mass index (BMI), history of diabetes, smoking, presence of PCOS, age at menarche, and parity status were recorded. Patients were divided into two groups based on BMI: obese and non-obese. BMI over 30 were included in the obese group, and BMI under 30 were included in the non-obese group.

Patients with a BMI of 40 or higher were classified as super-obese. Obese and non-obese patients were analyzed for risk factors related to EH. Additionally, differences in regression and treatment success were assessed between control endometrial biopsies taken at 6 and 12 months in the obese and non-obese groups.

The endometrial curretage materials and the control curretages performed at 6 months and 12 months after therapy are examined by a consultant pathologist.(Figure-1) In an endometrial curretage specimen, increased gland to stroma ratio with irregular, branching and dilated glands devoid of atypia is diagnosed as ‘endometrial hyperplasia without atypia’. Regression and treatment success is regarded as if there is no hyperplasia in the control curretage materials. (Figure-2)

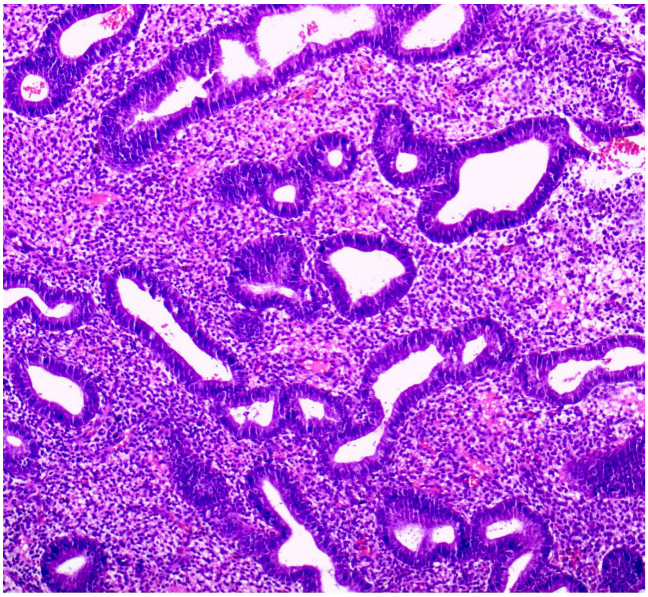

Figure 1. Endometrial hyperplasia without atypia, HE x200, Increased gland/stroma ratio, irregular branching and dilated endometrial glands

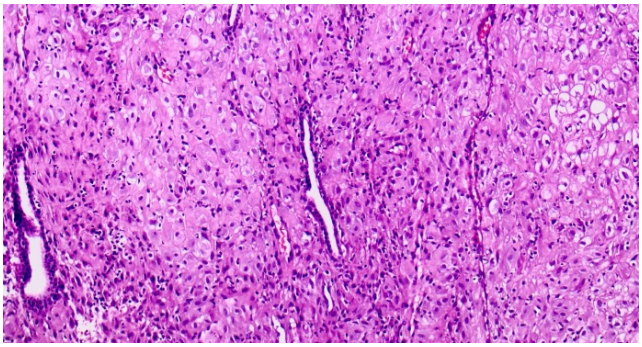

Figure 2. Regression at 6 months after LNG-IUD therapy, HE x200, pseudodecidualization in endometrial stroma due to progestin effect, no hyperlasia remained.

The study was approved by the ethics committee of Alanya Training and Research Hospital. (20-5 11/09/24)

**Exclusion Criteria:** Patients who could not tolerate intrauterine levonorgestrel therapy or experienced side effects, those with uncontrolled abnormal uterine bleeding, those who experienced expulsion of the intrauterine device, patients with concurrent gynecological conditions requiring surgery, and patients in whom control biopsies at the 6th or 12th month revealed atypical hyperplasia, endometrial intraepithelial neoplasia, or invasive carcinoma were excluded from the study.

**Statistical Analysis:** Descriptive statistics of the data include mean, standard deviation, median, minimum, maximum, frequency, and ratio values. The distribution of variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For independent quantitative variables with a normal distribution, an independent samples t-test was used, while the Mann-Whitney U test was employed for independent quantitative variables with a non-normal distribution. Chi-square tests were applied for independent qualitative data analysis. SPSS 27.0 software was used for the analysis.

## Results

A total of 115 patients were included in the study. One patient with uncontrolled abnormal uterine bleeding, two patients who expelled the intrauterine device, and two patients whose control pathology during treatment indicated atypical hyperplasia were excluded. The final analysis was conducted on 110 patients, who were categorized into two groups according to BMI as obese and non-obese. Data of 32 patients in the obese patient group and 78 patients in the non-obese patient group were examined.

The overall regression rate at the 6th month for all patients was calculated to be 86.3%, while the regression rate at the 12th month was 95.4%. Demographic data of the patients and regression rates are presented in Table 1. In obese patients, the regression rate at the 6th month was 62.5%, and the regression rate at the 12th month was 90.6%. In the obese patient group, both the 6th-month regression rate and the 12th-month regression rate were statistically significantly lower compared to the non-obese patient group ($p < 0.05$).

There was no statistically significant difference between the obese and non-obese patient groups regarding height, age at menarche, smoking status, and parity ($p > 0.05$). However, there was a statistically significant difference between the two groups in terms of age, diabetes, and PCOS data ($p < 0.05$). Data for the obese and non-obese patient groups are presented in Table 2.

Table 1. Demographic data of all patients

| | | Mean.±ss/n-% | | |
|---|---|---|---|---|
| Age | | 47.3 | ± | 2.0 |
| BMI | | 28.3 | ± | 4.4 |
| Menarche age | | 12.1 | ± | 0.8 |
| Smoking | (-) | 86 | - | 81.1% |
| | (+) | 24 | - | 18.9% |
| Diabetes Mellitus | (-) | 95 | - | 90.1% |
| | (+) | 15 | - | 9.9% |
| PCOS | (-) | 97 | - | 67.6% |
| | (+) | 13 | - | 32.4% |
| Parite | Nullipar | 3 | - | 2.7% |
| | Primipar | 35 | - | 95.5% |
| | Multipar | 72 | - | 1.8% |
| 6th month regression rate | | 95 | - | 86.3% |
| 12th month regression rate | | 105 | - | 95.4% |

Table 2. Comparison of obese and non-obese patients

| | | Obese Patients (n:32 29,1%) | | | Non-Obese Patients (n:78 70,9%) | | | P value |
|---|---|---|---|---|---|---|---|---|
| | | Mean.±ss/n-% | | | Mean.±ss/n-% | | | |
| Age | | 45.6 | ± | 2.0 | 47.8 | ± | 1.7 | 0.000 |
| Weight(kg) | | 89.8 | ± | 9.5 | 68.2 | ± | 6.5 | 0.000 |
| Length(m) | | 1.6 | ± | 0.0 | 1.6 | ± | 0.0 | 0.381 |
| BMI | | 33.9 | ± | 3.4 | 26.0 | ± | 2.2 | 0.000 |
| Menarche age | | 12.0 | ± | 0.7 | 12.2 | ± | 0.9 | 0.457 |
| Smoking | (-) | 25 | - | 78.1% | 61 | - | 78.2% | 0.993 |
| | (+) | 7 | - | 21.9% | 17 | - | 21.8% | |
| Diabetes Mellitus | (-) | 23 | - | 71.8% | 72 | - | 92.3% | 0.004 |
| | (+) | 9 | - | 28.2% | 6 | - | 7.7% | |
| PCOS | (-) | 24 | - | 75% | 73 | - | 93.5% | 0.006 |
| | (+) | 8 | - | 25% | 5 | - | 6.5% | |
| 6th month biopsy | Benign | 20 | - | 62.5% | 75 | - | 96.0% | 0.000 |
| | Hyperplasia without atypia | 12 | - | 37.5% | 3 | - | 4.0% | |
| 12th month biopsy | Benign | 29 | - | 90.6% | 76 | - | 97.4% | 0.073 |
| | Hyperplasia without atypia | 3 | - | 9.4% | 2 | - | 2.6% | |

BMI: Body mass index, PCOS:polycystic ovarian syndrome, IUD:ıntrauterine device

## Discussion

The incidence of EH in America is approximately 1-2 per 100,000 women [8]. Hyperplasias are precursor lesions of endometrial cancers and based on the presence of atypia, the risk of progression to invasive carcinoma in hyperplasias is less than 1% for non- atypical hyperplasias and around 29% for atypical endometrial hyperplasias. The recommended and widely used method for atypical hyperplasias is surgical intervention, while the most common treatment for non-atypical hyperplasias is progesterone therapy due to the low progression risk [9]. Although different regression rates for non-atypical hyperplasia have been reported after the oral and intrauterine use of progesterone in various studies, intrauterine administration of progesterone has been shown to be more successful than oral use [10-14]. In several studies, regression rates with oral progesterone usage range from 54% to 84% [10,13], whereas one study reported a regression rate of 94.8% with LNG-IUD [11]. One of the most important factors affecting the treatment response in non-atypical endometrial hyperplasia is the duration of treatment. In a meta-analysis examining the effect of treatment duration on regression, 13 studies involving 3,174 patients comparing LNG-IUD therapy and systemic progesterone therapy were evaluated, and 2 studies were excluded due to insufficient data on treatment duration. In the meta-analysis, patients receiving treatment for less than 6 months were included in the untreated group. Six months after the end of treatment, the regression rate in LNG-IUD patients was found to be 86%, while in patients receiving systemic progesterone, it was 72%. After the 12th month following treatment, these rates were 80% and 51%, respectively [15]. In our study, premenopausal patients who had been on LNG-IUD treatment for at least 1 year were included, and the regression rates for all patients in the study were found to be 86.3% at 6 months and 95.4% at 1 year.

Risk factors for endometrial cancer are associated with high levels of unopposed estrogen exposure. Among these, the most significant factors include early menarche, late menopause, exogenous estrogen therapy, tamoxifen treatment, nulliparity, infertility, and PCOS. Other risk factors include advanced age, hypertension, diabetes, hereditary nonpolyposis colorectal cancer, and obesity [16]. Obesity is also an important risk factor in the development of EH. The risk of developing

endometrial cancer in untreated obese patients with atypical endometrial hyperplasia is 1.6%, while the risk of cancer development in untreated obese patients with atypical hyperplasia ranges from 20% to 30%. Although hysterectomy is known as a treatment option for atypical patients, due to the increased comorbidities in obese patients, progesterone therapy is again recommended as a treatment option [17]. Furthermore, studies have reported that intrauterine progesterone therapy is more effective than oral treatment in patients with obesity [18,19].

Obesity is known to increase endometrial proliferation due to both causing anovulation and increased estrogen synthesis [4]. Furthermore, obesity significantly affects the pharmacokinetic properties of many medications, influencing their absorption, metabolism, and distribution, which reduces the effectiveness of drugs compared to those in individuals of normal weight [20,21]. For these reasons, obesity is a risk factor for EH, it also reduces the effectiveness of its medical treatment. Additionally, although there are only a few studies in the literature that specifically examine obese patients with EH, it has been reported that the progression rates of hyperplasia increase as BMI rises. In one study, the regression rate in patients with endometrial hyperplasia and a BMI below 30 who used LNG-IUD was reported to be 100%, while in patients with a BMI over 40, this rate was reported to be 77.4% [17]. Another study found that in obese patients with atypical endometrial hyperplasia treated with progesterone, the reported regression rate (46%) was significantly lower than that of normal-weight patients documented in the literature [22]. Moreover, in obese patients receiving systemic progesterone therapy for EH, there was an increase in comorbidities such as cardiovascular issues and hypertension due to weight changes, which negatively impacted the treatment process, decreased regression rates, and increased hyperplasia recurrences. These conditions are particularly more common in super obese patients, highlighting the need for monitoring and managing comorbid conditions that may affect treatment outcomes in patients receiving progesterone therapy [23].

In our study, the responses of patients with atypical endometrial hyperplasia to LNG-IUD treatment and their regression levels were examined. While no statistically significant differences were found between obese and non-obese patients regarding smoking habits, height, menarche age, and parity values, it was determined that hyperplasia began statistically earlier in obese patients. In the obese patient group, the prevalence of diabetes and PCOS was found to be significantly higher compared to normal-weight patients. In our study, the regression rate in obese patients was 62.5% at the 6th month and 90.6% at the 12th month, while in non-obese patients, these rates were 96% and 97.4%, respectively, indicating a statistically significant difference. Among the 32 obese patients classified by BMI, no regression was observed in 2 super obese patients (BMI over 40) at the 6th month (0%), while regression was detected in 1 patient at the 12th month, resulting in a regression rate of 50% among super obese patients.

**Limitations:** The most restrictive point of this study is its conducted retrospectively. Another limitation is the relatively small number of patients examined in the study.

In conclusion, our study, which examined the effects of obesity on the response to LNG-IUD treatment in patients without atypical endometrial hyperplasia, demonstrated that the risks of PCOS and diabetes are higher in obese patients. Additionally, it showed that obesity negatively affects the response to progesterone treatment and that regression rates decrease as BMI increases. Therefore, it highlights the need for closer and more careful monitoring of obese patients with endometrial hyperplasia, both regarding their response to treatment in terms of regression and progression, and in terms of the development of comorbidities that could affect the treatment process and increase the risk of endometrial cancer.

**Conflict of Interest:** The authors declare no conflicts of interest

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**Peer-review:** Externally peer reviewed.

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# Correlation Between Suicidal Behavior and Depression, Anxiety, Stress Levels and Sociodemographic Characteristics in University Students

## Üniversite Öğrencilerinde İntihar Davranışının Depresyon, Anksiyete, Stres Düzeyleri ve Sosyodemografik Özellikler ile İlişkisi

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## ABSTRACT

**Aim:** Studies conducted on university students have reported high levels of depression, anxiety and stress as well as suicidal thoughts and suicide attempts. This study aimed to determine the correlation between suicidal behavior and depression, anxiety, stress levels and sociodemographic characteristics in university students.

**Method:** Participants who agreed to participate in this online study were asked to fill in the sociodemographic data form and the Depression Anxiety Stress Scale-21 (DASS-21). Among the 530 participants, 517 (97.6%), having read information about the study, agreed to participate, while 13 (2.4%) declined.

**Results:** In this study, 36% of the participating university students had a history of major suicidal ideation, 6.4% currently experienced major suicidal ideation and 14.7% had attempted suicide. Depression, anxiety and stress scores were found to be higher in university students who had attempted suicide or currently experienced major suicidal ideation compared to those who had/did not (p≤0.001). With regard to sociodemographic factors; perceived and actual academic performance levels, socioeconomic status, current dieting status, sleep problems, smoking, daily time spent online, chronic diseases, and past or current psychiatric treatment were found to be common risk factors for both current major suicidal ideation and suicide attempt status (p≤0.05).

**Conclusion:** Having found high levels of depression, anxiety and stress among university students in this study, we consider that it is necessary to investigate the factors associated with suicidal ideation and suicide attempts, and that comprehensive psychosocial support units and programs should be developed to protect students' mental health and reduce risk of suicide.

Keywords: Suicide, university students, depression, anxiety, stress, sociodemographic characteristics

## ÖZ

**Amaç:** Üniversite öğrencileri ile yapılan çalışmalarda, depresyon, anksiyete ve stres düzeylerinin, intihar düşünce ve girişimlerinin yüksek oranlarda olduğu bildirilmektedir. Bu çalışmada üniversite öğrencilerinde intihar davranışının depresyon, anksiyete, stres düzeyleri ve sosyodemografik özellikler ile ilişkilisinin belirlenmesi amaçlanmıştır.

**Yöntem:** İnternet ortamında gerçekleştirilen çalışmada, araştırmaya katılmayı kabul eden katılımcılardan sosyodemografik veri formu ve Depresyon Anksiyete Stres Ölçeği-21 (DASÖ-21) ölçeklerini doldurmaları istenmiştir. Çalışmaya katılan 530 katılımcının 517'si (%97,6) çalışma hakkındaki bilgilendirmeyi okuyup, çalışmaya katılmayı kabul ederken 13'ü (%2,4) çalışmaya katılmayı reddetmiştir.

**Bulgular:** Çalışmamızda üniversite öğrencilerinin %36'sında geçmişte ciddi intihar düşüncesi, %6,4'ünde mevcut ciddi intihar düşüncesi ve %14,7'sinde intihar girişimi olduğu tespit edilmiştir. İntihar girişiminde bulunan veya mevcut ciddi intihar düşüncesi olan üniversite öğrencilerinde olmayanlara kıyasla depresyon, anksiyete ve stres puanları daha yüksek olarak belirlenmiştir (p≤0,001). Sosyodemografik etkenlerdense akademik başarı düzeyi ve algısı, sosyoekonomik düzey, güncel diyet yapma durumu, uyku sorunu varlığı, sigara kullanımı, günlük internet kullanım süresi, kronik hastalık varlığı, geçmişte veya halen psikiyatrik tedavi alma durumu hem mevcut ciddi intihar düşüncesi hem de intihar girişiminde bulunma durumu için ortak risk faktörleri olarak belirlenmiştir (p≤0,05).

**Sonuç:** Üniversite öğrencilerinde depresyon, anksiyete ve stres düzeylerini yüksek olarak saptadığımız çalışmamızda intihar düşüncesi ve girişimi ile belirlenen ilişkili faktörlerin araştırılmasının gerekli olduğunu, öğrencilerin ruh sağlığını korumak ve intihar riskini azaltmak amacıyla kapsamlı psikososyal destek birimleri ve programlarının geliştirilmesi gerektiğini düşünmekteyiz.

Anahtar kelimeler: İntihar, üniversite öğrencileri, depresyon, anksiyete, stres, sosyodemografik özellikler

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## Introduction

University years are a period of transition from adolescence to adulthood during which individuals face many social, economic, academic, emotional and societal psychosocial challenges [1,2]. Students may also experience various mental problems such as depression and anxiety disorders, as well as attention deficit hyperactivity disorder, social media addiction, sleep problems, alcohol and substance use disorders. Depression, anxiety and stress symptoms are reported to be common in university students, although they vary depending on gender, economic status and other sociodemographic variables [2]. In a study conducted by Bayram and Bilgel (2008) in Turkey, the prevalence of depression, anxiety and stress in university students was found to be 27.1%, 47.1% and 27%, respectively [3]. A study conducted in Malaysia on university students (2013) found that 37.2% of the participants had depression, 63% anxiety and 23.7% stress [4]. Depression and anxiety can cause university students to feel sad, anxious, guilty and worthless, lead to loss of interest, sleep problems and impaired concentration, thereby creating problems such as poor academic performance [5]. Stress is defined as an individual's physical, mental or emotional response to conflicts, pressures and environmental tensions [6]. In addition to the fact that anxiety and stress have common biological bases, the stress experienced by students may increase their anxiety levels and facilitate the emergence of anxiety disorders [7]. Factors such as family problems, economic difficulties, academic failure, lack of social support and chronic physical illness may increase the risk of developing depression and anxiety symptoms, and negatively affect quality of life. In studies on suicide, it is stated that university students are in a more risky group in terms of suicide due to their age. In addition, it is stated that university students with suicidal behaviour experience more stressful life events in their lives than those without suicidal behaviour [8].

It has been reported in the literature that high levels of depression, anxiety and stress increase the likelihood of suicide attempts in university students [9]. According to the World Health Organization (WHO), suicide is the second most common cause of death among young people [10]. We hypothesised that, university students experience more stress, anxiety and depression and therefore have a higher risk of suicidal behaviour and also factors such as romantic relationship status, perceived academic failure and low socioeconomic status have an effect on students suicidal behaviour. In this study, it was aimed to determine the relationship between suicidal behavior and depression, anxiety and stress levels and sociodemographic characteristics among the students of a state university. Identifying students' mental problems (depression, anxiety, suicidal thoughts/suicide attempts, etc.) and supporting them psychosocially will contribute positively to their academic and social lives.

## Methods

Students of Alanya Alaaddin Keykubat University were included in this study conducted between January 2024 and March 2024. The link to the survey form was shared on the homepage of Alanya Alaaddin Keykubat University website and also sent to students' e-mail addresses under the university domain. Students who gave written consent to participate in the study were asked to fill out the Sociodemographic data form and the Depression Anxiety Stress Scale-21 (DASS-21).

Permission for the study was obtained from the Clinical Research Ethics Committee of Alanya Alaaddin Keykubat University on January 9, 2024 under decision no. 2024/04, and the Declaration of Helsinki was complied with. Among the 530 students who participated in the study, 517 (97.6%), having read the information about the study, agreed to participate, while 13 (2.4%) declined. Students who were 18 years of age or older and still continuing their education at the university were accepted. The study sample consisted of the 517 students who agreed to participate.

### Data collection tools

#### Sociodemographic data form

The sociodemographic data form created by the researcher surveys information such as age, gender, romantic relationship status, faculty satisfaction, overall weighted grade point average

(OWGP), perception and level of course success, socioeconomic level, accommodation, internet usage time, body mass index, past and current psychiatric treatment status, smoking and alcohol use, and past and current major suicidal ideation and suicide attempts.

**DASS-21**

The first version of the scale developed by Lovibond and Lovibond in 1995 included a total of 42 items to measure depression, stress and anxiety under 14 items each [10]. In 2005, Henry and Crawford modified the scale into a short version with 21 items. The resulting DASS-21 has 7 items each for the depression, anxiety and stress sub-dimensions.

Each item in the scale has a 4-point Likert-type rating namely "0" did not apply to me at all, "1" applied to me to some degree, "2" applied to me to a considerable degree and "3" applied to me very much, consisting of 21 questions in total. The adaptation, validity and reliability of the scale into Turkish were conducted by Sarıçam (2018) [11].

**Statistical analysis**

The statistical analyses were conducted by the SPSS Statistics 27.0 software package. In the assessment of data, in addition to descriptive statistical techniques (mean, standard deviation), categorical characteristics of the groups were compared using chi-square or Fisher's test. Independent samples t-test was used to compare two groups for quantitative data with normal distribution, whereas nonparametric Mann-Whitney U test was used for non-normally distributed data. In the comparison of more than two groups, ANOVA and post-hoc Tukey test were used for normally distributed data, and Kruskal Wallis test was used for non-normally distributed data. Statistical significance level was accepted as $p \leq 0.05$ in all tests.

## Results

A total of 517 university students participated in the study. The mean age of the participants was 21.85±3.47 years, among whom 62.7% were female and 37.3% were male. One-fifth of the students were employed, and about half of them lived in dormitories. It was determined that 32.5% of the students had received psychiatric treatment in the past, and 12.4% were currently under psychiatric treatment. 36% percent of the students reported experiencing major suicidal ideation in the past, 6.4% percent of students still have serious suicidal ideation, and 14.7% reported having attempted suicide. The Depression Anxiety Stress Scale-21 (DASS-21) was performed on the participants as a result of which the mean scores of depression, anxiety and stress were found to be 9.98±6.10, 8.42±5.76 and 11.25±5.14, respectively. In the DASS-21, 31.5% of the students scored very severe depression, 39.3% very severe anxiety, and 17.6% very severe stress. Information on the sociodemographic characteristics of the students is summarized in Table-1.

Comparisons were made between students with and without current major suicidal ideation in terms of sociodemographic and clinical variables. Faculty dissatisfaction (p=0.019) perceived academic failure (p=0.004), poor socioeconomic status (p=0.035), current diet status (p=0.043), sleep problems (p<0.001), smoking (p<0.001), high internet use time (p=0.023), presence of chronic diseases (p<0.001), past psychiatric treatment status (p=0.005), and current psychiatric treatment status (p=0.001) were found to be associated with current serious suicidal ideation. Depression scores 6.59 (p<0.001), anxiety scores 5.76 (p<0.001), and stress scores were 2.94 (p=0.001) points higher in university students with current serious suicidal ideation compared to those without. In addition, the overall weighted grade point average (GPA) of these students was 0.38 points lower (2.42 & 2.80) (p<0.001). The comparison of students with and without current serious suicidal ideation in terms of sociodemographic and clinical variables is summarized in Table-2.

When students with and without previous suicide attempts were compared in terms of sociodemographic and clinical variables; variables such as having a romantic relationship (p=0.049), perceived academic failure (p=0.012), poor socioeconomic status (p=0.014), parental divorce (p<0.001), current dieting status (p<0.001), past dieting status (p=0.030), sleep problems (p<0.001), smoking (p<0.001), and daily time spent online (p=0.031), chronic disease status

Table 1. The sociodemographic characteristics and clinical scale scores of the participants

| | | N / Mean | % / SD |
|---|---|---|---|
| Gender | Female | 324 | 62.7 |
| | Male | 123 | 37.3 |
| Age | | 21.85 | 3.47 |
| Emotional Relationship | Yes | 232 | 44.9 |
| | No | 285 | 55.1 |
| Working Status | Working | 59 | 11.4 |
| | Part-time | 43 | 8.3 |
| | Not-Working | 415 | 80.3 |
| Faculty Satisfaction | Satisfied | 153 | 30 |
| | Partly | 271 | 53.1 |
| | Not-Satisfied | 86 | 16.9 |
| Perception of Academic Performance | High | 150 | 29 |
| | Moderate | 294 | 56.9 |
| | Low | 73 | 14.1 |
| OWGP | | 2.78 | 0.58 |
| Socioeconomic Status | High | 75 | 14.5 |
| | Moderate | 342 | 66.2 |
| | Low | 100 | 19.3 |
| Accommodation | Alone | 45 | 8.7 |
| | With Friend | 100 | 19.3 |
| | With Family | 96 | 18.6 |
| | Private Dormitory | 34 | 6.6 |
| | State Dormitory | 242 | 46.8 |
| Parental Marriage Status | Married | 432 | 83.6 |
| | | 85 | 16.4 |
| BMI | | 22.92 | 4.22 |
| Current Diet Status | Yes | 90 | 17.4 |
| | No | 427 | 82.6 |
| Past Diet Status | Yes | 240 | 46.4 |
| | No | 277 | 53.6 |
| Sleep Problems Status | Yes | 216 | 41.8 |
| | Partly | 182 | 35.2 |
| | No | 119 | 23 |
| Smoking | Yes | 204 | 39.5 |
| | No | 313 | 60.5 |
| Cigarettes Per a Day | 0 | 312 | 60.3 |
| | 1-10 | 86 | 16.6 |
| | 11-20 | 80 | 15.5 |
| | +21 | 39 | 7.5 |
| Alcohol Usage | Yes | 247 | 47.8 |
| | No | 270 | 52.2 |
| Frequency of Alcohol Use | Never | 226 | 43.7 |
| | Sometimes | 157 | 30.4 |
| | Oftenly | 113 | 21.9 |
| | Usually | 21 | 4.1 |
| Substance Missuse | Yes | 3 | 0.6 |
| | No | 514 | 99.4 |

| | | | |
|---|---|---|---|
| Daily Usage of İnternet | Less than one hour | 24 | 4.7 |
| | 1-3 hours | 185 | 36.3 |
| | 3-6 hours | 211 | 41.5 |
| | More than six hours | 89 | 17.5 |
| Presence of Chronic Diseases | Yes | 85 | 16.4 |
| | No | 432 | 83.6 |
| Past Psychiatric Treatment | Yes | 168 | 32.5 |
| | No | 349 | 67.5 |
| Current Psychiatric Treatment | Yes | 64 | 12.4 |
| | No | 453 | 87.6 |
| Past serious suicidal ideation | Yes | 186 | 36 |
| | No | 331 | 64 |
| Attempted Suicide | Yes | 76 | 14.7 |
| | No | 441 | 85.3 |
| Current Serious Suicidal İdeation | Yes | 33 | 6.4 |
| | | 484 | 93.6 |
| DASS-Depression Point | | 9.98 | 6.10 |
| DASS-Anxiety Point | | 8.42 | 5.76 |
| DASS-Stress Point | | 11.25 | 5.14 |
| DASS Depression Score | Normal | 112 | 21.7 |
| | Mild | 54 | 10.4 |
| | Moderate | 122 | 23.6 |
| | Severe | 66 | 12.8 |
| | Extremely Severe | 163 | 31.5 |
| DASS Anxiety Score | Normal | 124 | 24 |
| | Mild | 61 | 11.8 |
| | Moderate | 68 | 13.2 |
| | Severe | 61 | 11.8 |
| | Extremely Severe | 203 | 39.3 |
| DASS Stress Score | Normal | 101 | 19.5 |
| | Mild | 91 | 17.6 |
| | Moderate | 109 | 21.1 |
| | Severe | 125 | 24.2 |
| | Extremely Severe | 91 | 17.6 |

N. number of participants; SD. standard deviation; DASS. Depression. Anxiety. and Stress Scale. OWGP. overall weighted grade point; BMI. body mass index

Table 2. The comparison of students with and without current major suicidal ideation in terms of sociodemographic and clinical variables

| | | N / With Current Serious Suicidal İdeation | N / Without Current Serious Suicidal İdeation | N / Total/ Mean Differance | Chi Squared Value / F | p |
|---|---|---|---|---|---|---|
| Gender | Female | 18 | 306 | 324 | 0.994 | 0.319a |
| | Male | 15 | 178 | 193 | | |
| | Total | 33 | 484 | 517 | | |
| Age | | 21.64±1.71 | 21.86±3.56 | 0.225 | 2.187 | 0.720b |
| Emotional Relationship | Yes | 11 | 221 | 232 | 1.898 | 0.168a |
| | No | 22 | 263 | 285 | | |
| | Total | 33 | 484 | 517 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Working Status | Working | 8 | 51 | 59 | 5.923 | 0.052a |
| | Part-time | 3 | 40 | 43 | | |
| | Not-Working | 22 | 393 | 415 | | |
| | Total | 33 | 484 | 517 | | |
| Faculty Satisfaction | Satisfied | 6 | 147 | 153 | 7.902 | 0.019a |
| | Partly | 15 | 256 | 271 | | |
| | Not-Satisfied | 11 | 75 | 86 | | |
| | Total | 32 | 478 | 510 | | |
| Perception of Academic Performance | High | 6 | 144 | 150 | 11.077 | 0.004a |
| | Moderate | 16 | 278 | 294 | | |
| | Low | 11 | 62 | 73 | | |
| | Total | 33 | 484 | 517 | | |
| OWGP Mean ±SD | | 2.42±0.56 | 2.80±0.57 | -0.38 | 0.058 | <0.001b |
| Socioeconomic Status | High | 3 | 72 | 75 | 6.710 | 0.035a |
| | Moderate | 18 | 324 | 342 | | |
| | Low | 12 | 88 | 100 | | |
| | Total | 33 | 484 | 517 | | |
| Accommodation | Alone | 2 | 43 | 45 | 1.012 | 0.908a |
| | With Friend | 8 | 92 | 100 | | |
| | With Family | 7 | 89 | 96 | | |
| | Private Dormitory | 2 | 32 | 34 | | |
| | State Dormitory | 14 | 228 | 242 | | |
| | | 33 | 484 | 517 | | |
| Parental Marriage Status | Married | 24 | 408 | 432 | 3.010 | 0.083a |
| | Divorced | 9 | 76 | 85 | | |
| | Total | 33 | 484 | 517 | | |
| BMI Mean±SD | | 24.43±5.64 | 22.81±4.09 | 1.62 | 6.902 | 0.114b |
| Current Diet Status | Yes | 10 | 80 | 90 | 4.077 | 0.043a |
| | No | 23 | 404 | 427 | | |
| | Total | 33 | 484 | 517 | | |
| Past Diet Status | Yes | 20 | 220 | 240 | 2.851 | 0.091a |
| | No | 13 | 264 | 277 | | |
| | Total | 33 | 484 | 517 | | |
| Sleep Problems Status | Yes | 28 | 188 | 216 | 27.103 | <0.001a |
| | Partly | 4 | 178 | 182 | | |
| | No | 1 | 118 | 119 | | |
| | Total | 33 | 484 | 517 | | |
| Smoking | Yes | 22 | 182 | 204 | | |
| | No | 11 | 302 | 313 | | |
| | Total | 33 | 484 | 517 | | |
| Cigarettes Per a Day | 0 | 11 | 301 | 312 | 2.326 | 0.127a |
| | 1-10 | 7 | 79 | 86 | | |
| | 11-20 | 7 | 73 | 80 | | |
| | +21 | 8 | 31 | 39 | | |
| | Total | 33 | 484 | 517 | | |
| Alcohol Usage | Yes | 20 | 227 | 247 | 4.216 | 0.239a |
| | No | 13 | 257 | 270 | | |
| | Total | 33 | 484 | 517 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Frequency of Alcohol Use | Never | 12 | 214 | 226 | | |
| | Sometimes | 8 | 149 | 157 | | |
| | Oftenly | 10 | 103 | 113 | | |
| | Usually | 3 | 18 | 21 | | |
| | Total | 33 | 484 | 517 | | |
| Substance Missuse | Yes | 1 | 2 | 3 | | |
| | No | 32 | 482 | 514 | | |
| | Total | 33 | 484 | 517 | | |
| Daily Usage of İnternet | Less than one hour | 4 | 20 | 24 | 9.487 | 0.023a |
| | 1-3 hours | 10 | 175 | 185 | | |
| | 3-6 hours | 9 | 202 | 211 | | |
| | More than six hours | 10 | 79 | 89 | | |
| | Total | 33 | 476 | 509 | | |
| Presence of Chronic Diseases | Yes | 13 | 72 | 85 | 13.518 | <0.001a |
| | No | 20 | 12 | 432 | | |
| | Total | 33 | 484 | 517 | | |
| Past Psychiatric Treatment | Yes | 18 | 150 | 168 | 7.813 | 0.005a |
| | No | 15 | 334 | 349 | | |
| | Total | 33 | 484 | 517 | | |
| Current Psychiatric Treatment | Yes | 10 | 54 | 64 | 10.441 | 0.001a |
| | No | 23 | 430 | 453 | | |
| | Total | 33 | 484 | 517 | | |
| Past serious suicidal ideation | Yes | 32 | 154 | 186 | 56.932 | <0.001a |
| | No | 1 | 330 | 331 | | |
| | Total | 33 | 484 | 517 | | |
| Attempted Suicide | Yes | 16 | 60 | 76 | 32.087 | <0.001a |
| | No | 17 | 424 | 441 | | |
| | Total | 33 | 484 | 517 | | |
| DASS-Depression Point Mean±SD | | 16.15±3.58 | 9.56±6.01 | 6.59 | 11.666 | <0.001b |
| DASS- Anxiety Point Mean±SD | | 13.82±5.60 | 8.05±5.59 | 5.76 | 0.100 | <0.001b |
| DASS-Stress Point Mean±SD | | 14.00±4.58 | 11.06±5.13 | 2.94 | 1.101 | 0.001b |
| DASS Depression Score | Normal | 0 | 112 | 112 | 41.041 | <0.001a |
| | Mild | 0 | 54 | 54 | | |
| | Moderate | 2 | 120 | 122 | | |
| | Severe | 5 | 61 | 66 | | |
| | Extremely Severe | 26 | 137 | 163 | | |
| | Total | 33 | 484 | 517 | | |
| DASS Anxiety Score | Normal | 3 | 121 | 124 | 23.226 | <0.001a |
| | Mild | 1 | 60 | 61 | | |
| | Moderate | 2 | 66 | 68 | | |
| | Severe | 1 | 60 | 61 | | |
| | Extremely Severe | 26 | 177 | 203 | | |
| | Total | 33 | 484 | 517 | | |
| DASS Stress Score | Normal | 1 | 100 | | 10.680 | 0.030a |
| | Mild | 5 | 86 | | | |
| | Moderate | 6 | 103 | | | |
| | Severe | 10 | 115 | | | |
| | Extremely Severe | 11 | 80 | | | |
| | Total | 33 | 484 | 517 | | |

N. number of participants; SD. standard deviation; DASS. Depression. Anxiety. and Stress Scale. OWGP. overall weighted grade point; BMI. body mass index. pa statistical signifance p ≤0.05 Chi-square test. pb statistical signifance p ≤0.05 t test for independent groups. * Chi-square test not applied.

Table 3. The comparison of students with and without previous suicide attempts in terms of sociodemographic and clinical variables

| | | N / With Current Serious Suicidal İdeation | N / Without Current Serious Suicidal İdeation | N / Total/ Mean Differance | Chi Squared Value / F | p |
|---|---|---|---|---|---|---|
| Gender | Female | 55 | 269 | 324 | 3.583 | 0.058a |
| | Male | 21 | 172 | 193 | | |
| | Total | 76 | 441 | 517 | | |
| Age | | 21.47±3.00 | 21.91±3.55 | -0.43 | 0.572 | 0.312b |
| Emotional Relationship | Yes | 42 | 190 | 232 | 3.887 | 0.049a |
| | No | 34 | 251 | 285 | | |
| | Total | 76 | 441 | 517 | | |
| Working Status | Working | 8 | 51 | 59 | 0.099 | 0.952a |
| | Part-time | 6 | 37 | 43 | | |
| | Not-Working | 62 | 353 | 415 | | |
| | Total | 76 | 441 | 517 | | |
| Faculty Satisfaction | Satisfied | 18 | 135 | 153 | 1.573 | 0.456a |
| | Partly | 44 | 227 | 271 | | |
| | Not-Satisfied | 13 | 73 | 56 | | |
| | Total | 75 | 435 | 510 | | |
| Perception of Academic Performance | High | 18 | 132 | 150 | 8.825 | 0.012a |
| | Moderate | 39 | 255 | 294 | | |
| | Low | 19 | 54 | 73 | | |
| | Total | 76 | 441 | 517 | | |
| OWGP Mean ±SD | | 2.62±0.64 | 2.80±0.56 | -0.17 | 2.889 | 0.016b |
| Socioeconomic Status | High | 10 | 65 | 75 | 8.606 | 0.014a |
| | Moderate | 42 | 300 | 342 | | |
| | Low | 24 | 76 | 100 | | |
| | Total | 76 | 441 | 517 | | |
| Accommodation | Alone | 8 | 37 | 45 | 3.680 | 0.451a |
| | With Friend | 18 | 82 | 100 | | |
| | With Family | 9 | 87 | 96 | | |
| | Private Dormitory | 4 | 30 | 34 | | |
| | State Dormitory | 37 | 205 | 242 | | |
| | | 76 | 441 | 517 | | |
| Parental Marriage Status | Married | 54 | 378 | 432 | 10.144 | 0.001a |
| | Divorced | 22 | 63 | 85 | | |
| | Total | 76 | 441 | 517 | | |
| BMI Mean±SD | | 23.01±4.56 | 22.90±4.16 | 0.11 | 1.162 | 0.831b |
| Current Diet Status | Yes | 26 | 64 | 90 | 17.495 | <0.001a |
| | No | 50 | 377 | 427 | | |
| | Total | 76 | 441 | 517 | | |
| Past Diet Status | Yes | 44 | 196 | 240 | 4.715 | 0.030a |
| | No | 32 | 245 | 277 | | |
| | Total | 76 | 441 | 517 | | |
| Sleep Problems Status | Yes | 51 | 165 | 216 | 24.415 | <0.001a |
| | Partly | 18 | 164 | 182 | | |
| | No | 7 | 112 | 119 | | |
| | Total | 76 | 441 | 517 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Smoking | Yes | 49 | 155 | 204 | 23.339 | <0.001a |
| | No | 27 | 286 | 313 | | |
| | Total | 76 | 441 | 517 | | |
| Cigarettes Per a Day | 0 | 27 | 285 | 312 | 26.380 | <0.001a |
| | 1-10 | 19 | 67 | 86 | | |
| | 11-20 | 17 | 63 | 80 | | |
| | +21 | 13 | 26 | 39 | | |
| | Total | 76 | 441 | 517 | | |
| Alcohol Usage | Yes | 44 | 203 | 247 | 3.657 | 0.056a |
| | No | 32 | 238 | 270 | | |
| | Total | 76 | 441 | 517 | | |
| Frequency of Alcohol Use | Never | 26 | 200 | 226 | 6.423 | 0.093a |
| | Sometimes | 23 | 134 | 157 | | |
| | Oftenly | 21 | 92 | 113 | | |
| | Usually | 6 | 15 | 21 | | |
| | Total | 76 | 441 | 517 | | |
| Substance Missuse | Yes | 1 | 2 | 3 | | * |
| | No | 75 | 439 | 514 | | |
| | Total | 76 | 441 | 517 | | |
| Daily Usage of İnternet | Less than one hour | 4 | 20 | 24 | 8.870 | 0.031a |
| | 1-3 hours | 21 | 164 | 185 | | |
| | 3-6 hours | 29 | 182 | 211 | | |
| | More than six hours | 22 | 67 | 89 | | |
| | Total | 76 | 433 | 509 | | |
| Presence of Chronic Diseases | Yes | 22 | 63 | 85 | 10.144 | 0.001a |
| | No | 54 | 378 | 432 | | |
| | Total | 76 | 441 | 517 | | |
| Past Psychiatric Treatment | Yes | 46 | 122 | 168 | 31.915 | <0.001a |
| | No | 30 | 319 | 349 | | |
| | Total | 76 | 441 | 517 | | |
| Current Psychiatric Treatment | Yes | 18 | 46 | 64 | 10.498 | 0.001a |
| | No | 58 | 395 | 453 | | |
| | Total | 76 | 441 | 517 | | |
| Past serious suicidal ideation | Yes | 69 | 117 | 186 | 116.217 | <0.001a |
| | No | 7 | 324 | 331 | | |
| | Total | 76 | 441 | 517 | | |
| DASS-Depression Point Mean±SD | | 13.04±5.41 | 9.45±6.06 | 3.588 | 2.612 | <0.001b |
| DASS- Anxiety Point Mean±SD | | 13.16±5.50 | 7.60±5.41 | 5.557 | 0.039 | <0.001b |
| DASS-Stress Point Mean±SD | | 13.88±4.51 | 10.79±5.11 | 3.088 | 1.816 | <0.001b |
| DASS Depression Score | Normal | 5 | 107 | 112 | 21.495 | <0.001a |
| | Mild | 4 | 50 | 54 | | |
| | Moderate | 18 | 104 | 122 | | |
| | Severe | 11 | 55 | 66 | | |
| | Extremely Severe | 38 | 125 | 163 | | |
| | Total | 76 | 441 | 517 | | |
| DASS Anxiety Score | Normal | 5 | 119 | 124 | 48.562 | <0.001a |
| | Mild | 5 | 56 | 61 | | |
| | Moderate | 4 | 64 | 68 | | |
| | Severe | 5 | 56 | 61 | | |
| | Extremely Severe | 57 | 146 | 203 | | |
| | Total | 76 | 441 | 517 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| DASS Stress Score | Normal | 4 | 97 | 101 | 23.263 | <0.001a |
| | Mild | 9 | 82 | 100 | | |
| | Moderate | 18 | 91 | 109 | | |
| | Severe | 20 | 105 | 125 | | |
| | Extremely Severe | 25 | 66 | 91 | | |
| | Total | 76 | 441 | 517 | | |

N. number of participants; SD. standard deviation; DASS. Depression. Anxiety. and Stress Scale. OWGP. overall weighted grade point; BMI. body mass index. pa statistical signifance p ≤0.05 Chi-square test. pb statistical signifance p ≤0.05 t test for independent groups. * Chi-square test not applied.

(p=0.001), past psychiatric treatment history (p<0.001) and current psychiatric treatment status (p=0.001) were determined to be associated with attempted suicide. Depression scores 3.58 (p<0.001), anxiety scores 5.55 (p<0.001) and stress scores were 3.08 (p=0.001) points higher in university students who attempted suicide compared to those who did not. In addition, the overall weighted grade point average (GPA) of these students was 0.17 points lower (2.62 & 2.80) (p=0.016). The comparison of students with and without previous suicide attempts in terms of sociodemographic and clinical variables is summarized in Table-3.

## Discussion

In this study investigating the relationship between suicidal behavior and depression, anxiety and stress levels and sociodemographic characteristics in university students, depression, anxiety and stress levels were found to be higher in university students with current serious suicidal ideation or suicide attempt. In addition, faculty satisfaction, romantic relationship status, overall weighted grade point average, perceived and level of academic performance, socioeconomic status, parental divorce, past and current dieting status, sleep problems, smoking, internet usage time, presence of chronic disease, past and current psychiatric treatment status were determined as factors associated with suicidal behavior.

It was found that 12.8% of the students in this study had severe and 31.5% very severe depression, 11.8% had severe and 39.3% very severe anxiety, and 24.2% had severe and 17.6% very severe stress scores. Our results were higher compared to the results of the study conducted by Bayram and Bilgel (2008) in Turkey using the DASS for depression, anxiety and stress levels in university students (severe depression 6.1% and very severe depression 22%, severe anxiety 14.5% and very severe anxiety 6.3%, and severe stress 6.1% and very severe stress 0.8%) [3]. This difference may be attributed to factors such as the different sociodemographic structures of the students participating in the study, the methods used in the data collection process and the characteristics of the measurement tools. The use of the online survey method in our study may have caused students with higher psychiatric complaints (32,5% past psychiatric treatment, 12,4% current psychiatric treatment) to show interest in the survey. As for studies conducted worldwide, it was found that 9.7% of university students in Malaysia had severe or very severe depression, 29% had severe or very severe anxiety, and 5.1% had severe or very severe stress [4]. Our study results are in parallel with the findings of the study conducted abroad, but the high anxiety levels are particularly noteworthy. The unique cultural, economic, educational and social dynamics of each country may affect individuals' stress, anxiety and depression levels, and coping styles.

This study determined that 36% of university students had a history of serious suicidal ideation, 6.4% had current serious suicidal ideation, and 14.7% had a history of suicide attempts. Another study conducted among university students in Turkey (Gürkan B et al, 2009), in parallel with our results, determined suicidal ideation and suicide attempt rates to be high (serious suicidal ideation 12.99% and attempted suicide 5.5%) [12].

In our study, when the sociodemographic characteristics of university students with and without serious suicidal ideation were compared, no significant relationship was found between gender and suicidal ideation. This finding coincides with some studies in the literature showing that the effect of gender on suicidal ideation is not always significant [13,14]. In our study, it was determined that the rates of suicidal ideation and suicide attempts were higher in students with

lower socioeconomic status compared to those with higher socioeconomic status. Students with lower socioeconomic status may experience higher levels of stress due to financial difficulties and problems concerning living standards, which may increase symptoms of depression and anxiety [15]. Thus, lower socioeconomic status may indirectly influence suicidal ideation and suicide attempts.

It was determined that 39.5% of the students who participated in this study smoked cigarettes and 47.8% consumed alcohol, and suicidal behavior was higher in students who smoked cigarettes. In a study conducted at Ege University, smoking and alcohol consumption rates were reported as 43.3% and 52.5%, respectively. The results of both studies were similar in terms of the frequency of smoking and alcohol consumption and revealed that smoking and alcohol consumption were common among university students [16]. Although smoking and alcohol are commonly used to cope with stress, it is known that especially heavy alcohol consumption may trigger risky behavior and suicide attempts [17]. In our study, it was determined that approximately one fifth of the students daily spent more than 6 hours online, and similar to the literature, suicidal thoughts and suicide attempts were more common in this group. [18]. Although internet use can be beneficial for students in terms of social connections and access to information, excessive use can lead to social isolation and various mental problems such as depression, anxiety and suicidal behavior [18].

Eating habits and mental health are known to be related [19]. Our study revealed that 46.4% of the students had been on a diet at some point in their lives and 17.4% were still dieting, and suicidal behavior was more common in those students who were currently on a diet. Some studies in the literature have shown that students who remain on a diet for a long time or who are at risk of eating disorders have high levels of depression and anxiety, which may be associated with suicidal thoughts [19]. In our study, it was found that suicide attempts were significantly more common in students whose parents have separated. However, no significant difference was observed in terms of current suicidal ideation. Other studies in the literature on the role of family structure in suicidal behavior among university students found that serious suicidal ideation was more common in students whose parents were divorced or separated. This result reveals that parental separation may negatively affect the mental health of students [20]. On the other hand, there are also studies reporting that continuation of parental unity does not always have a protective effect, on the contrary, may increase suicidal behaviors in some cases [21]. Parental separation may have contributed to an increase in major suicide attempts in the past, but in our study, we found that it did not have a direct effect on current suicidal thoughts. This suggests that not only family structure, but also other factors may play an important role in the formation of suicidal thoughts. In our study, it was observed that suicidal behavior was more common in students with lower faculty satisfaction, lower perceived and level of academic performance. In the literature, it is emphasized that students who are satisfied with their faculty have lower levels of depression, anxiety and stress, and are therefore less prone to suicidal thoughts [22]. The feeling of academic failure may lead students to feel inadequate, hence negatively affect their mental health and trigger suicidal thoughts [22].

In our study, 16.4% of university students had chronic diseases and 41.8% had sleep problems, and there was a significant relationship between the presence of chronic diseases and sleep problems and suicidal behavior. Chronic diseases and sleep disorders may negatively affect the general mental health of individuals [23]. The constant physical and mental stress caused by chronic diseases can increase depression and anxiety levels, making individuals more prone to suicidal thoughts [23]. Similarly, it has been reported in the literature that sleep disorders disrupt emotional regulation and increase stress levels, hence may trigger suicidal behavior [23].

In our study, suicidal behavior was found to be higher in students who had romantic relationships. The literature reports that this situation may develop due to stress sources such as conflicts experienced during the relationship process and separation anxiety, and emotional fluctuations experienced by individuals while in a relationship, hence the resulting increased anxiety levels may

affect suicidal behavior [24]. In our study, students with a history of receiving psychiatric treatment in the past or currently were found to have higher levels of depression, anxiety and stress and more suicidal thoughts and suicide attempts. These students may have difficulty coping with stressful life events. Individuals with a history of psychiatric treatment may have a higher risk of suicidal thoughts, especially when they encounter similar stressful life events again [25].

This study has some limitations. Since it is a cross-sectional study, a cause-and-effect relationship cannot be established for the results. The scales were performed online rather than face-to-face. In addition, our sample includes the students of only one state university. This study concluded that depression, anxiety and stress levels are high in university students, and depression, anxiety and stress levels may be related to suicidal thoughts and attempts. In addition, it was concluded that various individual factors such as faculty satisfaction, romantic relationship status, perception and level of academic performance, past or current dieting status, sleep problems, smoking, internet usage time, presence of chronic disease and past or current psychiatric treatment status, and various environmental factors such as parental separation and socioeconomic level may be associated with suicidal thoughts and attempts. Considering our research results, we conclude that it is necessary to establish psychosocial support units where students can get help with the problems identified. It seems necessary that these units should provide social and psychological support to students and be organized in a way to provide intervention especially in vital crisis situations such as suicidal thoughts/suicide attempts.

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# Impact of Serum Sodium Levels on Treatment Efficacy and Prognosis in Advanced Renal Cell Carcinoma Patients Receiving Subsequent Line Nivolumab

## İkinci Sıra veya Sonrasında Nivolumab ile Tedavi Edilen Metastatik Renal Hücreli Karsinom Hastalarında Serum Sodyum Düzeyinin Sağkalım Üzerine Etkisi

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## ABSTRACT

**Aim:** We aimed to evaluate the effect of serum sodium levels on treatment efficacy and prognosis in metastatic renal cell cancer (RCC) patients receiving subsequent line Nivolumab.

**Methods:** This retrospective, single-center study include 55 patients (n=55). Clinicopathological factors and serum sodium levels were recorded before nivolumab (pre-ICI) initiation and at the eighth week of nivolumab (post-ICI). Patients were divided into two groups according to the median sodium levels for pre-ICI (138 mEq/L) and post-ICI 137 (mEq/L). Cox regression analysis was used to determine proportional hazards.

**Results:** The median age of the study population was 63 (33-90) and 44 (78.6%) patients were male. Progression-free survival (PFS) ans overall survial (OS) was similar for pre-ICI sodium low and high patients. However, post-ICI sodium-high patients had significantly longer PFS [30.9 months, 95% CI; (2.0-59.9) ve 3.4 months, %95 CI; (0.0-7.1); respectively (p<0.001)] and OS [NR vs 9.1 months, 95% CI; (0.0-22.6); (p<0.001)] than the patients with low post-ICI sodium levels. In the multivariate analyses, the only independent predictor was post-ICI sodium level for both PFS [HR: 0.288; 95% CI 0.149-0.559, (p<0.001)] and OS [HR: 0.239; 95% CI, 0.107-0.533, (p<0.001)].

**Conclusion:** Our results are consistent with those of previous studies showing the prognostic and predictive value of serum sodium levels. As serum sodium is an easy, fast, and affordable marker, it may be a feasible prognostic marker. More comprehensive studies are needed to highlight this topic.

Key Words: Renal cell carcinoma, Immunotherapy, Sodium, Prognosis

## ÖZ

**Amaç:** Bu çalışmada, ikinci sıra ve ötesinde Nivolumab ile tedavi edilen metastatik renal hücreli karsinom (RCC) hastalarında serum sodyum düzeyinin tedavi etkinliği ve prognoz üzerindeki etkisini değerlendirmeyi amaçladık.

**Yöntem:** Tek merkezli retrospektif bir çalışma olarak tasarlanan bu araştırmaya 55 hasta (n=55) dahil edildi. Klinikopatolojik faktörler ve serum sodyum seviyeleri, Nivolumab başlamadan önce ve Nivolumab'ın sekizinci haftasında olmak üzere kaydedildi. Hastalar medyan sodyum değerline (Nivolumab öncesi için 138 mEq/L ve sekizinci hafta için 137 mEq/L) göre dikotomize edildi. Sodyum dahil progresyona etki eden faktörler cox-regresyon ile incelendi.

**Bulgular:** Çalışma popülasyonunun medyan yaşı 63 (33-90) olup, 44'ü (%78.6) erkekti. Tedavi öncesi düşük sodyum (≤138 mEq/L) ve yüksek sodyum (>138 mEq/L) değerine sahip hastalar arasında progresyonsuz sağkalım (PFS) açısından fark bulunmazken (p=0.507), sekizince hafta yüksek sodyum seviyesine (>137 mEq/L) sahip hastalarda PFS, düşük sodyum seviyesine (≤137 mEq/L) sahip hastalardan belirgin şekilde daha uzundu [30.9 ay, %95 GA; (2.0-59.9) ve 3.4 ay, %95 GA; (0.0-7.1); sırasıyla (p<0.001)]. Çok değişkenli analizlerde yalnızca sekizinci hafta sodyum seviyeleri anlamlı bulundu (p<0.001). Nivolumab öncesi düşük ve yüksek sodyum değerine sahip hastalar arasında genel sağkalım (OS) benzerdi (p=0.292). Ancak, sekizinci haftada yüksek sodyum değerine sahip hastalar, düşük değere sahip olanlardan anlamlı şekilde daha uzun OS'ye sahipti [Yüksek sodyum grubu için ulaşılmamış ve düşük sodyum hastalar için 9.1 ay, %95 GA; (0.0-22.6); (p<0.001)].

**Sonuç:** Bulgularımız, serum sodyum seviyelerinin prognostik ve prediktif değerine işaret eden eski çalışmalarla uyumluydu. Serum sodyumunun kolay, hızlı ve uygun maliyetli bir belirteç olması nedeniyle bu konuyu daha fazla vurgulamak için daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Renal kanser, İmmünoterapi, Sodyum, Prognoz

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## Introduction

Renal cell carcinoma (RCC) is the fourteenth most commonly diagnosed malignancy globally, with 431,288 new cases reported in 2020 [1]. Between 20% and 40% of RCC cases present with metastatic disease at the time of diagnosis. The median overall survival is estimated to be approximately 4 years for advanced stage disease. The prognostic factors that influence survival outcomes include age, performance status, and comorbid conditions [2]. Recent analyses derived from the United States Surveillance, Epidemiology, and End Results (SEER) database have indicated a notable reduction in mortality associated with metastatic RCC since 2012, suggesting that advancements in therapeutic approaches have substantially improved survival rates [3].

Therapeutic strategies for metastatic RCC have progressed significantly over the past two decades. Initial treatments, centered on first-generation immunotherapies (e.g., interferon and interleukin-2), have evolved to include targeted therapies targeting vascular endothelial growth factor (VEGF), immune checkpoint inhibitors (ICI), and combination regimens.[4] Immune checkpoint inhibitors, originally approved as second-line or later therapies, are now incorporated into the first-line treatment protocols in combination regimens. Historically, RCC management was primarily palliative; however, the advent of checkpoint inhibitors has extended survival and created a potential for long-term complete response. Nonetheless, the benefits of ICIs are not universal; some patients may experience immune-related adverse effects without achieving therapeutic benefits. The IMDC risk score remains a critical instrument in clinical practice, although it primarily serves as a prognostic marker rather than a predictive marker of immunotherapy efficacy [5,6]. Although biomarkers such as PD-L1 expression, immune infiltration, and tumor mutation burden have predictive relevance across multiple malignancies, they remain inadequate for reliably predicting immunotherapy outcomes in RCC. Emerging studies suggest that genomic expression profiles and loss of pro-angiogenic proteins, including VHL and PBRM-1, may have predictive value, although their clinical applicability remains unclear [7].

Ongoing research efforts continue to explore biomarkers predictive of immunotherapy responses in RCC. Serum sodium (Na) levels have previously been investigated as potential markers, with hyponatremia (serum sodium ≤ 135 mEq/L) serving as an independent prognostic factor across various malignancies, including metastatic RCC [8,9]. Furthermore, serum sodium levels in the low-normal range have been associated with poor prognosis in patients with metastatic RCC receiving tyrosine kinase inhibitors and immunotherapy [10,11]. Moreover, hyponatremia occurs frequently in this population. Altered kidney functions, syndrome of inappropriate antidiuresis due to uncontrolled cancer, immune-related diarrhea, adrenalitis, or hypophysitis are possible causes of hyponatremia in RCC patients [12,13].

This study aimed to evaluate the impact of serum sodium levels measured before the initiation of nivolumab and at the eighth week of nivolumab treatment on the efficacy and prognosis of immunotherapy in patients with metastatic RCC undergoing nivolumab as second-line therapy or beyond.

## Method

### Study Population

This retrospective study examined patients diagnosed with metastatic RCC who were treated with single-agent nivolumab at Antalya Training and Research Hospital between January 2016 and July 2024. Eligible patients were aged 18 years or older. Patients who received immunotherapy as a first-line treatment or had incomplete follow-up or treatment data were excluded from the study. Data were obtained from the hospital records and electronic health information systems. This study complies with the Declaration of Helsinki, and ethical committee approval was obtained from Antalya Training and Research Hospital (Approval No: 10/37, 11.07.2024).

### Management Policy and Data Collection

Patients with metastatic RCC were managed according to current clinical guidelines and best practices. Nivolumab was administered at a dose of 3 mg per kilogram of total body weight or 240 mg flat dose once every 2 weeks (Q2W) [14]. Staging

was conducted according to the American Joint Cancer Committee (AJCC) 8th Edition Criteria. Response evaluation criteria in solid tumors (version 1.1; RECIST v1.1) was the main guide used to determine treatment response in routine practice. Data collected included demographic and clinical variables as age, sex, Eastern Cooperative Oncology Group Performance Score (ECOG PS), body mass index, smoking history, primary tumor surgery, RCC histological subtype (grouped as clear cell and non-clear cell), histological grade (grouped as grade 1-2 and grade 3-4), presence of sarcomatoid differentiation, date of diagnosis for metastatic stage, IMDC risk classification, initial treatment regimen, nivolumab initiation date, baseline and post-treatment laboratory parameters such as sodium and glomerular filtration rate (GFR), best response to nivolumab, progression date if occurred, and date of death if occurred. Baseline (pre-ICI) sodium levels were defined as those recorded within two weeks before nivolumab initiation, and sodium levels at the eighth week of nivolumab (post-ICI) were recorded for each patient. The normal range of sodium was 135-145 mEq/L.

The data of this study are available upon request from the corresponding author.

### Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics version 26.0. Continuous variables were reported as mean ± standard deviation (SD). Otherwise, the median value (min-max) was used. Progression-free survival (PFS) was defined as the time from the initiation of nivolumab to disease progression, death, or the last recorded follow-up for patients without progression. Overall survival (OS) was defined as the time from the initiation of nivolumab treatment to death or the latest control date. For statistical comparisons, patients were stratified based on the median values of baseline (pre-ICI) and eighth-week (post-ICI) sodium levels. Kaplan-Meier estimates were used for univariate survival analysis. Certain clinically relevant variables and variables with a $p<0.3$ in the univariate analysis were included in multivariate analysis. Multivariate analyses were performed using Cox regression analysis. Statistical significance was defined as $P<0.05$.

## Results

### Clinicopathological Characteristics of The Study Population

We retrospectively screened 85 patients diagnosed with metastatic RCC who received nivolumab (n=85). However, 27 (n=27) were excluded due to missing data, and 6 (n=6) were excluded because they had received first-line immunotherapy, resulting in a final cohort of 55 patients (n=55). The median age of the study population was 63 (33-90) and 44 (78.6%) patients were male. The clear cell subtype was the dominant histological subtype, accounting for 45 patients (81.8%). The median value of pre-ICI sodium was 138 (130-145) mEq/L, 29 patients (n=29) had pre-ICI Na≤138 mEq/L, and 26 patients (n=26) had pre-ICI sodium >138 mEq/L. The median value was 137 (127-144) for post-ICI sodium, and 28 patients (n=28) had post-ICI Na≤137 mEq/L, while 27 (n=27) had >137 mEq/L. Clinicopathological feature distributions per median pre-ICI and post-ICI sodium values are provided separately. (Table 1)

### Efficacy Analyses

The median follow-up was 50.2 (38.6-61.9) months for the study population. During the follow-up period, 40 patients (71.4%) had disease progression and 30 patients (53.6%) died in the entire population. The pre-ICI low (≤138 mEq/L) and high (>138 mEq/L) sodium groups were similar in terms of objective response rates (ORR), [%44.8 and %50.0; respectively (p=0.701)] and disease control rates (DCR) [%72.4 and %73.1; respectively (p=0.956)]. The post-ICI low (≤137 mEq/L) and high (>137 mEq/L) sodium groups were similar in terms of ORR, [%35.7 and %59.3; respectively (p=0.08)] while DCR was significantly better in those with high post-ICI sodium levels [%60.2 and %85.7; respectively (p=0.042)].

### Progression-Free Survival Analyses

According to the univariate Kaplan-Meier analyses, the median PFS did not differ significantly between the pre-ICI low [13.8 months 95% CI; (0.0-33.1)] and high [11.7 months 95% CI; (4.5-18.9)] sodium subgroups (log-rank, p=0.507). (Figure 1A) However, patients with higher post-ICI sodium had significantly longer PFS [30.9 months

95% CI; (2.0-59.9)] than those with lower post-ICI sodium levels [3.4 months 95% CI; (0.0-7.1)], (log-rank, p<0.001). (Figure 1B). Moreover, ECOG PS and histological grade were the other significant factors that influenced PFS in univariate analysis. (Table 2)

**Table 1. Clinicopathological Characteristics According to the Baseline and 8th Week Sodium Values**

| | All Patients | Pre-ICI Med. Sodium Based Dichotom | | Post-ICI Med. Sodium Based Dichotom | |
|---|---|---|---|---|---|
| | (n=55) n, (%) | Na≤13 (n=29) n, (%) | Na>138 (n=26) n, (%) | Na≤137 (n=28) n, (%) | Na>137 (n=27) n, (%) |
| **Age** | | | | | |
| <65 years | 33 (60.0) | 13 (44.8) | 20 (76.9) | 13 (46.4) | 20 (74.1) |
| ≥65 years | 22 (40.0) | 16 (55.2) | 6 (23.1) | 15 (53.6) | 7 (25.9) |
| **Sex** | | | | | |
| Female | 11 (20.0) | 5 (17.2) | 6 (23.1) | 7 (25.0) | 4 (14.8) |
| Male | 44 (80.0) | 24 (82.8) | 20 (76.9) | 21 (75.0) | 23 (85.2) |
| **ECOG PS** | | | | | |
| 0-1 | 41 (75.5) | 19 (65.5) | 22 (84.6) | 17 (60.7) | 24 (88.9) |
| 2 | 14 (24.5) | 10 (34.5) | 4 (15.4) | 11 (39.3) | 3 (11.1) |
| **Smoking History** | | | | | |
| Non-smoker | 22 (40.0) | 10 (34.5) | 12 (46.2) | 10 (35.7) | 12 (44.4) |
| Smoker | 33 (60.0) | 19 (65.5) | 14 (53.8) | 18 (64.3) | 15 (55.6) |
| **History of Nephrectomy** | | | | | |
| No | 14 (24.5) | 7 (24.1) | 7 (26.9) | 9 (32.1) | 5 (18.5) |
| Yes | 41 (75.5) | 22 (75.9) | 19 (73.1) | 19 (67.9) | 22 (81.5) |
| **Histological Type** | | | | | |
| Clear Cell RCC | 45 (81.8) | 23 (79.3) | 22 (84.6) | 23 (82.1) | 22 (81.5) |
| Non-Clear Cell RCC | 10 (18.2) | 6 (22.7) | 4 (15.4) | 5 (17.9) | 5 (18.5) |
| **Histological Grade** | | | | | |
| 1-2 | 14 (24.5) | 9 (31.0) | 5 (19.2) | 11 (39.3) | 3 (11.1) |
| 3-4 | 41 (75.5) | 20 (69.0) | 21 (80.8) | 17 (60.7) | 24 (88.9) |
| **Sarcomatoid Differantiation** | | | | | |
| No | 8 (14.5) | 24 (82.8) | 23 (88.5) | 24 (85.7) | 23 (85.2) |
| Yes | 47 (85.5) | 5 (17.2) | 3 (11.5) | 4 (14.3) | 4 (14.8) |
| **First-Line Treatment** | | | | | |
| Sunitinib | 37 (67.3) | 17 (58.6) | 20 (76.9) | 19 (67.9) | 18 (66.7) |
| Pazopanib | 14 (25.5) | 11 (37.9) | 3 (11.5) | 9 (32.1) | 5 (18.5) |
| Other | 4 (7.3) | 1 (3.4) | 3 (11.5) | 0 (0.0) | 4 (14.8) |
| **Nivolumab Treatment Line** | | | | | |
| Second Line | 49 (89.0) | 26 (89.7) | 23 (88.5) | 26 (92.9) | 23 (85.2) |
| Subsequent Line | 6 (11.0) | 3 (10.3) | 3 (11.5) | 2 (7.1) | 4 (14.8) |
| **IMDC Risk** | | | | | |
| Good Risk | 14 (25.5) | 5 (17.2) | 9 (34.6) | 4 (14.3) | 10 (37.0) |
| Intermediate Risk | 33 (40) | 20 (69.0) | 13 (50.0) | 18 (64.3) | 15 (55.6) |
| Poor Risk | 8 (14.5) | 4 (13.8) | 4 (15.4) | 6 (21.4) | 2 (7.4) |
| Body Mass Index | | | | | |
| <30 kg/m2 | 46 (83.6) | 25 (86.2) | 21 (80.8) | 25 (89.3) | 21 (77.8) |
| ≥30 kg/m2 | 9 (16.4) | 4 (13.8) | 5 (19.2) | 3 (10.7) | 6 (22.2) |
| **Glomerular Filtration Rate** | | | | | |
| <60 ml/min/1.73m2 | 22 (40.0) | 13 (44.8) | 9 (34.6) | 14 (50.0) | 8 (29.6) |
| ≥60 ml/min/1.73m2 | 33 (60.0) | 16 (55.2) | 17 (65.4) | 14 (50.0) | 19 (70.4) |

ECOG PS: Eastern Cooperative Oncology Group Performance Status, IMDC: International Metastatic RCC Database Consortium, Na: Sodium, Med.: Median RCC: Renal Cell Carcinoma

**Table 2. Univariate and Multivariate Analysis For Progression Free Survival for Nivolumab**

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| Variables | P Value | HR | 95% CI | P Value |
| Age | | | | |
| <65 years | 0.442 | 1.00 (Ref.) | | 0.732 |
| ≥65 years | | 0.873 | (0.401-1.900) | |
| Sex | | | | |
| Female | 0.494 | 1.00 (Ref.) | | 0.142 |
| Male | | 1.880 | (0.810-4.366) | |
| ECOG PS | | | | |
| 0-1 | 0.009 | 1.00 (Ref.) | | 0.496 |
| 2 | | 1.292 | 0.618-2.705 | |
| Smoking History | | | | |
| Non-smoker | 0.721 | | | |
| Smoker | | | | |
| History of Nephrectomy | | | | |
| No | 0.591 | | | |
| Yes | | | | |
| Histological Type | | | | |
| Clear Cell RCC | 0.707 | | | |
| Non-Clear Cell RCC | | | | |
| Histological Grade | | | | |
| 1-2 | 0.099 | 1.00 (Ref.) | | 0.684 |
| 3-4 | | 1.191 | (0.513-2.768) | |
| Sarcomatoid Differantiation | | | | |
| No | 0.720 | | | |
| Yes | | | | |
| Body Mass Index | | | | |
| <30 kg/m2 | 0.259 | 1.00 (Ref.) | | 0.722 |
| ≥30 kg/m2 | | 0.840 | (0.321-2.200) | |
| IMDC Risk | | | | |
| Good Risk | 0.229 | 1.00 (Ref.) | | 0.272 |
| Intermediate Risk | | 0.533 | (0.225-1.264) | |
| Poor Risk | | 0.800 | (0.260-2.459) | |
| Glomerular Filtration Rate | | | | |
| <60 ml/min/1.73m2 | 0.215 | 1.00 (Ref.) | | 0.743 |
| ≥60 ml/min/1.73m2 | | 0.888 | (0.436-1.807) | |
| Pre-ICI Na | | | | |
| ≤138 mEq/L | 0.507 | 1.00 (Ref.) | | 0.128 |
| >138 mEq/L | | 1.781 | (0.847-3.745) | |
| Post-ICI Na | | | | |
| ≤137 mEq/L | <0.001 | 1.00 (Ref.) | | <0.001 |
| >137 mEq/L | | 0.288 | (0.149-0.559) | |

CI: Confidence Interval, ECOG PS: Eastern Cooperative Oncology Group Performance Status, HR: Hazard Ratio IMDC: International Metastatic RCC Database Consortium

According to the multivariate analysis of PFS, the sole factor reaching statistical significance was post-ICI sodium levels, favoring the group with high sodium levels (>137 mEq/L) [HR: 0.288; 95% CI 0.149-0.559, (p<0.001)]. Pre-ICI sodium levels, age, sex, ECOG PS, histological grade, IMDC risk score, and GFR were not statistically significant. (Table 2)

### Overall Survival Analyses

Univariate OS analyses showed that the median OS was similar between the low [24.0 months 95% CI; (15.9-32.1)] and high [36.8 months 95% CI; (NA-NA)] pre-ICI sodium value (log-rank, p=0.292). (Figure 2A) However, patients with higher post-ICI sodium levels had significantly longer OS than those with lower sodium levels [9.1 months 95% CI; (0.0-22.6)], (log-rank, p<0.001). (Figure 2B) The median OS in the high post-ICI group was not reached. Age and ECOG PS also reached statistical significance in univariate analyses for OS. (Table 3)

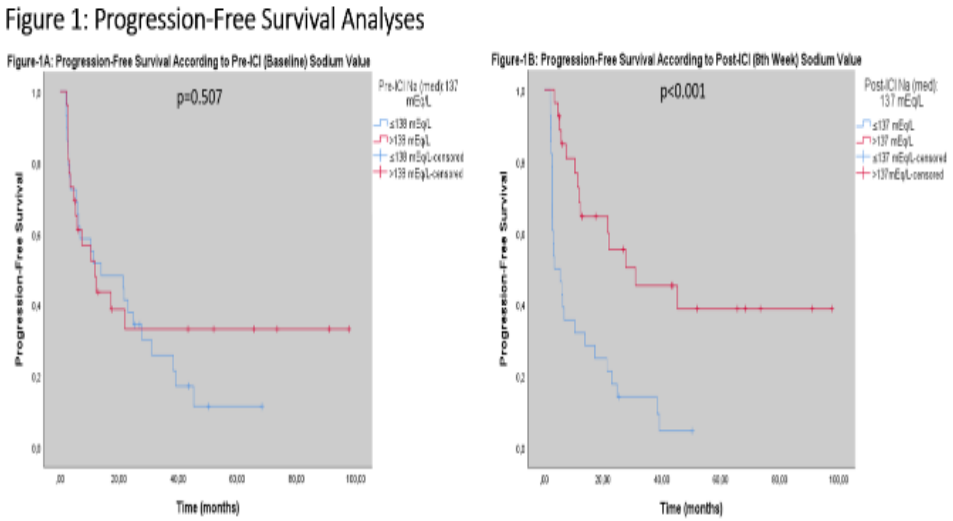


Figure 1- A: The PFS was similar for pre-ICI low [13.8 months 95% CI; (0.0-33.1)] and high [11.7 months 95% CI; (4.5-18.9)] sodium subgroups (log-rank, p=0.507). B: The PFS was longer for post-ICI sodium group [30.9 months 95% CI; (2.0-59.9)] than those with lower post-ICI sodium levels [3.4 months 95% CI; (0.0-7.1)], (log-rank, p<0.001).

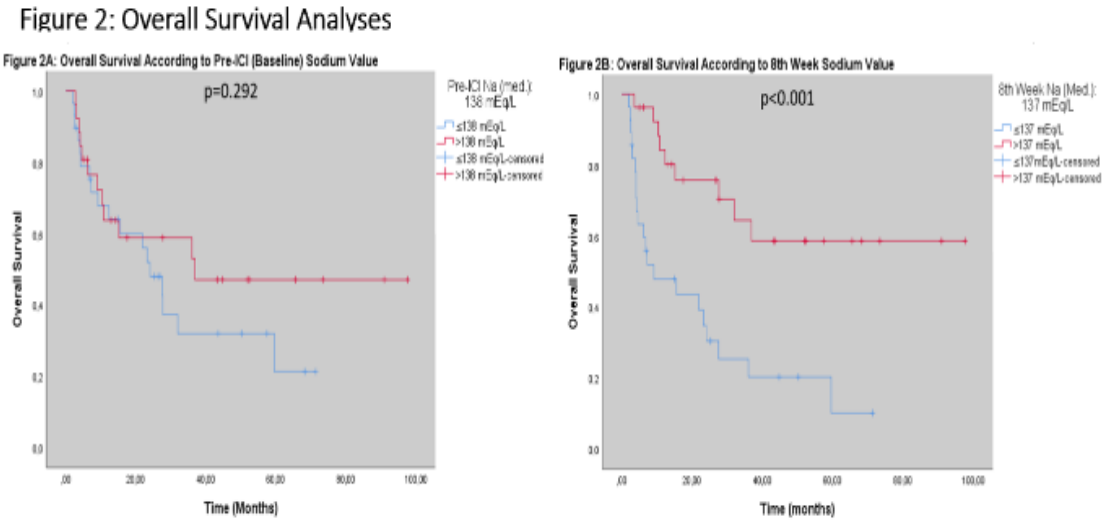


Figure 2-A: The median OS was similar between the low [24.0 months 95% CI; (15.9-32.1)] and high [36.8 months 95% CI; (NA-NA)] pre-ICI sodium value (log-rank, p=0.292). B: The patients with higher post-ICI sodium levels (the median OS was not reached) had significantly longer OS than those with lower sodium levels [9.1 months 95% CI; (0.0-22.6)], (log-rank, p<0.001).

Table 3. Univariate and Multivariate Analysis For Overall Survival for Nivolumab

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| Variables | P Value | HR | 95% CI | P Value |
| Age | | | | |
| <65 years | 0.034 | 1.00 (Ref.) | | 0.218 |
| ≥65 years | | 1.704 | (0.730-3.977) | |
| Sex | | | | |
| Female | 0.981 | 1.00 (Ref.) | | 0.293 |
| Male | | 1.704 | (0.730-3.977) | |
| ECOG PS | | | | |
| 0-1 | 0.006 | 1.00 (Ref.) | | 0.452 |
| 2 | | 1.419 | (0.570-3.534) | |
| Smoking History | | | | |
| Non-smoker | 0.622 | | | |
| Smoker | | | | |
| History of Nephrectomy | | | | |
| No | 0.472 | | | |
| Yes | | | | |
| Histological Type | | | | |
| Clear Cell RCC | 0.209 | 1.00 (Ref.) | | 0.076 |
| Non-Clear Cell RCC | | 2.129 | 0.924-4.904 | |
| Histological Grade | | | | |
| 1-2 | 0.850 | 1.00 (Ref.) | | |
| 3-4 | | 1.191 | (0.513-2.768) | |
| Sarcomatoid Differantiation | | | | |
| No | 0.785 | | | |
| Yes | | | | |
| Body Mass Index | | | | |
| <30 kg/m2 | 0.311 | 1.00 (Ref.) | | |
| ≥30 kg/m2 | | 0.840 | (0.321-2.200) | |
| IMDC Risk | | | | |
| Good Risk | 0.103 | 1.00 (Ref.) | | 0.337 |
| Intermediate Risk | | 0.721 | (0.248-2.093) | |
| Poor Risk | | 1.485 | (0.366-6.013) | |
| Glomerular Filtration Rate | | | | |
| <60 ml/min/1.73m2 | 0.665 | | | |
| ≥60 ml/min/1.73m2 | | | | |
| Pre-ICI Na | | | | |
| ≤138 mEq/L | 0.292 | 1.00 (Ref.) | | 0.398 |
| >138 mEq/L | | 1.426 | (0.626-3.247) | |
| Post-ICI Na | | | | |
| ≤137 mEq/L | <0.001 | 1.00 (Ref.) | | <0.001 |
| >137 mEq/L | | 0.239 | (0.107-0.533) | |

CI: Confidence Interval, ECOG PS: Eastern Cooperative Oncology Group Performance Status, HR: Hazard Ratio IMDC: International Metastatic RCC Database Consortium

In multivariate analyses for OS, it was observed that the post-ICI sodium value significantly affected OS [HR: 0.239; 95% CI, 0.107-0.533, (p<0.001)]. The pre-ICI sodium level, age, sex, ECOG PS, histological subtype, and IMDC risk score did not reach statistical significance. (Table 3)

## Discussion

We demonstrated that a higher sodium value measured at the 8th week of subsequent

nivolumab treatment was a positive independent prognostic factor for PFS and OS in patients with metastatic RCC. Sodium levels above 137 mEq/L were associated with a better prognosis than those with lower post-ICI eighth-week sodium levels. In addition, the DCR was significantly higher in the high post-ICI high sodium group. However, the baseline pre-ICI sodium levels measured before the beginning of nivolumab treatment, with a cut-off median value of 138 mEq/L did not significantly affect the response rates, PFS, or OS.

Sodium is an easy, fast, and affordable test that is feasible for almost all patients. Therefore, many studies have investigated sodium levels. The effect of serum sodium on immunity is not well-defined. However there are hypothetic theories. The direct pathway is the activation of T cells and macrophages by elevated sodium concentration. The indirect pathway is the immunmodulation through endocrine system [15]. The clinical implication of this effect is still being investigated.

In Checkmate 025, the pivotal study of second-line nivolumab, there is no effective biomarker for ICI response in later-line treatment [14]. Therefore, the search for a convenient marker continued. In 2021, the Meet-Uro Score was highlighted as outperforming the IMDC risk score as a prognostic factor in patients who received second- or later-line nivolumab by the Meet-Uro 15 study [16]. In the bone-metastatic subset analysis of the Meet-Uro 15 study, pre- and post-ICI (4th-week) sodium levels were tested as prognostic markers in 120 patients, and the cut-off sodium value was set as 140 for both sets. Multivariate analysis showed that post-ICI high sodium levels significantly reduced the risk of progression and death. However, the pre-ICI sodium levels showed modest significance only for OS (p=0.04) [17]. Consistent with our results, they reported that previous nephrectomy history did not significantly affect PFS and OS. In addition, post-ICI sodium levels were prognostic factors in our study, despite the different cut-off values and measurement times. Another study by Catalano et al., which is a multicenter, retrospective analysis composed of 355 patients receiving second or later-line nivolumab reported that post-ICI (4th-week) sodium median levels significantly altered the OS outcomes favoring the high sodium groups but not PFS. Nevertheless, pre-ICI sodium levels were significant for OS but not for PFS in multivariate analyses. Unlike our study, they found that previous nephrectomy, better Karnofsky Performance Score (≥80%), and being in the good-risk group at the IMDC risk categorisation were significantly associated with improved PFS and OS [10]. Although the 4th-week sodium levels significantly affected the prognosis in these two studies, we demonstrated that the 8th-week sodium level was the sole strong prognostic factor. Our results are consistent with the literature since higher post-ICI sodium levels were associated with a better prognosis in our study.

A recent post-hoc analysis of serum electrolytes of IMvigor 221 and IMmotion 151 which included metastatic RCC patients receiving first-line atezolizumab plus bevacizumab, reported that elevated baseline serum sodium reported that elevated baseline sodium levels directly associated with an increased benefit from immunotherapy. These results suggestthat a high sodium level might serve as a predictive biomarker for immunotherapy response [18]. Beyond the predictive value for immunotherapy, there are many studies in metastatic RCC patients treated with the tyrosine kinase inhibitors, everolimus reporting that hyponatremia is associated with a worse prognosis regardless of the IMDC risk score and the treatment agent [9,11,19,20].

Age, ECOG PS, and IMDC risk score have proven to be independent prognostic factors for metastatic RCC [5]. Nevertheless, the small size of our study cohort might have prevented the identification of these variables from reaching prognostic significance.

## Limitations

The major limitations of our study were its retrospective design and the limited number of study patients. Moreover, the single-center data could have led to unintentional patient selection bias. In contrast, the strong prognostic effect of the post-ICI 8th-week sodium level is a unique result despite its limitations.

## Conclusions

In conclusion, our study revealed that high levels

of post-ICI 8th-week sodium (>137 mEq/L) were associated with longer PFS and OS than lower levels (≤137) in metastatic RCC patients treated with second or later-line nivolumab. However, baseline sodium levels were not associated with either PFS or OS. These results suggest that the patients with lower 8th-week sodium levels may be followed closer for progression and the therapeutic stragies should be managed knowing the poor prognosis these patients might have. The accumulating data in the literature are promising for both the predictive and prognostic value of higher sodium levels in metastatic RCC patients treated with ICI. However, comprehensive, randomized studies are needed to determine the consequences of this evolving subject, as it is feasible and affordable.

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**Ethics Committee Approval:** Antalya Eğitim ve Araştırma Hastanesi Etik Kurul Komitesi (Onay No: Approval No: 10/37, 11.07.2024) / Antalya Training and Research Hospital Ethical Committee (Approval No: 10/37, 11.07.2024).

**ORCID and Author contribution:** **HGG; (0000-0001-8310-1752,** Data curation, Writting the original draft, Literature research, Methodology **BÖ; (0000-0003-0290-8787)** Supervision and menthorship, Reviewing and editing the original draft, Methodology, Literature research, Sources

**Peer-review:** Externally peer reviewed.

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# The Link Between Anxiety Sensitivity and Social Anxiety Symptoms: Cognitive Flexibility as a Mediating Factor

## Anksiyete Duyarlılığı ve Sosyal Anksiyete Semptomları Arasındaki Bağlantı: Aracı Faktör Olarak Bilişsel Esneklik

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## ABSTRACT

**Aim:** The purpose of this study was to explore the relationship between symptoms of social anxiety and anxiety sensitivity, as well as the role of cognitive flexibility as a mediator.
**Methods:** A total of 552 people between the ages of 18-35, with no history of psychiatric follow-up and treatment, were included in the study. A sociodemographic data form, the Liebowitz Social Anxiety Scale, Anxiety Sensitivity Index-3 and Cognitive Flexibility Inventory were applied to the participants.
**Results:** It was determined that social anxiety scores were significantly higher in female participants (86.11 ± 23.50) compared to male participants (79.43 ± 26.10) ($p < 0.001$). There was a positive relationship between social anxiety symptoms and anxiety sensitivity and its subscales ($p < 0.001$) and a negative relationship with cognitive flexibility ($p < 0.001$). According to the mediation analysis results, cognitive flexibility mediates 13% of the total effect of anxiety sensitivity on social anxiety symptoms.
**Conclusion:** The findings of the study draw attention to the strong relationship between social anxiety symptoms and anxiety sensitivity and show that cognitive flexibility may be an important mediating mechanism in this process. Accordingly, it is thought that interventions aimed at increasing cognitive flexibility in the treatment of social anxiety may be useful.

Key Words: Social anxiety, Anxiety sensitivity, Cognitive flexibility

## ÖZ

**Amaç:** Bu çalışmanın amacı, sosyal anksiyete belirtileri ile anksiyete duyarlılığı arasındaki ilişkiyi ve bilişsel esnekliğin aracı rolünü araştırmaktır.
**Yöntem:** Çalışmaya psikiyatrik takip ve tedavi öyküsü olmayan, 18-35 yaş aralığında toplam 552 kişi dahil edildi. Katılımcılara sosyodemografik veri formu, Liebowitz Sosyal Anksiyete Ölçeği, Anksiyete Duyarlılığı İndeksi-3 ve Bilişsel Esneklik Envanteri uygulandı.
**Bulgular:** Kadın katılımcılarda sosyal anksiyete puanlarının (86.11 ± 23.50) erkeklere kıyasla (79.43 ± 26.10) anlamlı derecede yüksek olduğu belirlenmiştir ($p < 0.001$).Sosyal anksiyete belirtileri ile anksiyete duyarlılığı ve alt ölçekleri arasında pozitif ($p < 0.001$), bilişsel esneklik ($p < 0.001$) ile negatif ilişki bulunmuştur. Aracılık analizi sonuçlarına göre, bilişsel esneklik, anksiyete duyarlılığının sosyal anksiyete belirtileri üzerindeki toplam etkisinin %13'üne aracılık etmektedir.
**Sonuç:** Çalışmanın bulguları, sosyal anksiyete belirtileri ile anksiyete duyarlılığı arasındaki güçlü ilişkiye dikkat çekmekte ve bilişsel esnekliğin bu süreçte önemli bir aracı mekanizma olabileceğini göstermektedir. Bu doğrultuda, sosyal anksiyete tedavisinde bilişsel esnekliği artırmaya yönelik müdahalelerin faydalı olabileceği düşünülmektedir.

Anahtar Sözcükler: Sosyal anksiyete, Anksiyete duyarlılığı, Bilişsel esneklik

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## Introduction

Social anxiety, alternatively referred to as social phobia, is a prevailing and incapacitating ailment that significantly impacts the overall well-being of an individual. The apprehension of adverse assessment or peer criticism may induce withdrawal from communal gatherings, thereby causing substantial hindrances to day-to-day operations and interpersonal connections [1]. In addition, social anxiety has the potential to augment the likelihood of acquiring other mental health afflictions, such as depression and substance abuse disorders, exacerbating the negative effects on an individual's general state of being [2]. The cognitive framework of social anxiety suggests that unfavourable convictions concerning oneself, others and the social realm, are instrumental in the emergence and perpetuation of the disorder. These negative beliefs may encompass thoughts of being inferior, unattractive or incompetent, as well as perceptions of the social world as dangerous or threatening. Individuals with social anxiety may engage in safety behaviours and avoidance strategies as coping mechanisms to manage their anxiety, inadvertently reinforcing their negative beliefs and perpetuating the disorder [1].

Anxiety sensitivity is a phenomenon characterized by increased fear or distress in response to an individual's bodily sensations associated with anxiety. Anxiety sensitivity, originally conceptualized as a one-dimensional trait reflecting the tendency to fear the consequences of anxiety, has evolved into a multidimensional construct with three sub-dimensions: physical, cognitive and social [3]. The physical subtype of anxiety sensitivity encompasses concerns about the physical symptoms of anxiety, while cognitive anxiety sensitivity involves worries about the loss of cognitive control due to anxiety. Social anxiety sensitivity, on the other hand, relates to concerns about the unfavourable social consequences of others observing anxiety symptoms [4]. Research has shown that anxiety sensitivity is not limited to specific anxiety disorders but rather serves as a transdiagnostic factor associated with various mental illnesses. This suggests that it plays a significant role in the development and maintenance of psychological distress. Furthermore, anxiety sensitivity has been found to influence an individual's perception of stress, as it is closely linked to the assessment of events and the importance attributed to those events. High levels of anxiety sensitivity have been associated with increased stress perception, indicating its role as a significant determinant of stress-related experiences [5].

Cognitive flexibility is the capacity to modify one's thought processes by modifying environmental circumstances. It involves the capacity to generate alternative thoughts that are better suited to the situation at hand, rather than being stuck in rigid or maladaptive thought patterns that may lead to distress. Cognitive flexibility encompasses the ability to approach problems from multiple angles, think creatively and employ different strategies to effectively navigate challenging situations. Cognitive flexibility can promote resilience and facilitate psychological well-being, especially in the face of uncontrollable stressors. By cultivating cognitive flexibility through interventions and practices that promote adaptable thinking, individuals can enhance their ability to cope with stressful situations and maintain their mental health in the midst of adversity [6].

Social anxiety is a complex and debilitating disorder sustained by several cognitive processes. To better conceptualise this disorder, it is vital to identify its underlying factors. The relationship between social anxiety and anxiety sensitivity has been investigated in a limited number of studies [7]. In addition, research has shown that individuals with social anxiety tend to exhibit higher levels of anxiety sensitivity, than those without social anxiety. Cognitive flexibility has been posited as a potential mechanism underlying the emergence of anxiety, as it denotes the capacity to shift between diverse modes of emotional stimulus processing, contingent on situational demands and personal objectives [8]. The presence of cognitive inflexibility weaknesses among those with social anxiety, may play a role in the origin and perpetuation of the condition. When the literature is examined, no study investigating the relationship between social anxiety sensitivity and cognitive flexibility has been observed. The present research endeavoured to examine the correlation that exists between anxiety sensitivity of social anxiety and cognitive flexibility, as its

main objective.

## Methods

### Study design

This research undertaking was planned as a descriptive cross-sectional study and was executed during the period of March to April 2023, at the Family Medicine outpatient facility of Kütahya Health Sciences University. The study was approved by the ethics committee of Kütahya Health Sciences University and Kütahya Provincial Health Directorate.

The G*Power 3.1.9.7 program was used for sample size calculation. The "Chi-square test" was taken into consideration in sample size calculation. For effect size (Cohen w)=0.3, d(f)=1, □ error=0.05, 1-□ error=0.9 and two-way p-value; a total of 117 patients were evaluated. The research was executed using a sample size of 552 individuals who fulfilled the eligibility criteria and gave their informed consent to partake in the investigation. Participants were between the ages of 18 to 35, who applied to the family medicine outpatient clinic for non-psychiatric reasons (screening, driving licence, starting work, health report, administrative reasons, etc.), who had no history of psychiatric admission, follow-up and treatment in their medical records, who did not describe any mental complaints in the clinical evaluation made by the family physician specialist, who did not have any neurological and internal problems that would affect any cognitive performance during the interview and who agreed to participate in the study.

### Data collection

A sociodemographic form collecting the age, gender, years of education, marital status, smoking and alcohol consumption status of the patients, was completed by the family physician specialist. The Anxiety Sensitivity Index-3, Liebowitz Social Anxiety Scale and Cognitive Flexibility Inventory were applied to all individuals who met the inclusion criteria.

### The Anxiety Sensitivity Index-3

The Anxiety Sensitivity Index-3 (ASI-3) consists of a total of 18 items and is divided into three sub-dimensions: physical, social and cognitive. Each sub-dimension contains six items. The scale is a five-point Likert-type scale ranging from 0 (strongly disagree) to 4 (strongly agree). The total score that can be obtained from the scale ranges from 0 to 72; higher scores indicate higher anxiety sensitivity. This scale was developed by Stewart, Taylor and Watt to assess the level of individuals' perception of anxiety symptoms as threatening, and its Turkish adaptation and validity-reliability study was conducted by Mantar et al. [9].

### The Liebowitz Social Anxiety Scale

Liebowitz Social Anxiety Scale (LSAS) is a scale that shows the social relationship and performance situations in which individuals show fear and avoidance behaviours. It consists of a total of 24 items, 11 of which are related to social relationships and 13 of which are related to performance. Each item is scored between 0 and 3. The total score of the scale ranges from 0 to 144, with higher scores indicating more severe social anxiety. This scale was developed by Michael R. Liebowitz in 1987 to assess for social anxiety disorder and its validity and reliability study in Turkey was conducted by Soykan et al. [10].

### The Cognitive Flexibility Inventory

The Cognitive Flexibility Inventory (CFI) was formulated to measure cognitive flexibility, which is related to the ability to replace incompatible thoughts with appropriate and compatible ones. The scale, which consists of a total of 20 items, has two subscales: 'control' and 'alternatives'. Each item is scored from 1 (strongly disagree) to 7 (strongly agree). The total score of the scale ranges from 20 to 140; higher scores indicate a higher level of cognitive flexibility. This scale was developed by Dennis C. Dennis and John M. Vander Wal and its validity and reliability study in Turkey was conducted by Dilbaz and Güz [11].

### Statistical analysis

The statistical analysis was conducted using the SPSS version 21 (IBM®, Chicago, USA). The examination of the variables' distribution, whether normal or abnormal, was conducted through the utilization of the Shapiro-Wilk test. The distribution of data was summarized using descriptive statistics.

In the case of normally distributed numerical data, the mean and standard deviation were employed, while the median (minimum-maximum) was used for abnormally distributed data. For nominal data, the number and percentage were reported. For the analysis of normally distributed numerical variables, the "Student's T-test" and "One-way ANOVA" were utilized. For the analysis of non-normally distributed variables, the "Mann-Whitney U" and "Kruskal-Wallis test" were applied. The "chi-square analysis" was employed to compare nominal data. The mediating effect of cognitive flexibility on the relationship between social anxiety and anxiety sensitivity, was analysed using Process Macro based on bootstrapping. A statistical significance was attributed to p values that were below 0.05 during the execution of statistical analyses.

## Results

The study included 552 participants. Table 1 presents the means, standard deviations and percentages of the participants' socio-demographic characteristics and questionnaire scores. The mean age of all participants was 26.54±4.67 years. Of all participants, 67.4% were female and 63.8% were single. The mean number of years of education was 14.89±2.42. The mean LSAS score was 83.93±24.58, ASI 24.88±13.73 and CFI 65.42±5.79. The comprehensive and detailed summary of the participants' socio-demographic characteristics and the scores obtained from the questionnaire can be found in Table 1.

The comparison of scale scores according to gender is given in detail in Table 2. The mean LSAS score of women (86.11 ± 23.50) was significantly higher than that of men (79.43 ± 26.10) (p<0.001). Women's LSAS-Avoidance score was 43.24 ± 11.72, while men's score was 41.52 ± 13.92. Women scored significantly higher than men (p = 0.016). For the LSAS-Concern subscale, women's worry scores were also significantly higher (42.87 ± 12.68) compared to men's (37.91 ± 13.63) (p<0.001). The overall ASI score of women (26.00 ± 14.39) was higher than that of men (22.57 ± 11.91) (p = 0.018). ASI-Physical subscale score was significantly higher in women (8.50 ± 6.03) compared to men (6.93 ± 4.99) (p=0.009). In the ASI-Cognitive subscale, women (9.04 ± 5.58) scored significantly higher than men (7.75 ± 4.64) (p=0.033). There was no significant difference between women (8.45 ± 4.95) and men (7.88 ± 4.94) on the ASI-Social subscale (p=0.176). There was no significant difference between women (65.32 ± 5.90) and men (65.63 ± 5.55) in overall CFI scores (p=0.113).

**Table 1. Sociodemographic characteristics and questionnaire scores of all participants (N=552)**

| | All participants (N=552) |
|---|---|
| **Age (years)*** | 26.54±4.67 |
| **Gender, female**** | 372 (67.4) |
| **Education level (years)*** | 14.89±2.42 |
| **Marital status, single**** | 352 (63.8) |
| **Smoking (+)**** | 188 (34.1) |
| **Alcohol consumption (+)**** | 92 (16.7) |
| **LSAS*** | 83.93±24.58 |
| LSAS-Avoidance | 42.68±12.51 |
| LSAS-Worry | 41.25±13.20 |
| **ASI*** | 24.88±13.73 |
| ASI-Physical | 7.99±5.76 |
| ASI-Cognitive | 8.62±5.33 |
| ASI-Social | 8.26±4.96 |
| **CFI*** | 65.42±5.79 |
| CFI-Alternative | 48.82±8.21 |
| CFI-Control | 16.59±3.80 |

*Mean±sd, Mann Whitney U Test; **N(%), Chi-square. ASI: Anxiety Sensitivity Index, LSAS: Liebowitz Social Anxiety Scale, CFI: Cognitive Flexibility Inventory

The Spearman correlation analysis was performed to evaluate the linear relationship between the questionnaire scores. In the correlation analysis, a significant positive correlation was observed between ASI and sub-scores of ASI (p<0.001) and LSAS total score (p<0.001) and LSAS sub-scores (p<0.001). A significant negative correlation was found with CFI (p<0.001). In addition, a significant negative correlation was observed between CFI-A and ASI (p<0.001), ASI-S (p<0.001) and ASI-C (p<0.001). A significant positive correlation was observed between CFI-C and ASI (p=0.009), ASI-S (p=0.004) and ASI-C (p=0.002).

The mediating role of cognitive flexibility in the effect of anxiety sensitivity on social anxiety symptoms is shown in Figure 1. The direct effect of anxiety sensitivity on social anxiety symptoms (standardised effect) was β = 0.351 (p<0.001).

Taking into account the mediating role of cognitive flexibility (M-mediator variable), the effect of anxiety sensitivity (antecedent variable) on social anxiety symptoms (Y) (standardised effect) was β = 0.306 (p<0.001).

Table 2. Comparison of scale scores according to gender (N=552)

| | Female (n=372) | Male (n=180) | p value |
|---|---|---|---|
| LSAS | 86.11± 23.50 | 79.43± 26.10 | <0.001 |
| LSAS-Avoidance | 43.24± 11.72 | 41.52± 13.92 | 0.016 |
| LSAS-Worry | 42.87± 12.68 | 37.91± 13.63 | <0.001 |
| ASI | 26.00± 14.39 | 22.57± 11.91 | 0.018 |
| ASI-Physical | 8.50± 6.03 | 6.93± 4.99 | 0.009 |
| ASI-Cognitive | 9.04± 5.58 | 7.75± 4.64 | 0.033 |
| ASI-Social | 8.45± 4.95 | 7.88± 4.94 | 0.176 |
| CFI | 65.32± 5.90 | 65.63± 5.55 | 0.113 |
| CFI-Alternative | 48.51± 8.39 | 49.47± 7.79 | 0.118 |
| CFI-Control | 16.80± 3.81 | 16.15± 3.76 | 0.053 |

Mean±sd, Mann Whitney U Test. ASI: Anxiety Sensitivity Index, LSAS: Liebowitz Social Anxiety Scale, CFI: Cognitive Flexibility Inventory

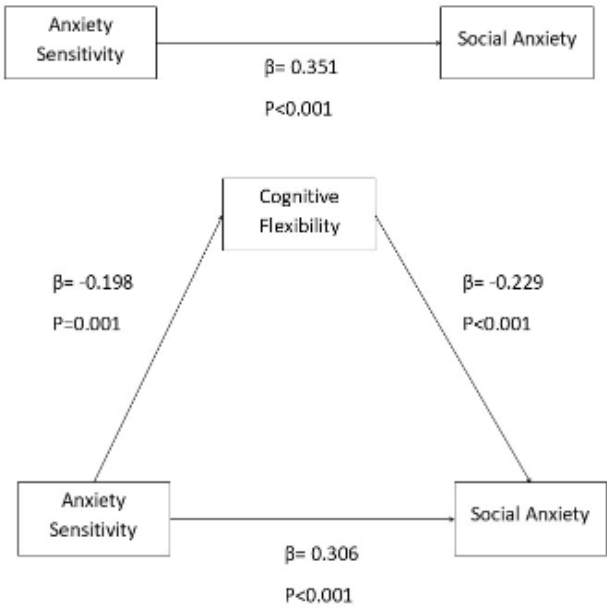


Figure 1. Mediation model results in predicting social anxiety, p< 0.05

The mediating effect of cognitive flexibility on the relationship between social anxiety symptoms and anxiety sensitivity, was analysed on a bootstrapping basis and summarised in detail in Table 3. The difference between the direct and indirect effects of anxiety sensitivity and cognitive flexibility on social anxiety symptoms, emphasises the importance of the mediating role of cognitive flexibility. The indirect effect, that is, the effect of cognitive flexibility on social anxiety symptoms, constitutes approximately 12.88% (0.081/0.629) of the total effect. This can be interpreted as approximately 13% of the total effect of anxiety sensitivity on social anxiety is mediated by cognitive flexibility.

Table 3. Bootstrapping coefficients

| | Effect | Estimate | SE | 95%CI (LL/UL) | β | z | p |
|---|---|---|---|---|---|---|---|
| Indirect | ASI ⇒ CFI ⇒ LSAS | 0.0813 | 0.0234 | (0.0357/ 0.1276) | 0.0454 | 3.47 | <0.001 |
| Component | ASI ⇒ CFI | -0.0838 | 0.0178 | (-0.1192/ -0.0494) | -0.1985 | -4.70 | <0.001 |
| | CFI ⇒ LSAS | -0.9706 | 0.1830 | (-1.3274/ -0.6102) | -0.2288 | -5.30 | <0.001 |
| Direct | ASI ⇒ LSAS | 0.5475 | 0.0709 | (0.4081/ 0.6859) | 0.3058 | 7.73 | <0.001 |
| Total | ASI ⇒ LSAS | 0.6288 | 0.0742 | (0.4829/ 0.7737) | 0.3512 | 8.48 | <0.001 |

ASI: Anxiety Sensitivity Index, LSAS: Liebowitz Social Anxiety Scale, CFI: Cognitive Flexibility Inventory

## DISCUSSION

The complex and multifaceted nature of the relationship between social anxiety symptoms, anxiety sensitivity and cognitive flexibility is remarkable. The results of our investigation indicate a substantial correlation between symptoms of social anxiety and anxiety sensitivity. Furthermore, the observed link was mediated by cognitive flexibility.

Although anxiety sensitivity was initially associated with panic disorder, transdiagnostic approaches have reported that it may be an important transdiagnostic factor in the aetiology, assessment and treatment of multiple affective disorders, including social anxiety disorder [12]. However, there are a limited number of studies investigating the relationship between anxiety

sensitivity and social anxiety disorder in the literature [13].

In some studies in the literature, it has been reported that there is a relationship between high anxiety sensitivity and social anxiety disorder and that anxiety sensitivity may be a sustaining factor in social anxiety symptoms [13]. In our study, a strong relationship was found between social anxiety symptoms and anxiety sensitivity. This relationship indicates that individuals with high levels of anxiety sensitivity may be more prone to experience symptoms related to social anxiety.

In our study, social anxiety scores were significantly higher in women than in men. The results of the ASI were similarly higher in women than in men, suggesting that women may experience higher levels of social anxiety and may also have higher levels of anxiety sensitivity. The significant differences observed in the ASI-Physical and ASI-Cognitive subscales suggest that women are more sensitive to the physical symptoms of anxiety and are more likely to interpret these symptoms as dangerous. This increased sensitivity to physical sensations may contribute to the higher prevalence of anxiety disorders among women [14]. These results are consistent with other studies that found women are more likely than males to report having greater social anxiety symptoms. It is similar to the literature suggesting that women would be more likely to exhibit anxiety and avoidant behaviours in social settings. These gender differences in social anxiety can be attributed to a variety of socio-cultural and biological factors.

Anxiety sensitivity has a multidimensional structure consisting of physical, cognitive and social sub-dimensions. This hierarchical structure is important in understanding the links between certain subscales of anxiety sensitivity and different anxiety-related psychopathologies [15]. The physical subscale related to dread of physical sensations is linked to panic disorder, whereas the cognitive subscale concerning fear of diminished cognitive control is connected with depression and generalized anxiety disorder (GAD) [16]. However, the findings on the relationship between the sub-dimensions of anxiety sensitivity and social anxiety are inconsistent. While some studies found a significant relationship between the social subscale of anxiety sensitivity and social anxiety, others reported different results [17, 18]. In a further study, it was reported that none of the subscales predicted social anxiety symptoms, one year later [12]. Ölmez et al. emphasised the importance of anxiety sensitivity in individuals with social anxiety disorder and drew attention to the role of the social, cognitive and physical subscales of the Anxiety Sensitivity Index (ASI) in assessing the severity of the condition [19]. Similarly, a significant correlation was found between social anxiety symptoms and all subscales of anxiety sensitivity in our study. Observable physical symptoms such as facial flushing, trembling and sweating are common in individuals with social anxiety and it is known that individuals show increased sensitivity to these symptoms [19]. The establishment of continuous rumination, a negative interpretation tendency in cognitive processes and a fear of being negatively evaluated in social situations, are all factors that lead to the development and maintenance of social anxiety. These detrimental cognitive processes are thought to be more common in those with high levels of cognitive anxiety sensitivity [19, 20]. Social anxiety is a complex and debilitating disorder sustained by various cognitive processes. Identifying the factors underlying this disorder is critical for a more comprehensive conceptualisation. Anxiety sensitivity can lead to a cascading cycle of social anxiety, with cognitive, somatic and behavioural symptoms of social anxiety disorder. Given the links between anxiety sensitivity and specific features of social anxiety in the current theoretical framework, further research is needed to integrate anxiety sensitivity with cognitive-behavioural models of social anxiety disorder.

There is a small number of research investigations that have been conducted to investigate the connection between social anxiety and cognitive flexibility in the existing body of literature. Some studies suggest that there is no relationship between social anxiety and cognitive flexibility [20, 21]. On the other hand, other research demonstrates a negative association between cognitive flexibility and social anxiety, which is consistent with the findings of our study. Findings from research on cognitive flexibility suggest a potential relationship between cognitive flexibility and various psychopathologies, including social

anxiety [22]. When the findings of the study were analysed comprehensively, it was found that social anxiety, cognitive flexibility and anxiety sensitivity exhibited a complex reciprocal relationship. During the mediation analysis aiming to better understand the dynamics underlying this relationship, it was found that cognitive flexibility functions as a mediator in the effect of anxiety sensitivity on social anxiety. It was found that approximately 13% of the total effect of anxiety sensitivity on social anxiety was mediated by cognitive flexibility. Similarly, it has been reported in the literature that cognitive flexibility functions as a mediator for social anxiety and this mediation is associated with high anxiety levels.

According to the cognitive model, it is emphasised that individuals' cognitive distortion tendencies, dysfunctional attitudes and negative automatic thoughts are the basis of social anxiety. According to the investigations, dysfunctional beliefs were a predictor of cognitive flexibility [23]. The ability to adjust to unfamiliar social contexts and react suitably to social cues plays a pivotal role in the dynamics of cognitive flexibility. The absence of adaptable cognitive abilities can potentially contribute to the development of social anxiety through the manifestation of repetitive negative interpretations within social relationships [24]. Attention to and interpretation of information plays a critical role in cognitive processes. Biases in this information processing process cause a vicious cycle of negative thoughts, behavioural avoidance and increased feelings of anxiety. For this reason, anxiety sensitivity has been associated with a cognitive defence against negative reactions to anxiety symptoms, caused by attention and interpretation biases related to anxiety. In contrast, cognitive flexibility is an asset that enables one to concentrate on pertinent information while disregarding non-essentials and flexibly reorienting attention among various information sources. This involves the ability to identify multiple alternative evaluations or explanations when confronted with stressful circumstances [25]. This role may explain the mediating function of cognitive flexibility on anxiety sensitivity and social anxiety symptoms.

The limitations of our study are that self-report scale-based assessments were utilized and cognitive flexibility was assessed using an inventory, rather than neuropsychological comprehensive tests. The sample size, the fact that the participants were evaluated by a clinician prior to the study and the fact that past psychiatric history was determined and controlled as an exclusion criterion, constitute the strengths of our study.

In conclusion, this study provides a significant addition to the current body of knowledge regarding the interplay among symptoms of social anxiety, anxiety sensitivity and cognitive flexibility. The findings suggest that individuals who exhibit high levels of anxiety sensitivity and low cognitive flexibility, are more likely to experience higher social anxiety symptoms compared to their counterparts. The effect of anxiety sensitivity on social anxiety symptoms as a transdiagnostic approach and the mediating role of cognitive flexibility is significant. Therefore, considering the relationship between anxiety sensitivity and cognitive flexibility, it is critical to recognise patients with high anxiety sensitivity and to offer therapies and interventions that include cognitive flexibility for better treatment of social anxiety symptoms.

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RESEARCH ARTICLE

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# Pediatric Thoracic and Lumbar Spinal Fractures

## Pediatrik Torakal ve Lomber omurga kırıkları

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## ABSTRACT

**Aim:** Vertebral body fractures in childhood are rarely observed and differ from those in adults due to incomplete ossification. There is no guideline for the management of pediatric thoracolumbar spinal fractures. The aim of this study is to examine the epidemiological data of our pediatric patients treated for thoracic and lumbar vertebral fractures and to contribute to the decision-making processes regarding the diagnosis and treatment of these patients.
**Methods:** Patients under 16 years of age who were admitted to the emergency department of Alanya Education and Research Hospital with a history of spinal trauma and diagnosed with thoracic and lumbar vertebral fractures between 2016-2023 were included. Our study included patients whose demographic data, causes of trauma, diagnostic tests, and treatments were accessed using the hospital's clinical database.
**Results:** Among 154 patients admitted to our hospital with a diagnosis of spinal trauma, 21 patients who met the inclusion criteria were included in the study. Thirteen patients had a single vertebral body fracture, five had fractures in two vertebral bodies, and three had pars fractures leading to traumatic spondylolisthesis. Four patients underwent surgery due to vertebral fractures.
Conclusion: The pediatric spine's biomechanical structure and self-healing ability differ from adults. Pediatric spinal traumas are important pathologies that need to be studied due to their rarity, difficulty in diagnosis, lack of experience in treatment, and potential complications that may develop in the long term.

Key words: Lumbar, Thoracic, Spine, Trauma, Pediatric

## ÖZ

**Amaç:** Çocukluk döneminde vertebra korpus kırıkları kemikleşme tam olmadığı için yetişkinden farklılıklar gösterir ve oldukça nadir görülür. Pediatrik torakolomber spinal fraktürlerin yönetimi hakkında bir klavuz yoktur. Bu çalışmanın amacı torakal ve lomber vertebra kırığı nedeniyle tedavi ettiğimiz pediatrik hastalarımızın epidemiyolojik verilerini incelemek ve bu hastaların tanı ve tedavisine ilişkin karar alma süreçlerine katkıda bulunmaktır.
**Yöntem:** Alanya Eğitim Araştırma Hastanesi acil servisine 2016-2023 yılları arasında spinal travma hikayesi ile gelen torakal ve lomber vertebra kırığı tanısı alan 16 yaş altındaki hastalar dahil edilmiştir. Çalışmamıza, hastanemiz klinik veri tabanı kullanılarak, demografik verilerine, travma nedenlerine, tanısal testlerine ve tedavilerine ulaşılan hastalar dahil edilmiştir.
**Bulgular:** Hastanemize omurga travması tanısı ile yatırılan 154 hasta arasından dahil edilme kriterlerini karşılayan 21 hasta çalışmaya dahil edilmiştir. Hastaların 13 tanesinde tek vertebra korpus kırığı, 5 tanesinde 2 vertebra korpusunda kırığı, 3 tanesinde travmatik spondilolistezise yol açan pars kırığı vardı. Hastaların 4 tanesine vertebra kırığı nedeniyle operasyon uygulandı.
**Sonuç:** Pediatrik omurganın biomekanik yapısı ve kendini iyileştirme yeteneği yetişkinden farklıdır. Pediatrik spinal travmalar nadir görülmesi, tanısının zor konulması, tedavisi konusundaki tecrübenin azlığı ve uzun dönemde gelişebilecek komplikasyonlar nedeniyle üzerinde çalışılması gereken önemli patolojilerdir.

Anahtar kelimeler: Lomber, Torakal, Omurga, Travma, Pediatrik

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## Introduction

The spine shows different biomechanical and structural characteristics in different age groups as it changes throughout life. The approach to spinal trauma varies in parallel with the development of the spine. Spinal traumas occurring in the pediatric period account for 1-4% of all spinal traumas. Although spinal traumas are more commonly observed in the cervical region due to the head-to-body ratio in the first years of life, they are observed in the thoracic and lumbar vertebrae at older ages. In adults, vertebral fractures are primarily caused by high-energy trauma, whereas in children, they are typically observed following low-energy trauma, such as falls and sports injuries [1,2,3]. 20-40% of pediatric spinal traumas are observed in the thoracic and lumbar regions. Pediatric thoracic and lumbar fractures account for less than 1% of all spinal traumas. Although it has been reported to be more commonly observed in male children between the ages of 13 and 16, it exhibits different epidemiological characteristics across different populations [1-5].

The pediatric spine differs from the adult spine in several aspects.

In the thoracolumbar region of the pediatric spine, there are three ossification centers: one in the center and two in the neural arches. Ossification of the vertebral body begins at the 10th week of gestational life, with less than 70% ossified at birth. This process accelerates between the ages of 2 and 6 and is typically complete by around the age of 10 [6, 7]. The facet joints of pediatric vertebrae are horizontally oriented before the age of 8, allowing for greater mobility, but they become more inclined during childhood and resemble the adult structure by the age of 15. The ligaments and connective tissues that provide spinal stability are more lax compared to adults, allowing for greater movement. Consequently, due to the increased mobility and elasticity of the pediatric thoracolumbar vertebrae in early life, fractures in this region are relatively rare [2,7,8,].

As vertebral fractures developed during the pediatric period can lead to various neurological problems and spinal deformities in the long term due to the growing skeleton, patients need to be followed up in the long term. In this study, we aimed to discuss the epidemiological data, treatment approaches, and prognosis of our pediatric patients treated for thoracic and lumbar vertebral fractures, whose treatment decision-making processes differ from those of adult patients, in the light of the literature.

## Methods

Patients under the age of 16 with a history of spinal trauma who were diagnosed with thoracic and lumbar fractures and presented to the emergency department of Alanya Education and Research Hospital between 2016 and 2023 were included in the study. Patients whose demographic data, causes of trauma, diagnostic tests and treatments were accessed in the clinical database of our hospital were included in the study. Patients with vertebral body fractures were evaluated according to the AO-Spine Magerl Thoracolumbar Injury Classification system, while patients with spondylolisthesis were assessed using the Meyerding classification. Patients with incomplete epidemiological data, as well as those whose diagnostic tests and treatment methods were unavailable, were excluded from the study.

### Statistical analysis

We used SPSS version: 23 to evaluate the data of our study. The data obtained from our patients were analyzed with frequency and percentage distributions from descriptive statistical methods.

## Results

21 patients who met the inclusion criteria among 154 patients hospitalised in our hospital with the diagnosis of spinal trauma were included in the study. Ten (48%) of the patients were female and 11 (52%) were male. The mean age at the time of injury was 10.4 years (5-16). Seven of the patients were fall from height, 8 were pedestrian injuries, 2 were in-vehicle traffic accidents and 4 were sports or game injuries. All patients had multiple trauma. Seventeen (81%) of the patients were treated conservatively and 4 (19%) were treated surgically. The diagnosis of all patients was made by tomography. Spinal MRI was performed in a total of 11 patients, 3 of whom were sedated to investigate the presence of additional spinal

Table1: Patient list

| N | M/F | Age | Vertebrea | Trauma | Treatment | Hospit. | AO Magerl Cl. |
|---|---|---|---|---|---|---|---|
| 1 | F | 7 | L5 Pars F | Spor | Conservative | 9 | 1.°Listhesis |
| 2 | M | 10 | T7, T8 | Fall H. | Conservative | 8 | A1-A3 |
| 3 | F | 12 | T12 | Fall H. | Surgery | 15 | A4 |
| 4 | M | 9 | L2 | Out-TA | Conservative | 11 | A2 |
| 5 | F | 11 | T6, T7 | İn-TA | Conservative | 16 | A1-A3 |
| 6 | M | 9 | L1 | Spor | Conservative | 6 | A3 |
| 7 | F | 5 | T7, L2 | İn-TA | Conservative | 5 | A1-A4 |
| 8 | M | 14 | L2 | Out-TA | Surgery | 18 | A4 |
| 9 | M | 15 | T10 | Fall H. | Conservative | 7 | A1 |
| 10 | F | 9 | L3 | Spor | Conservative | 3 | A3 |
| 11 | F | 16 | L3 | Out- TA | Conservative | 6 | A3 |
| 12 | M | 10 | L4 Pars F | Fall H. | Conservative | 4 | 1.°Listhesis |
| 13 | F | 14 | L2, L3 | Fall H. | Surgery | 35 | C-C |
| 14 | M | 7 | T12 | Out-TA | Conservative | 7 | A1 |
| 15 | M | 13 | L1 | Out-TA | Surgery | 14 | A4 |
| 16 | F | 9 | L2 | Spor | Conservative | 4 | A2 |
| 17 | M | 8 | T7 | Fall H. | Conservative | 6 | A1 |
| 18 | M | 10 | L5 Pars F | Out-TA | Conservative | 2 | 1.°Listhesis |
| 19 | F | 8 | T6 | Out-TA | Conservative | 17 | A2 |
| 20 | M | 11 | L3, L4 | Fall H. | Conservative | 13 | A3-A1 |
| 21 | F | 13 | L2 | Out-TA | Conservative | 5 | A3 |

**M:Male, F: Female, Fall H.:Fall From Height, İn-TA: In-Car Traffic Accident, Outs-TA: Outside Vehicle Traffic Accident, AO Magerl Cl: AO-Spine Magerl Thoracolumber İnjury Classification System, Hospit: Hospitalization, Pars F: pars fracture.**

pathology. Three of the patients (14.2%) had a pars fracture leading to traumatic spondylolisthesis. Five of the patients had fractures in 2 vertebral body. Among these patients, a single patient had fracture in the thoracic region, two patients had in the lumbar region and two patients had in both thoracic and lumbar regions. Within the group of patients with one vertebral body fracture, 5 were in the thoracic and 8 in the lumbar region. According to the AO-Spine classification, the most common types of vertebral body fractures observed were wedge compression (31%) (Type A1) and incomplete burst (31%) (Type A3). Older children and adolescents had higher grade injuries based on the AO-spine classification. The most commonly affected vertebra was L2 (n=6, 28.5%). Permanent neurological deficit developed in very few patients without mortality (n=2, 9.5%). The mean length of hospital stay was 10.04 (2-35) days and, followed up duration for patients was 6.7 months (3-64 months).

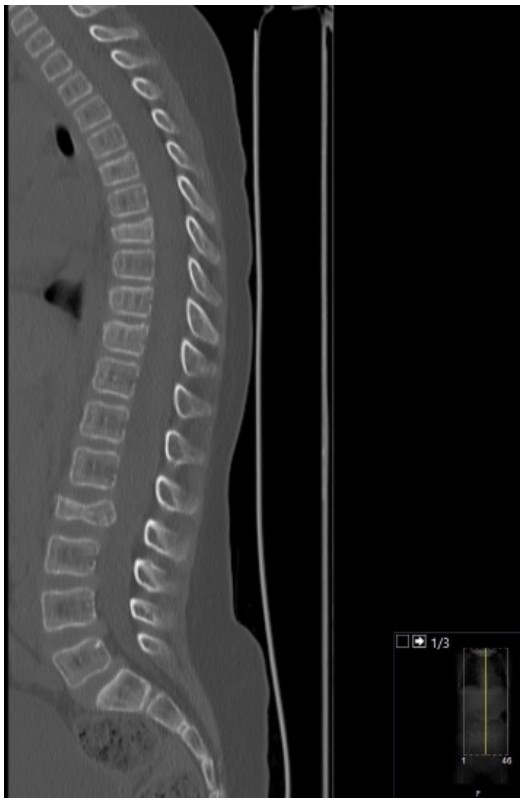


**Figure 1. T7 and L2 vertebra fracture of a 5 year old girl injured due to in-car traffic accident**

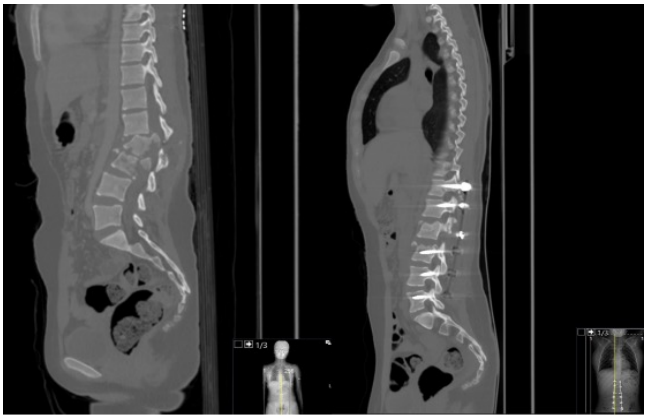

Figure 2. L2 and L3 vertebra fractures of a 14-year-old girl injured as a result of falling from a height and postoperative

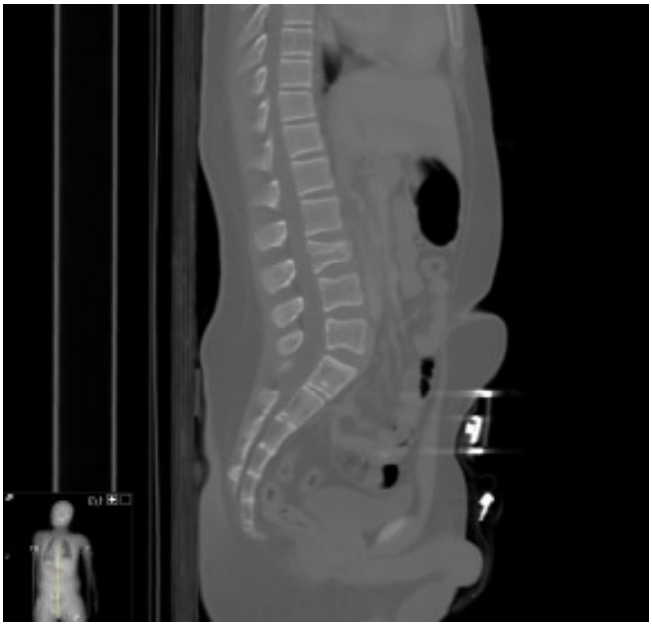

Figure3. L3 vertebra fracture of 9 year old boy injured due to a fall during sports

## Discussion

1-3% of all paediatric fracture cases are in the spinal region. The incidence of pediatric spinal fractures increases during the first five years of life and again after the age of 10 [9]. Compared to adults, the pediatric spine exhibits greater elasticity due to incomplete ossification, underdevelopment of paraspinal muscles, anatomical position of facet joints, and changes in the amount of collagen and water in the nucleus pulposus. After the age of eight, the differences gradually diminish. After 15 years of age, it shows fracture characteristics similar to adults [2,8]. As the head-to-body ratio is larger in children younger than 8 years old, cervical traumas are more frequently encountered in early childhood. Multiple vertebral fractures are observed more frequently since the body of the vertebrae are wedge-shaped and smaller in adults to carry high forces [10,11]. Spinal cord injuries without fracture are also observed in this age group because of vertebral flexibility. Saul et al. reported that 9% of paediatric vertebral fractures occurred in the cervical region, 56% in the thoracic region and 31% in the lumbar region [4]. Mendoza et al. reported that 40.9% of paediatric traumas occurred in the lumbosacral region, 32.9% in the cervical region and 26.2% in the thoracic region [10].

In the thoracolumbar region, collapse fractures of the vertebral body are observed most frequently in children as in adults. Unlike adults, L2 vertebral fracture is observed most frequently in the thoracic and lumbar region in childhood [1,2,12]. Similar to these findings, we also observed L2 vertebra fractures as the most frequent occurence in our study.

Herren et al. reported that although the thoracolumbar region is more commonly affected in childhood, middle thoracic vertebrae are more frequently injured in older children and adolescents . Vertebral fractures are frequently observed as compression fractures in the thoracic region and burst fractures in the lumbar region [2]. We could not make such a distinction in our study.

Although in various studies, different results have been reported, it is observed that the ratio is equal in larger series [1,2,4]. In our study, a higher number of male patients were found.

Vertebral body fractures in the sagittal plane are more frequently observed than those in the coronal plane. Ligament injuries, epiphyseal detachments or fractures of the ossification centres are observed more frequently in paediatric cases compared to adults due to the high elasticity. In children less than 8 years old, dislocation or spondylolisthesis without fracture is observed more frequently [2,11]. In our study, we observed grade 1 spondylolisthesis due to 3 pars fractures. The mean of our patients' age was below the overall mean.

Multiple vertebral fractures are observed more frequently because the body of the vertebrae are

wedge-shaped and smaller in adults to carry high forces. Multiple vertebral injuries in the paediatric spine were found to be 32% [13]. Herren et al. found an additional injury in another spinal segment in maximum 1.2% of patients [2]. In our study, 2 vertebral segments were involved with a rate of 23%. It is thought that vertebral fractures are overlooked in paediatric patients because the whole spine is not scanned to avoid radiation exposure. In a series evaluating paediatric vertebral fractures, 6% were found to be 3 levels away from the primary injury. MRI has been recommended to show lesions that may be missed on CT such as epidural haematoma, discoligamentous injuries, traumatic disc herniation and low-grade vertebral fractures. However, it is difficult to perform MRI without sedation in childhood because of the acquisition conditions [13].

Surgical treatment is less commonly used in children due to their high healing and remodelling capacity. Conservative treatment is recommended for wedge-shaped compression fractures without neurological deficit. In order to prevent kyphosis, the use of orthoses that maintain the spine in extension is often sufficient for the treatment of the patient [14]. Surgical treatment is considered appropriate in cases when kyphosis exceeds 30 degrees. In pediatric cases with burst fracture in paediatric cases as in adults, treatment plan is made according to neurological deficit and stability of the fracture. The most common vertebral fractures requiring surgery in the paediatric period are in the lumbar region [4,15]. Surgical treatment is performed in 7.5-30% of patients with paediatric thoracolumbar spinal trauma [5,16]. In our study, surgical procedures were required in 19% of patients.

Spinal injuries overlooked during childhood may result in impaired spinal range of motion and deformities in later adulthood. Early surgical decompression and stabilisation in patients with spinal cord injury have a positive affect clinical outcomes [17]. It has been reported that 90% of patients who develop cord injury due to spinal trauma in childhood may develop spinal deformities in the following years. Instability has been reported to develop in cases in which decompression was performed without stabilisation [6,15]. Decrease in vertebral body height by more than 40%, kyphosis of 15°-30°, 35-50% spinal canal compression, translation by more than 2.5 mm and involvement of the posterior tension band are considered as signs of instability in the thoracolumbar region [3,18].

Gavira et al. conducted a study to differentiate between conservative and surgical treatment in paediatric thoracolumbar vertebral fracture patients. A road map was prepared by determining physiological bone age according to the Risser classification and fracture type according to the Magerl classification. A conservative treatment for patients with bone age Risser 1 and fracture type A1-A2-A3-B was recommended. In addition to this, It is recommended to determine the treatment method applied to the the Risser 2-4 patient groups according to kyphosis and canal compression. Moreover, in the Risser 5 patient group, it has been found that applying the same treatment protocol as in adults is indicated [3]. In our study, surgery was performed in 4 patients, 3 of whom had A4 and 1 had C group fractures. Open decompression and instrumentation were performed as the surgical procedure. Similarly, in a study conducted on 153 patients in Germany, 1/3 of the patients needed surgery. In this study, it was suggested that the application of minimally invasive percutaneous screw placement technique in paediatric cases requiring thoracolumbar surgery without fusion is an appropriate treatment method for the patient [13].

## Limitations

As bone age was not routinely determined during hospitalisation, its contribution to treatment-decision-making process could not be evaluated. Additionally, limitations in our study includes the inability to identify the duration of brace use and assessing patients' long- term deformity and neurological complications.

## Conclusion

Pediatric spine traumas are rare lesions that can be overlooked. The treatment plan should be made taking into account the growth of the spine. Larger patient groups with longer follow-up periods are needed to establish a treatment protocol for pediatric spinal trauma.

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**Author contribution:** **B.Ö. (0000- 0002-4056-6936) and K.T. (0000-0001-8725-8044),** All authors contributed to all stages. All authors read and approved the final manuscript.

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CASE REPORT

OLGU SUNUMU

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# Case Report: Tetris Ball In The Left Atrium

## Vaka raporu: Sol Atriyal Tetris Topu Trombüs

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**ABSTRACT**

A free-floating ball thrombus in the left atrium is a rare and serious medical problem that can cause fatal systemic emboli or block the flow of blood into the left ventricle, which usually ends in sudden death.This report discusses a case of a significant left atrial thrombus that was found to be free-floating in an enlarged left atrium. A 73-year-old male, who had experienced a cerebrovascular infarction and hemorrhage five days earlier, along with a history of chronic atrial fibrillation, was referred to the cardiology department to investigate the embolic cause. A transthoracic echocardiogram identified a free-floating ball thrombus. Thrombolytic therapy was not recommended because there were areas of bleeding within the cerebrovascular infarction and the patient had a high risk profile The individual, with several comorbid conditions, a Glasgow Coma Scale score of 8, and right-sided hemiplegia, was classified as high-risk by the cardiovascular surgery team. In spite of the potential for bleeding complications, treatment with warfarin and unfractionated heparin was started. Subsequent evaluations indicated that the thrombus did not diminish in size. We lost our patient due to progressive heart failure and cardiogenic shock while anticoagulant treatment was continuing. As a result, in such cases, it is important to determine the treatment according to the patient's general condition, glaskow coma score, embolization and the risk of fatal bleeding.

Keywords: Tetris Ball Thrombus; Left Atrium; Mitral Valve

**ÖZ**

Sol atriyumda serbest yüzen bir top trombüs, ölümcül sistemik embolilere veya sol ventrikül girişinin tıkanmasına yol açabilen, genellikle ani ölümle sonuçlanan nadir ve ciddi bir tıbbi sorundur. Bu vaka raporunda, genişlemiş sol atriyumda serbestçe yüzdüğü tespit edilen önemli bir sol atriyal trombüs vakasını tartıştık. Beş gün önce serebrovasküler enfarktüs ve kanama geçiren ve kronik atriyal fibrilasyon öyküsü olan 73 yaşındaki erkek hasta, embolik nedenin araştırılması için kardiyoloji bölümüne sevk edildi. Transtorasik ekokardiyogramda serbest yüzen bir top trombüs tespit edildi. Serebrovasküler enfarktüs içinde hemorajik bölgelerin varlığı ve hastanın yüksek risk profili nedeniyle trombolitik tedavi uygun görülmedi. Komorbiditesi yüksek olan, Glasgow Koma Skalası skoru 8 olan ve sağ taraflı hemiplejisi bulunan hasta, kardiyovasküler cerrahi ekibi tarafından yüksek riskli olarak sınıflandırıldı. Kanama komplikasyonu potansiyeline rağmen, varfarin ve fraksiyone olmayan heparin ile tedaviye başlandı. Daha sonraki değerlendirmeler trombüsün boyutunun küçülmediğini gösterdi. Vakamızı antikoagulan tedavisi devam etmekteyken ilerleyen kalp yetmezliği ve kardiyojenik şok tablosundan kaybettik. Sonuç olarak bu gibi vakalarda hastada kar zarar oranına göre klinik kararı hastanın genel durumu glaskow koma skoru, embolizasyon ve ölümcül kanama riskine göre tedavi belirlenmesi önemlidir.

Anahtar Sözcükler: Trombüs, Sol Atriyum, Mitral Kapak

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## Introduction

The left atrial free-floating ball thrombus is a rare clinical entity. The diagnosis of this condition has been made easier thanks to the availability and advancement of echocardiography and multi-detector row computed tomography (MDCT), and a considerable number of cases have been published.[1] An unattached, free-floating thrombus in the left atrium that is not touching the atrial wall or mitral leaflet is a rare condition that can lead to serious problems. It can have different signs and symptoms. Peripheral embolization of thrombus fragments can cause ischemia or infarction in the heart, brain, organs, or limbs. Syncope and/or pulmonary congestion occur due to partial or total obstruction of the normal opening of the mitral valve. We present a case of a free-floating ball thrombus in the left atrium. [2]

## Case

A 77-year-old male patient was referred to cardiology while being monitored in the general intensive care unit due to a low glasgow coma scale following an acute cerebrovascular infarction 5 days prior. He had a history of hypertension and smoking, as well as known chronic atrial fibrillation. On physical examination, the patient was right hemiplegic, unconscious, and responded to painful stimuli by pulling away. Cardiac examination revealed a 3/6 systolic murmur, and his bilateral lower extremities were in a flexion posture. His electrocardiogram showed a heart rate of 65 beats per minute, consistent with atrial fibrillation. Vital signs included a blood pressure of 120/60 mmHg, a pulse rate of 65 beats per minute, and a respiratory rate of 20 breaths per minute, with no fever present.

We performed transthoracic echocardiography to investigate the embolic focus in this patient, who was in poor general condition. A ball-shaped thrombus, resembling a Tetrix ball, was observed in the left atrium, moving towards the mitral valve and then circulating back to the left atrium. The heart's ejection fraction was 45%, anterior wall is akinetic, and the aortic valve was calcified with mild aortic stenosis. The left atrium was enlarged, but there was only mild mitral regurgitation.

We classified the case as high-risk and sought the expertise of a cardiovascular surgeon.

It was concluded that surgery would be high-risk and that medical follow-up would be more appropriate. It was recommended that if treatment with warfarin did not result in regression, surgery should be considered. The risks were explained to the patient and their relatives, and a joint decision was made to proceed with warfarin treatment due to the high risk of surgery. The patient continues to receive treatment with heparin and warfarin in the intensive care unit. On follow up, we lost our patient due to progressive heart failure and cardiogenic shock while anticoagulant treatment was continuing.

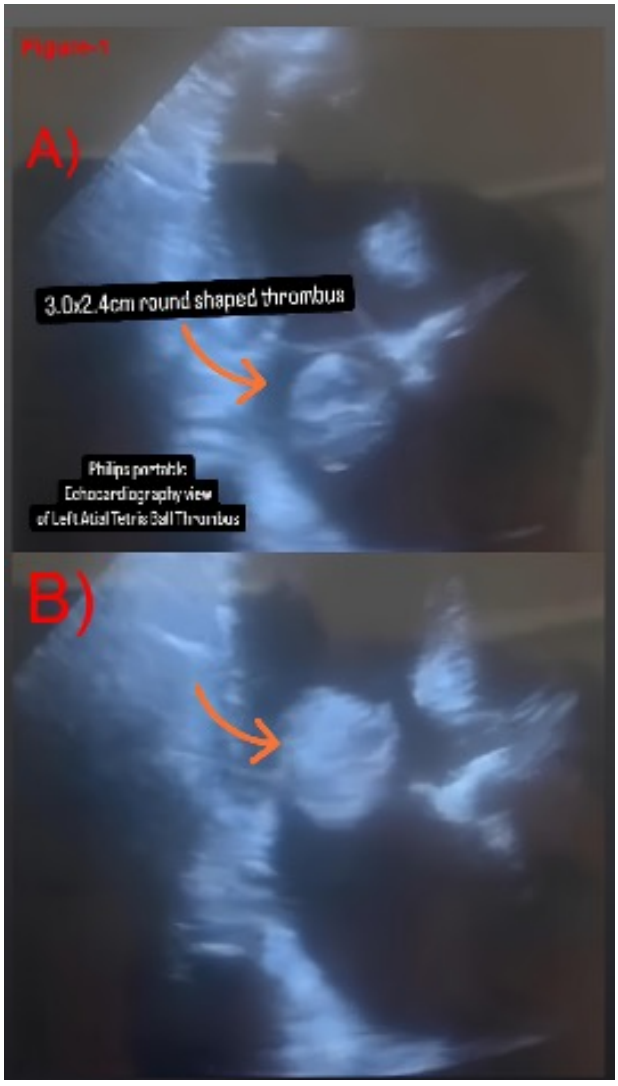


Figure 1- A) Echocardiographic image of a moving tetrix ball thrombus in the left atrium with Philips portable echocardiography device. B) Ping Pong Ball Thrombus in Left Atrium : A ball-shaped thrombus, resembling a Tetrix ball, was observed in the left atrium, moving towards the mitral

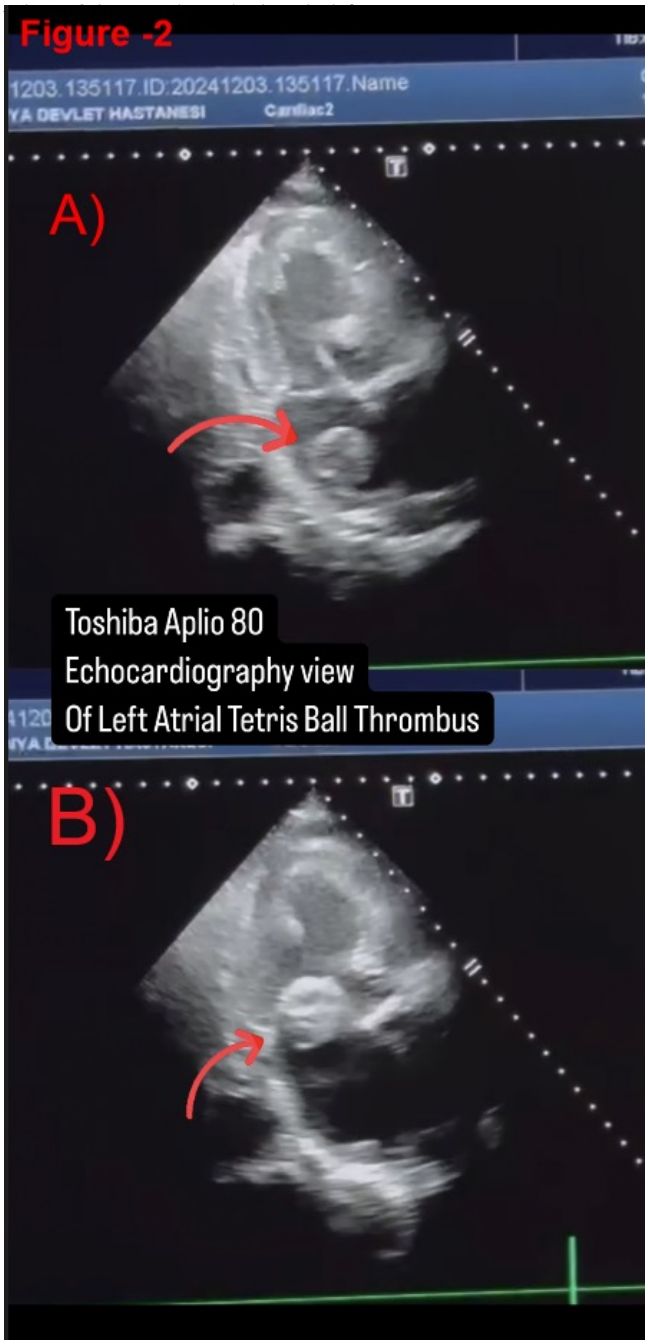


Figure 2- A) Echocardiographic image of moving tetrix ball thrombus in the left atrium with Toshiba Aplio 80 echocardiography device. B) Toshiba Aplio 80 echocardiogram showing a moving tetrix ball thrombus in the left atrium trying to pass through the mitral valve

## Discussion

Medical conditions that may result in left atrial thrombi include stenotic mitral valves, atrial fibrillation, an enlarged left atrium, prior mitral valve replacement, congestive heart failure, bradycardia, occluder material in the left atrium, thrombophilia, reduced cardiac output, myocarditis, hypertrophic cardiomyopathy, and infectious endocarditis. [2-5]

About 12% of patients with atrial fibrillation have a left atrial (LA) thrombus. Very seldom, a "ball thrombus" can form. Certain specialists believe this occurs due to the thrombus rotating and frequently impacting the left atrial wall and mitral valve apparatus, hence altering the heart's structure. Differentiating thrombi from myxomas is important because it affects treatment options. Differentiating myxomas from thrombi can be difficult, but the medical history and unique features are usually helpful. Echocardiography represents one of the most valuable non-invasive imaging modalities. Cardiac myxomas typically present as mobile masses with a thinly stalk connected to the atrial septum, demonstrating both movement and flexibility. [6-7] Thrombi, on the other hand, are typically non-mobile and have a broad-based attachment to the left atrial wall. However, if thrombi are pedunculated and mobile, as in our case, it is difficult to differentiate. The ultimate diagnosis is based on pathology. A medical history of mitral stenosis and left atrial enlargement supports the diagnosis of thrombus. Anticoagulation and follow-up care can help explain further. Anticoagulation therapy can resolve thrombi, but it won't alter myxomas. [7]

Ball thrombus is regarded as highly prone to embolism, but treatment is not formalized. Immediate thrombectomy is typically considered the best option, with a 90% survival rate. We offered the patient mitral valve replacement for valvular stenosis and ligation of the left atrial appendage. Although an occasional case of thrombus resolution by anticoagulation alone has been reported, this should only be attempted in very high-risk cases or patients refusing surgery because of some risk of fragmentation and embolization and postoperative regime will require anticoagulation therapy. İn clinical practice, ball thrombosis is a rare phenomenon. Urgent thrombectomy is recommended, and echocardiography may be employed for instantaneous monitoring throughout the time. [7] A number of managerial alternatives were taken into account. It was feared that anticoagulation or lysis might change the mass's size enough to pass through the mitral orifice but not the left ventricular outflow tract, which has a smaller cross-sectional area and lacks the mitral leaflets' protective mobility effect. This could result in a potentially fatal consequence. Transcatheter

options that employ electrocautery and/or aspiration procedures are new approaches to treating masses in the heart chambers. However, because of its size, the LA mass may be difficult to remove via a trans-septal technique. [8]

We looked for "ball thrombus" on PubMed to evaluate this rare condition, and we found 19 examples in the last ten years. The average age of the 12 females and 7 males is 54.8 years. There are several thrombi in three cases. Regarding the first symptom, cerebral embolism occurred in 4 cases and heart failure in 11 cases, whereas twelve cases underwent surgery. Two people died, one from increasing heart failure and the other from thrombosis obstructing the left ventricular inflow tract. [7] And in our case, we lost our patient to cardiogenic shock due to progressive heart failure.

In conclusion, in such cases, which may rarely occur in the elderly population with rheumatic valvular disease and atrial fibrillation, it is recommended to make a clinical decision according to the patient's general condition, glasgow coma scale, embolization and the risk of fatal bleeding.

**Conflict of Interest:** The authors declare no conflict of interest related to this article.

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**Ethics Committee Approval:** The study followed the ethical principles outlined in the 1964 Declaration of Helsinki and its later amendments. Informed consent form for case presentation was obtained from the patient and/or his/her relatives.

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CASE REPORT

OLGU SUNUMU

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# A Rare Coronary Anomaly: Single Coronary Artery; Two Cases

## Nadir Bir Koroner Anomali: Tek Koroner Arter; İki Olgu

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**ABSTRACT**

We present two cases of a rare coronary anomaly—single coronary artery—identified incidentally during routine coronary angiography. Both patients presented with symptoms of chest pain and exertional angina. In both cases, the anomaly is located in the right sinus of Valsalva (R-1-A) and crosses the heart anterior to the right ventricle. (Figure 3) The first patient experienced significant stenosis in the proximal left anterior descending artery, which was successfully treated with percutaneous stent implantation. The second patient's chest pain was managed effectively with medical therapy alone. These cases highlight that a single coronary artery, often asymptomatic, can exist as a congenital anomaly in patients experiencing myocardial ischemia due to atherosclerotic coronary artery disease. Furthermore, they demonstrate that percutaneous coronary intervention, including stent placement, offers a promising treatment approach. In the literature, coronary artery bypass surgery should particularly be considered as a treatment option for these coronary anomalies. However, it has also been shown that in selected cases, percutaneous intervention or medical therapy can be viable alternatives.

Keywords: Coronary Angiography, Coronary Artery Anomalies, Single Coronary Artery, Chest Pain

**ÖZ**

Bu makalede, rutin koroner anjiyografi esnasında rastlantısal olarak keşfedilen iki tek koroner arter anomalisi vakası anlatılmaktadır. Hastaların semptomları arasında, eforla tetiklenen göğüs ağrısı ve anjina bulunmaktadır. Her iki olguda da anomali, sağ Valsalva sinüsünde (R-1-A) yer almaktadır ve sağ ventrikül önünden kalbi çaprazlamaktadır (Şekil -3). İlk hastanın proksimal sol ön inen arterinde ciddi bir darlık saptanmış ve bu darlık, perkütan stent implantasyonu ile etkin bir şekilde tedavi edilmiştir. İkinci hastanın göğüs ağrısı ise medikal tedavi ile giderilmiştir. Bu olgular, aterosklerotik koroner arter hastalığı sonucu miyokardiyal iskemi yaşayan kişilerde, sessiz bir konjenital koroner arter anomalisi olarak tek koroner arterin bulunabileceğini ve stent implantasyonu ile perkütan koroner müdahalenin uygun bir tedavi yöntemi olabileceğini ortaya koymaktadır. Bu koroner anomalilerde literatürde bypass cerrahisi tedavi seçeneği olarak özellikle akılda tutulmalı ancak seçilmiş vakalarda perkütan girişim veya medikal tedavinin de seçenek olabildiği gösterilmiştir.

Anahtar Sözcükler: Koroner Anjiyografi, Koroner Arter Anomalileri, Tek Koroner Arter, Göğüs Ağrısı

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## Introduction

The detection of coronary artery anomalies has become more common due to the increasing use of angiography, with reported incidences ranging from 0.6% to 1.6%. Among these, a single coronary artery anomaly—where one coronary artery arises from a solitary ostium in the aortic arch—is rare, occurring in just 0.024% to 0.04% of cases [1]. First identified in 1967 via angiography, this anomaly is often associated with congenital heart defects like tetralogy of Fallot, pulmonary atresia, and persistent truncus arteriosus, found in about 40% of patients. Though typically benign and asymptomatic, certain variants of this anomaly can lead to severe cardiac events, such as sudden death or myocardial infarction, especially during physical activity. Furthermore, isolated single coronary artery anomalies may present as chest pain, arrhythmias, syncope, and heart failure. This article explores two cases of single coronary artery anomalies. Unlike the usual surgical interventions seen in the literature, we chose coronary stent implantation in the first case and medical management in the second, based on anatomical considerations. The cases emphasize the importance of an individualized approach to diagnosing and treating patients with single coronary artery anomalies, factoring in anatomical differences and the potential for percutaneous intervention [2].

## CASE 1

A 56-year-old male with a five-year history of hypertension presented with substernal chest pain, described as pressure and burning, which had persisted for three months. The pain typically occurred during exertion and subsided with rest. He was on perindopril and amlodipine for hypertension and had a smoking history. His family history included renal failure, cardiovascular disease, and kidney transplantation. On examination, there was a left-deviated apical sound and a firm S1 heart sound, but no additional murmurs. Electrocardiography showed normal sinus rhythm at 75 bpm with nonspecific T wave negativity in leads V1-V6. Transthoracic echocardiography revealed an ejection fraction (EF) of 60%, left ventricular hypertrophy, mild aortic regurgitation, and ascending aortic dilatation (41 mm). Given the symptoms and normal lab results, coronary angiography was performed, revealing that all coronary arteries arose from the right coronary artery. There was severe (90%) stenosis in the proximal left anterior descending artery, which crossed over aorta and the pulmonary artery before continuing normally (Figure 1). Due to the lesion's accessibility and favorable catheter engagement, a decision was made for coronary intervention. A right 6F guiding catheter was used to access the single coronary artery, and after crossing the lesion with a floppy wire, a 2.75x18 drug-eluting stent (Mitigator) was deployed at 16 atm in the proximal left anterior descending artery. The procedure was successful, with full patency and no complications. The following day, the patient showed no electrocardiographic changes, no chest pain, and normal troponin levels. His treatment plan was adjusted, and he was discharged on the third day with a follow-up coronary CT angiography scheduled, as no further issues were observed during the follow-up. Ct angiography was performed one month later and showed a single coronary artery and patent stent (Figure 2 and 3).

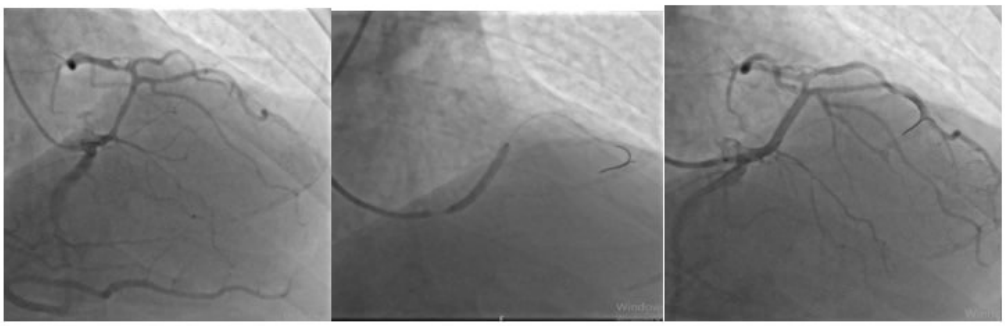


Figure 1. A) Single coronary artery with right sinus of valsalva origin and critical stenosis in the proximal left anterior descending artery B )Insertion of a 2.75x24mm drug-eluting stent after 2x20 balloons after JR4 guiding catheter placement C) Final image of the left anterior descending artery after successful stent implantation

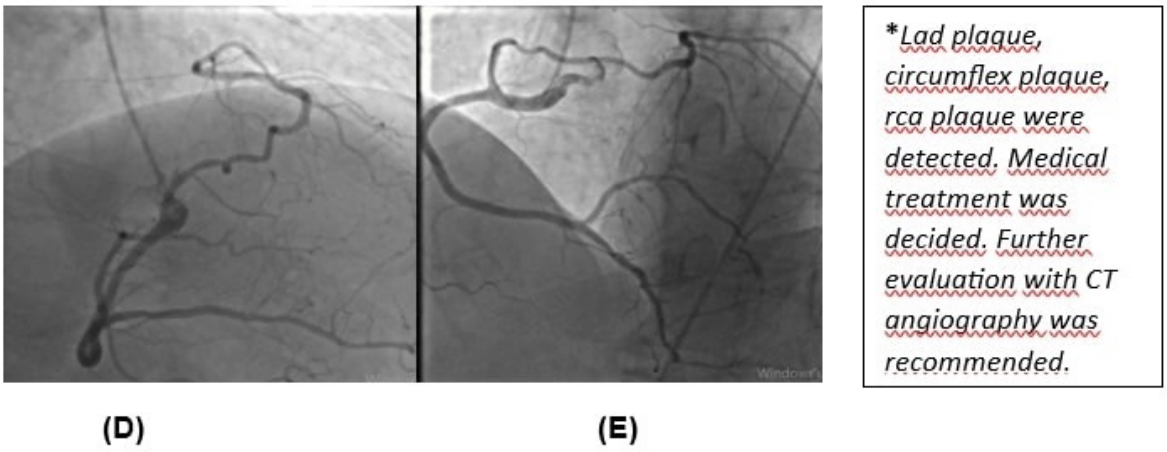


Figure 2. D) Image of single coronary artery exiting right sinus valsalva (AP cranial) E) Image of single coronary artery exiting right sinus valsalva (left oblique) *

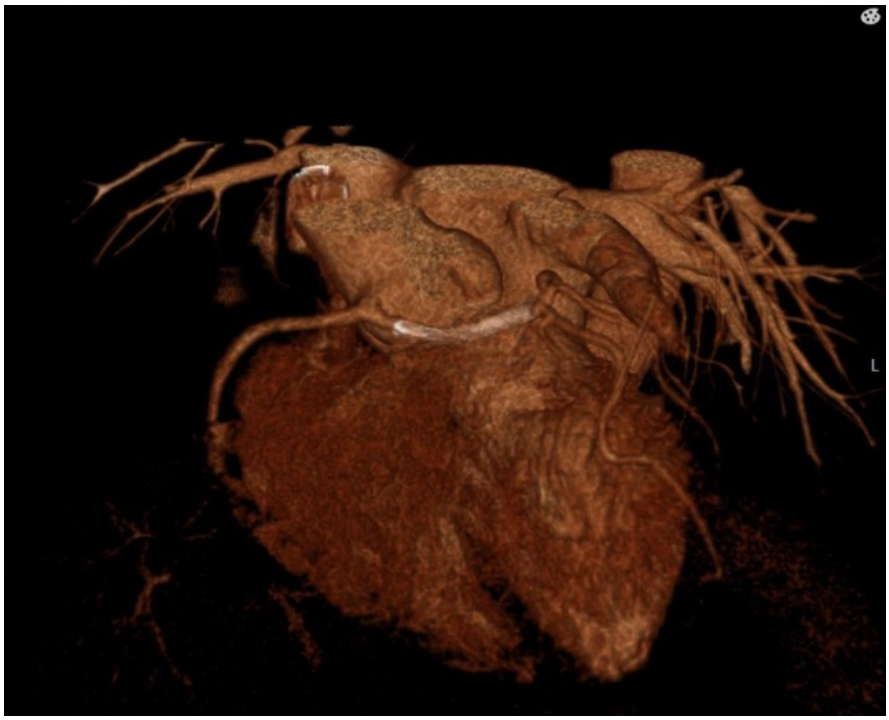

Figure 3. Case 1 – Coronary CT 3D ViEW Type R-1-A Single Coronary Artery ve Patent Stent in Left Main Coronary Artery

## CASE 2

A 45-year-old male presented to the cardiology clinic with intermittent chest pain and tightness that worsened with exertion over the past month. His electrocardiogram was normal, and echocardiography showed normal valve structures and an EF of 60%, with no other abnormalities. He had a smoking history and recently diagnosed diabetes mellitus, but no significant family history. Following a high-risk result on an exertional stress test and normal blood tests, he underwent coronary angiography. The results revealed a single coronary artery arising from the right sinus of Valsalva, with the left anterior descending artery crossing the pulmonary artery and continuing normally. No significant lesions were found, though plaques were noted in the left anterior descending and right coronary arteries (Figure 2). The patient's symptoms improved with medical treatment, and he was discharged with plans for follow-up and a coronary CT angiography. And in the control he refused to have a CT scan due to risk of contrasyt nephropathy.

## Discussion

The term "coronary anomaly" encompasses a wide

variety of conditions, the most common being the separate origins of the left anterior descending and circumflex arteries from the left sinus of Valsalva, the origin of the circumflex artery from the right sinus of Valsalva, and coronary artery fistulas. An isolated single coronary artery anomaly is one of the rarest, accounting for only 2-4% of all coronary anomalies. The prognosis for patients with a single coronary artery depends on its anatomical path. For example, when the left coronary artery originates from the right coronary sinus, the mortality rate before age 20 is alarmingly high at 59%. While some individuals may have a favorable prognosis, others are at significant risk of sudden death, with up to 15% developing severe cardiac issues before the age of 40. A particularly dangerous variant occurs when the coronary artery passes between the aorta and pulmonary artery in anomalies originating from the right sinus of Valsalva. Patients with this condition may remain asymptomatic for years, only showing symptoms when atherosclerotic changes occur [3].

Lipton et al.'s 1979 classification system for single coronary arteries, which builds upon earlier work by Smith (1950) and Ogden and Goodyer (1970), uses 'R' and 'L' to indicate the right or left sinus of Valsalva origin, along with 'A', 'P', and 'B' to describe the artery's path relative to the pulmonary artery: 'A' for anterior, 'P' for posterior, and 'B' for between the aorta and pulmonary artery (Table -1) [4].

Currently, there is no universally accepted guideline for managing patients with single coronary artery anomalies. Surgical intervention is recommended for those unresponsive to medical therapy or those with coronary arteries passing between the aorta and pulmonary artery, as these carry a higher mortality risk. Some cases in the literature, however, show that single coronary arteries—when not fitting these high-risk categories—can be treated with coronary stenting, as seen in studies by Raddino et al. (2006) and more recently by Altun et al. Moreover, Mirchandani et al. (2005) explored both surgical and medical management of single coronary arteries in children [5-6]. Therefore, for patients with myocardial ischemia due to atherosclerosis, a single coronary artery might present as a benign congenital anomaly, and percutaneous coronary angioplasty with stenting could be an effective solution.

Table 1: Single Coronary Artery Classification Lipton et al.

| Classification of single coronary arteries | | |
|---|---|---|
| Osteal placement | r | Right sinus valsalva |
| | l | Left sinus valsalva |
| Anatomic distrubution | 1 | Single coronary artery follows right or left coronary course |
| | 2 | Crosses the basal part of heart in a broad transverse body |
| | 3 | The cx and lad arise seperately from a single coronary trunk |
| Course of transverse part of coronary vessel | a | İn front of the big vessels |
| | b | Between aorta and pulmonary artery |
| | p | Behind to big vessels |
| | s | Septal type |
| | | Combined type |

İn a case presentation by Canbay and colleagues(2008), they presented three cases of single coronary artery, which were classified as R-1, R-1, and R-2-B. Surgical intervention was decided for two of the cases, while medical treatment was chosen for one case [7].

However, it's essential to thoroughly define the morphology of the anomalous artery before initiating treatment to rule out other potential causes of myocardial ischemia, such as vascular compression. Imaging techniques like coronary CT or MRI can provide crucial insights into the origin and path of the anomalous coronary arteries [5]. In the cases discussed here, we opted for follow-up coronary CT angiography to classify the single coronary artery, despite the patients being symptom-free during follow-up and still under observation.

The optimal treatment approach for single coronary artery remains uncertain. Management should be tailored based on the anatomical course of the artery and the presence of associated coronary atherosclerosis. Coronary artery bypass surgery may be advantageous for patients with an anomalous coronary artery that passes between

the aorta and the main pulmonary artery, as well as for those with significant atherosclerosis, who might benefit from revascularization. Additionally, successful outcomes with percutaneous coronary intervention have been documented in certain cases [5,6].

**Conflict of Interest:** The authors declare no conflict of interest related to this article.

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**Ethics Committee Approval: :** The study followed the ethical principles outlined in the 1964 Declaration of Helsinki and its later amendments. Informed consent form for case presentation was obtained from the patient and/or his/her relatives.

**ORCID and Author contribution:** **S.A. (0000-0003-3482-5900)** All authors contributed to the manuscript conception, **C.K:(0000-0001-8911-3340)** design, **S.A. (0000-0003-3482-5900)** literature research, writing,**C.R.Ö : ( 0000-0001-5422-6847)** critical review and final approval.

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