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Efficacy of Therapeutic Plasma Exchange and Hemodialysis in the Treatment of Theophylline Intoxication

Teofilin İntoksikasyonunun Tedavisinde Terapötik Plazma Değişimi ve Hemodiyalizin Etkinliği

Mehmet Emin Menentoğlu, Nihal Akçay, Esra Şevketoğlu

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Dear Editor,

Theophylline is a methylxanthine derivative used to treat bronchospastic disorders in children and adults, and to address apnea and bradycardia in newborns (1,2). As a methylxanthine derivative, theophylline increases intracellular cyclic adenosine monophosphate by inhibiting phosphodiesterase, thereby inducing smooth muscle relaxation. Blood theophylline levels above 15 µg/mL are associated with a risk of toxicity, whereas serum concentrations between 5-15 µg/mL are considered safe and effective (3). Because of its narrow therapeutic window, both chronic use and acute ingestion can cause serious poisoning. Management aims to reduce gastrointestinal absorption, monitor serum levels, and treat cardiac, neurological, and metabolic complications. Although extracorporeal elimination methods such as hemoperfusion, hemodialysis, and therapeutic plasma exchange (TPE) have been employed in intoxication cases, supportive care remains the cornerstone of treatment (4).

We report the case of a 15-year-old female who developed severe toxicity following the intentional ingestion of 30 tablets of sustained-release theophylline (Teokap® SR 200 mg) and who was admitted to our pediatric intensive care unit approximately 10 hours later. At the initial center, gastric lavage and activated charcoal were administered one hour after ingestion, but treatment was discontinued because the family refused further care. Eight hours later, the patient re-presented with palpitations and hand tremors, and was transferred to our hospital. On admission, she was conscious (Glasgow Coma Scale 15), with a blood pressure of 90/68 mmHg, a heart rate of 153 bpm, a respiratory rate of 19/min, and a temperature of 37 °C. Tremor, nystagmus, and hyperreflexia were observed, whereas examinations of other systems were unremarkable. The patient's serum theophylline level was 49.4 µg/mL at admission.

Laboratory findings revealed leukocytosis (20,110/mm^3), serum potassium of 3.2 mmol/L, lactate of 5.6 mmol/L, and metabolic alkalosis (pH 7.45, HCO_3 21.7 mmol/L). The electrocardiography showed sinus tachycardia. Intravenous hydration was initiated with 0.9% NaCl, followed by maintenance fluids containing 5% dextrose+0.9% NaCl and 40 mEq/L KCl. Ondansetron (8 mg IV) was administered for severe nausea and vomiting. Since the ingested formulation was extended-release, multiple-dose activated charcoal (50 g every 6 hours) and polyethylene glycol were administered to enhance elimination (5,6). Within the first hour of admission, continuous venovenous hemodiafiltration was initiated due to ventricular ectopy and tachycardia reaching 220 bpm. A 12 Fr femoral dialysis catheter was inserted; dialysate flow was 2000 mL/1.73 m^2/hr and replacement was 35 mL/kg/hr, using standard solutions containing 2 mmol/L K^+, without net ultrafiltration.

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Additionally, TPE with 4% albumin was performed once. Electroencephalography showed periodic epileptiform discharges, and midazolam infusion was started. After 32 hours of hemodialysis, blood pressure stabilized, sinus rhythm was restored, and dialysis was terminated. Following 92 hours of intensive care monitoring, the patient was discharged for psychiatric and social services follow-up.

All types of arrhythmias can develop during theophylline intoxication, ranging from sinus tachycardia to ventricular fibrillation. Extracorporeal treatment methods such as hemodialysis and hemoperfusion are preferred in severe ventricular arrhythmias, while calcium channel blockers or β-blockers may be used in supraventricular tachycardia (7). In our patient, sinus tachycardia and ventricular extrasystoles improved following the combined use of hemodialysis and TPE.

We consider that the uninterrupted combined use of hemodialysis and TPE contributed to the rapid improvement in hemodynamic findings. Although the literature suggests that TPE is less effective than hemodialysis or hemoperfusion for theophylline elimination, our experience indicates that TPE may still be beneficial in selected cases (8).

In conclusion, close monitoring is essential because acute theophylline intoxication can be fatal, particularly from cardiac and neurological complications. The combined use of hemodialysis and TPE may provide rapid resolution of symptoms and should be considered in severe cases that are unresponsive to supportive therapy.

FOOTNOTES

Authorship Contributions

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Review

The Role of *Saccharomyces boulardii* over Probiotics in Prevention and Treatment of Colorectal Cancer and Gastrointestinal Disorder in Potential High-Risk Individuals, Review of Current Evidence

Potansiyel Yüksek Riskli Bireylerde Kolorektal Kanser ve Gastrointestinal Bozuklukların Önlenmesi ve Tedavisinde Probiyotiklere Kıyasla *Saccharomyces boulardii*'nin Rolü: Mevcut Kanıtların Gözden Geçirilmesi

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ABSTRACT

Saccharomyces boulardii, a widely used non-pathogenic yeast used as a probiotic in different regions of the world,was first isolated from litchi fruit *(Litchi chinensis)* in 1923 by Dr. Henri Boulard. From that time, it became well known tool in prevention and treatment of many gastrointestinal tract diseases like inflammatory bowel disease, *Clostridium difficile* infections, antibiotics associated with diarrhea, eradication of *Helicobacter pylori* and irritable bowel syndrome, this is done usually by two major ways, first, *Saccharomyces boulardii* founded to inhibit release or inhibit the effect of bacterial toxins, second; it founded to have direct effect on intestinal mucosa, The aim of this systematic review is to focus on recent studies about probiotic, then addresses the role *Saccharomyces boulardii* in prevention and treatment of various intestinal tract pathologies like inflammation and cancer by providing recent clinical based trials with numerous meta-analysis studies. Multiple studies from PubMed and Google Scholar, including clinical trials, meta-analyses, and experiments published from (2010-2025), suggest a beneficial effect of *Saccharomyces boulardii* in the prevention and treatment of colorectal cancer and various acute or chronic intestinal disorders. Despite the risk of fungemia, previous studies have not reported other adverse effects.

Keywords: *Saccharomyces boulardii*, colorectal cancer, gastrointestinal disorder

ÖZ

Saccharomyces boulardii, dünyanın farklı bölgelerinde probiyotik bir unsur olarak yaygın olarak kullanılan patojenik olmayan bir mayadır ve ilk olarak 1923 yılında Dr. Henri Boulard tarafından liçi meyvesinden (*Litchi chinensis*) izole edilmiştir. O zamandan beri, enflamatuvar barsak hastalığı, *Clostridium difficile* enfeksiyonları, antibiyotik kaynaklı ishal, *Helicobacter pylori* eradikasyonu ve irritabl bağırsak sendromu gibi birçok gastrointestinal sistem hastalığının önlenmesi ve tedavisinde bilinen bir araç haline gelmiştir. Bu genellikle iki ana yolla yapılır: Birincisi, *Saccharomyces boulardii*'nin bakteriyel toksinlerin salınımını veya etkisini inhibe ettiği bulunmuştur; ikincisi, barsak mukozası üzerinde doğrudan bir etkiye sahip olduğu bulunmuştur. Bu sistematik incelemenin amacı, probiyotikler hakkındaki son çalışmalara odaklanmak ve ardından *Saccharomyces boulardii*'nin enflamasyon ve kanser gibi çeşitli barsak sistemi patolojilerinin önlenmesi ve tedavisindeki rolünü, çok sayıda meta-analiz çalışmasıyla desteklenen son klinik çalışmalar sunarak ele almaktır. PubMed ve Google Schoolar'da (2010-2025 yılları arasında yayınlanan) klinik çalışmalar, meta-analizler ve deneyler de dahil olmak üzere çok sayıda çalışma, *Saccharomyces boulardii* kolorektal kanser ve çeşitli akut veya kronik bağırsak rahatsızlıklarının önlenmesi ve tedavisinde faydalı etkisini göstermektedir. Bu çalışmalar, fungemi riski olmasına rağmen, önceki çalışmalarda bildirilen herhangi bir yan etkiye dair kanıt bulunmamaktadır.

Anahtar Kelimeler: *Saccharomyces boulardii*, kolorektal kanser, gastrointestinal bozukluklar

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INTRODUCTION

Colorectal carcinomas considered as the third cancer in incidence over the world and second most killer especially after 50 years of age with 10% incidence rate (1,2). There are various risk factors that help in development of colorectal cancer like genetic predisposition, lifestyle, diet, eating processed meat, low fiber diet like fruits, vegetable, also alcohol consumption and cigarettes smoking considered as important variables (3).

Numerous microorganisms are also reported to be influenced positively or negatively in the development of colorectal cancer (4). It accounts for about one hundred trillion microorganisms living digestive tract from mouth to rectum, so it is important to rule out the function of these organisms in immune, absorption, and metabolism of intestinal tract, these organisms called gut microbiome or gut flora (5).

Any change or disruption in gut microbiome may predispose to colorectal cancer by modifying metabolism, epithelial lining, immune response and deoxyribonucleic acid (DNA) change or damage, all these factors leading to abnormal cellular events and function of colorectal cells (6), Conditions such as malnutrition, obesity, diabetes mellitus, and chronic inflammatory bowel disease are considered important leading causes of colorectal cancer (7,8).

The gut microbiome is a dynamic complex system of microorganism that inhabits the gastrointestinal tract in planned matter, according to multiple factors including age, lifestyle, antibiotic treatment, genetic predisposition in addition to environmental factors and exposure to pathological agents (9-11).

Bioactive material that is consumed by population like probiotics is very important, where recent studies showed the benefit of these materials upon human health (12-14). So, probiotics are considered an important alternative pathway in treatment and prevention of various pathological diseases of intestinal tract (15).

The aim of this review is to focus on recent studies on probiotics, especially *Saccharomyces boulardii,* and their role in the prevention and treatment of various intestinal tract pathologies, such as inflammation and cancer.

Probiotics

The probiotics define as "live microorganisms which when administered in an adequate amount, confer health benefits on the host" (16). This definition established by Food and Agriculture Organization of the united nation and World Health Organization (WHO) 2001 (17). Where the probiotic term came or derived from Greek word "for-life," the FAO and WHO discuss the anti-disease activity of probiotic in few areas of effectiveness (16). We will review the latest evidence.

Saccharomyces boulardii

A widely used non-pathogenic yeast as probiotic element in number of regions of world, first isolated from litchi fruit (*Litchi chinensis*) in 1923 by Dr. Henri Boulard (18). From that time, it became well known tool in prevention and treatment of many gastrointestinal tract diseases like inflammatory bowel disease, *Clostridium difficili* infections, antibiotics associated with diarrhea (ADD), due to *Saccharomyces boulardii* had resistance to all antibacterial antibiotics making it typical antibiotic companion agent in treatment various GIT pathologies and in same time regarded as cost-effective treatment (19). *Saccharomyces boulardii*, considered a safe agent for use in children and the elderly, sometimes requires 2-3 days to reach a viable concentration in the gut and 2-5 days to be cleared after oral use (20). The mood of action of this yeast by two major ways, first, *Saccharomyces boulardii* founded to inhibit release or inhibit the effect of bacterial toxins, second; it founded to have direct effect on intestinal mucosa (21).

Role of Probiotics in Colorectal Cancer In Clinical Trials on Humans

There are myriad studies focused on the role of probiotics in colorectal cancer that conducted beyond *in vitro* or *in vivo* levels but as clinical trials such what examined by Hibberd et al. (22). In this trial he studied the influence of probiotics on gut microbiomes in patients with colorectal carcinoma staged from I-III, where the participants received probiotics doses of [$7x10^9$ colony forming unit (CFU)] of *Lactobacillus acidophilus* and 1.4x10 (10) CFU of *Bifidobacterium lactis* with as two tablet with 630 mg of inulin daily for 8-78 days based on date of their surgery, after which he collected biopsies from all groups of participants (probiotics with colorectal cancer patients, patients with colorectal cancer without probiotics supplementations and normal control group) also he took fecal samples from all participants during colonoscopy, he conclude after the trial have been completed; the colorectal cancer patient have different microbial signature in cancerous tissue and normal mucosa of safe margin that have been alter after probiotics treatment (2,22).

The probiotics enhance the quality of life in patients who survive from cancer as suggest by another study of Lee et al. (23). Also, multiple studies explained the role of probiotics in infections after routine therapy of cancer due to immune suppression which can be lethal where probiotics can improve the rate of infection and complication after surgery (24).

In Laboratory Design Studies

After appearance of potential effect of probiotics in modulating cell immunity, myriad studies and research focused on effects of probiotics on colorectal cancer and the ways in which they act (25). From standpoint of nature of cancerous cells to proliferate and migrate; some laboratory design studies focused on proliferation, that explore the effects of probiotics (*Enterococcus faecium* and *Lactobacillus fermentum*) on caco-2 cancer cells, where they suggest there was antiproliferative effect of aforementioned bacteria on cancerous cells by about 21-29% (26).

In terms of migration and spreading, recent data refer; introducing the probiotics CT26 cells line derived from mouse and fed them to mice with BALB/c tumor and follow them for 21 days, they suggest that; there was reducing in CT26 cells ability to proliferate, invade and migrate in comparing to control cells, also he found the tumor in mice that fed with probiotics was statistically significant smaller in size than control group (27).

At the molecular level, several studies explore the probiotics effects and alteration in apoptotic activity of CRC cells, where recent study examined and explore the effect of probiotics (*Lactobacillus acidophilus, Lactobacillus casei*) on LS513 cell line and suggest that, there was increase in activity of apoptotic factors after increasing in dose also there was increase in Caspase-3 activity and decreased in P21 expression (28). Other studies using diverse types of bacteria reported similar results. Similar studies at the molecular level revealed decreased expression of CD166, CD44, CD133, and ALDH1 in addition to decrease in formation of colon spheres and increase the activity of caspase-3 (29-31).

In general, most used way to treat colorectal cancer is curative chemotherapy (32,33). Chemotherapy induced mucositis (CIM) nearly happen in 40-100% of patients undergo chemotherapy treatment for CRC, those patients may need supportive measures like parenteral feeding, fluid replacement therapy, and preventive measure against infections (34).

Saccharomyces boulardii Over Probiotic in Treatment of CRC

Recent studies have focused on using *Saccharomyces boulardii* in the treatment of CIM because of its stability at low pH, resistance to antibiotics, and ability to withstand normal body temperature, allowing prolonged residence in the gastrointestinal tract. In treatment of CIM, The *Saccharomyces boulardii* affects the GIT lumen through restoring gut dysbiosis in addition to production of spermidine, spermine, polyamines that stimulate enzymes production, protein synthesis and DNA replication that promote cell growth, regeneration control apoptosis through mitogen-activated protein kinase and nuclear factor kappa B (35). *Saccharomyces boulardii* increases the strength of the mucosal barrier by increasing mucosal production which protects the intestinal mucosa from physical and chemical damage (36).

Immune System of Gastrointestinal Tract and Probiotics

Probiotics can adhere to intestinal mucosa by about 80%, so it is considered a crucial factor in modulating immune response of intestinal tract and preventing serious illness, such as intestinal infections, inflammatory bowel disease and relieving lactose intolerance (37,38).

Probiotics can stimulate both innate and adaptive immune response, by enhancing phagocytosis and increasing the cytotoxicity of NK cells leading to inhibiting tumor and infection development (39).

Different studies have shown that probiotics increase the expression of immunoglobulin A (IgA) and IgM, thereby enhancing adaptive immunity. These studies also suggest probiotics can enhance production and differentiation of T1 helper lymphocytes and alter the balance of Th1 and Th2 lymphocytes as a results probiotic's supplementation can enhance both innate and adaptive immunity (37,40).

Saccharomyces boulardii Over Probiotics in Immune Modulation

Early studies on *Saccharomyces boulardii* showed this yeast can triggered the complement and reticuloendothelial systems that lead to migration of monocyte and granulocyte in addition to enhancing number of Kupffer cells, these studies indicate that *Saccharomyces boulardii* stimulate innate immunity of gastrointestinal tract (41,42).

Qamar et al. (43) found that after oral administration of *Saccharomyces boulardii* to rat, there was increasing in production in secretory IgA in duodenal fluid by 56.9% and in other study increase by 62.8%, also IgA increased in villous cells by 69% and in the crypt cells by 80%, so these study conclude that *Saccharomyces boulardii* can stimulate and triggered the adaptive immunity.

Recent studies show that *Saccharomyces boulardii can decrease* pro-inflammatory molecules in response to infections such as *Salmonella typhimurium,* including interleukin-8 (IL-8), nuclear factor kappa B, and mitogen-activated protein kinase (44). In the same manner the *Saccharomyces boulardii* can increase anti-inflammatory cytokines like (IL-4, IL-10) and decrease pro-inflammatory

factors (IL-8) in response to *Escherichia coli* infection, likewise it found to increase in IgA and IgG in response to *Clostridium difficili* toxins (45).

Another study showed that *Saccharomyces boulardii* can induce pro-inflammatory cytokines like (interferon-γ) in early *Salmonella typhimurium* infection and suppress production of anti-inflammatory cytokines (IL-10) in small intestine but increase production of both cytokines in cecum as a result, *Saccharomyces boulardii* can modulate immune response throughout GI in different manner (46,47).

Saccharomyces boulardii in Chronic Inflammatory Bowel Diseases

The efficacy of *Saccharomyces boulardii* has been assessed in multiple inflammatory bowel diseases, such as ulcerative colitis, Crohn's disease (CD), irritable bowel syndrome, and other illnesses related to diarrhea.

Saccharomyces boulardii Role in Ulcerative Colitis

Saccharomyces boulardii used as a complementary therapy in ulcerative colitis patients to achieve remission state in active disease (47). Recent data suggest that treatment with *Saccharomyces boulardii* and rifaximin for 3 months seems to be effective in prevention of disease relapsing early, this study was a pilot study with small sample size and short duration of treatment time with no control group or follow up measures (48).

Saccharomyces boulardii supplementation in UC can restore normal gut flora and diminished development of harmful flora leading to restoring normal intestinal environment (49,50).

Very recent studies proposed that additive treatment of *Saccharomyces boulardii* to sulfasalazine in UC patients promote remission in active disease in addition to relief associate symptoms and restore normal mucosal barrier furthermore enhancing quality of life, then using sulfasalazine alone (50-52).

Saccharomyces boulardii Role in Crohn's Disease

Recent studies mentioned CD incidence increased since 1990 in previous century with 3.5 per 100,000 persons\year specially in newly industrialized countries in Africa, Asia, and south America (52).

Most of systematic review of literatures mentions the role of *Saccharomyces boulardii* as probiotics in treatment of CD and they mentioned there was a marked reduction in clinical relapses of CD after six months of treatment with *Saccharomyces boulardii* in combination with Mesalamine, also there was increase in function of intestinal barrier by decreasing of lactulose\mannitol ratio in other studies (53-55).

Compared with *Lactobacillus rhamnosus* GG, which was not found to improve or prolong remission nor to be effective in reducing relapse, *Saccharomyces boulardii* showed effectiveness in prolonging remission in CD and in improving the permeability of the intestinal wall when combined with standard therapy (36,56).

Saccharomyces boulardii in Irritable Bowel Syndrome

Irritable bowel disease (IBS) considered as most common disease identified in people attending gastroenterologist clinics with about 12% of all cases, the prevalence of IBS differs from one country to another where myriad studies reach to incidence of 10-15% of population have IBS (57). IBS had no sure treatment, the most drug modalities merely had supportive and palliative role in treatment of IBS (58).

Different studies declare that the IBS result as changing in gut micro-flora superimposed by enteric infection, so the best treatment is to restore normal microflora by using probiotic (59,60). As IBS characterized by disturbance in normal function of GI tract so its manifestation as abdominal pain or changing in intestinal habits (61).

Recent data suggest that *Saccharomyces boulardii* can improve the abdominal pain, diarrhea and eructation and gas release from stomach, also there was no benefit on using probiotics upon flatulence (57), while other studies suggest that using *Saccharomyces boulardii* along with Mebeverine can exert an additional benefit on treatment of IBS (49).

Role of *Saccharomyces boulardii* in Antibiotic Associated Diarrhea

This type of diarrhea is considered the most common complication of using antibiotics that result from disruption of normal intestinal microbiome (62,63).

Moreover, the antibiotics ADD can display or lead to *Clostridium difficili* infection that is present in more than 50% of infants, 10% of hospitalized patients and 1-5% of normal adults (64). Treatment of *Clostridium difficili* with antibiotics can lead to more turmoil, so the goal of treatment is to restore normal gut microtropia through completion of clinically improve antibiotic course and time with suitable supportive probiotics (65). The European Society for Pediatric Gastroenterology, Hepatology and Nutrition, The World Gastroenterology Organization's Global Guideline and American Gastroenterology association all state on administration of specific probiotics in risky patients upon initiation of antibiotics thus prevent ADD and *Clostridium difficili* infection (65,66).

The yeast *Saccharomyces boulardii* is not normally part of the intestinal microbiota and, unusually, is a eukaryote;

therefore, it is resistant to the effects of antibiotics, making it a more suitable probiotic for administration to patients with an elevated risk of developing ADD (65).

Recent studies and Szajewska and Kołodziej's (67) meta-analysis suggest that *Saccharomyces boulardii* treatment reduced the risk of developing ADD by 18% and significantly reduced the risk of developing *Clostridium difficile* infections.

Role of *Saccharomyces boulardii* in Traveler's Diarrhea

One of the frequent and common GI illnesses is traveler's diarrhea (TD), that affected both sexes equally with rate of up to 70% depending on term and residence, where there were 10-40 million people who had TD yearly (68). TD is usually resolved within 2 days but 10% need medical intervention and 3% need hospital admission (69,70).

Avoiding contaminated food and beverages through effective education about the risk of TD is the best preventive method; prophylactic antibiotics may disrupt the intestinal microbiome and are therefore strongly not recommended (71).

Using prophylactic probiotics nowadays have special attention, Alharbi et al. (71) in her metanalysis study in 2024 suggest that using of *Saccharomyces boulardii* is an effective method in preventing and\or treating of TD depending on dose and strain of *Saccharomyces boulardii*.

Role of *Saccharomyces boulardii* in Persistent Diarrhea

Persistent diarrhea is defined by WHO as "an episode which start acutely but persist for 14 days or longer." Recent studies from clinical trials improve the effectiveness of using *Saccharomyces boulardii* in treatments of persistent diarrhea in children with significant rate of 50% in comparison with placebo (72,73).

Role of *Saccharomyces boulardii* in Enteral Nutrition-Related Diarrhea

Diarrhea is considered most common complications in patients with total enteral nutrition (TEN) that involve change in intestinal short chain fatty acids (SCFAs), recent studies of Schneider et al. (73) and Abid et al. (21) showed there was increased in SCFAs concentrations in patients with *Saccharomyces boulardii* treatment that explained the preventive role of this yeast on TEN patients in comparison to normal control patients.

Role of *Saccharomyces boulardii* in Eradication of Pylori Infection

Multiple studies evaluate the effectiveness of *Saccharomyces boulardii* supplementation in *Helicobacter pylori* eradication; these studies improve that the *Saccharomyces boulardii* can improve eradications rate and reduce the side effects related to triple eradication module of *Helicobacter pylori* like diarrhea also it found to induce morphological changes and decrease the colonization rate of *Helicobacter pylori* in children (74).

CONCLUSION

Extensive research, including clinical trials and meta-analyses, has demonstrated that *Saccharomyces boulardii* therapeutic potential for the prevention and treatment of colorectal cancer, as well as for a number of acute and chronic gastrointestinal illnesses.

Although fungemia remains a recognized clinical concern, no notable side effects have been documented in the literature to date. However, small sample sizes frequently limit the strength of current evidence for illnesses such as TD. Large-scale clinical trials are therefore required to confirm the effectiveness of this yeast in larger populations. To optimize treatment outcomes for various intestinal diseases, further experimental research is needed to evaluate the synergistic benefits of combining *Saccharomyces boulardii* with other probiotics.

FOOTNOTES

Authorship Contributions

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Research

Evaluation of ChatGPT's Performance in the Turkish Orthopedic Speciality Education Development Examination (UEGS)

ChatGPT'nin Türk Ortopedi Uzmanlık Eğitimi Gelişim Sınavı'ndaki (UEGS) Performansının Değerlendirilmesi

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ABSTRACT

Objective: Artificial intelligence (AI) technologies are revolutionizing many fields, including health sciences, engineering, and art education. This article aims to evaluate the Speciality Education Development Examination (UEGS) for orthopedics and traumatology residents in Türkiye, in light of Chat Generative Pre-Trained Transformer's (ChatGPT) potential contributions, and to compare ChatGPT's performance with the actual exam results.

Methods: To evaluate ChatGPT's performance, the questions from the Turkish Orthopedics and Traumatology Education Council UEGS from the last three years were entered into the dataset. The results of ChatGPT were classified as correct or incorrect and compared with the actual exam results. The results were analyzed statistically.

Results: Of the 600 questions, 599 were used as data in this study. ChatGPT received 21%, 9.3%, and 5.6% in the 2021, 2022, and 2023 UEGS, respectively. Over the past three years, the average UEGS performance of ChatGPT was 11.9%. No significant difference was found between ChatGPT and actual exam results (p=0.109).

Conclusion: This study showed that ChatGPT's exam performance exceeded that of assistants with first-year residents and was comparable to that of assistants with second-year residents. The findings highlight the importance of continuously updating and customizing these tools while exploring the potential of AI technologies in education.

Keywords: ChatGPT, general orthopedics, Turkish orthopedics exam, UEGS

ÖZ

Amaç: Yapay zeka (YZ) teknolojileri, sağlık bilimlerinden mühendisliğe ve sanat eğitimine kadar birçok alanda devrim yaratmaktadır. Bu makale, Türkiye'de ortopedi ve travmatoloji uzmanlık eğitimi kapsamında uygulanan Uzmanlık Eğitimi Gelişim Sınavı'nın (UEGS) değerlendirilmesinde üretken önceden eğitilmiş dönüştürücü ChatGPT'nin potansiyel katkılarını incelemeyi ve performansını gerçek sınav sonuçlarıyla karşılaştırmayı amaçlamaktadır.

Gereç ve Yöntem: ChatGPT'nin performansını değerlendirmek için, son üç yılın Türk Ortopedi ve Travmatoloji Eğitim Konseyi UEGS soruları veri olarak kullanıldı. ChatGPT'nin sonuçları doğru ve yanlış olmak üzere iki parametre altında değerlendirildi ve gerçek sınav sonuçlarıyla karşılaştırıldı. Sonuçlar istatistiksel olarak analiz edildi.

Bulgular: Toplamda 600 soru bulunmaktaydı, bunlardan 599'u bu çalışmada veri olarak kullanıldı. ChatGPT, 2021, 2022 ve 2023 UEGS'lerinden sırasıyla %21, %9,3 ve %5,6 puan aldı. Son üç yılın ortalama UEGS performansı %11,9 olarak belirlendi. ChatGPT sonuçları ve gerçek sınav sonuçları istatistiksel olarak analiz edildiğinde, anlamlı bir fark bulunmadı (p=0,109).

Sonuç: Bu çalışma, ChatGPT'nin sınav performansının, 1. yıl asistanlarının sınav sonuçlarından daha yüksek ve 2. yıl asistanlarının sınav sonuçlarına benzer olduğunu göstermiştir. Bulgular, bu araçların sürekli olarak güncellenmesinin ve özelleştirilmesinin önemini vurgularken, eğitimde YZ teknolojilerinin potansiyelini keşfetmenin önemini de ortaya koymaktadır.

Anahtar Kelimeler: ChatGPT, genel ortopedi, Türk ortopedi sınavı, UEGS

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INTRODUCTION

Artificial intelligence (AI) technologies are revolutionizing many fields, from health sciences to engineering and art education. The opportunities offered by these innovative technologies have significant potential, especially in transforming education and training methods. While medical education constitutes one of the most critical stages of this transformation, the effectiveness of educational processes in specialties such as orthopedics and traumatology plays a crucial role in training future health professionals. Specialty training for orthopedics and traumatology residents in Türkiye requires an intensive, comprehensive curriculum, and successful management of this process directly affects both the quality of education and the standards of patient care. In this context, the Specialty Education Development Examination (UEGS), developed by the Turkish Orthopedics and Traumatology Education Council (TOTEK), is an essential tool for assessing residents' knowledge and skills and for measuring the effectiveness of training programs. However, the objectivity and comprehensiveness of such assessments and the effectiveness of feedback processes have always been subject to critical scrutiny. AI technologies, especially Chat Generative Pre-Trained Transformer (ChatGPT), are prominent in natural language processing and provide a novel perspective on these evaluation processes (1-4).

UEGS has been conducted by the TOTEK within the Turkish Orthopedics and Traumatology Association (TOTBID) since 2010 to evaluate the personal and institutional development of resident physicians trained in orthopedics and traumatology. The true-false question format is used instead of the multiple-choice question format. To ensure that test takers are more careful in selecting answers, each wrong answer cancels one correct answer (5).

ChatGPT's ability to analyze complex data sets, personalize learning materials, and create interactive learning experiences can make valuable contributions to existing methods in medical education. This article aims to evaluate the UEGS organized for orthopedics and traumatology residents in Türkiye in light of ChatGPT's potential contributions and to compare ChatGPT's performance with the actual exam results. It will analyse how ChatGPT's ability to comprehend and summarise the training materials and to answer questions correlates with the exam results.

METHODS

This study aimed to compare ChatGPT's performance with the results of the UEGS taken by orthopedics and traumatology residents in Türkiye. The study consists of two main phases: first, the accuracy of ChatGPT's answers to the UEGS sample questions was evaluated; second, these answers were compared with the actual exam results.

Data Collection

The UEGS questions published by TOTEK and the actual exam results formed the study's primary dataset. These questions covered a variety of clinical scenarios and theoretical knowledge. During interactions with ChatGPT, the model was asked to answer these questions. ChatGPT's first response to each question was recorded. Sample answers given by ChatGPT are shown in Figures 1 and 2.

Method of Analysis

The answers given by ChatGPT were evaluated by comparing them with the correct answers to the questions. For each question, the model's answer was scored for accuracy, and an overall success rate was calculated by summing these scores. This method allowed us to determine the extent to which ChatGPT could correctly answer the UEGS exam questions.

Comparison

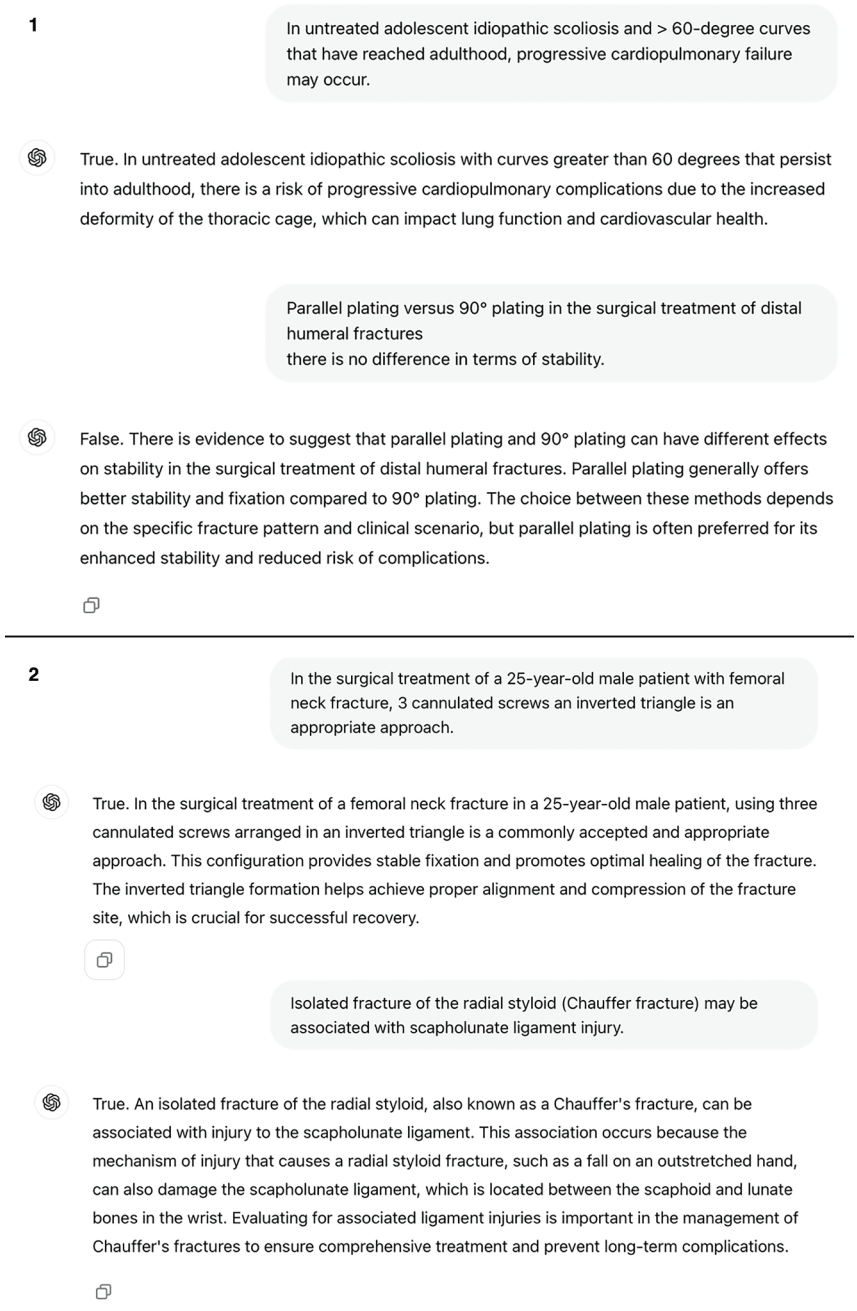
The actual UEGS results of the resident physicians were obtained from the anonymized dataset provided by TOTEK. The model's performance was evaluated by comparing ChatGPT's overall success rate to these accurate exam results. In addition, the model's performance for each question type was analyzed separately, thereby identifying the model's strengths and weaknesses in specific subject areas.

Evaluation

Evaluation of the results yielded inferences regarding how ChatGPT's UEGS performance compares with that of actual physicians. These conclusions are intended to provide information about the applicability and potential of ChatGPT in the field. Versions of ChatGPT-3.5 and GPT-4 were used in this study, and average values were calculated. The answers given by ChatGPT were evaluated in two groups, and the variables were statistically analyzed. Data were analyzed using a Python software package. $p<0.05$ was considered statistically significant.

Ethical Considerations

All data used in the study were anonymized to exclude personal information. The research was designed and conducted in accordance with ethical guidelines. ChatGPT was incorporated into the educational process under licenses permitting both open-source and commercial use. This study was conducted with the written approval of the TOTBID board of directors, as documented in their official correspondence (approval no: 159, date: 26.04.2024).



Figures 1 and 2. ChatGPT's sample answers to UEGS exam questions
ChatGPT: Chat Generative Pre-Trained Transformer, UEGS: Speciality Education Development Examination

This study was conducted using publicly available examination questions and did not involve human participants or patient data. Therefore, informed consent was not required.

Statistical Analysis

The data were analyzed using the Python software package. The normality of the quantitative data distribution was assessed using the Shapiro-Wilk test and graphical methods. The Mann-Whitney U test was used to compare two independent, non-normally distributed samples. The Pearson chi-square test was used to compare qualitative data. Statistical significance was evaluated at $p<0.05$.

RESULTS

Questions that were canceled or that contained visual images were excluded, leaving 599 of 600 questions for

analysis. ChatGPT scored 21%, 9.3%, and 5.6% in the 2021, 2022, and 2023 TOTEK UEGS, respectively. When the TOTBID period books were examined, the average UEGS results for 2021, 2022, and 2023 were 30.4%, 18.7%, and 22.5%, respectively (6,7). These results indicate that ChatGPT's performance on examinations has declined over time. This decrease may be due to an increase in exam difficulty, changes in assessment criteria, or changes in ChatGPT's performance in specific subjects.

When analyzed by subject area, ChatGPT demonstrated the highest success rates in basic orthopedics and trauma (26.67% each) and the lowest in foot and ankle surgery (3.33%) and spine surgery (13.33%). Further year-by-year analysis revealed performance fluctuations across different topics. For instance, ChatGPT's accuracy in pediatric orthopedics increased from 40% in 2021 to 50% in 2022, but dropped to 20% in 2023, whereas its performance in trauma declined to 4% in 2022 before improving to 32% in 2023. These results indicate that ChatGPT's ability to answer UEGS-style questions varies by subject and exam structure (Figures 3-5).

Figure 6 shows annual changes in the performance of both groups, comparing ChatGPT results with actual exam results. The graph shows how the scores of both groups change from 2021 to 2023. While ChatGPT's scores decrease over time, the actual exam results fluctuate. The graph shows trends and changes in performance over time.

No significant difference was found when ChatGPT and the actual exam results were compared using the Mann-Whitney U test (p=0.109). This indicates that the differences between the results of the two groups may be due to random variation and that neither group performed statistically significantly better or worse.

Analysis of the actual exam results from the last three years in the TOTBID 10th- and 11th-term books shows that the average exam success score for residents with one-year seniority was 11.3%, and for residents with two-year seniority was 12.1% (6,7). The average UEGS performance of ChatGPT for the last three years was 11.9%. When these data are analyzed, they show that ChatGPT's

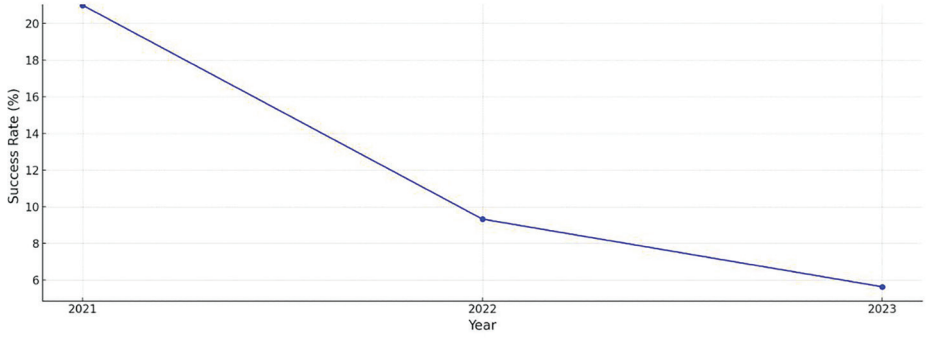


Figure 3. ChatGPT's success graph by years

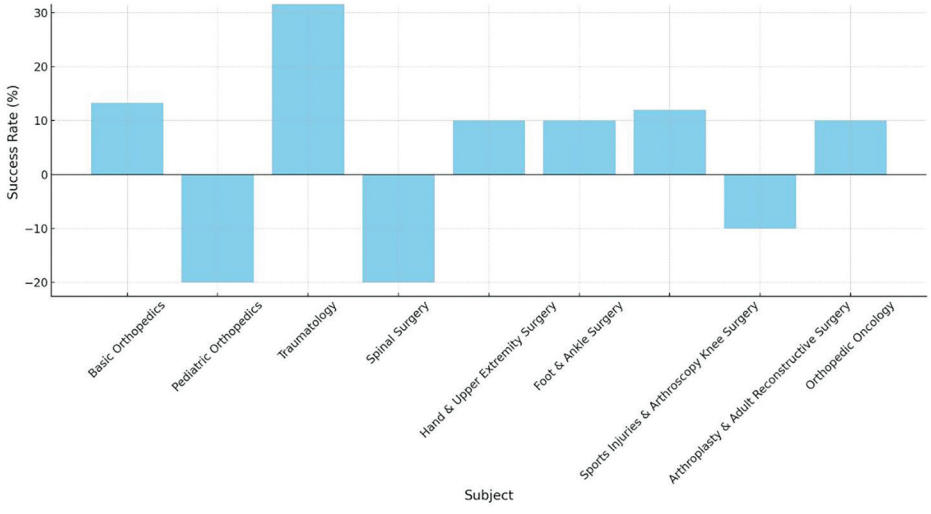


Figure 4. ChatGPT's average success percentage by subjects

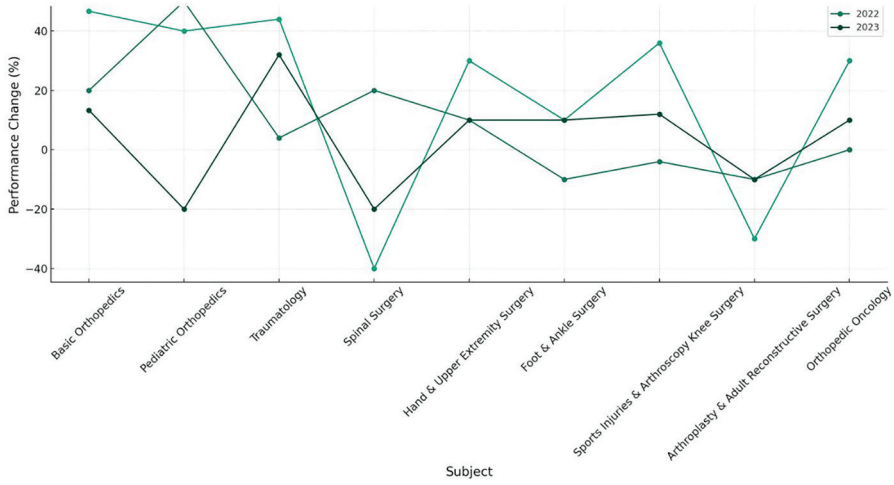


Figure 5. Graph showing the annual subject-based performance change of ChatGPT

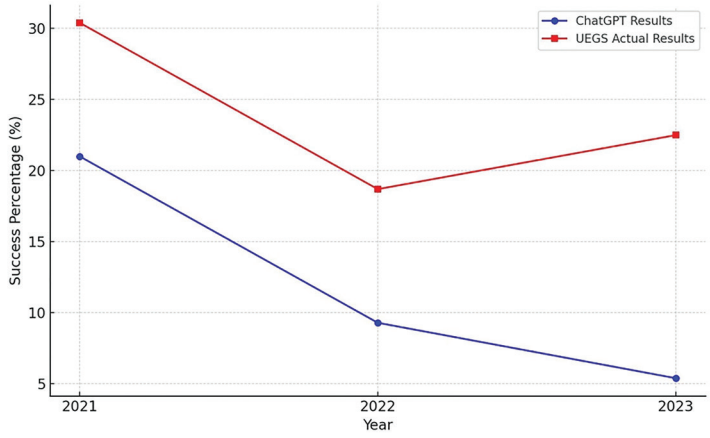


Figure 6. Comparison of "ChatGPT results" and "real exam results" by years
ChatGPT: Chat Generative Pre-Trained Transformer's, UEGS: Speciality Education Development Examination

exam performance is higher than the average results for residents with one year of seniority and comparable to those for residents with two years of seniority.

DISCUSSION

This study analyzed ChatGPT's annual examination results and their relationship to the actual examination results for the corresponding years. Our analyses revealed that ChatGPT's performance varied significantly over the years and in various subject areas. In particular, ChatGPT achieved high accuracy rates in some subjects but performed poorly in others. This suggests that the knowledge and skills of AI-based systems, as human learners do, may vary across subject areas.

In 2021, a moderately positive correlation was observed between ChatGPT and accurate exam results, while in 2022 this relationship was weakly negative. In 2023, the relationship turned positive again, but was less intense than in 2021. These fluctuations may be due to changes in exam content, updates to ChatGPT's training datasets, or specificities of subject areas.

The high success rates of ChatGPT in subjects such as basic orthopedics and trauma indicate that it understands and processes knowledge and terminology in these areas effectively. In contrast, the low performance in other areas, such as spine surgery and paediatric orthopedics, may be due to the complexity of these topics or ChatGPT's insufficient training in them. These findings offer important lessons for integrating AI-based learning and assessment tools into educational processes. Tools such as ChatGPT can enrich students' learning experiences by leveraging their strengths. However, it is essential to be aware of the

limitations of these tools and to integrate guidance from human teachers and other educational materials to provide students with a comprehensive learning experience.

A review of the literature indicates that few studies have evaluated ChatGPT's performance in orthopedics and traumatology examinations. Cuthbert and Simpson (8) evaluated whether ChatGPT could pass part 1 of the Royal College of Surgeons' Fellowship in Trauma and Orthopedic Surgery (FRCS) examination. They stated that ChatGPT could not perform the high-level and multistep logical reasoning required to pass the FRCS examination. Lum (9) evaluated whether ChatGPT could pass the American Board of Orthopedic Surgery Examination and found that ChatGPT was unlikely to pass the exam, but reported that ChatGPT's performance was comparable to that of a first-year orthopedic surgery resident. Saad et al. (10) evaluated ChatGPT's performance on the Orthopedic FRCS (FRCS Orth) part A exam, but reported that ChatGPT did not achieve a passing score. In a multinational study, Alfertshofer et al. (11) manually entered 300 questions from the medical licensing examinations in the United States of America, Italy, France, Spain, the United Kingdom, and India to evaluate the performance of ChatGPT and compare the accuracy of the answers. The study reported significant differences in ChatGPT test accuracy across countries. The highest performance was reported in the Italian exam (73% correct), and the lowest in the French exam (22% correct). ChatGPT's performance on the Examen Nacional de Medicina in Peru was evaluated, and it achieved expert-level performance (12). A study conducted in Japan reported that ChatGPT met the passing standards of the National Medical Licensing Examination (13). ChatGPT's performance on Anesthesiology Board-Style Examination Questions was evaluated in another study, which reported that ChatGPT needed to improve to pass the exam (14).

The use of true-false questions rather than multiple-choice questions in the UEGS exam presents both advantages and disadvantages, which are reflected in ChatGPT's performance. One key advantage of the true-false format is its ability to assess fundamental knowledge efficiently, requiring examinees to make definitive judgments about statements. Additionally, this format discourages random guessing through negative marking. However, a major limitation is its reduced capacity to evaluate complex reasoning and problem-solving skills, which are better assessed by multiple-choice questions that include nuanced answer choices. In our study, ChatGPT's performance varied significantly across different subject areas; its relatively lower performance on the UEGS may be partly attributable to the true-false format, as large language models perform better with contextualized multiple-choice questions. Furthermore, the 50% chance of guessing correctly on true-false questions may have introduced variability in ChatGPT's accuracy. Future evaluations could explore whether a hybrid approach incorporating both question types would enhance the exam's ability to measure a broader range of competencies and to provide more meaningful insights into AI-assisted medical education.

CONCLUSION

ChatGPT's mean reported score on the 2021-2023 UEGS examinations was 11.9%, numerically above the mean for first-year residents (11.3%) and close to that for second-year residents (12.1%). Its scores were lower than the overall resident mean in each examination year, although the reported comparison did not reach statistical significance (p=0.109). This finding should not be interpreted as evidence of equivalent performance.

Performance varied across examination years and subject areas, indicating limitations in the consistency of ChatGPT's responses to orthopedics and traumatology questions. These findings support further investigation of ChatGPT as a supplementary educational resource, but do not establish its effectiveness in improving learning or examination outcomes. Future studies should evaluate individual model versions separately, clearly define scoring procedures, and assess educational outcomes before drawing conclusions about its role in residency training.

ETHICS

Ethics Committee Approval: This study was conducted with the written approval of the TOTBID board of directors, as documented in their official correspondence (approval no: 159, date: 26.04.2024).

Informed Consent: This study was conducted using publicly available examination questions and did not involve human participants or patient data. Therefore, informed consent was not required.

FOOTNOTES

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

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Research

Evaluation of Cervical Lordosis Loss in Patients Undergoing Posterior Cervical Laminectomy Without Instrumentation

Enstrümantasyon Uygulanmayan Posterior Servikal Laminektomi Hastalarında Servikal Lordoz Kaybının Değerlendirilmesi

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ABSTRACT

Objective: Various surgical techniques, including ventral and dorsal approaches, exist for cervical spondylotic myelopathy (CSM). We present the results in patients with CSM who underwent cervical laminectomy without fusion. Our aim was to remind readers of the advantages of this nearly forgotten technique.

Methods: Our study is a single-center, non-randomized, retrospective observational study. Our study was carried out in University of Health Sciences Türkiye, Bakırköy Prof. Dr. Mazhar Osman Training and Research Hospital between 01.01.2013 and 31.12.2022. In our study, we included patients admitted to the neurosurgery inpatient service who underwent posterior cervical laminectomy without fusion.

Results: Between 2013 and 2022, 24 patients underwent posterior cervical laminectomy without fusion. Neurological improvement was observed in 16 patients. No major complications were experienced in any of the 24 cases. Preoperative C2-7 Cobb angles averaged 15.75 degrees. At the 1 year follow-up, the mean C2-7 Cobb angle was 10.25 degrees.

Conclusion: Cervical laminectomy without fusion can be a suitable, low-complication, and easily applicable alternative to other techniques for the appropriate patient group.

Keywords: Brain and nerve surgery, cervical spondylotic myelopathy, cervical laminectomy

ÖZ

Amaç: Servikal spondilotik myelopatide (SSM) ventral ve dorsal olmak üzere çeşitli ameliyat teknikleri mevcuttur. SSM'de füzyonsuz sadece servikal laminektomi yaptığımız hastaların sonuçlarını sunduk. Artık daha az tercih edilen bu tekniğin avantajlarını hatırlatmayı amaçladık.

Gereç ve Yöntem: Çalışmamız tek merkezli, randomize olmayan, retrospektif ve gözlemsel bir çalışmadır. Çalışmamız Sağlık Bilimleri Üniversitesi, Bakırköy Prof. Dr. Mazhar Osman Ruh Sağlığı ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi'nde 01.01.2013-31.12.2022 tarihleri arasında gerçekleştirildi. Çalışmamıza nöroşirürji servisine yatırılan ve füzyon yapılmadan posterior servikal laminektomi uygulanan servikal spondilotik miyelopati hastaları dahil edildi.

Bulgular: 2013 ve 2022 yılları arasında 24 hastaya füzyonsuz posterior servikal laminektomi uygulandı. On altı hastada nörolojik iyileşme gözlemlendi. Yirmi dört olguda majör komplikasyon yaşanmadı. Ameliyat öncesi C2-7 Cobb açıları ortalama 15,75 derece olarak ölçüldü. Bir yıllık takipte, C2-7 Cobb açıları ortalama 10,25 derece olarak ölçüldü.

Sonuç: Füzyonsuz sadece servikal laminektomi uygun hasta grubunda diğer tekniklere göre uygun ve kolay uygulanabilir bir alternatif olabilir.

Anahtar Kelimeler: Beyin ve sinir cerrahisi, servikal spondilotik myelopati, servikal laminektomi

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INTRODUCTION

Cervical spondylotic myelopathy (CSM) is a complex syndrome characterized by chronic compression and ischemia of the spinal cord, and by pathologies of the spinal canal and spine (1). CSM is characterized by the progressive loss of integrity and function of the cervical cord (2). It is characterized by specific symptoms and clinical findings, depending on the location and severity of spinal cord damage. It presents with symptoms and findings such as decreased manual dexterity, impaired balance, reduced muscle strength in the extremities, and urinary dysfunction (3). Magnetic resonance imaging can detail the location and extent of the damage (2).

In severe cases, surgery appears to be the best option (4). Approximately half of patients initially managed non-surgically undergo surgery because of worsening symptoms (4). During follow-up, 23%-54% of patients who were not initially recommended for surgery underwent surgery within 70 months (4).

Both anterior and posterior techniques can be applied in surgical treatment. Different techniques within the anterior and posterior approaches can be beneficial for surgical treatment. Cervical posterior laminectomy, laminoplasty, and full endoscopic techniques are associated with favorable outcomes (5). Therefore, there is no consensus on the surgical technique for CSM.

Our aim is to report neurological improvement and C2-7 Cobb angle values at 1 year after surgery in patients who underwent posterior cervical laminectomy without fusion. We planned to measure and compare the preoperative and postoperative C2-7 Cobb angles.

METHODS

Patient Population

Our study is a single-center, non-randomized, retrospective, and observational study. Our study was carried out in University of Health Sciences Türkiye, Bakırköy Prof. Dr. Mazhar Osman Training and Research Hospital between 01.01.2013 and 31.12.2022. In our study, we included patients who were admitted to the neurosurgery inpatient service and underwent posterior cervical laminectomy without fusion.

From hospital records, the patients' genders, ages, complaints (such as decreased manual dexterity, loss of balance, loss of muscle strength in the extremities, and urinary dysfunction), and physical examination findings were recorded. Findings from preoperative cervical computed tomography, cervical X-rays (anteroposterior and lateral), and magnetic resonance imaging were retrieved from the hospital's electronic database. Postoperative cervical X-ray and magnetic resonance imaging findings were also obtained from the hospital's electronic database.

Cervical X-rays taken during the patients' monthly and annual follow-ups were obtained from the hospital's electronic records. Visual analogue scale (VAS) scores used to assess pain in all patients who underwent surgery at our hospital were extracted from patients' discharge summaries. Recorded VAS scores for neck pain and sensory problems were extracted from hospital records.

All procedures conducted in studies involving human participants adhered to the ethical guidelines set forth by the institutional and/or national research committees and were in accordance with the 1964 Declaration of Helsinki and its subsequent amendments or equivalent ethical standards. This study received approval from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no: 2024-09-11, date: 02.09.2024). Informed consent was not required because the study was retrospective.

Surgical Technique

A routine posterior cervical surgical approach was performed using a midline incision at the necessary levels. Paravertebral muscles were dissected from the spinous processes using cautery. Muscle tissue over the lateral mass was preserved (Figure 1). Laminectomies were performed using Kerrison rongeurs, numbers 1 and 2. Facet resection was not performed. After decompression was achieved, hemostasis was performed. A drain was placed, and the anatomical layers were sutured appropriately.

Radiological Measurements

C2-7 Cobb angles were measured by a single physician, a neurosurgeon with 25 years' experience in spine disorders, using the hospital's electronic database. The Cobb angle values were remeasured from the electronic database preoperatively and 1 year postoperatively.

Statistical Analysis

IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Normally distributed data were presented as mean±standard deviation, whereas non-normally distributed data were presented as median (min-max). When comparing preoperative and postoperative data, the paired t-test was used for normally distributed data, and the Wilcoxon test was used when at least one dataset was not normally distributed. A significance level of 0.05 was adopted.

Inclusion and Exclusion Criteria

Only patients who underwent posterior cervical laminectomy for CSM were included in the study. Patients who underwent laminoplasty or lateral mass instrumentation were excluded. Patients without preoperative cervical X-rays were excluded. Patients who did not attend postoperative follow-ups were excluded from the study. Patients without cervical X-rays at 1 year postoperatively were excluded. Those who had two or more neck surgeries were not included in the study.

RESULTS

Demographic Findings

Between 2013 and 2022, 24 patients underwent posterior cervical laminectomy without fusion (Figures 1 and 2). There were 8 female (33.3%) and 16 male patients. The average age of the patients was found to be 59.25±11.80. Cervical laminectomy was performed at a mean of 2.62±0.85 levels. Neurological improvement was observed in 16 patients (66.6%). Complaints and findings are presented in Table 1.

Changes in Neck Pain and Cobb Angles

Preoperative C2-7 Cobb angles were measured at an average of 15.75 degrees. At the 1-year follow-up, the C2-7 Cobb angle averaged 10.25° (Figures 3 and 4). After surgery, C2-7 Cobb angles were significantly reduced compared with preoperative values (p=0.001, paired-samples t-test).

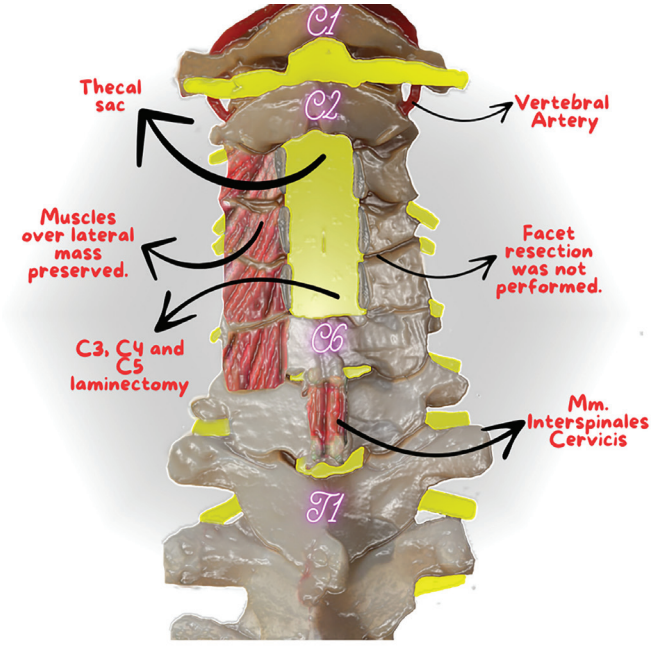

Figure 1. The muscles over the lateral mass were preserved. Facet resection was not performed. The technique of cervical laminectomy without fusion has been illustrated

However, we did not have any patient who developed cervical kyphosis. VAS scores before and after treatment are presented in Figure 5. Neck VAS scores were significantly reduced after treatment compared with before treatment (Wilcoxon test, p<0.001).

DISCUSSION

Posterior cervical laminectomy without fusion was performed on 24 patients (Figures 1 and 2). Our rate of neurological improvement is 66.6% (n=16). Arnold et al. (6) reported improvement rates of 52% for patients who underwent laminectomy and 83% for patients who underwent laminectomy plus fusion (5/6 patients). Carol and Ducker (7) reported long-term improvement rates of 68% in the patient group who underwent posterior laminectomy.

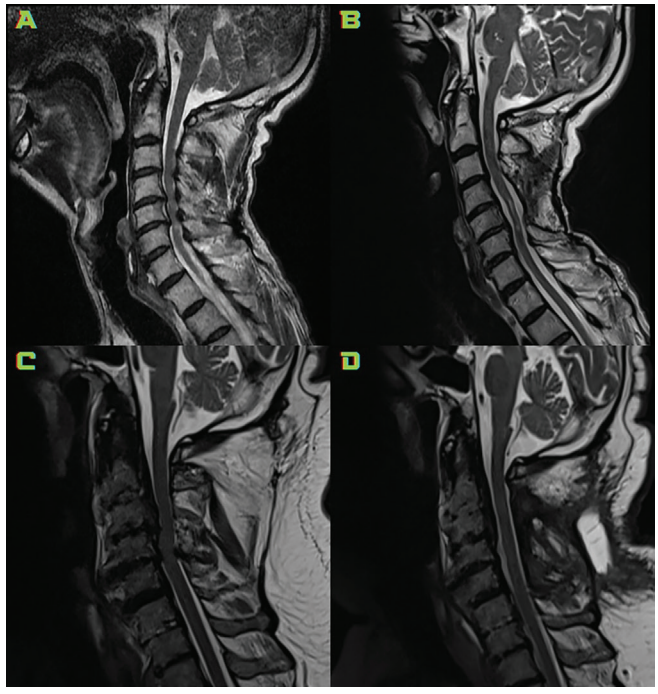

Figure 2. The preoperative and postoperative MRI images of 2 patients with cervical spondylotic myelopathy undergoing cervical laminectomy without fusion are shown
MRI: Magnetic resonance imaging

Table 1. The complaints and findings of the patients

Variables	n (percentage or standard deviation)
Motor deficits	21 (87.5%)
Upper motor neuron signs	17 (70.8%)
Sensory abnormalities	16 (66%)
Incontinence	3 (12.5%)
Impairment of gait and/or falls	18 (75.0%)
Decreased fine manual skills	16 (66.6%)

They reported long-term improvement rates of 73% in their series of patients who underwent anterior cervical discectomy and fusion (7). Ebersold et al. (8) reported long-term recovery rates of 37% following posterior laminectomy and 55% following anterior cervical intervention. Compared with studies published before 2000, our neurological

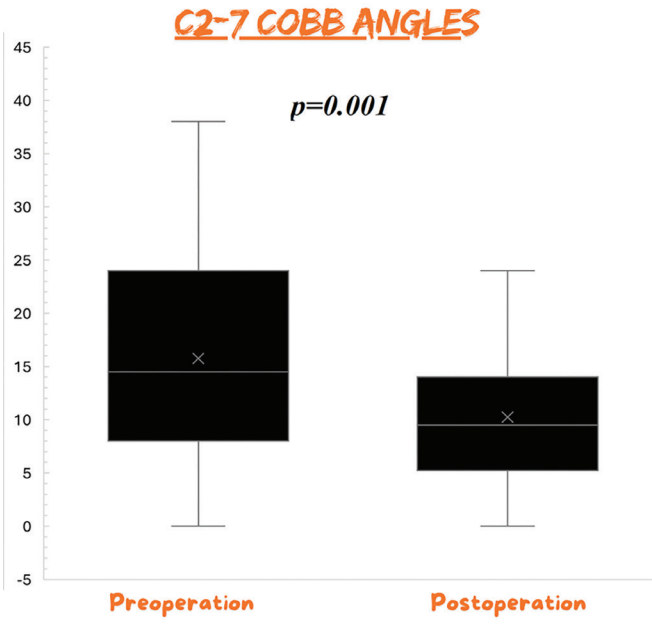

Figure 3. After surgery, Cobb C2-7 angles were significantly reduced compared to before treatment (p=0.001) (paired samples t-test)

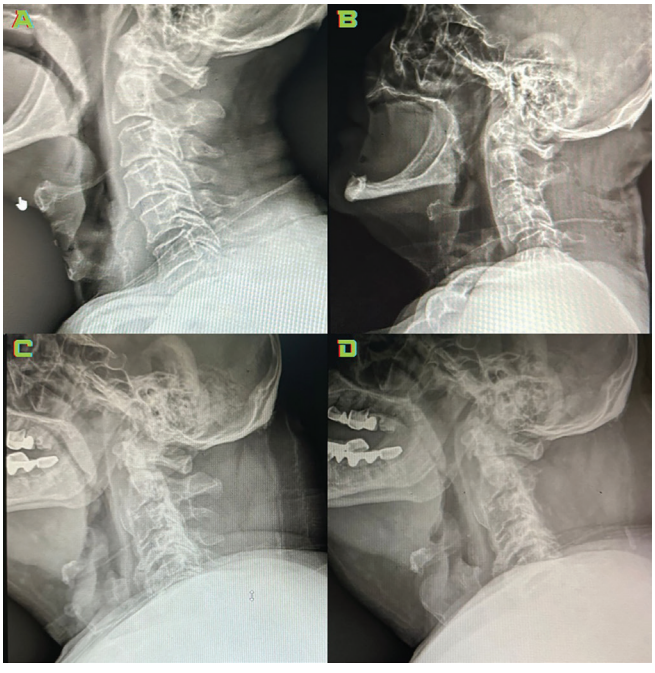

Figure 4. Preoperative Cobb C2-7 angles were measured at an average of 15.75 degrees. At the 1-year follow-up, Cobb C2-7 angles were measured at an average of 10.25 degrees

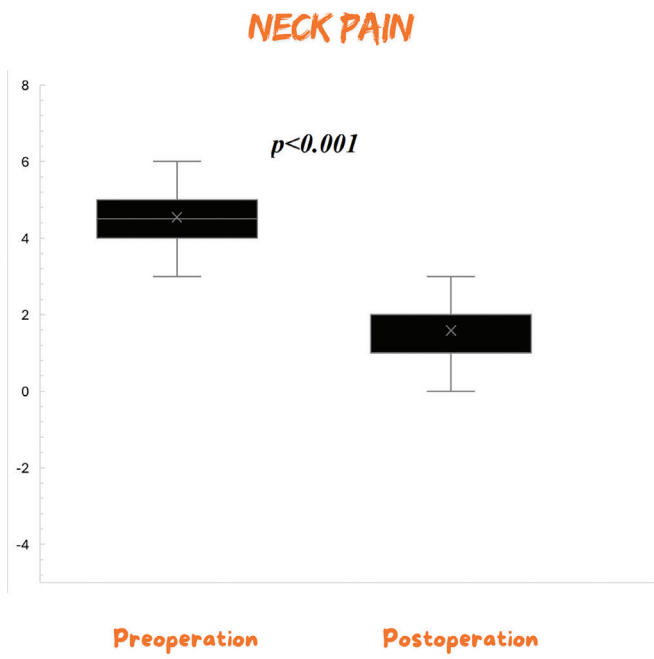

Figure 5. Neck VAS scores after treatment were significantly reduced compared to before treatment (p<0.001) (Wilcoxon test)
VAS: Visual analogue scale

improvement rate (66.6%) following posterior cervical laminectomy without fusion appears more favorable.

This may be due to increased knowledge, preservation of muscle tissue over the lateral mass, avoidance of facetectomy, and use of a microscope (Figure 1). Sakaura et al. (9) reported improvement rates (evaluated with Japanese Orthopedic Association) of 71% in the group who underwent the anterior approach and 70% in the group who underwent laminoplasty. The improvement rate in our study (66.6%) is consistent with that reported by Sakaura et al. (9).

Pathophysiology of Cervical Spondylotic Myelopathy

CSM results from chronic cord compression due to degenerative changes in the intervertebral discs, the facet joints and the uncovertebral joints, and associated ligamentous hypertrophy. The resulting canal narrowing causes ischemia, demyelination, and neuronal loss (10-12). The zygapophyseal joint also absorbs multidirectional compressive, shearing, and torsional forces (13,14). The Luschka joint functions in concert with the facet joint. It assists in lateral bending and rotational movements. It restricts cervical spine movements that exceed its physiological or anatomical limits and could therefore be considered pathological (15,16). This complex anatomical structure is accompanied by fibrotic ligaments that connect different regions (10). Particularly, the anterior longitudinal ligament, posterior longitudinal ligament, interspinous ligament,

ligamentum flavum, and capsular ligaments contain elastin and collagen. The functions of these units depend on their anatomical localization and biochemical composition, such as elastin and collagen. They are resistant to normal and abnormal loads (10).

Across studies, the average loss of lordosis is 5 degrees even after laminoplasty (17,18). In our study, the average lordosis loss was 5 degrees (Figure 3). It is consistent with previous studies. In fact, given the nature of the surgical technique (a procedure in which no fusion is performed), it can be considered a more favorable outcome.

Surgical Options or Preferences in Cervical Spondylotic Myelopathy

The results of studies comparing anterior and posterior approaches, the latter with or without fusion, are inconclusive (19,20). Surgical techniques include ventral decompression and fusion; multilevel discectomy and plating; corpectomy; posterior fusion using lateral mass or pedicle screws; various laminoplasty techniques; and posterior cervical laminectomy without fusion (20-23). In the United States, posterior fusion surgeries increased until 2002, and expenditures exceeded $2 billion (20).

Both anterior and posterior surgical techniques are associated with effective improvements (20,21). Among posterior surgical techniques, laminoplasty or laminectomy combined with posterior fusion is used (24). In our study, we presented the results of cases in which posterior cervical laminectomy without fusion was performed. Some authors reference Albert and Vaccaro's (23) 1998 paper, stating that posterior cervical laminectomy without fusion can lead to complications, such as post-laminectomy kyphosis (24). We believe this situation is misinterpreted. Albert and Vaccaro (23) specifically noted that the rates of post-laminectomy kyphosis are higher in children due to the immaturity of their musculoskeletal system. However, they state that in adults the rates of post-laminectomy kyphosis are low when preoperative cervical alignment is normal and there is no instability (23). They state that aggressive muscle dissection, unnecessary facet resection, age, and preoperative kyphosis can lead to post-laminectomy kyphosis (23). If the patient has kyphosis, the following can be applied: anterior decompression with fixation, and pedicle screw system fixation with decompression (22,25). Small or insufficient pedicles, abnormal pedicle axis, preoperative posterior cervical infection, and abnormal vertebral artery positions are dangerous and constitute contraindications to posterior fusion (22). If the outer diameter of the cervical pedicle is less than 4 mm, safe screw placement is considered technically infeasible (22). Moreover, during posterior cervical instrumentation, degeneration of the lateral mass can make determining the entry point difficult (22). Karaikovic et al. (26) also noted that there is no safe zone in the anterior parts of the C3-C7 cervical vertebral bodies. Prior to posterior instrumentation, the vertebral artery anatomy and its variations should be evaluated in detail (22,27). Neurovascular structures should be evaluated individually (22,27). Although Abumi (22) noted that posterior cervical instrumentation with pedicle screw fixation is a strong method for correcting cervical deformity, he also stated that it can cause neurovascular complications. Cases of cerebral infarction due to posterior cervical instrumentation have also been reported in the literature (28). Brachial plexus injury is also a complication that can develop from positioning (22). Abumi (22) states that pedicle screw fixation provides stronger stabilization than other internal fixation methods. However, he notes that even experienced and careful surgeons have relatively high rates of screw malposition and neurovascular complications (22).

Lau et al. (24) demonstrated that laminectomy combined with spinal fusion results in greater blood loss than laminoplasty. Laminectomy with spinal fusion resulted in longer hospital stays than laminoplasty. Laminectomy with posterior spinal fusion was associated with more long-term complications than laminoplasty (24). However, laminectomy with posterior spinal fusion (pedicle screw or lateral mass) was associated with greater neurological improvement than laminoplasty (24,25). Reports indicate that dorsal laminoplasty showed greater improvement on the short form-36 (SF-36) at 1 year compared with dorsal and ventral fusion (20). No statistically significant difference was found in postoperative neck pain between the two groups. However, when fixation is performed with lateral mass screws, there is a risk of iatrogenic nerve root compression if preoperative foraminal stenosis is present (22,29,30). Excessive traction on the shoulder girdle during C-arm projection can also cause brachial plexus palsy (22). A considerably more invasive technique, combined pedicle-screw instrumentation at C2 and C7 with lateral-mass instrumentation at C3-C6, is technically demanding and laborious (22).

Piazza et al. (19) reported that posterior laminectomy produced greater radiological decompression and expansion of the posterior cerebrospinal fluid space than anterior cervical discectomy. However, they included both fusion and non-fusion patients in the same posterior group, without dividing them into two distinct groups (19). They showed that the posterior approach is better when ligament hypertrophy predominates in posterior spinal cord compression (19). Dorsal surgery for CSM produced greater improvements in physical functioning than ventral surgery

at 1 and 2 years (20). Lawrence et al. (31) also stated that laminoplasty provided sufficient decompression. In terms of infection rates and postoperative pain syndromes, anterior approaches appear to be superior (19). Ghogawala et al. (20) reported that ventral surgery was associated with a higher risk of complications (dysphagia, reoperation, readmission within 1 month) and of new neurological deficits. Nunna et al. (32) compared posterior decompression and fusion to anterior discectomy and fusion and reported different outcomes. In the posterior fusion group, they found higher rates of complications , including urinary tract infection, deep vein thrombosis, pulmonary embolism, infarction, wound dehiscence, surgical site infection, readmission, revision surgery, and pseudoarthrosis (32). In patients who underwent posterior fusion, the use of narcotic medications was also found to remain high for up to 120 days (32).

In cervical laminoplasty, which is less invasive than other techniques, complications such as spinal cord injury, infection, readmission within 30 days, and fever of unknown origin have been reported (20). The rate of C5 palsy in patients who underwent cervical laminoplasty was reported to be 2.4% (33). Morishita et al. (34) reported the following systemic complications in a large series of patients who underwent laminoplasty: cardiovascular disease, cerebrovascular disease, respiratory failure, pneumonia, dysphagia, renal failure, hepatic failure, gastric ulcer and hemorrhage, deep venous thrombosis, pulmonary embolism, sepsis, and delirium. In the same study, local complications such as surgical site infection, paralysis, meningitis, spinal fluid leakage, and hematoma were also reported (34).

The surgical technique is closely related to the types and variety of complications (20). It remains unclear which technique is optimal for the treatment of CSM (20,22,24,25). Moreover, complication rates and types vary and may even be contradictory depending on the surgical technique (19,20,22,23,32-34). In our opinion, among the various techniques, posterior cervical laminectomy without fusion is the least invasive. In our study, no minor or major complications occurred. Although the decrease in the C2-7 Cobb angle is significant (Figure 3), posterior cervical laminectomy without fusion offers many advantages. These advantages include being less invasive than other surgical approaches, avoiding the potential risks associated with instrumentation, having a shorter operative time, having a lower risk of immediate postoperative complications, and being technically easier than other surgical approaches.

Finally, we would like to note an additional consideration. In patients with advanced spondylotic change—where substantial osteophytic formation (Figure 6) has already contributed to a degree of auto-stabilization—we do not consider routine application of further instrumentation necessarily advantageous. While this observation should be interpreted cautiously, it reflects our clinical impression that, in selected cases, additional fixation may offer limited benefit relative to its potential risks.

Study Limitations

Our study has some scientific limitations. The most significant limitation is its retrospective nature. Additionally, the number of patients was limited. The patients' histories, comorbidities, and physical examination data may not have been adequately documented. In our clinic, examinations such as the hyperactive pectoralis reflex, the inverted radial reflex, the positive finger escape sign, and the release test were not recorded. Tests assessing quality of life, such as the SF-36, were not administered preoperatively or postoperatively. This makes it difficult to evaluate the impact of the results on patients' quality of life. A one-year follow-up period may not provide sufficient information about long-term results and complications. The lasting

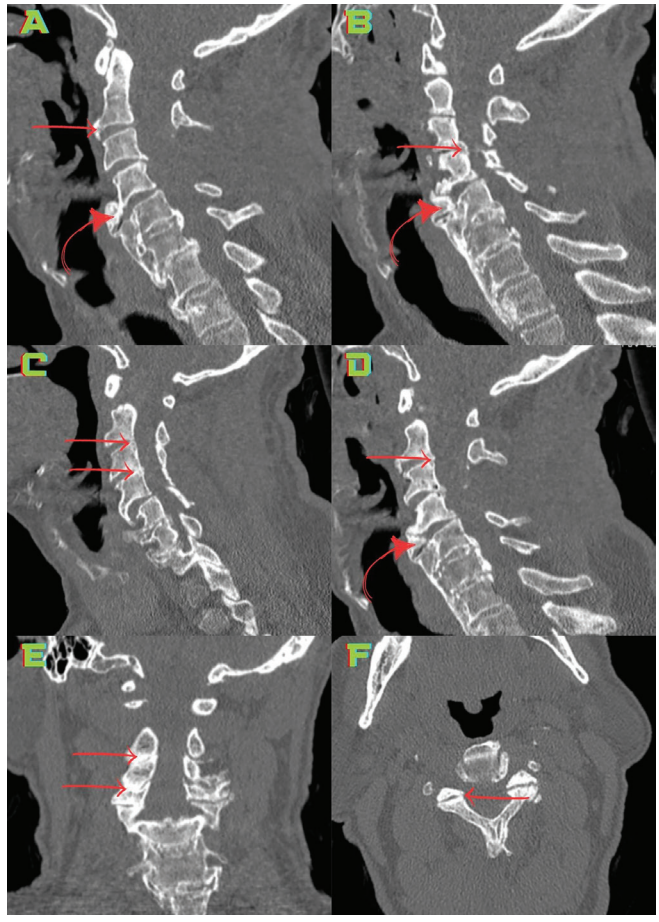

Figure 6. A cervical spine attempting to stabilize itself with osteophytosis is being observed

effects of the method can be evaluated with longer-term follow-up studies.

CONCLUSION

CSM is a serious condition that significantly affects patients' quality of life and is characterized by progressive neurological deficits. For treatment, surgery is preferred to conservative therapy. Among the surgical techniques are ventral decompression and fusion, multilevel discectomy with plating, corpectomy, posterior fusion with lateral mass screws, posterior fusion with pedicle screws, various laminoplasty techniques, and laminectomy without fusion. A posterior cervical laminectomy without fusion can be a suitable and readily applicable alternative to other techniques for the appropriate patient group. One of its advantages is lower complication rates.

ETHICS

Ethics Committee Approval: This study received approval from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no: 2024-09-11, date: 02.09.2024).

Informed Consent: Informed consent was not required because the study was retrospective.

FOOTNOTES

Authorship Contributions

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

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

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Research

Investigation of the Relationship Between Suicidal Behavior and Anxiety Sensitivity and Somatosensory Amplification in Patients with Tinnitus

Tinnitus Hastalarında İntihar Davranışı, Anksiyete Duyarlılığı ve Somatosensoriyal Amplifikasyon Arasındaki İlişkinin İncelenmesi

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ABSTRACT

Objective: Some patients with tinnitus experience substantial psychosocial challenges. This study aimed to investigate the relationships among tinnitus severity, anxiety sensitivity, somatosensory amplification, and suicidal behavior. Additionally, the study examined whether tinnitus patients and healthy controls on these factors.

Methods: The study consisted of 45 patients admitted to the otorhinolaryngology clinic with complaints of tinnitus; and 45 healthy individuals. We administered the sociodemographic and clinical data form, Tinnitus Handicap Inventory (THI), anxiety sensitivity index-3 (ASI-3), somatosensory amplification scale (SSAS), and suicidal behaviors questionnaire (SBQ) to the study participants.

Results: No significant differences were found between the patient and control groups in ASI-3, SSAS, and SBQ scores (all $p>0.05$). However, in the tinnitus group, positive correlations were observed between THI total scores and ASI-3 ($r=0.55$; $p<0.001$), SSAS ($r=0.47$; $p=0.001$), and SBQ ($r=0.72$; $p<0.001$). According to the multiple regression analysis, 44% of the variance in SBQ scores was explained by THI ($F=34.37$; $p<0.001$). When ASI-3 was added to the model, the explained variance increased to 49% ($F=20.22$; $p<0.001$), and with the addition of SSAS, it increased further to 50% ($F=13.55$; $p<0.001$). However, in this model, only THI ($p<0.001$) and ASI-3 ($p=0.043$) made significant contributions, while the effect of SSAS was not statistically significant ($p=0.443$). Mediation analysis revealed that ASI-3 partially mediated the relationship between THI and SBQ, whereas SSAS had no significant mediating effect.

Conclusion: Our findings suggest that tinnitus severity may be closely associated with suicidal tendency, particularly as anxiety sensitivity increases.

Keywords: Subjective tinnitus, anxiety, somatosensory amplification, suicidal ideation

ÖZ

Amaç: Tinnitus hastası bazı bireyler, önemli psikososyal zorluklar yaşamaktadır. Bu çalışma, tinnitus şiddeti, anksiyete duyarlılığı, somatosensoryal amplifikasyon ve intihar davranışı arasındaki ilişkileri araştırmayı amaçlamıştır. Ayrıca, tinnitus hastaları ile sağlıklı kontrol grupları arasında bu faktörler açısından farklılık olup olmadığını incelemiştir.

Gereç ve Yöntem: Çalışma, tinnitus şikayetiyle kulak burun boğaz kliniğine başvuran 45 hasta ve 45 sağlıklı bireyden oluşmuştur. Çalışma katılımcılarına sosyodemografik ve klinik veri formu, Tinnitus Handikap Envanteri (THE), anksiyete duyarlılığı indeksi-3 (ADİ-3), somatosensoryal amplifikasyon ölçeği (SAÖ) ve intihar davranışı ölçeği (İDÖ) uygulanmıştır.

Bulgular: Gruplar arasında ADİ-3, SAÖ ve İDÖ puanları açısından kontrol grubuna göre anlamlı fark saptanmamıştır (tümü $p>0,05$). Bununla birlikte, tinnitus tanılı hasta grubunda THE toplam puanı ile ADİ-3 ($r=0,55$; $p<0,001$), SAÖ ($r=0,47$; $p=0,001$) ve İDÖ ($r=0,72$; $p<0,001$) arasında pozitif korelasyonlar bulunmuştur. Çok değişkenli regresyon analizine göre, İDÖ puanlarındaki varyansın %44'ü THE ile ($F=34,37$; $p<0,001$) açıklanmıştır. ADİ-3 eklendiğinde açıklanan varyans %49'a yükselmiş ($F=20,22$; $p<0,001$), SAÖ'nün de eklenmesiyle %50'ye ulaşmıştır ($F=13,55$; $p<0,001$). Ancak bu modelde yalnızca THE ($p<0,001$) ve ADİ-3 ($p=0,043$) anlamlı katkı sağlamış; SAÖ'nün etkisi anlamlı bulunmamıştır ($p=0,443$). Mediasyon analizi, ADİ-3'ün THE ile İDÖ arasındaki ilişkiyi kısmen aracıladığını, SAÖ'nün ise anlamlı bir aracılık etkisine sahip olmadığını göstermiştir.

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ÖZ

Sonuç: Bulgularımız tinnitus şiddetinin, özellikle anksiyete duyarlılığı arttıkça intihar eğilimiyle yakından ilişkili olabileceğini göstermektedir.
Anahtar Kelimeler: Subjektif tinnitus, anksiyete, somatosensoryal amplifikasyon, intihar düşüncesi

INTRODUCTION

Tinnitus is the perception of sound without an external source, commonly described as buzzing, ringing, whistling, or hissing. It affects a significant portion of the population, with prevalence rates ranging from 8% to 30%, and becomes more common with age (1). While some individuals tolerate tinnitus without seeking medical attention, others experience substantial psychosocial challenges (2). The condition is heterogeneous in clinical presentation and etiology, and no reliable objective measure exists to diagnose tinnitus (3).

Tinnitus is associated with various factors, including exposure to loud noise, head and neck injuries, and underlying medical conditions such as hearing loss, neurological disorders, and psychiatric illnesses (4). Its pathophysiology involves both auditory and central nervous system dysfunctions, with neuroimaging studies showing changes in brain areas such as the limbic system and prefrontal cortex, which may contribute to the psychological distress experienced by patients with tinnitus (5,6).

The relationship between tinnitus and psychiatric conditions, particularly anxiety, depression, and suicidal behavior, has been well-documented (7). Previous studies suggest that tinnitus may be both a consequence and a trigger of psychiatric symptoms, creating a vicious cycle in which tinnitus exacerbates psychological distress, which in turn worsens the perception of tinnitus (8,9). Suicidal behavior has also been linked to tinnitus, particularly in individuals with underlying psychiatric conditions, although the exact nature of this relationship remains complex and multifactorial (10).

While psychiatric comorbidities of tinnitus, such as anxiety and depression, have been extensively studied, fewer investigations have focused on the combined roles of anxiety sensitivity, somatosensory amplification, and suicidal behavior in tinnitus patients. Understanding how these factors interact may provide deeper insight into the psychological mechanisms that exacerbate tinnitus severity and contribute to the distress experienced by patients. This study aims to explore the association between tinnitus severity and psychiatric factors such as anxiety sensitivity, somatosensory amplification, and suicidal behavior in adults diagnosed with subjective tinnitus. Additionally, we aim to determine whether these factors differ between tinnitus patients and healthy controls.

METHODS

Participants

This cross-sectional case-control study was conducted at the otorhinolaryngology outpatient clinic between December 2019 and June 2022 and enrolled patients clinically diagnosed with subjective tinnitus. Eligibility criteria required participants to be over 18 years of age, to have no severe medical or neurological disorders, and not to be receiving active psychiatric treatment at the time of assessment. Individuals with a documented psychiatric diagnosis or psychotropic medication use within the preceding 6 months were excluded to minimize potential confounding effects of acute psychiatric symptomatology. Participants with a more distant psychiatric history but without any current diagnosis or medication record in the institutional health system and who were evaluated as clinically stable based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria were considered eligible for inclusion. Detailed otorhinolaryngological evaluations were performed to exclude secondary causes, such as otologic or systemic diseases. Patients with mild sensorineural hearing loss, defined as thresholds of 25-40 dB HL on pure-tone audiometry, were included because mild hearing loss is commonly observed in idiopathic tinnitus and does not directly affect the psychological variables under investigation. Individuals with moderate to severe hearing loss (>40 dB HL) or conductive hearing loss were excluded. Idiopathic tinnitus was defined as subjective tinnitus without any identifiable cause. Patients underwent otoscopic examination, pure tone audiometry, and basic laboratory screening. The control group consisted of age- and sex-matched healthy individuals recruited from hospital staff and patient relatives who reported no tinnitus or hearing loss. Written informed consent was obtained from all participants prior to enrollment.

The sample size was determined a priori based on effect sizes reported in the literature examining the relationship between tinnitus severity and psychological variables. In a reference study, the correlation between Tinnitus Handicap Inventory (THI) and anxiety symptoms was reported as

r=0.532 (11). This value was adopted as the target effect size, and a power analysis was conducted using G*Power 3.1.9.7 under the option linear multiple regression: fixed model, R2 deviation from zero. Assuming α=0.05, power (1-β)=0.80, and f^2=0.395 (derived from r=0.532), the minimum required sample size was estimated to be approximately n=30 (for 3 predictors). As the tinnitus group in the present study consisted of n=45, the sample size provides sufficient power to detect the moderate-to-large effects reported in previous research.

A total of 45 patients with idiopathic tinnitus were included in the case group, while the control group consisted of 45 healthy volunteers with no physical or psychiatric disorders. The study received ethical approval from the Recep Tayyip Erdoğan University Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (approval no: 2019/202, date: 12.12.2019).

Measures

Sociodemographic and Clinical Data Form

The researchers designed a questionnaire to collect data on the study's independent variables, including sociodemographic and clinical characteristics of patients and healthy volunteers. The form collected data on age, sex, education, smoking, alcohol consumption, occupation, chronic diseases, history of psychiatric treatment, history of suicide attempts, and family history of suicide attempts.

The somatosensory amplification scale (SSAS), developed by Barsky et al. (12), consists of 10 statements that assess participants' sensitivity to bodily sensations. Each item is scored on a 5-point scale, with higher scores indicating greater symptom amplification. The Turkish validity and reliability study was conducted by Güleç and Sayar (13).

The anxiety sensitivity index-3 (ASI-3) is the latest version of the ASI. It is an 18-item self-report scale that assesses anxiety sensitivity across 3 domains: social, physical, and cognitive. Each item is rated on a five-point scale, with total possible scores ranging from 0 to 72; higher scores indicate greater anxiety sensitivity (14). The Turkish version was validated by Mantar et al. (15).

Suicidal Behaviors Questionnaire

The suicidal behaviors questionnaire (SBQ) is a self-reported measure that assesses suicidal thoughts and behaviors. It consists of four items, with a total score ranging from 0 (no suicidal thoughts or behaviors) to 14. Items cover topics such as suicidal ideation (including ideation within the past year), suicide attempts, threats of suicide attempts, and self-reported likelihood of future suicidal behavior. It was developed by Linehan et al. (16), and the Turkish version was validated by Bayam et al. (17).

Tinnitus Handicap Inventory

The THI is a 25-item questionnaire used to assess the severity of tinnitus-related handicap. Each item is scored as yes (4 points), sometimes (2 points), or no (0 points), with total scores ranging from 0 to 100. Higher scores indicate greater tinnitus-related handicap. The THI includes three subscales: functional (11 items), emotional (9 items), and catastrophic (5 items). It was developed by Newman et al. (18), and its Turkish version was validated by Aksoy et al. (19).

Statistical Analysis

The demographic characteristics of the cases evaluated in the study were analyzed using descriptive statistics (such as frequencies, percentages, means, and standard deviations). Proportions of demographic characteristics were compared between groups using the chi-square test. Mean scores for age, ASI, and SSAS were compared between the patient and control groups using the independent-samples t-test. The Mann-Whitney U test was used to compare median SBQ scores between groups.

In the patient group, correlations among THI, ASI, SSAS, and SBQ were examined using Pearson and Spearman correlation analyses. We evaluated the effectiveness of ASI and SSAS in explaining tinnitus symptoms, and that of THI, ASI, and SSAS in explaining SBQ scores in the patient group, using multivariate linear regression analysis. The significance level was set at $p<0.05$ for all analyses. The normality of the data was assessed using skewness and kurtosis, with acceptable values within ±1.5. All analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Sociodemographic and Clinical Data Form

The sample consisted of 90 individuals: 44.4% (n=40) male and 55.6% (n=50) female. The mean age of the participants was 41.99±13.46 years. There were no significant differences between the tinnitus and control groups in terms of age, sex, marital status, education, or employment status. However, educational level (p=0.013) and history of psychiatric treatment (χ^2=6.64; p=0.036) significantly differed between groups. Detailed sociodemographic and clinical data are shown in Table 1.

In the patient group, 11.1% reported a family history of tinnitus. The onset was predominantly gradual (62.2%).

Stress (26.7%) and exposure to loud noise (13.3%) were the most frequently reported precipitating factors. Almost all participants perceived tinnitus in one or both ears; only 4.4% localized it to the head. The symptom pattern was intermittent in 53.3% of participants and continuous in 46.7%. Stress was identified as the most common aggravating factor (64.4%), followed by head or neck movements (33.3%), which appeared to modulate tinnitus perception. Loud sounds exacerbated symptoms in 55.6% of patients, had no effect in 37.8%, and had an uncertain effect in 6.7%. The influence of daytime naps was less consistent, as 11.1% reported worsening, 22.2% reported improvement, and 66.7% reported no change. The average duration of tinnitus in the patient group was 25.49±35.69 months. The mean scores of the THI and its subscales (functional, emotional, and catastrophic) as well as the total THI score are presented in Table 2.

No statistically significant differences were observed between the patient and control groups in any ASI-3 subscale or total score, nor in SSAS or SBQ scores, as determined by the independent-samples t-test and the Mann-Whitney U test. Table 3 presents the comparative results.

According to the Pearson correlation analysis, total THI scores showed significant positive correlations with ASI-3 physical (r=0.416; p=0.004), social (r=0.516; p<0.001), cognitive (r=0.530; p<0.001), total (r=0.553; p<0.001), and SSAS (r=0.474; p=0.001) scores in the patient group. Similar positive correlations were observed between the THI subscales (functional, emotional, and catastrophic) and ASI-3 dimensions and SSAS scores (all p<0.05). Furthermore, SSAS scores were strongly correlated with ASI-3 subscales, particularly ASI-physical (r=0.584; p<0.001) and ASI-total (r=0.576; p<0.001). According to the Spearman correlation analysis, SBQ scores were positively correlated with THI total (r=0.724; p<0.001) and its subscales, and with ASI-3 and SSAS measures (r=0.356-0.572; all p<0.05). Table 4 presents the detailed correlation coefficients.

Multivariate linear regression analysis indicated that total THI scores accounted for 44% of the variance in SBQ scores in the patient group (F=34.37; p<0.001).

After ASI scores were added to model 1, 49% of the variance in SBQ scores was explained by total THI and ASI scores, a statistically significant proportion (F=20.22; p<0.001).

Table 1. Sociodemographic features of patients and healthy controls

Features		Patient group (n=45)	Healthy controls (n=45)	p
Age† (mean)		43.82	40.16	
Sex‡	Female	25 (27.8)	25 (27.8)	1.00
	Male	20 (22.2)	20 (22.2)	
Education‡	Primary school	17 (18.9)	4 (4.4)	0.013
	Secondary school	6 (6.7)	10 (11.1)	
	High school	14 (15.6)	18 (20)	
	University	8 (8.9)	13 (14.4)	
Marital status§	Single	12 (13.3)	14 (15.6)	0.820
	Married	32 (35.6)	29 (32.2)	
	Widowed	0 (0)	1 (1.1)	
	Divorced	1 (1.1)	1 (1.1)	
Occupation§	Unemployed	15 (16.7)	9 (10)	0.218
	Employee	6 (6.7)	9 (10)	
	Officer	4 (4.4)	8 (8.9)	
	Independent	3 (3.3)	6 (6.7)	
	Housewife	10 (11.1)	11 (12.2)	
	Retired	7 (7.8)	2 (2.2)	
Chronic disease‡	Yes	19 (21.1)	13 (14.5)	0.186
	No	26 (28.9)	32 (35.6)	
History of psychiatric‡ treatment	Yes	18 (20)	16 (17.8)	0.036
	No	27 (30)	29 (32.2)	
Suicide attempt§	Yes	1 (1.1)	0 (0)	1.00
	No	44 (48.9)	45 (50)	

p<0.05 was considered statistically significant
†: Independent samples t-test, ‡: Pearson chi-square test, §: Fisher's exact test

Table 2. Descriptive statistics for tinnitus duration and THI scores

Variable	Mean±SD	Min-max
Tinnitus duration	25.49±35.69	1.00-180.00
THI functional	17.64±11.30	0.00-42.00
THI emotional	14.47±9.68	0.00-36.00
THI catastrophic	7.87±5.68	0.00-20.00
THI total	39.98±24.34	2.00-88.00

THI: Tinnitus Handicap Inventory, Min-max: Minimum-maximum, SD: Standard deviation

Table 3. Comparison of patient and control groups on suicidal behavior and anxiety sensitivity measures

Variable	Patient mean±SD	Control mean±SD	p
SBQ	0.87±1.65	0.64±1.19	0.465
ASI physical	7.78±6.24	7.40±4.15	0.736
ASI social	7.22±5.87	7.60±4.26	0.728
ASI cognitive	5.38±5.08	5.56±3.96	0.854
ASI total	20.38±15.05	20.60±10.70	0.936
SSAS	26.20±8.20	25.00±6.26	0.437

p<0.05 was considered statistically significant
ASI: Anxiety sensitivity index, SSAS: Somatosensory amplification scale, SBQ: Suicidal behaviors questionnaire, SD: Standard deviation

Upon examining model 2, only total THI scores [p<0.001; 95% confidence interval (CI): 0.017-0.053] had a statistically significant effect on SBQ scores. When SSAS scores were added to the model, the explained variance increased slightly to 50% (F=13.55; p<0.001). However, SSAS was not a significant predictor (p=0.443), whereas THI (p<0.001) and ASI (p=0.043) remained significant (Table 5).

According to the multivariate linear regression analysis, it was found that 31% of the variance in tinnitus symptoms was statistically significantly explained by ASI scores (F=18.91; p<0.001).

When SSAS scores were added to model 1, ASI and SSAS scores together accounted for 34% of the variance in tinnitus symptoms (F=10.91; p<0.001). Upon examining model 2, only ASI scores (p=0.009, 95% CI: 0.177-1.176) were found to have a statistically significant effect in explaining tinnitus symptoms, as shown in Table 6.

Based on these findings, a mediation analysis was conducted to examine whether ASI-3 and SSAS mediate the relationship between THI and SBQ. The mediation model indicated that ASI-3 partially mediated the relationship between THI and SBQ, whereas SSAS did not have a significant indirect effect. Standardized path coefficients are presented in Figure 1.

Table 4. Correlation between THI, ASI, SSAS, and SBQ in patients group

		1	2	3	4	5	6	7	8	9
1) THI total	r	-								
	p	-								
2) THI functional	r	0.922								
	p	<0.001								
3) THI emotional	r	0.943	0.776							
	p	<0.001	<0.001							
4) THI catastrophic	r	0.845	0.638	0.794						
	p	<0.001	<0.001	<0.001						
5) ASI physical	r	0.416	0.314	0.474	0.352					
	p	0.004	0.036	0.001	0.018					
6) ASI social	r	0.516	0.474	0.488	0.437	0.628				
	p	<0.001	0.001	0.001	0.003	<0.001				
7) ASI cognitive	r	0.530	0.485	0.526	0.411	0.593	0.732			
	p	<0.001	0.001	<0.001	0.005	<0.001	<0.001			
8) ASI total	r	0.553	0.479	0.564	0.455	0.860	0.898	0.869		
	p	<0.001	0.001	<0.001	0.002	<0.001	<0.001	<0.001		
9) SSAS	r	0.474	0.383	0.475	0.462	0.584	0.393	0.534	0.576	
	p	0.001	0.010	0.001	0.001	<0.001	0.008	<0.001	<0.001	
10) SBQ	rho	0.724	0.596	0.708	0.689	0.397	0.476	0.572	0.502	0.356
	p	<0.001	<0.001	<0.001	<0.001	0.007	0.001	<0.001	<0.001	0.017

r: Pearson correlation analysis, rho: Spearman correlation analysis, THI: Tinnitus Handicap Inventory, ASI: Anxiety sensitivity index, SSAS: Somatosensory amplification scale, SBQ: Suicidal behaviors questionnaire

Table 5. The effectiveness of THI, ASI, and SSAS scores in explaining SBQ in patients

Model		Unstandardized coefficients		Unstandardized coefficients	t	p	95% CI	
		B	SE	Beta			B	SE
1	(Constant)	-0.935	0.359		-2.606	0.013	-1.659	-0.212
	THI total	0.045	0.008	0.666	5.862	<0.001	0.030	0.061
2	(Constant)	-1.125	0.361		-3.117	0.003	-1.853	-0.397
	THI total	0.035	0.009	0.524	3.963	<0.001	0.017	0.053
	ASI	0.028	0.014	0.258	1.955	0.057	-0.001	0.057
3	(Constant)	-0.732	0.623		-1.174	0.247	-1.990	0.527
	THI total	0.037	0.009	0.548	4.017	<0.001	0.018	0.056
	ASI	0.034	0.016	0.307	2.091	0.043	0.001	0.066
	SSAS	-0.022	0.028	-0.108	-0.775	0.443	-0.078	0.035

Model 1: R^2=0.44, F=34.37, p<0.001; Model 2: R^2=0.49, F=20.22, p<0.001; Model 3: R^2=0.50, F=13.55, p<0.001
THI: Tinnitus Handicap Inventory, ASI: Anxiety sensitivity index, SSAS: Somatosensory amplification scale, SE: Standard error, SBQ: Suicidal behaviors questionnaire, CI: Confidence interval

Table 6. The effectiveness of ASI and SSAS in explaining tinnitus symptoms

Model		Unstandardized coefficients		Unstandardized coefficients	t	p	95% CI	
		B	SE	Beta			B	SE
1	(Constant)	21.768	5.186		4.198	<0.001	11.311	32.226
	ASI	0.894	0.205	0.553	4.349	<0.001	0.479	1.308
2	(Constant)	8.030	10.352		0.776	0.442	-12.861	28.922
	ASI	0.676	0.247	0.418	2.733	0.009	0.177	1.176
	SSAS	0.693	0.454	0.234	1.526	0.135	-0.224	1.611

Model 1: R^2=0.31, F=18.91, p<0.001; Model 2: R^2=0.34, F=10.91, p<0.001
ASI: Anxiety sensitivity index, SSAS: Somatosensory amplification scale, SE: Standard error, CI: Confidence interval

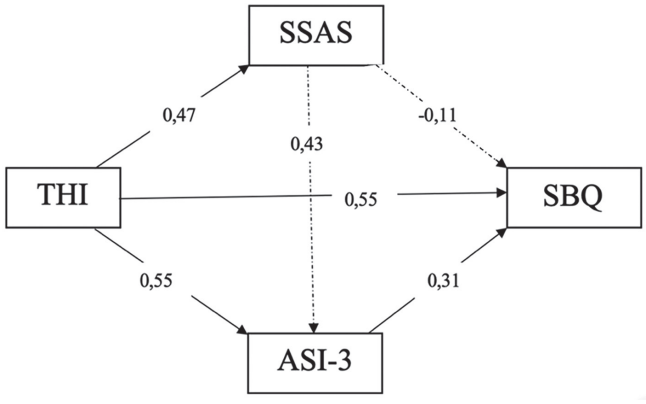

Figure 1. Mediation model demonstrating the indirect effects of ASI-3 and SSAS on the relationship between THI and suicidal behavior SBQ All coefficients are standardized (β). Solid lines represent significant paths (p<0.05), while the dashed line indicates a non-significant path
THI: Tinnitus Handicap Inventory, ASI-3: Anxiety sensitivity index-3, SSAS: Somatosensory Amplification scale, SBQ: Suicidal behaviors questionnaire

DISCUSSION

This study examined the relationships among tinnitus severity, anxiety sensitivity, somatosensory amplification, and suicidal behavior. No significant differences were observed between patients and controls in anxiety sensitivity, somatosensory amplification, or suicidal behavior scores. In the tinnitus group, however, tinnitus severity was positively correlated with anxiety sensitivity, somatosensory amplification, and suicidal behavior. Regression analyses showed that tinnitus severity significantly predicted suicidal behavior, with anxiety sensitivity partially mediating this relationship, while somatosensory amplification did not have a significant effect. These findings suggest that anxiety sensitivity plays a more prominent role than somatic amplification in the psychological distress and suicidal tendencies associated with tinnitus.

Previous studies with comparable sample sizes to ours similarly found no significant differences in anxiety and depression levels between tinnitus patients and healthy controls (7,20). In contrast, a recent population-based cohort study reported significantly higher rates of anxiety, depression, and somatic symptom disorders among individuals with tinnitus compared to those without, highlighting the considerable psychological burden associated with the condition (21). The discrepancy between these results and ours may be partly explained by methodological differences, particularly our smaller sample size and the inability to categorize participants according to tinnitus severity or disease duration. However, tinnitus represents a heterogeneous condition, a recent population-based cohort study reported that only a minority of individuals with tinnitus experienced tinnitus-related distress, emphasizing that the psychological impact of tinnitus is more closely associated with its perceived severity than with its mere presence (22). Moreover, several studies have demonstrated a significant positive association between self-reported tinnitus severity and stress levels, and patients with severe tinnitus, especially those presenting with comorbid anxiety or depression, are considered to be at elevated risk for suicidal ideation and behavior (21,23).

Studies have found a significant association between tinnitus severity and suicidal ideation; a recent meta-analysis has provided robust evidence supporting this association. The analysis demonstrated that individuals with tinnitus had nearly double the risk of suicidal ideation and suicide attempts compared to those without tinnitus, with a clear dose-response relationship indicating that higher tinnitus severity was associated with greater suicidality (23). However, a large-scale study of veterans showed that suicide rates were lower among veterans with tinnitus than among those without, possibly reflecting better coping mechanisms or increased healthcare engagement among individuals who seek treatment for tinnitus, which may confer some protection against suicidality (10). Although our study found no significant difference in SBQ scores between the tinnitus and control groups, suicidal thoughts were positively correlated with tinnitus severity, suggesting that the relationship between tinnitus and suicidality may differ across clinical subgroups and symptom profiles.

Study Limitations

The findings of our study should be interpreted in light of its limitations. It was a cross-sectional study with a small sample size. Therefore, causality cannot be established, and the small sample size reduces the power of the study. Additionally, other psychological factors, especially depression, known to be related to tinnitus, were not examined in this study. Future studies should include larger samples, classify participants by tinnitus severity, and examine a wider range of psychological factors to better elucidate the relationship between tinnitus and psychiatric symptoms.

CONCLUSION

In conclusion, although patients with tinnitus did not differ from healthy controls in anxiety sensitivity, somatosensory amplification, or suicidal behavior, greater tinnitus severity was associated with higher suicidal behavior scores. Anxiety sensitivity appeared to play a relevant role in this association and partially mediated the relationship between tinnitus severity and suicidal behavior, whereas somatosensory amplification showed no significant mediating effect. These findings highlight the importance of considering anxiety sensitivity and suicidality in the clinical assessment of patients with more severe tinnitus. Further longitudinal studies with larger samples are needed to clarify the direction and mechanisms of these associations.

ETHICS

Ethics Committee Approval: The study received ethical approval from the Recep Tayyip Erdoğan University Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (approval no: 2019/202, date: 12.12.2019).

Informed Consent: Written informed consent was obtained from all participants prior to enrollment.

FOOTNOTES

Authorship Contributions

Concept: G.V.Ç., A.E.K., E.D., Ç.H., Z.Ö.C., Design: G.V.Ç., A.E.K., E.D., Ç.H., Z.Ö.C., Data Collection or Processing: G.V.Ç., A.E.K., Analysis or Interpretation: G.V.Ç., A.E.K., Ç.H., Z.Ö.C., Literature Search: G.V.Ç., A.E.K., Ç.H., Writing: G.V.Ç., A.E.K., Ç.H., Z.Ö.C.

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Research

Prevalence and Associated Factors of Dyspepsia in Primary Care: A Descriptive Evaluation of Prescribing Patterns

Birinci Basamakta Dispepsinin Prevalansı ve İlişkili Faktörler: Reçeteleme Örüntülerinin Tanımlayıcı Değerlendirmesi

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ABSTRACT

Objective: This study aimed to determine the prevalence of dyspepsia, to identify associated factors, and to descriptively evaluate prescribing patterns for dyspepsia in a primary care setting.

Methods: This single-center, cross-sectional study included individuals aged 15-70 years registered at a family health center (n=4,453). The sample size was calculated assuming a dyspepsia prevalence of 20%, a 95% confidence level, and a 5% margin of error, yielding a minimum of 233 participants. Participants were selected using a population-based, age-stratified sampling approach. Dyspepsia was defined according to the Rome IV criteria. Data were collected through face-to-face interviews using a structured questionnaire assessing sociodemographic characteristics, lifestyle factors, anthropometric measurements, and anxiety levels using the Beck Anxiety Inventory. Prescription data were retrospectively obtained from electronic prescription records. Statistical analyses included chi-square tests, the Mantel-Haenszel test, and multivariate logistic regression analysis. A p-value <0.05 was considered statistically significant.

Results: The prevalence of dyspepsia was 19.3% [n=45; 95% confidence interval (CI): 14.2-24.4]. Prevalence increased significantly with age (p=0.003) and was higher in females than in males (25.2% vs. 8.5%, p=0.002). In multivariate analysis, increasing age [adjusted odds ratio (OR): 1.06 per year; 95% CI: 1.02-1.10; p=0.001] and a high anxiety level (adjusted OR: 14.30; 95% CI: 5.93-34.45; p<0.001) remained independently associated with dyspepsia. Prescription analysis showed that 20.5% of primary care prescriptions included a dyspepsia diagnosis, with proton pump inhibitors accounting for 82% of dyspepsia-related prescriptions.

Conclusion: Dyspepsia is common in primary care, with age and anxiety emerging as key independent factors. Identification of modifiable risk factors and rational prescribing practices may improve dyspepsia management.

Keywords: Primary care, dyspepsia, prevalence, anxiety, prescribing patterns

ÖZ

Amaç: Bu çalışmada, birinci basamak sağlık hizmeti ortamında dispepsi prevalansının belirlenmesi, dispepsi ile ilişkili faktörlerin saptanması ve dispepsiye yönelik reçeteleme örüntülerinin tanımlayıcı olarak değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu tek merkezli, kesitsel çalışma, bir aile sağlığı merkezine kayıtlı 15-70 yaş arası bireyler arasında yürütülmüştür (n=4.453). Örneklem büyüklüğü, dispepsi prevalansı %20, %95 güven düzeyi ve %5 hata payı varsayılarak hesaplanmış ve en az 233 katılımcı olarak belirlenmiştir. Katılımcılar, toplum temelli yaşa göre tabakalandırılmış örnekleme yöntemiyle seçilmiştir. Dispepsi Roma IV kriterlerine göre tanımlanmıştır. Veriler, sosyodemografik özellikler, yaşam tarzı faktörleri, antropometrik ölçümler ve Beck Anksiyete Envanteri ile değerlendirilen anksiyete düzeylerini içeren yapılandırılmış bir anket aracılığıyla yüz yüze görüşmelerle toplanmıştır. Reçete verileri, gerçek yaşam reçeteleme örüntülerini tanımlamak amacıyla elektronik reçete kayıtlarından geriye dönük olarak elde edilmiştir. İstatistiksel analizlerde ki-kare testi, doğrusal ilişki için Mantel-Haenszel testi ve çok değişkenli lojistik regresyon analizi kullanılmış, p<0,05 değeri istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular: Dispepsi prevalansı %19,3 olarak saptanmıştır [n=45; %95 güven aralığı (GA): 14,2-24,4]. Prevalans yaşla birlikte anlamlı olarak artmış (p=0,003) ve kadınlarda erkeklere göre daha yüksek bulunmuştur (%25,2'ye karşı %8,5; p=0,002). Çok değişkenli analizde, artan yaş [düzeltilmiş olasılık oranı (OR): 1,06/yıl; %95 GA: 1,02-1,10; p=0,001] ve yüksek anksiyete düzeyi (düzeltilmiş OR: 14,30; %95 GA: 5,93-34,45; p<0,001) dispepsi ile

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ÖZ

bağımsız olarak ilişkili bulunmuştur. Reçete analizinde, birinci basamakta yazılan reçetelerin %20,5'inde dispepsi tanısının yer aldığı ve dispepsiye yönelik reçetelerin %82'sinin proton pompa inhibitörlerinden oluştuğu saptanmıştır.

Sonuç: Dispepsi, birinci basamakta sık görülen bir durumdur ve yaş ile anksiyete düzeyi başlıca bağımsız belirleyiciler olarak öne çıkmaktadır. Değiştirilebilir risk faktörlerinin belirlenmesi ve rasyonel reçeteleme uygulamaları, dispepsi yönetiminin iyileştirilmesine katkı sağlayabilir.

Anahtar Kelimeler: Birinci basamak, dispepsi, prevalans, anksiyete, reçeteleme örüntüleri

INTRODUCTION

Dyspepsia is a common gastrointestinal disorder characterized by upper abdominal symptoms, including postprandial fullness, early satiety, epigastric pain, and epigastric burning (1,2). Due to its frequent occurrence and chronic nature, dyspepsia represents a common clinical problem in primary care, where most patients initially seek medical care (1,3). Although dyspepsia is not a life-threatening condition, it is associated with impaired quality of life and increased healthcare utilization (3-5).

Dyspepsia is broadly classified into organic and functional subtypes. Organic dyspepsia refers to cases in which a structural, metabolic, or systemic cause explaining the symptoms is identified through diagnostic evaluation (6). In contrast, functional dyspepsia (FD) is defined by the absence of an identifiable organic pathology (1). The Rome IV criteria provide a symptom-based diagnostic framework that is commonly used in clinical practice and epidemiological studies (4,7). According to these criteria, FD is diagnosed when one or more dyspeptic symptoms persist for at least three months, with symptom onset at least six months before diagnosis, in the absence of an underlying organic disease (4,8).

Epidemiological studies suggest that approximately 80-85% of individuals presenting with dyspeptic symptoms are classified as having FD (1,6). Reported prevalence rates of dyspepsia vary across studies depending on diagnostic criteria, geographic region, and study design (3,4,7). Systematic reviews and meta-analyses based on the Rome criteria have reported a global prevalence of FD of approximately 20% (3,4). Female sex, advancing age, and lower socioeconomic status have consistently been identified as factors associated with dyspepsia (1,4,9).

Recent global data based on Rome criteria indicate marked regional variation in dyspepsia prevalence, while contemporary primary care-based epidemiological data from Türkiye remain limited (4,10). In Türkiye, available studies are relatively scarce, and many rely on earlier diagnostic criteria or focus on secondary or tertiary care populations, limiting their generalizability to current primary care practice (10,11). Primary care physicians play a central role in the evaluation and management of dyspepsia, as a substantial proportion of individuals with dyspeptic symptoms first present to primary care facilities (12,13).

In addition to identifying demographic and lifestyle-related risk factors, evaluating prescribing patterns in primary care is important for understanding real-world management approaches and potential areas for improvement (14-16). However, real-world data that comprehensively address dyspepsia prevalence, associated factors, and prescribing patterns within primary care settings remain limited (14).

Therefore, the present study aimed to determine the prevalence of dyspepsia among individuals aged 15-70 years registered at a family health center, to identify factors independently associated with dyspepsia, and to evaluate the distribution of pharmacological drug groups prescribed for dyspepsia in a primary care setting.

METHODS

Study Design and Population

This single-center, cross-sectional study was conducted at a family health center among individuals aged 15-70 years. At the time of the study, a total of 4,453 individuals within this age range were registered at the family health center. The primary outcome of the study was the presence of dyspepsia. Independent variables included age, sex, body mass index (BMI), educational level, socioeconomic status, presence of chronic diseases, anxiety level, smoking status, coffee and alcohol consumption, and eating speed.

The sample size was calculated using a single-proportion formula to estimate the prevalence of dyspepsia, assuming a prevalence of 20%, a 95% confidence interval (CI), and a 5% margin of error, resulting in a minimum required sample size of 233 participants. Participants were selected using a population-based, age-stratified sampling method among individuals attending the family health center during the study period.

Data Collection Tools and Procedure

Data collection was carried out between July 1, 2020, and December 31, 2020. Individuals aged 15-70 years who visited the family health center for any reason and agreed to

participate were included in the study. All participants were informed about the purpose and procedures of the study. Written informed consent was obtained from participants aged 18 years and older, and from the parents or legal guardians of participants aged 15-17 years.

Data were collected through face-to-face interviews using a structured questionnaire based on the Rome IV diagnostic criteria for dyspepsia. The questionnaire included sections on sociodemographic characteristics, lifestyle habits, and anthropometric measurements. Anxiety levels were assessed using the 21-item Beck Anxiety Inventory (BAI), a widely used and internationally validated instrument. A score of ≥16 was used to define high anxiety level, in accordance with established severity classifications (17).

Individuals younger than 15 years or older than 70 years, those who were unable to respond to the questionnaire due to illness, and individuals reporting symptoms consistent with irritable bowel syndrome were excluded from the study. Participant recruitment was terminated once the target sample size of 233 individuals was reached.

Prescription Data

Prescription data related to the pharmacological treatment of dyspepsia in primary care were obtained retrospectively from the electronic prescription records of the same family health center. Prescriptions issued between December 1, 2020, and January 1, 2021, were reviewed using the electronic family medicine information system of the study center. This one-month period was selected to provide a pragmatic snapshot of real-world prescribing practices in a primary care setting. Prescription analysis was conducted in a separate patient population within the same primary care setting.

Ethical Considerations

This study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki. Ethical approval was obtained from the University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval no: 2020-124, date: 24.06.2020).

Statistical Analysis

Statistical analyses were performed using SPSS version 15.0. Categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using the chi-square test. Linear associations and trends across ordered categorical variables were assessed using the Mantel-Haenszel test.

Multivariate logistic regression analysis was performed to identify factors independently associated with dyspepsia. Variables included in the model were selected based on clinical relevance and previous literature, and included age, sex, obesity (BMI ≥30), socioeconomic status, and anxiety level (BAI score ≥16). Results were reported as odds ratios (ORs) with 95% CIs. A p-value <0.05 was considered statistically significant.

RESULTS

Participant Characteristics and Dyspepsia Prevalence

A total of 233 individuals were included in the study; 64.8% were female (n=151) and 35.2% were male (n=82). The mean age of the participants was 36.7±14.2 years.

According to the Rome IV criteria, dyspepsia prevalence in the study population was 19.3% (n=45; 95% CI: 14.2-24.4) (Table 1).

Univariate Analysis

The prevalence of dyspepsia increased significantly across age groups, rising from 8.6% in the 15-20-year age group to 43.8% among individuals aged 61-70 years (p=0.003). Dyspepsia was more common in females than in males (25.2% vs. 8.5%, p=0.002) (Table 1).

In univariate analyses, dyspepsia prevalence increased as educational level decreased (p<0.001). Low socioeconomic status was also associated with a higher prevalence of dyspepsia (p=0.001). Dyspepsia prevalence was significantly higher among individuals not engaged in income-generating employment (p<0.001) (Table 1).

Dyspepsia prevalence increased with higher BMI and reached 67.6% among individuals with obesity (BMI ≥30) (p<0.001). Participants with chronic diseases had a significantly higher prevalence of dyspepsia compared with those without chronic conditions (p<0.001) (Table 1).

Regarding lifestyle factors, dyspepsia prevalence increased with higher coffee and tea consumption (both p<0.001). Although overall smoking status was not significantly associated with dyspepsia (p=0.126), a significant positive association was observed between the number of cigarettes smoked per day and dyspepsia prevalence (p=0.002). Eating speed was strongly associated with dyspepsia, with the highest prevalence observed among individuals who reported eating quickly (44.1%, p<0.001). Alcohol consumption was not significantly associated with dyspepsia (p=1.000) (Table 1).

Participants with high anxiety levels (BAI score ≥16) had a markedly higher prevalence of dyspepsia compared with those with lower anxiety scores (54.5% vs. 8.4%, p<0.001) (Table 1).

Table 1. Distribution of sociodemographic, clinical, and lifestyle variables according to dyspepsia status

		Dyspepsia				
		Present		Absent		
		n	%	n	%	p#
Age group	15-20	3	8.6	32	91.4	0.003
	21-30	5	9.6	47	90.4	
	31-40	8	14.5	47	85.5	
	41-50	12	26.7	33	73.3	
	51-60	10	33.3	20	66.7	
	61-70	7	43.8	9	56.3	
Gender	Male	7	8.5	75	91.5	0.002
	Female	38	25.2	113	74.8	
Participants by BMI	Underweight	3	18.8	13	81.3	<0.001
	Normal	6	7.3	76	92.7	
	Overweight	11	11.2	87	88.8	
	Obese	25	67.6	12	32.4	
BMI (≥30 vs. <30)*	Less than 30	20	12.3	142	87.7	<0.001
	30 and older	25	35.2	46	64.8	
Marital status	Never married	8	12.9	54	87.1	0.275
	Married/partner	36	21.7	130	78.3	
	Widowed or divorced	1	20.0	4	80.0	
Education level	No formal education	11	50.0	11	50.0	<0.001
	Primary education graduate	28	27.7	73	72.3	
	High school graduate	4	4.9	77	95.1	
	University, college, doctorate	2	6.9	27	93.1	
Employment status in an income generating job	Employee	11	9.2	108	90.8	<0.001
	Not working	31	38.3	50	61.7	
	Student	3	9.1	30	90.9	
Chronic disease	There is	40	45.5	48	54.5	<0.001
	No	5	3.4	140	96.6	
Socio economic status	Low	33	28.9	81	71.1	0.001
	Middle	11	10.3	96	89.7	
	High	1	8.3	11	91.7	
Smoking	Smokes cigarettes	13	27.1	35	72.9	0.126
	Does not smoke or quit smoking	32	17.3	153	82.7	
Coffee and dyspepsia	Occasional coffee consumption	18	10.7	150	89.3	<0.001
	Drinks coffee daily	21	80.8	5	19.2	
	Doesn't drink coffee	6	15.4	33	84.6	
Tea and dyspepsia	Does not consume tea	0	0.0	11	100	0.001
	Sometimes consumes tea	2	3.8	51	96.2	
	Consumes tea regularly	43	25.4	126	74.6	
Alcohol and dyspepsia	Drinking alcohol	1	14.3	6	85.7	1.000
	Does not drink alcohol	44	19.5	182	80.5	
Eating speed and dyspepsia	Eating quickly	15	48.4	16	51.6	<0.001
	Eating at normal speed	26	19.0	111	81.0	
	Slow eater	4	6.3	59	93.7	
Anxiety level and dyspepsia	Anxiety level normal and below	15	8.4	163	91.6	<0.001
	Anxiety level above normal	30	54.5	25	45.5	

*Body mass index was analyzed both as a categorical variable and as a dichotomous variable (BMI ≥30 vs. <30) for univariate analysis, #: Chi-square test, BMI: Body mass index

Multivariate Analysis

In multivariate logistic regression analysis, increasing age (OR: 1.06 per year; 95% CI: 1.02-1.10; p=0.001) and high anxiety level (OR: 14.30; 95% CI: 5.93-34.45; p<0.001) remained independently associated with dyspepsia after adjustment for potential confounders. Female sex, obesity, and low socioeconomic status were not independently associated with dyspepsia in the adjusted model (Table 2).

Symptom Distribution

Among individuals diagnosed with dyspepsia, postprandial fullness was the most frequently reported symptom (51.1%), followed by postprandial fullness combined with early satiety (31.1%). Other symptom combinations were observed less frequently (Table 3).

Prescription Analysis

During the one-month prescription review period, 487 prescriptions and 2,578 medication boxes were issued. Dyspepsia-related medications accounted for 13.0% of all prescribed medication boxes, and 20.5% of prescriptions included a diagnosis of dyspepsia. Among these prescriptions, 82% contained proton pump inhibitors.

DISCUSSION

Dyspepsia is a common gastrointestinal disorder worldwide, with reported prevalence rates ranging from 10% to 40% in Western European countries and from 5% to 30% in Asian populations. The global pooled prevalence has been estimated at approximately 21.8%, while substantial regional variation has been emphasized in recent Rome-based systematic reviews and meta-analyses (3,4). These differences are mainly related to variations in diagnostic criteria, study populations, and healthcare settings (1,4,8).

In a comprehensive review by Ford et al. (1), the prevalence of uninvestigated dyspepsia varied substantially across regions, with the lowest prevalence reported in Central America (7%) and the highest in South America (37.7%). The authors highlighted that heterogeneity in diagnostic definitions, particularly the use of different Rome criteria, contributed significantly to these differences. In Türkiye, epidemiological data on dyspepsia remain limited. Özmen's (11) study conducted in Bolu using Rome III criteria reported a dyspepsia prevalence of 18.6% among individuals aged 20-70 years. Using Rome IV criteria and a population-based, age-stratified sampling approach, our study identified a dyspepsia prevalence of 19.3%, which is comparable to both national and international findings (4,7,11).

Increasing age has been frequently reported as a factor associated with dyspepsia. Previous studies have demonstrated peak prevalence rates in individuals aged 45-54 years in Canada, 41-50 years in China, and 50-59 years in Japan (18). Similarly, studies from Saudi Arabia and multinational cohorts from low- and middle-income countries have reported higher dyspepsia prevalence with advancing age (9,19). In the present study, dyspepsia prevalence increased with advancing age, and age remained independently associated with dyspepsia in multivariate analysis.

Table 2. Factors independently associated with dyspepsia according to multivariate logistic regression analysis

Variable	OR	95% CI	p-value
Age (per year)	1.06	1.02-1.10	0.001
Female sex	2.01	0.74-5.47	0.170
Obesity (BMI≥30)	1.49	0.60-3.66	0.388
High anxiety level	14.30	5.93-34.45	<0.001
Low socioeconomic status	2.38	0.99-5.74	0.053

BMI: Body mass index, OR: Odds ratio, CI: Confidence interval

Table 3. Distribution of dyspeptic symptoms according to Rome IV criteria*

Symptom pattern	n	%
Postprandial fullness	23	51.1
Postprandial fullness+early satiety	14	31.1
Postprandial fullness+epigastric pain	3	6.7
All three symptoms	3	6.7
Epigastric pain only	1	2.2
Epigastric pain+early satiety	1	2.2

*Symptoms were assessed using a Rome IV-based structured questionnaire. Percentages may not total 100% due to rounding

Sex-related differences in dyspepsia prevalence have also been described in the literature. A large meta-analysis reported higher dyspepsia prevalence in females compared to males (1). Additionally, a large multinational study involving more than 250,000 participants found that women were more likely to experience FD than men (9). In this study, dyspepsia prevalence was higher among women. However, sex did not remain independently associated with dyspepsia after adjustment in multivariate analysis.

Similar findings have been reported in previous studies, and no significant association was observed between dyspepsia and marital status in our study (9,19,20). In contrast, BMI showed a clear association with dyspepsia prevalence. Several studies have reported higher rates of dyspepsia and other functional gastrointestinal disorders among individuals with obesity (10,21-24). Similarly, in our study, dyspepsia prevalence increased with higher BMI and was highest among obese participants. The relatively small number of obese participants should be considered when interpreting these findings.

Lower educational attainment has been reported to be associated with higher dyspepsia prevalence in population-based studies. In univariate analyses, our findings demonstrated an increase in dyspepsia prevalence as educational level decreased. Likewise, lower socioeconomic status has been associated with increased dyspepsia prevalence in international studies (4,9,25), and a similar pattern was observed in our study.

Lifestyle-related factors have also been examined in relation to dyspepsia. Smoking has been identified as a potential risk factor, particularly in relation to postprandial distress syndrome (26). While smoking status itself was not significantly associated with dyspepsia in our study, dyspepsia prevalence increased with the number of cigarettes smoked per day. In addition, faster eating speed and higher coffee and tea consumption were associated with increased dyspepsia prevalence, consistent with previous reports (27,28).

Psychological factors have been consistently associated with FD in previous studies. A recent meta-analysis reported a strong association between gastrointestinal symptoms and anxiety (29,30). In our study, dyspepsia prevalence was markedly higher among individuals with elevated anxiety scores, and high anxiety level remained independently associated with dyspepsia in multivariate analysis.

The frequent use of proton pump inhibitors is consistent with evidence supporting their efficacy in FD (15,16).

Similar concerns regarding proton pump inhibitor prescribing in primary care have been reported in studies from the United Kingdom, particularly England (14).

While proton pump inhibitors are widely recommended for dyspepsia management in international guidelines (12,16), these findings underscore the need for evaluating prescribing practices in primary care settings (13). In this context, the coexistence of prevalence findings and prescription data may provide a more comprehensive perspective on the burden and management of dyspepsia in primary care.

The findings of this study are generally consistent with previously reported national and international data and demonstrate that dyspepsia is associated with multiple demographic, clinical, and lifestyle-related factors in a primary care population. These findings should be interpreted in light of the cross-sectional design of the study and the reliance on self-reported data.

Study Limitations

This study has several limitations. First, it was conducted in a single primary care center, which may limit the generalizability of the findings to other regions. Second, the cross-sectional design precludes causal inferences between dyspepsia and associated factors. Third, dyspeptic symptoms and lifestyle characteristics were assessed using self-reported data, which may be subject to recall bias. In addition, prescription data were obtained from a different patient population within the same primary care setting, which may limit the direct interpretation of prescription patterns in relation to prevalence findings. Furthermore, the relatively short prescription review period reflects a pragmatic snapshot of routine primary care practice rather than longitudinal prescribing trends. Despite these limitations, the use of Rome IV diagnostic criteria and the integration of epidemiological, psychosocial, and prescribing data provide valuable real-world insights into dyspepsia in a primary care context.

CONCLUSION

In this primary care-based study, the prevalence of dyspepsia among individuals aged 15-70 years was 19.3%. Advancing age and high anxiety level were identified as independent factors associated with dyspepsia, while several sociodemographic and lifestyle-related variables showed associations in univariate analyses. These findings support the multifactorial nature of dyspepsia and indicate the need to consider both clinical and psychosocial factors in patient evaluation in primary care settings.

Dyspepsia is a common and clinically relevant condition that negatively affects quality of life and is frequently encountered in primary care practice. As first-contact and continuing care providers, primary care physicians are well positioned to identify individuals at risk for dyspepsia and to support individualized, evidence-based management strategies.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval no: 2020-124, date: 24.06.2020).

Informed Consent: Written informed consent was obtained from participants aged 18 years and older and from the parents or legal guardians of participants aged 15-17 years.

FOOTNOTES

Authorship Contributions

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

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Research

Platelet Count Abnormalities and Mortality in Pediatric Sepsis: The Dual Role of Thrombocytopenia and Thrombocytosis

Pediatrik Sepsiste Trombosit Sayısı Anormallikleri ve Mortalite: Trombositopeni ve Trombositozun Çift Yönlü Rolü

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ABSTRACT

Objective: Platelet abnormalities are frequent in pediatric sepsis and have been associated with disease severity. However, the prognostic significance of thrombocytopenia and thrombocytosis in children remains unclear. This study aimed to evaluate the relationship between platelet count patterns and in-hospital mortality in pediatric sepsis.

Methods: We retrospectively analyzed children who were admitted to a tertiary pediatric intensive care unit with sepsis. Patients were categorized into thrombocytopenia (<150,000/mm^3), normal (150,000-450,000/mm^3), and thrombocytosis (>450,000/mm^3) groups based on admission platelet counts. Demographic, clinical, and laboratory parameters were collected. Logistic regression was used to identify independent predictors of mortality.

Results: A total of 162 patients were included and overall mortality was 16.2%. Thrombocytopenia was common and associated with illness severity; however, it did not independently predict mortality after adjusting for confounders. Thrombocytosis, although infrequent, was associated with mortality; however, this finding was limited by small numbers of cases. Lactate was the only consistent independent predictor of mortality.

Conclusion: In pediatric sepsis, thrombocytopenia appears to reflect the overall severity of illness rather than serve as an independent determinant of mortality, whereas thrombocytosis may indicate a distinct hyperinflammatory response phenotype. A single platelet count at admission is insufficient for prognostic assessment and should be interpreted in conjunction with metabolic and organ dysfunction indicators. Lactate remained the most reliable predictor of mortality in our cohort.

Keywords: Mortality, pediatric sepsis, platelet count, thrombocytopenia, thrombocytosis

ÖZ

Amaç: Pediatrik sepsiste trombosit anormallikleri sık görülmekte ve hastalık şiddeti ile ilişkili bildirilmektedir. Ancak trombositopeni ve trombositozun prognostik değeri çocuklarda tam olarak netleşmemiştir. Bu çalışmanın amacı, pediatrik sepsiste trombosit sayısı paternleri ile hastane içi mortalite arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif çalışmada, üçüncü basamak bir çocuk yoğun bakım ünitesine sepsis nedeniyle kabul edilen hastalar değerlendirildi. Hastalar başvuru trombosit sayılarına göre trombositopeni (<150.000/mm^3), normal (150.000-450.000/mm^3) ve trombositoz (>450.000/mm^3) olmak üzere üç gruba ayrıldı. Demografik, klinik ve laboratuvar verileri toplandı. Mortaliteyi bağımsız olarak öngören değişkenleri belirlemek için lojistik regresyon analizi kullanıldı.

Bulgular: Toplam 162 hasta çalışmaya dahil edildi ve genel mortalite oranı %16,2 idi. Trombositopeni sık görülmekteydi ve hastalık şiddeti ile ilişkiliydi; ancak düzeltme sonrası mortaliteyi bağımsız olarak öngörmedi. Trombositoz nadir görülmekle birlikte mortalite ile ilişki gösterdi, ancak olgu sayısının azlığı bu bulguyu sınırladı. Laktat, mortalitenin tek tutarlı bağımsız belirleyicisi idi.

Sonuç: Pediatrik sepsiste trombositopeni, mortalitenin bağımsız bir belirleyicisi olmaktan ziyade hastalık şiddetini yansıtmaktadır; trombositoz ise farklı bir hiperenflamatuvar yanıt fenotipini gösterebilir. Başvuru anındaki tek bir trombosit değeri prognoz için yeterli değildir ve metabolik/organ fonksiyon belirteçleri ile birlikte değerlendirilmelidir. Çalışmamızda laktat, mortalitenin en güvenilir öngördürücüsü olmuştur.

Anahtar Kelimeler: Mortalite, pediatrik sepsis, trombosit sayısı, trombositopeni, trombositoz

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INTRODUCTION

Sepsis is a life-threatening syndrome characterized by organ dysfunction resulting from an uncontrolled host inflammatory response to systemic infection. It poses a significant global health burden, particularly among children, with an estimated 25 million cases worldwide and over 3 million deaths annually (1,2). Early recognition and intervention are crucial for reducing mortality in patients with sepsis.

Platelets play a complex role in sepsis pathophysiology through their interactions with endothelial and immune cells, significantly influencing the clinical course and outcome. Thrombocytopenia, which is frequently observed in patients with sepsis, can result from increased platelet consumption, sequestration, or decreased production due to bone marrow suppression. Conversely, thrombocytosis may develop as part of the acute phase response, with platelets acting as inflammatory mediators (3).

Although severe thrombocytopenia has been independently associated with disease severity and mortality in adult intensive care patients, pediatric studies are limited and present conflicting results (4-7). Moreover, the prognostic value of thrombocytosis in sepsis has not been studied extensively.

This retrospective observational study aimed to evaluate the prognostic effect of platelet abnormalities (thrombocytopenia and thrombocytosis) on in-hospital mortality in pediatric patients admitted with sepsis. By examining the relationship between platelet counts (PCs) and clinical outcomes, this study seeks to contribute to the understanding platelet dynamics in pediatric sepsis and to potentially inform clinical decision-making and risk stratification strategies.

Methods

Study Design and Patient Selection

This study is a single-center, retrospective cohort study conducted using the retrospective file data of patients hospitalized in the 3rd-level pediatric intensive care unit (PICU) of University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital between 2022 and 2024. The study was performed in compliance with the Declaration of Helsinki. The study methodology was approved by University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Clinical Research Ethics Committee (approval no: 283, date: 27.08.2025), and all anonymized data linked to the study are accessible upon reasonable request.

A total of 162 pediatric patients, aged between 1 month and 18 years, who were followed up with a diagnosis of sepsis and had complete laboratory data from the first 24 hours of intensive care admission, were included in the study. Patients were excluded from the study if they had received a platelet transfusion prior to PICU admission, had a known platelet disorder (such as immunodeficiency syndromes associated with thrombocytopenia, e.g., Wiskott-Aldrich syndrome), or had been diagnosed with a hematological malignancy. Individuals with comorbid conditions or those who underwent interventions known to directly affect platelet levels (e.g., heparin therapy that can cause heparin-induced thrombocytopenia) were also excluded. Furthermore, patients with missing clinical or laboratory data were not included in the analysis. Data were collected on requirements for extracorporeal therapy and inotropic support, presence of acute kidney injury, laboratory parameters, and mortality. Blood samples were obtained from all patients upon admission, and the most severe values were recorded within the first 24 hours.

On the day of admission, the following were measured: complete blood count (including leukocyte and neutrophil counts), PC, mean platelet volume (MPV), red cell distribution width (RDW), lactate dehydrogenase, C-reactive protein, procalcitonin, albumin, and lactate levels.

To determine the Pediatric Risk of Mortality III (PRISM III) score, data on 16 variables were collected within the first 24 hours after admission to the intensive care unit. These variables included: body temperature, systolic blood pressure, heart rate, serum creatinine, blood urea nitrogen, serum potassium, blood glucose, partial arterial oxygen pressure, partial arterial carbon dioxide pressure, Glasgow Coma Scale, pupil reaction, prothrombin time, activated partial thromboplastin time, serum bicarbonate levels, and white blood cell count and PC.

Sepsis was diagnosed based on the presence of life-threatening organ dysfunction accompanying infection and, in accordance with the 2020 Surviving Sepsis Campaign International Guidelines. Organ dysfunction was evaluated based on cardiovascular (hypotension, need for vasopressors), respiratory, renal, neurological, or coagulation disorders (8).

Patients were divided into three groups according to their PC: thrombocytopenia (<150,000/mm^3), normal platelet levels (150,000-450,000/mm^3), and thrombocytosis (>450,000/mm^3).

Thrombocytopenia was defined as a PC <150×10⁹/L, consistent with the commonly used definition in the pediatric sepsis literature (4). In addition to absolute PC at admission, dynamic changes in platelet levels were also evaluated. Patients who did not have thrombocytopenia at admission but experienced a decrease of more than 50% in PC within the first 24 hours of PICU admission were identified and analyzed separately. Furthermore, the development of new-onset thrombocytopenia at any time during the PICU stay was recorded.

The primary outcome measure was in-hospital mortality, and the secondary outcome measures were the need for invasive mechanical ventilation (IMV), inotropic treatment, therapeutic plasma exchange (TPE), and continuous renal replacement therapy (CRRT).

The laboratory data were processed in the central laboratory of our hospital according to routine clinical protocols and blood samples were collected in EDTA tubes and analyzed using automated hematology analyzers.

Statistical Analysis

Statistical analyses were performed using the SPSS Statistics software. The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test; non-normally distributed data are presented as median (minimum-maximum). The Mann-Whitney U test was used for comparisons of continuous variables between groups to compare continuous variables between groups, and the chi-square test was used for categorical variables to compare categorical variables.

To identify independent risk factors for mortality, multivariable logistic regression analysis was conducted. The predictive performance of PC for mortality was evaluated using a receiver operating characteristic (ROC) curve, and the area under the ROC curve (AUC) was calculated. Statistical significance was set at $p<0.05$.

RESULTS

A total of 162 pediatric patients were included in this study. Of these patients, 90 (55.6%) were male and the median age was 21 months (1-208 months). The median length of hospital stay was 7 days (1-101 days), and the PRISM III score was 6 (0-40). The presence of PRISM III scores of zero reflects that patients were diagnosed with sepsis at an early stage, before the development of measurable physiological derangements included in the PRISM III scoring system.

IMV was required in 52.6% (n=82) of patients, and the median duration of IMV was 5 days (1-90). Inotropic agents were used in 41.4% (n=67) of patients; acute kidney injury (AKI) developed in 26.5% (n=43). TPE was required in 25.3% (n=41) of the patients, and CRRT was required in 21.7% (n=35). Mortality occurred in 27 patients (16.7%) (Table 1).

Patients were divided into two groups based on mortality status. Among patients who did not survive, PRISM III scores, need for inotropes, CRRT, AKI, need for mechanical ventilation, and need for TPE were higher ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, and $p=0.004$, respectively). In addition, the duration of IMV was significantly longer in patients who did not survive ($p=0.010$) (Table 2).

Thrombocytopenia and thrombocytosis were observed in 32% (n=52) and 18% (n=29) of patients diagnosed with sepsis, respectively. Thrombocytopenia was significantly more frequent in the non-survivors ($p=0.006$). Lactate levels were significantly higher in non-survivors ($p=0.014$). No significant relationships were found among the other laboratory parameters (Table 3).

Paired analysis demonstrated a significant decrease in PCs within the first 24 hours of PICU admission ($p<0.001$), whereas no significant temporal changes were observed in MPV or RDW values (Table 4).

Among patients who did not have thrombocytopenia at admission, a decrease in PC greater than 50% within the first 24 hours and the development of new-onset thrombocytopenia during the PICU stay were significantly more frequent among non-survivors.

In the multivariable logistic regression analysis, inotropic agent requirement [odds ratio (OR): 0.095, 95% confidence interval (CI): 0.022-0.414, $p=0.002$] and CRRT requirement (OR: 0.23, 95% CI: 0.057-0.927, $p=0.036$) were independently associated with mortality. After adjustment for disease severity and organ support therapies, the PRISM III score,

Table 1. Clinical features of patients

Total	**162**
Gender, male (n, %)	90 (55.6)
Age (months), median (min-max)	21 (1-208)
Length of hospital stay (day), median (min-max)	7 (1-101)
PRISM III score, median (range)	6 (0-40)
Mechanical ventilation requirement (n, %)	82 (52.6)
Duration of invasive mechanical ventilation (day), median (min-max)	5 (1-90)
Inotropic agent requirement (n, %)	67 (41.4)
Evidence of acute kidney injury	43 (26.5)
TPE requirement (n, %)	41 (25.3)
CRRT requirement (n, %)	35 (21.7)
Mortality (n, %)	27 (16.7)

CRRT: Continuous renal replacement therapy, PRISM III: Pediatric risk of mortality III score, TPE: Therapeutic plasma exchange

plasma exchange, and PC categories were not independently associated with mortality. Using thrombocytopenia as the reference category, neither normal platelet count nor thrombocytosis was independently significant in the multivariable model (Table 5).

At a cut-off value of 285,000/mm^3, the PC demonstrated a sensitivity of 88.9% and a specificity of 40.7% for predicting in-hospital mortality. The ROC analysis yielded an AUC of 0.667 (95% CI: 0.560-0.773). The positive predictive value and negative predictive value at this threshold were 23.1% and 94.8%, respectively (Table 6).

Table 2. Comparison of survivors and non-survivors with prognostic factors

		Mortality		p-value
		Yes (n=27)	No (n=135)	
PRISM III score, median (range)		13 (2-40)	5 (0-30)	<0.001
Length of hospital stay (day), median (range)		8 (1-90)	7 (1-101)	0.730
Duration of invasive mechanical ventilation (day), median (min-max)		7.5 (1-90)	4 (1-88)	0.010
Acute kidney injury, n (%)	Yes	17 (63.0)	26 (19.3)	<0.001
	No	10 (37.0)	119 (73.5)	
Inotropic agent requirement, n (%)	Yes	24 (88.9)	43 (31.9)	<0.001
	No	3 (11.1)	92 (68.1)	
TPE requirement, n (%)	Yes	13 (48.1)	28 (20.7)	0.004
	No	14 (51.9)	107 (79.3)	
CRRT requirement, n (%)	Yes	16 (61.5)	19 (14.1)	<0.001
	No	11 (38.5)	116 (85.9)	
Mechanical ventilation requirement, n (%)	Yes	27 (100)	55 (40.7)	<0.001
	No	0 (0)	80 (59.3)	

CRRT: Continuous renal replacement therapy, PRISM III: Pediatric risk of mortality III score, TPE: Therapeutic plasma exchange

Table 3. Comparison of survivors and non-survivors with laboratory parameters

		Mortality		p-value
		Yes (n=27)	No (n=135)	
Platelet (10^3/mL)		158 (8-533)	252 (6-680)	0.006
Platelet count categories	Thrombocytopenia	13 (48.1)	39 (28.9)	0.013
	Normal range	13 (48.1)	68 (50.4)	
	Thrombocytosis	1 (3.7)	28 (20.7)	
Leukocytes (10^3/mL)		9090 (20-32010)	11220 (50-86300)	0.080
Neutrophil (10^3/mL)		5090 (0-23160)	7895 (0-76700)	0.142
MPV(ƒL)		10.6 (7.5-13.6)	9.7 (6.7-13.5)	0.093
RDW (%)		14.9 (12.0-18.3)	14.4 (11.9-29.3)	0.635
LDH(U/L)		448 (180-4110)	363 (159-8460)	0.249
CRP, median (range) (mg/dL)		33.52 (0.60-313.60)	43.95 (0.60-443.98)	0.449
PCT (mg/L)		4.6 (0.4-334.2)	5.18 (0.1-593.5)	0.403
Lactate (mmol/L)		2.51 (1.0-16.0)	1.73 (1.0-17.0)	0.014
Albumin (mg/dl)		3.23 (2.6-4)	3.73 (2.0-5.0)	0.059
Δ$^{\varphi}$(0-24h)	Platelet (10^3/mL)	37000 (-129000 to 266000)	345000 (-177000 to 630000)	0.612
	MPV (ƒL)	0 (-1.10 to 2.20)	0 (-8.50 to 122.60)	0.533
	RDW (%)	0 (-2.40 to 2.20)	0 (-15.70 to 11.10)	0.675
Platelet count decrease >50% within 24 hours*, n (%)		6 (46.2)	20 (21.1)	0.047
Development of thrombocytopenia during PICU stay, n (%)		10 (76.9)	28 (29.5)	0.001

Δ$^{\varphi}$: Values represent the change between admission and 24 hours measurements in patients with available paired data. *Among patients without thrombocytopenia at admission
$^{\gamma}$RDW: Red cell distribution width, MPV: Mean platelet volume, LDH: Lactate dehydrogenase, PCT: Procalcitonin, CRP: C-reactive protein

DISCUSSION

Although numerous studies have investigated the relationship between PC and mortality in both adult and pediatric populations, accurately identifying high-risk patients remains a clinical challenge (8). A wide range of biomarkers and scoring systems has been proposed to aid in early risk stratification and improve outcomes; however, no single marker has demonstrated a definitive predictive value (9,10). Therefore, there is growing interest in cost-effective, widely accessible, and easy-to-interpret parameters that can be used not only in intensive care units but also in outpatient settings, emergency departments, and general wards. PC, due to its routine availability and low cost, remains a promising candidate for ongoing clinical evaluation.

The high incidence of thrombocytopenia observed in our cohort aligns with previous studies reporting increased platelet consumption, sequestration, and impaired production during systemic inflammation in sepsis (11,12). Although thrombocytopenia has been consistently associated with disease severity and mortality in both adult and pediatric sepsis (4,5,13), our adjusted analysis demonstrated that it did not independently predict mortality after accounting for confounders such as lactate level and organ dysfunction. This finding supports the concept that

Table 4. Changes in platelet count, MPV, and RDW within the first 24 hours of PICU admission

	n	Mean rank	Sum of ranks	z	p-value
Platelet					
Negative ranks	120	88.33	10599.50	-7.498	**<0.001**
Positive ranks	38	51.62	1961.50		
Ties	2				
Total	160				
MPV					
Negative ranks	77	73.93	5692.50	-0.344	0.731
Positive ranks	71	75.12	5333.50		
Ties	12				
Total	160				
RDW					
Negative ranks	76	66.73	5071.50	-0.587	0.557
Positive ranks	62	72.60	4519.50		
Ties	22				
Total	160				

RDW: Red cell distribution width, MPV: Mean platelet volume

Table 5. Multivariate logistic regression analysis of factors associated with in-hospital mortality

Independent variable		β	OR (95% CI)	p-value
Platelet counts	Normal range vs. thrombocytopenia	-1.535	0.215 (0.022-2.077)	0.184
	Thrombocytosis vs. thrombocytopenia	-1.592	0.203 (0.023-1.831)	0.155
PRISM score		-0.050	0.951 (0.880-1.027)	0.199
Inotropic agent requirement, n (%)		-2.350	0.095 (0.022-0.414)	0.002
TPE requirement, n (%)		1.155	3.173 (0.752-13.389)	0.116
CRRT requirement, n (%)		-1.471	0.230 (0.057-0.927)	0.036

Thrombocytopenia was used as the reference category for platelet count
OR: Odds ratio, CI: Confidence interval, PRISM: Pediatric Risk of Mortality, TPE: Therapeutic plasma exchange, CRRT: Continuous renal replacement therapy

Table 6. Predictive value of platelet count cut-off in sepsis-related mortality

	Cut-off point	Sensitivity (%)	Specificity (%)	AUC (95% CI)	PPV (%)	NPV (%)
Platelet (10^3/mL)	285000	88.9	40.7	0.667 (0.560-0.773)	23.1	94.8

AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

thrombocytopenia is more likely to reflect critical illness severity than to serve as a direct causal determinant of mortality.

Similarly, Zhang et al. (13) reported that PCs below 150×10^9/L were associated with increased 30-day mortality in pediatric septic shock patients. In contrast, Meliani et al. (6) found that non-survivors tended to have lower PCs; however, this difference was not statistically significant, and PC did not remain a significant factor in multivariable analysis, in which only RDW remained an independent predictor. These findings indicate that PC alone may not reliably predict mortality and should be interpreted within the broader clinical and laboratory context, rather than as a sole prognostic marker. Given these conflicting findings, some researchers have proposed that serial monitoring of PC may offer more valuable prognostic insights than baseline values alone (14). It has been suggested that a significant decrease in PC, particularly within the first four days of illness, may indicate disease progression in sepsis, and that persistent thrombocytopenia is more strongly associated with mortality (4,5,15). However, in our study, platelet measurements were limited to admission and early follow-up within the first 24 hours, which restricted our ability to assess longer-term platelet trajectories.

Importantly, our expanded analyses demonstrated that dynamic changes in PC were more strongly associated with mortality than admission values alone. A decrease in PC of greater than 50% within the first 24 hours and the development of new-onset thrombocytopenia during the PICU stay were both significantly more frequent among non-survivors. These findings support previous observations that early platelet decline reflects disease progression and systemic inflammatory burden in sepsis, underscoring the importance of serial platelet monitoring rather than reliance on a single baseline measurement.

In contrast, thrombocytosis, though less frequent, was associated with mortality in our analysis. However, given the limited number of cases and the wide CIs, this finding should be considered exploratory rather than definitive. It is plausible that thrombocytosis represents a distinct hyperinflammatory or cytokine-driven phenotype characterized by increased thrombopoietin and acute-phase reactant activity (3,12). Previous adult ICU studies have linked thrombocytosis to adverse outcomes, prolonged hospitalization, and increased sepsis-related complications (16). In another study, no statistically significant difference in mortality was found between patients with thrombocytosis and those with normal PC levels (17). Therefore, further prospective studies are needed to clarify whether thrombocytosis serves as a compensatory inflammatory marker or contributes to disease pathology in pediatric sepsis.

An increased MPV reflects enhanced platelet production in response to bone marrow stress, resulting in the release of younger and larger platelets into circulation. While several studies have demonstrated an association between MPV and the severity of sepsis (6,18), other studies have reported conflicting findings (17,19). In our study, no significant association was found between mortality and platelet indices, such as MPV and RDW. This discrepancy may be related to physiological differences in the pediatric population and to variations in the timing of MPV measurement. Consistent with our temporal analyses, MPV and RDW did not demonstrate significant changes within the first 24 hours, suggesting that these indices may reflect later or cumulative inflammatory processes rather than acute disease progression. Furthermore, these indices should not be evaluated in isolation but rather in conjunction with PC and other inflammatory markers to provide a more accurate and comprehensive risk prediction.

In this study, lactate was the only consistent independent predictor of mortality. As a biomarker reflecting tissue hypoperfusion and metabolic dysfunction. Elevated lactate levels, a biomarker reflecting tissue hypoperfusion and metabolic dysfunction, have been widely associated with poor outcomes in pediatric sepsis (20). Our findings support the role of lactate as a key parameter in early risk stratification and clinical decision-making in critically ill children.

Study Limitations

Our study had several limitations, including its retrospective design, single-center setting, and relatively small sample size. Additionally, the analysis was based solely on data obtained during the first 24 hours after admission, which limited the ability to assess longer-term dynamic changes. The microbiological findings and clinical complications were not included in the evaluation.

CONCLUSION

Our findings support the clinical value of assessing platelet patterns as adjunctive indicators rather than definitive predictors in pediatric sepsis. While thrombocytopenia appears to reflect disease severity and thrombocytosis may signify a distinct inflammatory phenotype, only lactate consistently predicted mortality. Thus, PC trends should be interpreted alongside clinical severity scores and metabolic markers such as lactate, particularly within the first days of critical illness. Serial platelet monitoring may improve prognostic accuracy, as dynamic trends, rather than a single

baseline value, have been associated with outcomes in prior studies.

ETHICS

Ethics Committee Approval: The study methodology was approved by University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Clinical Research Ethics Committee (approval no: 283, date: 27.08.2025).

Informed Consent: We obtained informed consent from all parents before hospitalization and during all procedures.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: K.B.G., C.D., Concept: E.G.Ş., C.D., Design: K.B.G., E.G.Ş., C.D., Data Collection or Processing: K.B.G., İ.A.Y., Analysis or Interpretation: C.D., Literature Search: K.B.G., E.G.Ş., F.V., Writing: İ.A.Y., F.V.

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

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Research

Comparison of Unilateral Biportal Endoscopic Discectomy and Microdiscectomy for Lumbar Disc Herniation: A Single-Center 1-Year Experience

Lomber Disk Hernisi Cerrahisinde Unilateral Biportal Endoskopik Diskektomi ile Mikrodiskektominin Karşılaştırılması: Tek Merkezli 1 Yıllık Deneyim

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ABSTRACT

Objective: The aim of this study was to compare the clinical, functional, and safety outcomes of unilateral biportal endoscopic (UBE) discectomy and lumbar microdiscectomy (LMD) in the surgical treatment of lumbar disc herniation.

Methods: This single-center, retrospective study included a total of 87 patients who underwent surgery for lumbar disc herniation. Patients were divided into two groups according to the surgical technique: LMD (n=40) and UBE (n=47). Clinical outcomes were assessed using preoperative and postoperative visual analogue scale (VAS) scores for back and leg pain, the Oswestry Disability Index (ODI), and the modified MacNab criteria at postoperative 3 months. Operative time and intraoperative and postoperative complications were also recorded.

Results: There were no significant differences between the groups in terms of preoperative VAS-back, VAS-leg, or ODI scores. The UBE group demonstrated significantly lower VAS-back scores in the early and mid-term postoperative periods compared with the LMD group ($p<0.001$). No significant differences were observed between the groups in postoperative 8 hours VAS-leg scores, ODI scores, or MacNab outcomes. Operative time was significantly longer in the UBE group ($p<0.001$). A limited number of complications, including recurrent disc herniation, dural tears, and epidural hematoma, were observed in the UBE group, while no permanent neurological deficits occurred in either group.

Conclusion: UBE is a safe and effective surgical alternative that provides advantages in early pain control while achieving functional outcomes and patient satisfaction comparable to those of microdiscectomy. The choice of surgical technique should be individualized based on patient characteristics and surgeon experience.

Keywords: Lumbar disc herniation, unilateral biportal endoscopy, microdiscectomy

ÖZ

Amaç: Bu çalışmanın amacı, lomber disk hernisi cerrahisinde unilateral biportal endoskopik (UBE) diskektomi ile lomber mikrodiskektominin (LMD) klinik, fonksiyonel ve güvenlik sonuçlarını karşılaştırmaktır.

Gereç ve Yöntem: Tek merkezli ve retrospektif olarak tasarlanan bu çalışmaya, lomber disk hernisi nedeniyle opere edilen toplam 87 hasta dahil edildi. Hastalar cerrahi tekniğe göre LMD (n=40) ve UBE (n=47) olmak üzere iki gruba ayrıldı. Klinik değerlendirmede preoperatif ve postoperatif görsel analog skala (VAS) (bel ve bacak), Oswestry Dizabilite İndeksi (ODI) ve postoperatif 3. ayda MacNab kriterleri kullanıldı. Ameliyat süresi ve intraoperatif/postoperatif komplikasyonlar kaydedildi.

Bulgular: Preoperatif VAS-bel, VAS-bacak ve ODI skorları açısından gruplar arasında anlamlı fark saptanmadı. UBE grubunda postoperatif erken ve orta dönemde VAS-bel skorları LMD grubuna göre anlamlı olarak daha düşük bulundu ($p<0,001$). Postoperatif 8. saat VAS-bacak skorları,

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ÖZ

ODI skorları ve MacNab kriterleri açısından gruplar arasında anlamlı fark izlenmedi. Ameliyat süresi UBE grubunda daha uzundu (p<0,001). UBE grubunda sınırlı sayıda nüks, dural hasar ve epidural hematom gözlendi; kalıcı nörolojik defisit her iki grupta da izlenmedi.

Sonuç: UBE, erken ağrı kontrolü açısından avantaj sağlayan, fonksiyonel sonuçlar ve hasta memnuniyeti bakımından mikrodiskektomi ile karşılaştırılabilir, güvenli bir cerrahi alternatiftir. Cerrahi teknik seçimi hasta özellikleri ve cerrah deneyimine göre bireyselleştirilmelidir.

Anahtar Kelimeler: Bel fıtığı, tek taraflı biportal endoskopi, mikrodiskektomi

INTRODUCTION

Lumbar disc herniation (LDH) is a common clinical condition characterized by low back and leg pain, numbness, and muscle weakness, all resulting from compression of the spinal nerve roots by herniated disc material. Its prevalence in the general population ranges from 15% to 45%, and approximately 75% of individuals experience at least one episode of low back pain during their lifetime (1-3). While conservative treatment is recommended for mild and non-progressive symptoms, surgical intervention becomes necessary in cases of pain refractory to medical treatment or in the presence of progressive motor and sensory deficits.

Open lumbar microdiscectomy (LMD) has long been considered the gold standard for the surgical treatment of LDH. With the introduction of high-resolution endoscopic systems, endoscopic techniques have gained increasing attention in recent years due to their advantages, including improved surgical visualization, reduced soft tissue damage, faster postoperative recovery, decreased intraoperative blood loss, shorter hospital stay, and a lower risk of infection (4-8).

Among endoscopic techniques, both uniportal and biportal approaches are currently used. Uniportal endoscopic surgery requires surgical instruments specifically designed for this technique. In contrast, the unilateral biportal endoscopic (UBE) technique has been developed by adapting conventional arthroscopic systems for spine surgery and has gained popularity in recent years. The UBE technique allows effective removal of herniated disc material via a posterior approach while aiming to preserve bony and muscular structures. Despite the growing use of endoscopic systems, studies comparing the clinical outcomes of UBE and microscopic discectomy—particularly in terms of pain control, quality of life, patient satisfaction, recurrence rates, and early and late complications—remain limited. Therefore, the present study aims to compare the clinical outcomes of UBE and LMD for the surgical treatment of LDH.

METHODS

Study Design

This study is a retrospective analysis of 87 patients with LDH who underwent surgery using two techniques—open LMD and UBE discectomy—at a single center in 2024. Data were obtained from the patients' medical records and intraoperative videos. Ethical approval for the study was obtained from the Institutional Human Research Ethics Committee of İstinye University (approval no: 2025-366, date: 13.01.2026).

Patient Selection

Patients were included in the study if they presented with low back pain or radicular pain associated with LDH, failed to respond to at least two weeks of conservative treatment, had symptoms that persisted for at least two weeks, had magnetic resonance imaging findings consistent with clinical symptoms, and had a minimum follow-up of one year. Prior to surgery, all patients underwent comprehensive neurological and radiological evaluations. Patients with previous lumbar surgery, extraforaminal disc herniation, recurrent disc herniation, multilevel disc herniation, severe scoliosis or spinal deformity, advanced osteoporosis, inflammatory rheumatologic diseases, traumatic disc herniation, or insufficient clinical or radiological follow-up data were excluded from the study.

Outcome Measures and Clinical Assessment

To evaluate surgical outcomes in a patient-centered and multidimensional manner, the visual analogue scale (VAS) was used to assess pain intensity, the Oswestry Disability Index (ODI) was used to evaluate functional status, and the MacNab criteria were used to determine overall clinical success and patient satisfaction. Low back and leg pain intensities were assessed preoperatively and postoperatively using the VAS (back and leg; range 0-10), while functional status was evaluated preoperatively and postoperatively using the ODI (range 0-100%). Back and leg pain were measured using the VAS 8 hours after surgery. Mid-term clinical outcomes were analyzed at

3 months postoperatively using VAS-back scores and the MacNab criteria (excellent, good, fair, and poor). Operative time was defined as the interval from the initial skin incision to the placement of the final skin suture. The operated lumbar level and the surgical side were recorded. In addition, intraoperative and postoperative complications were systematically evaluated.

Surgical Technique

Unilateral Biportal Endoscopic Discectomy

Visualization was achieved using a 4.0 mm-diameter, 0° HOPKINS® II arthroscope (Karl Storz, Tuttlingen, Germany) inserted through the endoscopic viewing portal. Bony decompression was performed using a 3 mm high-speed burr. Soft tissue ablation and hemostasis were achieved under continuous irrigation using a bipolar Coblation® radiofrequency probe (Smith & Nephew). During other stages of the procedure, standard surgical instruments from conventional open spine surgery—Kerrison rongeurs, dissectors, hooks, and pituitary forceps—were used for bone and soft tissue manipulation.

The patient was placed in the prone position under general anesthesia. After the surgical level was confirmed using C-arm fluoroscopy, skin incisions were planned. The cranial portal was created medial to the mid-inferior aspect of the cranial vertebral pedicle at the target level, while the caudal portal was created medial to the midline of the caudal vertebral pedicle. Triangulation of the working portal and the endoscope was achieved by targeting the spinolaminar junction. In right-sided disc herniations, the working portal could be positioned slightly more inferiorly. In cases of superiorly or inferiorly migrated disc herniations, portal placement was partially modified in the direction of the pathology.

The endoscope and surgical instruments were introduced through the two portals into the interlaminar window, which was maintained in a continuously irrigated fluid environment. After initiating irrigation, the operating table was placed in the reverse Trendelenburg position to reduce epidural pressure, prevent intracranial pressure elevation, and minimize the risk of retinal hemorrhage. Soft tissues overlying the lamina were dissected using a radiofrequency ablation probe, exposing the medial surface of the facet joint.

Subsequently, hemilaminectomy was performed using the 3 mm high-speed burr. Bone resection was terminated upon visualization of the characteristic medial "V-shaped" configuration of the ligamentum flavum and was followed by flavectomy. After removal of the ligamentum flavum, the dura mater and the corresponding nerve root were identified. Following safe mobilization of the nerve root, the disc space was explored, and the herniated disc material was removed, completing the discectomy.

Microdiscectomy

In patients undergoing LMD, the procedure was performed through a midline skin incision approximately 2-3 cm long, on the side corresponding to the disc herniation. The paraspinal muscles were dissected subperiosteally to expose the lamina and interlaminar space. The operation was carried out under microscopic magnification. After a partial hemilaminectomy and removal of the ligamentum flavum, the neural structures were exposed. Following safe mobilization of the nerve root, the herniated disc material was excised to achieve adequate decompression.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 29.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean±standard deviation, and categorical variables as counts and percentages. Comparisons were conducted between the LMD and UBE groups. Normality was assessed using visual methods and normality tests. As most variables were not normally distributed, non-parametric tests were primarily used. Postoperative 8-hours VAS-back and VAS-leg scores, postoperative 3-months VAS-back scores, preoperative and postoperative ODI scores, and changes in ODI scores were compared using the Mann-Whitney U test. Categorical variables, including 3-months postoperative MacNab outcomes, were analyzed using the chi-square test or Fisher's exact test when applicable. All analyses were two-tailed, and $p<0.05$ was considered statistically significant.

RESULTS

Between January and December 2024, 87 patients underwent lumbar discectomy at our center. The mean age of the patients was 46.75±10.70 years, and the female-to-male ratio was 41/46. Discectomy was performed on the right side in 39 patients (44.8%) and on the left side in 48 patients (55.1%). Regarding the operated levels, 1 patient (1.1%) underwent surgery at L2-3, 5 patients (5.7%) at L3-4, 41 patients (47.1%) at L4-5, and 40 patients (45.9%) at L5-S1. Of the total cohort, 40 patients (45.9%) were included in the LMD group, while 47 patients (54.0%) were included in the UBE group (Table 1).

In terms of surgical outcomes, the mean operative time was significantly longer in the UBE group compared with the LMD group (87.4±34.2 minutes vs. 61.6±16.6 minutes;

p<0.001) (Table 2). At 8 hours postoperatively, the VAS-leg score was 2.38±0.89 in the UBE group and 2.60±1.19 in the LMD group, with no statistically significant difference between the groups (p=0.305). In contrast, the postoperative 8-hours VAS-back score was significantly lower in the UBE group compared with the LMD group (3.65±1.32 vs. 4.77±0.94; p<0.001). Similarly, at mid-term follow-up, the postoperative 3-months VAS-back scores were significantly lower in the UBE group than in the LMD group (p<0.001).

Functional outcomes were evaluated using the ODI. Both groups showed a marked and statistically significant improvement in ODI scores postoperatively compared with preoperative values (p<0.001 for both groups). However, no statistically significant differences were found between the LMD and UBE groups in postoperative ODI scores or in the magnitude of ODI change (p=0.686). Clinical success and patient satisfaction were assessed at 3-months postoperatively using the MacNab criteria. No statistically significant difference was observed between the two groups in the distribution of MacNab outcomes (p=0.277); both groups showed a high proportion of excellent and good outcomes.

No postoperative infections, permanent neurological deficits, wound-related complications, or persistent radicular pain were observed. In the UBE group, one patient developed recurrent disc herniation that required reoperation; the reoperation was successfully performed using the UBE technique. One patient developed an epidural hematoma, confirmed by imaging, after the onset of radicular pain at the 4th postoperative hour and underwent emergent evacuation using the UBE technique. Two dural tears, identified intraoperatively, occurred in the UBE group; none required postoperative intervention. No irrigation-related retinal complications were observed in the UBE group.

DISCUSSION

In recent years, minimally invasive spine surgery techniques have become increasingly widespread, as endoscopic approaches offer notable advantages over traditional surgical methods, including faster postoperative recovery, reduced blood loss, a reduced risk of infection, shorter hospital stays, and reduced postoperative pain. The main finding of the present study is that unilateral biportal endoscopic surgery provides significant advantages in early- and mid-term pain control compared with microdiscectomy, while also achieving comparable clinical outcomes in terms of functional recovery and patient satisfaction. In particular, the significantly lower back pain scores observed in the UBE group during the early and mid-term postoperative periods support that minimally invasive approaches have a tissue-preserving effect on paraspinal soft tissues. Conversely, similar levels of functional improvement assessed by the ODI and comparable clinical success rates per the MacNab criteria indicate that UBE is a clinically equivalent alternative to microdiscectomy. These findings suggest that the choice of surgical technique in LDH should be guided not only by radiological decompression success but also by

Table 1. Demographic and clinical characteristics of the patients

	Total (n=87)	UBE (n=47)	LMD (n=40)
Age	46.75±10.70 (28-86)	48.23±11.41 (28-86)	45.02±9.67 (30-78)
Gender			
Female	41 (47.1%)	23 (26.4%)	18 (20.6%)
Male	46 (52.8%)	24 (27.5%)	22 (25.2%)
Side			
Right	39 (44.8%)	20 (22.9%)	19 (21.8%)
Left	48 (55.1%)	27 (31.0%)	21 (24.1%)
Level			
L2-3	1 (1.1%)	0	1 (1.1%)
L3-4	5 (5.7%)	5 (5.7%)	0
L4-5	41 (47.1%)	25 (28.7%)	16 (18.3%)
L5-S1	40 (45.9%)	17 (19.5%)	23 (26.4%)
Recurrence	1 (1.1%)	1 (1.1%)	0
Complication			
Dural injury	2 (2.2%)	2 (2.2%)	0
Epidural hematoma	1 (1.1%)	1 (1.1%)	0

UBE: Unilateral biportal endoscopy, LMD: Lumbar microdiscectomy

patient-centered outcomes, such as early pain relief and preservation of soft tissue integrity.

Although conventional microdiscectomy is an effective technique for symptomatic disc herniation, muscle and ligamentous injuries inherent to the procedure may lead to postoperative low back pain and muscle atrophy (9-11). Consequently, recovery and pain control may be prolonged, and some patients may require additional treatments. The incidence of postoperative low back pain after microdiscectomy has been reported to range between 30% and 70%, and approximately 8-10% of these patients may ultimately require fusion surgery for pain control (9,12-14). In contrast, the UBE technique, which avoids paravertebral muscle dissection and is performed under continuous saline irrigation, results in less tissue damage, a reduced inflammatory response, and decreased postoperative adhesion formation, thereby contributing to lower rates of postoperative low back pain (15). In the present study, the finding that patients in the UBE group experienced significantly less low back pain at the 8-hours postoperative and 3-months follow-up evaluations, compared with the LMD group, represents one of the notable advantages of the UBE technique.

The longer operative time observed in the UBE group than in the microdiscectomy group may be attributed to the inherent characteristics of endoscopic techniques and the associated learning curve. UBE requires two portals, continuous irrigation, and endoscope-specific hand-eye coordination, which may result in longer operative times during the initial phase of adoption. However, the literature indicates that operative times for UBE decrease significantly with increasing surgeon experience and eventually become comparable to those of microdiscectomy (2,16-18). This suggests that operative time should be regarded not as the sole indicator of technical efficiency, but rather as a dynamic parameter reflecting the surgeon's level of experience and progression along the learning curve. Despite longer operative time in the present study, lower postoperative VAS-back scores in the UBE group compared with the LMD group, together with the absence of significant differences in VAS-leg scores, support the effectiveness of UBE when used in appropriately selected patients and performed by experienced surgical teams. In terms of patient satisfaction, the lack of significant differences between the LMD and UBE groups in ODI and MacNab outcomes suggests that UBE's tissue-preserving nature, its contribution to early pain relief, and its support of functional recovery play a decisive role in clinical outcomes, despite its longer operative duration.

A limited number of complications were observed in the UBE group. Among patients who underwent UBE, one case of recurrent disc herniation, two dural tears identified intraoperatively, and one postoperative epidural

Table 2. Comparison of clinical outcomes between the UBE and LMD groups

	UBE	LMD	p
Back pain			
Preoperative VAS	6.23±1.30 (3-9)	6.57±1.23 (4-9)	p=0.255†
Postoperative 8 hours VAS	3.65±1.32 (1-6)	4.77±0.94 (3-6)	**p<0.001†**
Postoperative 3rd month VAS	2.23±1.00 (0-4)	3.02±0.94 (1-5)	**p<0.001†**
Leg pain			
Preoperative VAS	7.12±1.05 (4-9)	7.57±0.84 (6-9)	p=0.053†
Postoperative 8 hours VAS	2.38±0.89 (1-5)	2.6±1.19 (0-6)	p=0.305†
ODI			
Preoperative	77.46±8.15 (61-91)	79.85±7.31 (59-90)	p=0.165†
Postoperative	13.25±6.49 (4-36)	14.82±5.94 (7-32)	p=0.169†
Preoperative and postoperative changes	64.2±10.1 (39-80)	65.0±8.6 (47-82)	p=0.686†
MacNab criteria			p=0.277*
Excellent	35 (74.4%)	24 (60%)	
Good	7 (14.8%)	6 (15%)	
Fair	3 (6.3%)	8 (20%)	
Poor	2 (4.2%)	2 (5%)	
Operative time (minutes)	87.4±34.2 (40-180)	61.6±16.6 (28-93)	**p<0.001†**

†: Determined using the Mann-Whitney U test, *: Determined using the chi-square test, UBE: Unilateral biportal endoscopy, LMD: Lumbar microdiscectomy, VAS: Visual analogue scale, ODI: Oswestry disability index

hematoma were recorded. The dural tears were recognized intraoperatively and managed appropriately, with no need for additional intervention during the postoperative period. The epidural hematoma was diagnosed early and treated without resulting in a permanent neurological deficit. In the LMD group, no major complications requiring reoperation or resulting in serious neurological impairment were observed. No permanent neurological deficits or deaths occurred in either group. That most complications in the UBE group occurred during the learning-curve phase, along with the longer operative time observed, suggests that these complications may be related to technical experience. Nevertheless, when the overall complication profile is considered, UBE appears to have an acceptable and manageable safety profile when performed with appropriate patient selection and by experienced surgical teams (19-21).

Study Limitations

One of the major strengths of this study is the comparison of two patient groups who underwent surgery at the same center for similar surgical indications, based on detailed clinical and functional parameters. The similarity in preoperative pain and functional scores between groups enhances the internal validity of comparisons of postoperative outcomes. In addition, the combined evaluation of early and mid-term pain scores, functional recovery, and patient satisfaction allowed a comprehensive assessment of patient-centered outcomes related to the surgical techniques. However, the retrospective design of the study and the time-based group formation may introduce selection bias. The inclusion of cases from the early phase of the surgeon's learning curve in the UBE group may have influenced certain parameters, such as operative time. Furthermore, the lack of long-term clinical and radiological follow-up limits the generalizability of the findings to extended periods. Therefore, larger prospective studies with long-term follow-up are warranted to better define the role of UBE in the surgical treatment of LDH.

CONCLUSION

The results of this study indicate that in the surgical treatment of LDH, the UBE approach may provide advantages in early- and mid-term control of low back pain compared with LMD, while both techniques yield similar clinical outcomes in terms of functional recovery and patient satisfaction. While UBE offers potential benefits such as soft tissue preservation and early pain relief owing to its minimally invasive nature, longer operative time and learning curve-related complications should be considered limitations. Microdiscectomy, on the other hand, remains a reliable surgical technique supported by well-established efficacy, predictable operative duration, and extensive clinical experience. In this context, the selection of the optimal surgical technique for LDH should be individualized based on patient-specific clinical characteristics, surgeon experience, and institutional resources. When used in appropriately selected patients and by operators with sufficient expertise, UBE can be considered a safe and effective alternative to microdiscectomy.

ETHICS

Ethics Committee Approval: Ethical approval for the study was obtained from the Institutional Human Research Ethics Committee of İstinye University (approval no: 2025-366, date: 13.01.2026).

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

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: E.Y., A.G., A.E., Concept: S.C., Design: S.C., Data Collection or Processing: E.Y., A.E., Analysis or Interpretation: A.G., A.U., Literature Search: E.Y., A.U., Writing: E.Y., A.G.

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

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Research

Major, Midi and Multiple Mini Incisions in Inside-Out Meniscal Repair: Neurovascular Safety and Surgical Efficiency

Inside-Out Menisküs Tamirinde Majör, Midi ve Multipl Mini İnsizyonlar: Nörovasküler Güvenlik ve Cerrahi Verimlilik

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ABSTRACT

Objective: This study compared three skin incision strategies used in inside-out meniscal repair with respect to neurovascular complications, surgical parameters, and clinical outcomes.

Methods: Between January 2021 and June 2024, 224 patients who underwent arthroscopic inside-out repair for tears of the medial or lateral meniscal body or posterior horn were retrospectively reviewed. After applying the exclusion criteria, 192 patients were included and divided into three groups: conventional major incision (n=59), single midi incision (2-3 cm; n=65), and multiple mini incisions (n=68). The primary outcome was the overall complication rate, including vascular and neurological complications. Secondary outcomes included operative time and clinical outcomes; the clinical outcomes were assessed using the visual analogue scale (VAS), International Knee Documentation Committee (IKDC) score, and Tegner activity scale.

Results: Overall complication rates were 11.9% in the conventional group, 10.8% in the midi group, and 19.1% in the multiple mini-incision group, with no significant difference among groups (p=0.324). When complications were classified as local (incision-related) or systemic, local complication rates were 8.5%, 6.2%, and 13.2%. Neurological complications occurred more frequently in the multiple mini-incision group. Operative time was significantly longer in this group than in the other two groups (p<0.001). All groups demonstrated significant postoperative improvements in VAS, IKDC, and Tegner scores (all p<0.001), with comparable functional outcomes between the conventional and midi groups.

Conclusion: In this retrospective cohort, the midi-incision technique was not associated with a statistically significant difference in complication rates compared with the conventional major incision, but it demonstrated a shorter operative time than the multiple mini-incision technique. These preliminary findings suggest that the midi-incision approach is a promising alternative that warrants further prospective investigation.

Keywords: Meniscus repair, inside-out technique, skin incision, neurovascular complications, arthroscopy

ÖZ

Amaç: Bu çalışma, *inside-out* menisküs tamirinde kullanılan üç farklı deri insizyonu stratejisini; nörovasküler komplikasyonlar, cerrahi parametreler ve klinik sonuçlar açısından karşılaştırmayı amaçladı.

Gereç ve Yöntem: Ocak 2021 ile Haziran 2024 tarihleri arasında, medial veya lateral menisküs korpus ya da posterior boynuz yırtıkları nedeniyle artroskopik *inside-out* menisküs tamiri uygulanan 224 hasta retrospektif olarak incelendi. Dışlama kriterleri uygulandıktan sonra 192 hasta çalışmaya dahil edildi ve üç gruba ayrıldı: konvansiyonel majör insizyon (n=59), tek midi insizyon (2-3 cm; n=65) ve çoklu mini insizyonlar (n=68). Birincil sonlanım noktası, vasküler ve nörolojik komplikasyonları içeren toplam komplikasyon oranıydı. İkincil sonlanım noktaları ise ameliyat süresi ve görsel analog skala (VAS), I*nternational Knee Documentation Committee* (IKDC) skoru ve Tegner aktivite ölçeği ile değerlendirilen klinik sonuçlardı.

Bulgular: Toplam komplikasyon oranları konvansiyonel grupta %11,9, midi grupta %10,8 ve çoklu mini insizyon grubunda %19,1 olarak saptandı ve gruplar arasında anlamlı fark yoktu (p=0,324). Nörolojik komplikasyonlar çoklu mini insizyon grubunda daha sık görüldü. Ameliyat süresi bu grupta diğer iki gruba kıyasla anlamlı derecede daha uzundu (p<0,001). Tüm gruplarda VAS, IKDC ve Tegner skorlarında ameliyat sonrası anlamlı iyileşme gözlendi (tüm p<0,001) ve konvansiyonel ile midi gruplar arasında fonksiyonel sonuçlar benzerdi.

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ÖZ

Sonuç: Bu retrospektif kohortta, midi insizyon tekniği konvansiyonel majör insizyona kıyasla komplikasyon oranlarında istatistiksel olarak anlamlı bir fark göstermemiştir. Bu ön bulgular, midi insizyon yaklaşımının ileriye dönük araştırmalarla doğrulanması gereken umut verici bir alternatif olduğunu düşündürmektedir.

Anahtar Kelimeler: Menisküs tamiri, *inside-out* teknik, deri insizyonu, nörovasküler komplikasyonlar, artroskopi

INTRODUCTION

Arthroscopic inside-out meniscal repair has been widely used for decades because of its strong suture configurations and adaptability to various tear patterns, particularly corpus and posterior horn tears of the medial and lateral meniscus (1,2). Despite advances in all-inside devices, it remains a reference technique for many surgeons owing to its biomechanical reliability, its ability to tie knots over the capsule, and its durable clinical outcomes. However, the procedure requires an additional posteromedial or posterolateral incision, placing critical neurovascular structures at potential risk (1,3).

On the medial side, the saphenous nerve and its branches are vulnerable, whereas on the lateral side, the common peroneal nerve and popliteal vascular structures may be endangered depending on incision location and dissection depth (3,4). Traditionally, a 4-6 cm "safety incision" has been recommended prior to suture passage to allow placement of a retractor and protect adjacent structures (1). Although this conventional major incision provides adequate exposure, it may increase operative time, the extent of soft-tissue dissection, postoperative pain, and wound-related complications (5,6).

Recently, efforts to minimize soft-tissue trauma have led to alternative incision strategies. The "midi-incision" technique uses a single 2-3 cm shared incision after suture retrieval, whereas the multiple mini-incision technique creates separate small incisions for each knot (2). Consequently, in recent years, the feasibility of achieving comparable safety with more limited skin incisions during inside-out meniscal repair has gained increasing attention in clinical practice (3,7). While the general complication profile of inside-out repair has been extensively reported, direct comparisons of these incision strategies in terms of neurovascular safety and surgical efficiency remain limited (5,6,8).

The primary aim of this study was to compare three incision strategies for inside-out repair of medial and lateral meniscal body and posterior horn tears with respect to overall complication rates. As a secondary focus, neurovascular complications were analyzed separately to assess incision-related safety. Secondary aims included operative time, wound complications, early postoperative pain, and functional outcomes. We hypothesized that the single midi-incision technique would demonstrate no statistically significant difference in complication rates compared with the conventional major-incision technique, and would be associated with superior outcomes compared with the multiple mini-incision technique.

METHODS

This was a retrospective cohort study. The study protocol was approved by the Erzurum University Faculty of Medicine Scientific Researchs Ethics Committee (approval no: 288, date: 12.11.2025), and the study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, the ethics committee waived the requirement for study-specific informed consent. Routinely obtained preoperative surgical consent forms were used for all patients. All surgical procedures were performed by two experienced orthopedic surgeons specializing in arthroscopic surgery.

Patients who underwent arthroscopic inside-out meniscal repair for medial and/or lateral meniscal corpus (midbody) or posterior horn tears between January 2021 and June 2024 were identified retrospectively in hospital medical records. During this period, a total of 224 patients were screened. Based on predefined exclusion criteria, 32 patients were excluded, and 192 were included in the final analysis. Patients included in the study were divided into three groups according to the skin incision technique.

All three incision techniques were used concurrently during the study period (January 2021-June 2024). Both surgeons were experienced in all three techniques, and the choice of technique was based on individual surgeon preference rather than patient- or tear-specific factors. No systematic temporal trend or learning-curve effect was identified in the distribution of techniques over time.

Patients aged 14-55 years who underwent arthroscopic inside-out repair of repairable tears of the medial and/or lateral meniscal midbody or posterior horn were included in the study. Eligible tear patterns included longitudinal, horizontal, radial, bucket-handle, and complex types, provided intraoperative assessment confirmed sufficient meniscal tissue quality to allow stable repair. Inclusion

further required the availability of a minimum of 12 months of clinical and functional follow-up data. Patients with previous surgery on the same knee; patients who underwent revision meniscal repair or meniscectomy; patients requiring concomitant anterior cruciate ligament reconstruction or other major ligamentous procedures; patients with advanced cartilage degeneration; patients diagnosed with degenerative meniscal tears; and patients with a history of infectious or inflammatory arthritis, systemic rheumatologic disease, or postoperative follow-up shorter than 12 months were excluded from the study.

Pain and functional status were assessed in all patients preoperatively and at the final clinical follow-up using standardized patient-reported outcome measures. Pain intensity was recorded using the visual analogue scale (VAS), ranging from 0 to 10. Knee function and symptoms were evaluated using the International Knee Documentation Committee (IKDC) subjective knee evaluation form. Activity level was assessed using the Tegner activity scale. Changes in clinical outcomes were analyzed based on differences between preoperative and postoperative scores, and were used for both within- and between-group statistical comparisons.

Surgical Technique

All procedures were performed under general or spinal anesthesia with the patient in the supine position. The operative knee was positioned near the table edge to facilitate posteromedial or posterolateral access, and a lateral thigh post was used when necessary. Diagnostic arthroscopy was carried out through standard anteromedial and anterolateral portals to assess tear location and repairability. Corpus and posterior horn tears were treated using the inside-out technique.

Suture passage was performed with zone-specific cannulas based on tear location. For medial tears, cannulas were introduced through the anterolateral portal; for lateral tears, they were introduced through the anteromedial portal to ensure a safe needle exit trajectory. Sutures were placed in vertical or oblique mattress configurations at 3-5 mm intervals.

Posterior exposure was performed according to the assigned incision strategy. In the conventional major-incision technique, a 4-6 cm posteromedial or posterolateral incision was made before suture passage, and a blunt retractor was placed over the capsule to protect neurovascular structures (Figure 1a). In the single midi-incision technique, sutures were first retrieved through the skin, followed by the creation of a single 2-3 cm shared incision for knot-tying (Figure 1b). In the multiple mini-incision technique, separate small incisions were made for each knot with individual blunt dissection to the capsule (Figure 1c).

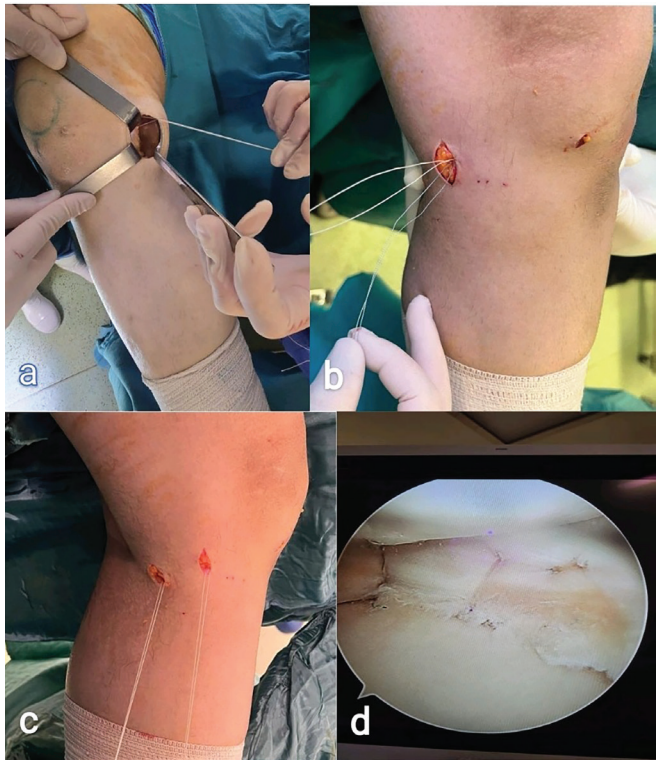

Figure 1. a. Conventional major incision technique using a blunt retractor to protect the posteromedial neurovascular structures during inside-out meniscal repair. **b.** Single midi-incision technique (2-3 cm), in which a single shared incision is created after all sutures are retrieved through the skin. **c.** Multiple mini-incision technique, in which separate millimetric skin incisions are made for each suture line and dissected individually down to the capsule. **d.** Arthroscopic view of inside-out repair of a horizontal tear involving the midbody-posterior horn of the medial meniscus

Care was taken to protect the saphenous nerve and vein medially and the common peroneal nerve and popliteal vessels laterally. Transillumination and anatomical landmarks were routinely used to identify safe incision sites. All sutures were tied over the capsule with the knee in near-full extension to reduce the risk of flexion contracture. Final meniscal stability was confirmed arthroscopically.

Deep vein thrombosis screening was performed based on clinical suspicion. Duplex ultrasonography was obtained when patients presented with clinical signs suggestive of deep-vein thrombose (DVT), including calf swelling, calf tenderness, or a positive Homans sign. Standardized universal DVT screening was not routinely performed, which may have resulted in underdetection of asymptomatic events.

Postoperative Rehabilitation

All patients used a knee brace postoperatively, with knee range of motion initially restricted to 0-90°. During the first 2 weeks, partial weight-bearing was allowed as tolerated for isolated repairs, with progression individualized according to tear characteristics and repair stability. Isometric quadriceps exercises, ankle pumps, and patellar mobilization were initiated early, and controlled knee flexion was gradually increased beginning in the second postoperative week.

By the fourth week, supervised closed kinetic chain exercises and light strengthening exercises were introduced, while deep flexion and rotational stress were avoided to protect the repair. After the sixth week, patients progressed to full weight bearing and advanced to active flexion beyond 120°. Running and low-impact activities were generally initiated between weeks 8 and 12. From the third postoperative month, sport-specific training with controlled directional changes was added, and return to contact or high-demand sports was permitted after 6 months, when clinical and functional assessments were satisfactory.

Statistical Analysis

Sample size calculation was based on detecting a clinically meaningful difference in complication rates between groups (α=0.05, power=0.80) and required approximately 60 patients per group. Continuous variables are presented as mean±standard deviation, and categorical variables as frequencies and percentages. Baseline comparisons were performed using one-way analysis of variance (ANOVA) for continuous variables and chi-square or Fisher's exact tests for categorical variables, with Levene's test assessing homogeneity of variances.

Complication rates were compared using the chi-square test, with 95% confidence intervals (CIs) calculated by the Wilson method. Operative time and changes in outcome scores were analyzed using ANOVA with Tukey post-hoc testing. Effect sizes were calculated using eta-squared (η^2) and Cohen's d. Within-group pre-post comparisons were evaluated using paired t-tests.

Multivariable logistic regression was used to identify independent predictors of complications, including surgical technique (with Classic Major Incision as the reference), age, gender, and tear complexity. Anlaysis of covariance (ANCOVA) was used to assess predictors of postoperative functional scores while adjusting for preoperative values and demographic variables. Spearman correlation analysis was used to examine associations between operative time, follow-up duration, and outcome changes. Statistical significance was set at $p<0.05$. Analyses were performed using Python (version 3.10).

RESULTS

Patient Characteristics

A total of 192 patients completed the study protocol (mean age 32.5±11.8 years, 70.8% male). The cohort comprised 59 patients (30.7%) in the Classic Major Incision group, 65 patients (33.9%) in the Midi Incision group, and 68 patients (35.4%) in the Multiple Mini Incisions group. Mean follow-up duration was 29.7±9.5 months, without significant difference between groups (Classic: 31.0±9.0 months, Midi: 30.5±10.0 months, Mini: 27.9±9.2 months). No patients were lost to follow-up.

Baseline demographic and clinical characteristics were generally comparable among groups (Table 1). No significant differences were observed in age (p=0.960), gender distribution (p=0.118), operative side (p=0.324), meniscus side (p=0.405), or tear type distribution (p=0.332). Preoperative VAS pain scores (p=0.159) and Tegner activity levels (p=0.657) were similar across groups. However, preoperative IKDC scores differed significantly among groups (Classic: 46.7±1.5, Midi: 47.3±1.7, Mini: 47.8±1.5; p=0.001), and this baseline imbalance was accounted for in all subsequent between-group functional outcome comparisons using ANCOVA adjustment.

Operative Parameters

The mean operation time differed significantly among groups ($F=135.7$, $p<0.001$, $\eta^2=0.590$), with a large effect size. The Classic Major Incision group had the shortest operative time (25.4±3.2 minutes), followed by the Midi Incision group (27.3±3.2 minutes), with the Multiple Mini Incisions group requiring significantly longer time (33.9±3.0 minutes). Post-hoc analysis revealed all pairwise differences were statistically significant (all $p\leq0.002$). The Multiple Mini Incisions technique required approximately 8.5 minutes longer than the Classic approach (95% CI: 7.2-9.8 minutes) and 6.6 minutes longer than the Midi approach (95% CI: 5.3-7.9 minutes).

Primary Outcome: Complication Rates

Overall complication rates were 11.9% (7/59) in the Classic Major Incision group, 10.8% (7/65) in the Midi Incision group, and 19.1% (13/68) in the Multiple Mini Incisions group, with no statistically significant difference among groups ($\chi^2=2.26$, p=0.324). The overlapping 95% CIs for each group (Classic: 5.9-22.5%, Midi: 5.3-20.6%, Mini: 11.5-30.0%) indicate that the observed differences may be attributable to chance. However, this should not be interpreted as evidence of equivalent

safety because the study was not designed as an equivalence or non-inferiority trial (Figure 2).

When complications were categorized as local (incision-related: neurological and wound complications) or systemic (DVT and thrombophlebitis) categories, the local complication rates were 8.5% (5/59) in the Classic group, 6.2% (4/65) in the Midi group, and 13.2% (9/68) in the Multiple Mini group (p=0.349). Systemic vascular complications occurred in 3.4% (2/59), 4.6% (3/65), and 8.8% (6/68), respectively. This separation provides a clearer assessment of incision-specific safety.

Individual complication types are presented in Table 2. Vascular complications occurred in 11 patients (5.7% overall): 2 (3.4%) in the Classic group, 3 (4.6%) in the Midi group, and 6 (8.8%) in the Mini group. Most were lower-extremity DVTs that were detected through clinical suspicion and managed successfully with anticoagulation. Two cases of superficial thrombophlebitis occurred in the Mini group. Neurological complications occurred in 9 patients (4.7% overall): 1 (1.7%) in the Classic group (saphenous neuropathy), 2 (3.1%) in the Midi group (saphenous neuropathy), and 6 (8.8%) in the Mini group (1 peroneal neuropathy, 5 saphenous neuropathies). Most neurological complications manifested as transient paresthesia

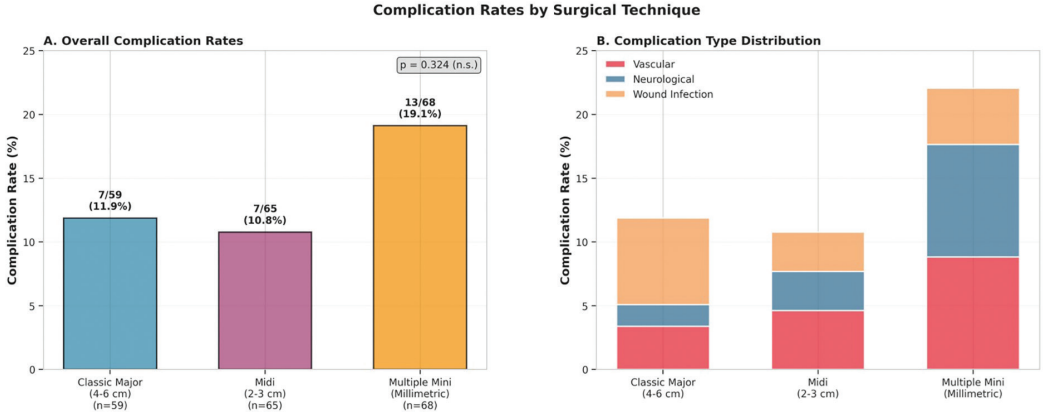

Figure 2. Complication rates by surgical technique. Complication rates comparison among three incision techniques. **A.** Overall complication rates show no statistically significant difference among groups (p=0.324, chi-square test). Multiple Mini Incisions group shows numerically higher rate (19.1%) compared to Classic Major (11.9%) and Midi (10.8%) techniques, but difference did not reach statistical significance. Note: The absence of statistical significance should not be interpreted as evidence of equivalent safety. **B.** Complication type distribution presented as stacked bar chart showing proportion of vascular, neurological, and wound infection complications in each group. Error bars represent 95% confidence intervals

n.s.: Not statistically significant (p>0.05)

Table 1. Patient demographics and baseline clinical characteristics

Characteristic	Classic major (n=59)	Midi incision (n=65)	Multiple mini (n=68)	p-value
Age (years), mean±SD	32.8±11.8	32.2±12.0	32.5±11.6	0.960
Male gender, n (%)	44 (74.6)	50 (76.9)	42 (61.8)	0.118
Right knee, n (%)	40 (67.8)	36 (55.4)	44 (64.7)	0.324
Medial meniscus, n (%)	34 (57.6)	41 (63.1)	47 (69.1)	0.405
Longitudinal, n (%)	15 (25.4)	9 (13.8)	18 (26.5)	0.332[a]
Horizontal, n (%)	20 (33.9)	18 (27.7)	22 (32.4)	—
Complex, n (%)	8 (13.6)	11 (16.9)	11 (16.2)	—
Radial, n (%)	11 (18.6)	14 (21.5)	7 (10.3)	—
Bucket-handle, n (%)	5 (8.5)	13 (20.0)	10 (14.7)	—
Follow-up (months), mean±SD	31.0±9.0	30.5±10.0	27.9±9.2	0.148
VAS pain score, mean±SD	7.3±1.5	7.3±1.7	6.8±1.5	0.159
IKDC score, mean±SD	46.7±1.5	47.3±1.7	47.8±1.5	0.001**
Tegner activity level, mean±SD	3.7±1.4	3.6±1.6	3.5±1.4	0.657

SD: Standard deviation, VAS: Visual analogue scale (0-10), IKDC: International Knee Documentation Committee (0-100), Tegner: Tegner activity scale (0-10). [a]: p-value for overall tear type distribution (chi-square test), **p<0.01

that resolved within 6-12 months; one case of common peroneal neuropathy in the Mini group persisted beyond 12 months with partial recovery. Wound infections occurred in 9 patients (4.7% overall): 4 (6.8%) in the Classic group, 2 (3.1%) in the Midi group, and 3 (4.4%) in the Mini group. All were superficial surgical site infections managed successfully with oral antibiotics; no deep infections or reoperations for infection occurred.

Multivariable logistic regression analysis of the composite complication risk revealed no significant association with surgical technique after adjustment for age, gender, and tear complexity. Compared with the Classic Major Incision group (reference), neither Midi Incision [odds ratio (OR): 0.88, 95% CI: 0.29-2.69, p=0.818] nor Multiple Mini Incisions (OR: 1.82, 95% CI: 0.66-4.98, p=0.247) demonstrated a significantly different risk of complications. Similarly, age, gender, and tear complexity were not independently associated with complication risk (all p>0.32).

Secondary Outcomes: Functional Scores

Within-Group Improvements

All three groups demonstrated statistically significant improvements in pain scores and functional scores from preoperative to postoperative assessments (all p<0.001, Table 3, Figure 3). VAS pain scores improved substantially in all groups: Classic (7.3→2.4, Δ=-4.9±2.0), Midi (7.3→2.2, Δ=-5.1±2.3), and Mini (6.8→3.2, Δ=-3.6±2.1). IKDC scores improved markedly in all groups: Classic (46.7→78.0, Δ=31.3±2.5), Midi (47.3→78.1, Δ=30.8±2.3), and Mini (47.8→68.1, Δ=20.3±2.2). Tegner activity levels also improved across groups: Classic (3.7→6.2, Δ=2.5±2.1), Midi (3.6→6.1, Δ=2.5±2.2), and Mini (3.5→4.8, Δ=1.3±2.2).

Multivariable regression analysis (ANCOVA) confirmed surgical technique as a significant predictor of postoperative IKDC score (R^2=0.915, F=398.0, p<0.001). The high R^2 value was primarily driven by the strong predictive contribution of preoperative IKDC scores. Model diagnostics, including residual analysis and multicollinearity assessment (all variance inflation factors <2.0), were satisfactory. After adjusting for preoperative IKDC, age, and gender, the Multiple Mini Incisions technique was associated with a 9.7-point lower postoperative IKDC score compared with the Classic Major Incision (β=-9.74, 95% CI: -10.3 to -9.2, p<0.001), while the Midi Incision showed no significant difference from the Classic Major Incision (β=0.20, p=0.457). Similar patterns were observed for Tegner activity scores.

Table 2. Complication rates and multivariable risk factor analysis

A. Complication rates by surgical technique

Complication type	Classic major (n=59)	Midi incision (n=65)	Multiple mini (n=68)	p-value
Any complication	7 (11.9%)	7 (10.8%)	13 (19.1%)	0.324
[95% CI]	[5.9-22.5%]	[5.3-20.6%]	[11.5-30.0%]	—
Local complications	5 (8.5%)	4 (6.2%)	9 (13.2%)	0.349
Systemic complications	2 (3.4%)	3 (4.6%)	6 (8.8%)	—
Vascular complication	2 (3.4%)	3 (4.6%)	6 (8.8%)	0.388
*Deep vein thrombosis	2	2	4	—
*Thrombophlebitis	0	1	2	—
Neurological complication	1 (1.7%)	2 (3.1%)	6 (8.8%)	0.117
*Saphenous neuropathy	1	2	5	—
*Peroneal neuropathy	0	0	1	—
Wound infection	4 (6.8%)	2 (3.1%)	3 (4.4%)	0.598

p-values from chi-square test for overall comparison; individual complication types presented descriptively due to low event rates

B. Multivariable logistic regression for any complication risk

Variable	Odds ratio	95% CI	p-value
Classic major incision	Reference	—	—
Midi incision	0.88	0.29-2.69	0.818
Multiple mini incisions	1.82	0.66-4.98	0.247
Age (per year)	1.01	0.98-1.05	0.441
Male gender	1.32	0.51-3.40	0.570
Complex tear	1.68	0.61-4.63	0.320

CI: Confidence interval. Model includes surgical technique (classic major incision as reference category), age, gender, and tear complexity. Pseudo R^2=0.026. No significant independent predictors identified

Given the statistically significant baseline difference in preoperative IKDC scores among groups (p=0.001), all between-group comparisons of postoperative functional outcomes were adjusted for preoperative IKDC values using ANCOVA, ensuring that the observed differences reflected true between-group effects rather than baseline imbalances.

Correlation Analysis

Spearman correlation analysis revealed significant associations between operative parameters and outcomes. Operation time correlated inversely with IKDC improvement (ρ=-0.64, p<0.001), indicating that longer procedures were associated with less functional improvement. Operation time also showed a moderate correlation with VAS change (ρ=0.26, p<0.001) and an inverse correlation with Tegner improvement (ρ=-0.21, p=0.004). Follow-up duration was weakly positively correlated with IKDC improvement (ρ=0.17, p=0.019), suggesting gradual functional gains. IKDC improvement correlated inversely with VAS change (ρ=-0.24, p<0.001), as expected, and correlated positively with Tegner improvement (ρ=0.19, p=0.008).

DISCUSSION

The principal finding is that complication rates did not differ significantly between the 2-3 cm midi incision and the

Table 3. Operative parameters and clinical outcomes

Outcome	Classic major (n=59)	Midi incision (n=65)	Multiple mini (n=68)	p-value[a]	η^2
Operation time (min)	25.4±3.2	27.3±3.2	33.9±3.0	<0.001***	0.590
VAS pain score					
Preoperative	7.3±1.5	7.3±1.7	6.8±1.5	0.159	—
Postoperative	2.4±1.4	2.2±1.5	3.2±1.7	<0.001***	—
Change (Δ)	-4.9±2.0	-5.1±2.3	-3.6±2.1	<0.001***	0.094
IKDC score					
Preoperative	46.7±1.5	47.3±1.7	47.8±1.5	0.001**	—
Postoperative	78.0±1.6	78.1±1.5	68.1±1.4	<0.001***	—
Change (Δ)	31.3±2.5	30.8±2.3	20.3±2.2[c]	<0.001***	0.834
Tegner activity score					
Preoperative	3.7±1.4	3.6±1.6	3.5±1.4	0.657	—
Postoperative	6.2±1.6	6.1±1.5	4.8±1.6	<0.001***	—
Change (Δ)	2.5±2.1	2.5±2.2	1.3±2.2[c]	0.001**	0.068

[a]: One-way ANOVA; [b]: Paired t-test; [c]: Significantly different from both Classic and Midi (Tukey honestly significant difference, p<0.01). **p<0.01; ***p<0.001. η^2 effect sizes: small 0.01-0.06, medium 0.06-0.14, large >0.14

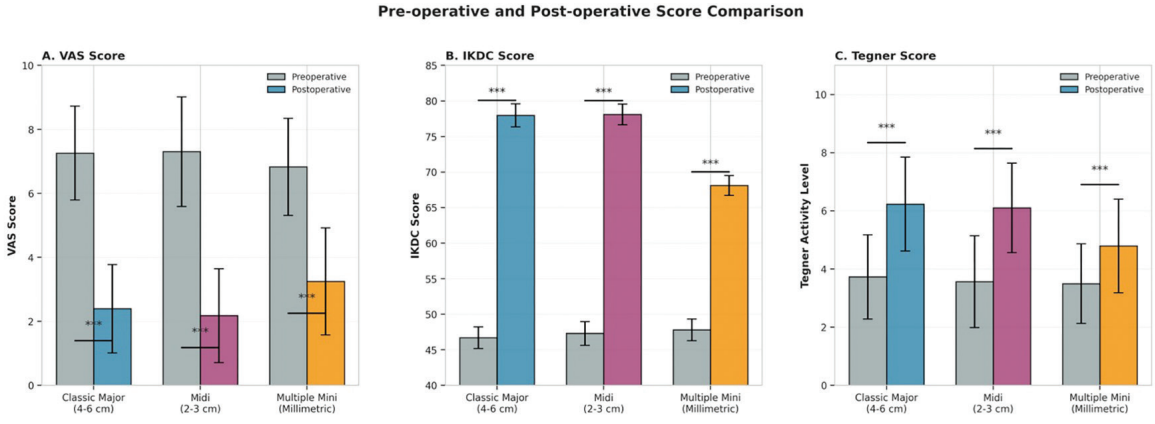

Figure 3. Preoperative and postoperative score comparison. Comparison of preoperative and postoperative functional scores among surgical techniques. **A.** VAS pain scores show significant improvement in all groups (***p<0.001). **B.** IKDC scores demonstrate substantial improvement in all groups (***p<0.001). Classic and Midi groups achieve postoperative scores near 78 points, while Multiple Mini Incisions group shows more modest improvement to 68 points. **C.** Tegner activity levels improve significantly in all groups (***p<0.001)

VAS: Visual analogue scale (0-10), IKDC: International Knee Documentation Committee (0-100): Tegner: Tegner activity scale (0-10)

conventional 4-6-cm major incision in inside-out meniscal repair (p=0.324). Because the study was not designed as an equivalence or non-inferiority trial, this result should not be interpreted as proof of equivalent safety. The multiple mini-incision technique was associated with numerically higher complication rates, significantly longer operative time, and significantly less functional improvement. By contrast, operative time and functional outcomes in the midi group were comparable to those of the conventional approach.

Inside-out meniscal repair is still widely preferred for corpus and posterior horn tears because of its strong suture configurations and durable outcomes (1-3,9). Despite advances in all-inside implants, its biomechanical reliability and capsular knot fixation keep it a reference technique (2,10,11). Its main drawback is the additional posteromedial or posterolateral incision, which exposes neurovascular structures to risk (1,3,12): medially, the variable branching of the saphenous nerve (13,14), and laterally, the proximity of the common peroneal nerve (15).

Traditionally, a 4-6 cm "safety incision" is created before suture passage to allow retractor placement (1). Although reliable, it requires more dissection and is linked to postoperative pain, wound complications, and sensory disturbances (5,6,16-19). The multiple mini-incision technique reduces total incision length but requires repeated dissection, potentially causing cumulative neurovascular manipulation (2,15-18,20,21).

Anatomical studies show that inconsistent saphenous nerve branching prevents a true "safe zone," and repeated small dissections may raise the risk of paresthesia (13,14,20). The numerically higher neurological complication rate and limited functional gains in the multiple mini-incision group align with these concerns, although, with only 9 events, the study was underpowered for a definitive comparison. The midi-incision technique offers a balanced compromise: a single 2-3 cm shared incision after suture retrieval permits controlled capsular dissection while limiting repeated neurovascular contact (2,3).

In our cohort, complication rates in the midi-incision group were not significantly different from those in the conventional group and were numerically lower than those in the multiple mini-incision group. Operative time in the midi group was similar to that in the conventional approach and significantly shorter than in the multiple mini-incision technique.

Prolonged operative time has been linked to greater postoperative pain, slower recovery, and more complications in arthroscopic knee surgery. The inverse correlation observed here between operative time and functional improvement is consistent with this. However, the retrospective design precludes causal inference; operative time may simply reflect technical difficulty. Both the midi and conventional groups achieved clinically meaningful and comparable improvements in VAS, IKDC, and Tegner scores. The smaller gains in the multiple mini-incision group may be related to increased surgical manipulation and neurosensory symptoms, but this is hypothesis-generating and requires prospective confirmation.

Study Limitations

This study has several limitations. The most critical limitation is the complete absence of meniscal healing and repair-failure endpoints: no second-look arthroscopy, magnetic resonance imaging confirmation, recurrent-tear assessment, revision-surgery tracking, or structural integrity evaluation were performed. Because meniscal healing is the definitive measure of repair success, the favorable VAS, IKDC, and Tegner results reported here reflect symptomatic and functional improvement only and must not be interpreted as evidence of successful biological healing or durable structural repair (22-24). Therefore, All comparative conclusions regarding incision techniques apply solely to perioperative safety and short- to mid-term functional outcomes, and not to the durability of the repair. Additional limitations include a retrospective, non-randomized design with surgeon-dependent technique selection, which may have introduced selection bias and unmeasured confounding; the single-center setting and inter-surgeon variability, which limit generalizability; reliance on clinical evaluation and patient-reported outcomes to ascertain neurological complications without routine electrophysiological testing; underpowered for rare events (only 9 neurological complications overall), therefore the numerical trend toward more neurological complications in the multiple mini-incision group (8.8% vs. 1.7% and 3.1%) should be interpreted cautiously; a multivariable model with a limited covariate set that did not adjust for meniscus side, tear zone (posterior horn vs. midbody), number of sutures, or individual surgeon; the unusually high R^2 (0.915) in the ANCOVA, which likely reflects a homogeneous population; and mid-term follow-up that did not allow evaluation of long-term function or healing rates.

CONCLUSION

In this retrospective cohort, the single 2-3 cm midi-incision technique for inside-out meniscal repair was associated with no statistically significant difference in overall complication rates compared with the conventional major-incision technique, while demonstrating shorter operative time

and a numerically lower rate of neurological complications than the multiple mini-incision technique. These findings suggest that the midi-incision approach may be a promising alternative to the conventional major incision; however, the retrospective, non-randomized design of this study precludes definitive conclusions regarding equivalence in safety. Prospective randomized studies with formal equivalence or non-inferiority designs, incorporating meniscal healing endpoints, are warranted to confirm these preliminary observations.

ETHICS

Ethics Committee Approval: The study protocol was approved by the Erzurum University Faculty of Medicine Scientific Researchs Ethics Committee (approval no: 288, date: 12.11.2025).

Informed Consent: Due to the retrospective nature of the study, the ethics committee waived the requirement for study-specific informed consent. Routinely obtained preoperative surgical consent forms were relied upon for all patients.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: N.A., F.E.T., Concept: E.Ö., E.D., Design: N.A., F.E.T., Data Collection or Processing: N.A., E.Ö., Analysis or Interpretation: E.Ö., E.D., Literature Search: E.D., F.E.T., Writing: N.A., E.Ö.

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

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Research

Challenging the 4 cm Rule: Nodule Size Does not Predict the Risk of Occult Malignancy in Cytologically Benign Thyroid Nodules

4 cm Kuralının Sorgulanması: Sitolojik Olarak Benign Tiroid Nodüllerinde Nodül Boyutu Gizli Malignite Riskinin Belirleyicisi Değildir

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ABSTRACT

Objective: Accurate differentiation between benign and malignant lesions remains a primary challenge in thyroid nodule management. This study evaluated the impact of nodule size on malignancy rates and on the incidence of occult malignancy among lesions that were preoperatively classified as benign, specifically questioning the reliability of the 4 cm threshold.

Methods: Between 2016 and 2019, 477 patients with preoperative benign cytology who underwent surgery were retrospectively analyzed. Patients were stratified into macro-nodules (≥4 cm, n=161) and smaller lesions (<4 cm, n=316). Multivariate logistic regression was used to identify independent predictors of malignancy, and a post-hoc power analysis was performed to evaluate the diagnostic strength of the findings.

Results: The overall malignancy rate was 11.5% (n=55/477). Malignancy rates were nearly identical between the groups: 11.8% [95% confidence interval (CI): 7.7-17.7%] for the ≥4 cm group and 11.4% (95% CI: 8.3-15.4%) for the <4 cm group (p=1.000). In the multivariate analysis, within the limits of the current regression model adjusted for age and sex, nodule size ≥4 cm did not emerge as a significant predictor of malignancy (odds ratio: 1.04, 95% CI: 0.58-1.86, p=0.885). A post hoc power analysis confirmed that the observed difference was clinically negligible (Cohen's h=-0.013). No significant differences were observed among histological subtypes, including papillary and follicular carcinomas, with respect to size (p>0.05).

Conclusion: Nodule size is an insufficient independent criterion for predicting malignancy specifically among surgically treated patients with benign cytology. Based on our findings in this surgically selected cohort, clinical decision-making should not rely solely on size thresholds. Instead, management should favor an integrated strategy that incorporates sonographic risk features and multidisciplinary evaluation to optimize patient outcomes and reduce unnecessary surgeries.

Keywords: Fine-needle aspiration biopsy, occult malignancy, thyroid cancer, thyroid nodule

ÖZ

Amaç: Tiroid nodülü yönetiminde benign ve malign lezyonların doğru şekilde ayırt edilmesi temel bir zorluk olmaya devam etmektedir. Bu çalışma, preoperatif olarak benign sitolojiye sahip lezyonlarda nodül boyutunun malignite oranları ve gizli malignite insidansı üzerindeki etkisini değerlendirmiş; özellikle 4 cm eşiğinin güvenilirliğini sorgulamıştır.

Gereç ve Yöntem: 2016-2019 yılları arasında, preoperatif sitolojisi benign olup cerrahi geçiren 477 hasta retrospektif olarak analiz edildi. Hastalar makro-nodüller (≥4 cm, n=161) ve daha küçük lezyonlar (<4 cm, n=316) olarak iki gruba ayrıldı. Malignitenin bağımsız öngördürücülerini belirlemek için çok değişkenli lojistik regresyon analizi kullanıldı ve bulguların tanısal gücünü değerlendirmek için post-hoc güç analizi yapıldı.

Bulgular: Genel malignite oranı %11,5 olarak saptandı. Gruplar arasındaki malignite oranları neredeyse aynıydı: ≥4 cm grubu için %11,8 [%95 güven aralığı (GA): %7,7-17,7] ve <4 cm grubu için %11,4 (%95 GA: %8,3-15,4) (p=1,000). Çok değişkenli analizde, ≥4 cm nodül boyutunun malignite için anlamlı bir belirleyici olmadığı görüldü (olasılık oranı: 1,04, %95 GA: 0,58-1,86, p=0,885). Post-hoc güç analizi, gözlemlenen farkın klinik olarak ihmal edilebilir olduğunu doğruladı (Cohen's h=-0,013). Papiller ve foliküler karsinomlar dahil olmak üzere histolojik alt tiplerde boyuta göre anlamlı bir fark saptanmadı (p>0,05).

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ÖZ

Sonuç: Benign sitolojiye sahip hastalarda nodül boyutu, malignite öngörüsünde yetersiz bir bağımsız kriterdir. Cerrahi olarak seçilmiş bu kohorttaki bulgularımıza dayanarak, klinik karar verme sürecinde yalnızca boyut eşiklerine güvenilmemelidir. Bunun yerine, hasta sonuçlarını optimize etmek ve gereksiz ameliyatları azaltmak için ultrasonografik risk özelliklerini ve multidisipliner değerlendirmeyi içeren entegre bir strateji tercih edilmelidir.

Anahtar Kelimeler: İnce iğne aspirasyon biyopsisi, gizli malignite, tiroid kanseri, tiroid nodülü

INTRODUCTION

Thyroid nodules are frequently encountered in clinical practice, and determining whether these nodules are benign or malignant is of great importance. The American Thyroid Association (ATA) guidelines recommend ultrasound-guided (US) biopsy for nodules >1 cm when suspicious features are identified on imaging (1). The biopsy results are classified into six categories based on the Bethesda system: non-diagnostic, benign, atypia of undetermined significance (AUS), follicular neoplasm, suspicion of malignancy, and malignant pathology. The Bethesda reporting system estimates a minimal risk of occult malignancy, typically spanning from 0% to 3%, for thyroid lesions initially diagnosed with benign cytopathology (2). These findings underscore that a benign cytological diagnosis does not entirely preclude the presence of malignancy, thereby mandating a rigorous and individualized clinical assessment.

Existing literature provides conflicting evidence as to whether a diameter exceeding 4 cm is an independent risk factor for thyroid carcinoma. While some authors suggest that increasing size correlates with a higher risk of malignancy, others maintain that size alone is a poor predictor of oncological outcomes. On the other hand, there is evidence suggesting that the sensitivity of fine needle aspiration biopsy (FNAB) may be compromised in the setting of macro-nodular disease, leading to disproportionately higher rates of missed malignancies compared to smaller nodules (3). Furthermore, certain clinical perspectives recommend immediate surgical intervention for large-volume nodules, regardless of their cytological status (4). This "size-based" surgical philosophy, however, remains a subject of intense debate, as it may lead to over-treatment of inherently benign lesions. Such discrepancies in the literature complicate the surgical decision-making and clinical triage for patients presenting with significantly enlarged nodules.

The primary objective of this research was to evaluate the correlation between thyroid nodule dimensions and clinical outcomes, specifically focusing on the comparative analysis of malignancy incidence and the rates of malignancies detected postoperatively between nodules ≥4 cm and those <4 cm. Using a large cohort of nodules that were benign preoperatively, this study aims to provide a robust framework for managing these nodules and optimizing clinical decision-making for surgery.

METHODS

A total of 1090 patients who underwent thyroid surgery at our clinic between January 2016 and December 2019 were retrospectively reviewed. The inclusion criteria comprised patients aged ≥18 years with preoperative benign thyroid cytology who subsequently underwent thyroidectomy at our institution. We excluded patients under the age of 18, patients without available preoperative biopsy results, and patients diagnosed with diffuse goiter or with an absence of nodules. Additionally, any cytological findings other than benign—including AUS, follicular neoplasms, suspicion of malignancy, and overt malignancy—as well as cases with missing clinical data were removed from the study cohort. The patient selection process is detailed in the study flow diagram (Figure 1). As a result, 477 patients were included in the study.

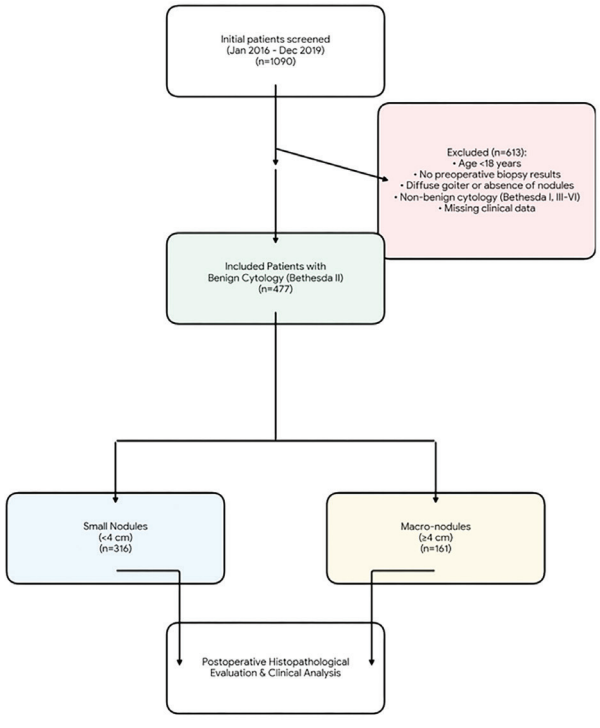

Figure 1. Flowchart of the patient selection process

The study population was categorized into two distinct cohorts according to a nodule diameter threshold of 4 cm: those with macro-nodules (≥4 cm) and those with smaller lesions (<4 cm). The patients' parameters, including gender, age, nodule size, postoperative pathology results, and histological subtypes, were retrospectively analyzed.

US-FNAB was systematically targeted at either the most sonographically suspicious lesion or the dominant nodule. The biopsy results were evaluated according to the Bethesda classification, and the cytological diagnosis was determined (2).

Surgical intervention was recommended based on several clinical criteria. For the macro-nodule group (≥4 cm), the primary indications were size-related concerns, including local compressive symptoms (dysphagia, neck pressure), potential for substernal extension, and the inherent risk of sampling failure in large lesions. For nodules <4 cm, surgery was indicated due to suspicious sonographic features (e.g., irregular margins, microcalcifications), rapid growth during follow-up, patient preference (anxiety regarding malignancy risk), or planned treatment for concomitant hyperthyroidism. Our institutional clinical approach followed the current evidence-based framework of the ATA guidelines (1).

This study was conducted after approval was obtained from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Research and Training Hospital Non-Interventional Clinical Research Ethics Committee (approval no: 2025-03-18, date: 05.02.2025).

Statistical Analysis

Statistical analyses were performed using Jamovi (version 2.3; the Jamovi project, 2022). Normality of continuous variables was assessed using the Shapiro-Wilk test and visual inspection of Q-Q plots. Quantitative outcomes were reported as mean ± standard deviation or median (minimum-maximum) as appropriate. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate. To identify independent predictors of malignancy, a multivariate logistic regression model was constructed, including age, gender, and nodule size as covariates. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to estimate the strength of associations. Furthermore, post hoc power analysis and effect-size estimation (Cohen's h) were performed to evaluate the diagnostic strength of comparisons of the primary outcomes. Statistical significance for all comparative analyses was predefined at a threshold of $p<0.05$.

RESULTS

The study included 477 cases, of whom 21.8% (n=104) were male and 78.2% (n=373) were female. The study cohort exhibited an age range of 18 to 80 years, with a calculated mean age of 47.6±13.1 years.

The overall malignancy rate in the study population was 11.5% (n=55/477). The malignancy rate was 11.4% (95% CI: 8.3-15.4%) in the <4 cm group and 11.8% (95% CI: 7.7-17.7%) in the ≥4 cm group. The overlapping CIs further support the absence of a statistically significant difference between the two cohorts (p=1.000) (Tables 1 and 2; Figure 2). In the multivariate logistic regression analysis, within the limits of the current regression model adjusted for age and sex, nodule size ≥4 cm did not emerge as a significant predictor of malignancy (OR: 1.04, 95% CI: 0.58-1.86, p=0.885) after adjusting for age and gender. A post-hoc power analysis was performed using the observed effect size (Cohen's h=-0.013). The analysis indicated that, given the nearly identical

Table 1. Comparative analysis of demographic data and clinical characteristics between the study cohorts

		Nodule ≥4 cm, n (%)	Nodule <4 cm, n (%)	p-value
Sex	Male	37 (7.8)	67 (14)	[b]0.65
	Female	124 (26)	249 (52.2)	
Age	Mean±SD	48.1±12	47.2±14	[a]0.48
	Median (min-max)	48 (23-80)	47.5 (18-80)	
Nodule size	Mean±SD	50.2±10.1	25.1±9.4	[c]<0.001*
	Median (min-max)	47 (40-94)	26 (3.5-39)	
Postoperative pathology	Benign	142 (88.2)	280 (88.6)	[d]1.00
	Malign	19 (11.8)	36 (11.4)	
Histological diagnosis	Benign	142 (88.2)	280 (88.6)	[d]0.89
	Papillary microcarcinoma	6 (3.7)	13 (4.1)	
	Papillary carcinoma	11 (6.8)	21 (6.6)	
	Follicular carcinoma	2 (1.2)	2 (0.6)	

SD: Standard deviation, [a]: Student-t test, [b]: Pearson chi-square test, [c]: Mann-Whitney U test, [d]: Fisher's exact test, *p<0.05

malignancy rates between the two groups, the study was not powered to detect such a negligible difference, thereby reinforcing the conclusion that nodule size alone does not clinically alter malignancy risk in this cohort. Similarly, no significant correlation was observed between nodule dimensions and specific histological subtypes, including papillary and follicular carcinomas (p>0.05) (Table 3).

Histopathological examination of the 55 malignant cases identified 32 cases of papillary thyroid carcinoma, 19 cases of papillary microcarcinoma, and 4 cases of follicular carcinoma (Table 1 and Figure 3). Histopathological examination identified 55 malignant cases. Of these, 19 (34.5%) were classified as incidental papillary thyroid microcarcinomas (iPTMCs), defined as tumors ≤10 mm in diameter that were not the primary target of the preoperative FNAB. After excluding these incidental cases, the clinical malignancy rate attributable to the targeted nodules was 7.5% (n=36/477).

Table 2. Comparison of malignancy rates with 95% CIS

Variable	<4 cm (n=316)	≥4 cm (n=161)	p-value
Malignancy rate, n (%)	36 (11.4%)	19 (11.8%)	1.000[d]
95% CI*	8.3%-15.4%	7.7%-17.7%	-

CI: Confidence interval, [d]: Fisher's exact test, *Calculated using the Wilson score method

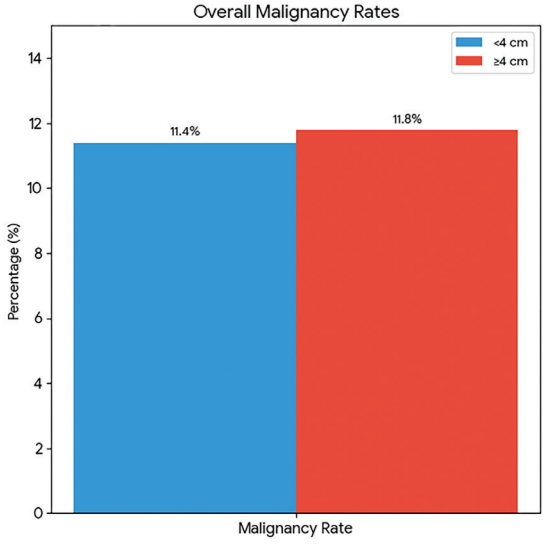

Figure 2. Comparison of overall malignancy rates between thyroid nodules <4 cm and ≥4 cm

Table 3. Multivariate logistic regression analysis of risk factors for malignancy

Variables	OR	95% CI	p-value
Age (>45 years)	1.12	0.85-1.48	0.420
Gender (male)	1.08	0.72-1.62	0.710
Nodule size (≥4 cm)	1.04	0.58-1.86	0.885

OR: Odds ratio, CI: Confidence interval

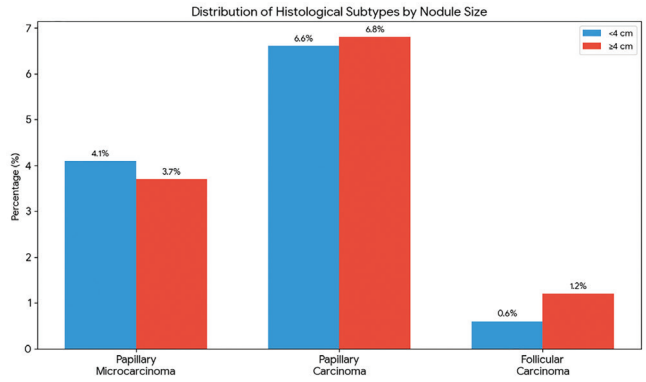

Figure 3. Distribution of histological malignancy subtypes stratified by nodule size

No statistically significant differences were identified between the study groups with respect to clinical parameters such as age, sex, and postoperative histological classifications (p>0.05).

DISCUSSION

The present investigation indicates that the incidence of postoperative malignancy does not differ significantly between thyroid nodules exceeding 4 cm and smaller nodules in patients with a preoperative benign cytological diagnosis. However, relatively high malignancy rates of 11.8% and 11.4% were observed in the two groups, respectively.

According to the ATA guidelines, no additional diagnostic methods or treatments are required for nodules with benign cytology. While prior investigations have reported malignancy incidences as low as 3.2% in benign cytology, our findings demonstrate a notably higher rate of 11.8% (5). This elevated rate likely points to technical challenges, including sampling errors—particularly in large or multinodular goiters, where the most suspicious focus may be missed—and the inherent diagnostic limitations of cytopathological interpretation. Furthermore, interobserver variability among cytopathologists may contribute to the higher-than-expected incidence of malignancy in lesions initially classified as benign. The inclusion of iPTMCs in our analysis is another key contributor to our reported malignancy rate. While these microlesions might not have been targeted by the initial FNAB, they represent a significant finding in the surgical specimens of patients with macronodular disease. Additionally, the standardized surgical indications used in our clinic help to contextualize the selection of certain

benign nodules for resection. Our findings highlight that the potential for malignancy should not be overlooked in the management of nodules with benign cytology. Future studies incorporating molecular testing or more stringent repeat-biopsy protocols could help mitigate these diagnostic errors.

Our institutional data revealed that the incidence of malignancy identified postoperatively in patients with benign cytology was 11.8% in the ≥4 cm cohort, which was comparable to the 11.4% observed in nodules below this size threshold. The literature reports occult malignancy rates in thyroid cytopathology that range from 3% to 24% (6-10). In multinodular glands, malignancy may arise from a non-biopsied nodule rather than the one targeted by FNAB. Therefore, these rates may reflect incidental malignancies or sampling limitations associated with multinodular disease rather than a technical failure of the cytopathological analysis. However, our study demonstrated that nodule size does not significantly influence the risk of a missed malignancy. Our findings demonstrate that a 4 cm diameter threshold does not reliably predict malignancy in preoperatively benign nodules. Although the literature documents a broad spectrum of false-negative outcomes, ranging 3% to 24%, our observed rate of 11.8% (95% CI: 7.3-17.9) underscores the limitations of US-FNAB for large nodules. This relatively high rate emphasizes that surgical decisions should not rely on size alone, but rather on a composite assessment of sonographic risk features and clinical judgment.

The debate continues regarding whether large nodule size is a risk factor for malignancy. Some studies have found that larger nodules increase the risk of malignancy (11). On the other hand, several reports in the literature fail to demonstrate a meaningful statistical relationship between increasing nodule size and the likelihood of a malignant diagnosis (12,13). According to our institutional results, nodule diameter was not a decisive predictor of thyroid carcinoma in patients preoperatively diagnosed with benign cytology. In the multivariate analysis, within the limits of the current regression model adjusted for age and sex, nodule size ≥4 cm was not a significant predictor of malignancy. We recognize that a more comprehensive model including sonographic risk features (such as microcalcifications, irregular margins, and hypoechoic appearance) and clinical risk factors (e.g., family history or radiation exposure), would provide a more nuanced understanding of the risk of malignancy. While our analysis focused on challenging the independent reliability of nodule size, sonographic characteristics remain the cornerstone of thyroid nodule triage. This finding is statistically supported by our post-hoc power analysis (Cohen's h=-0.013), which confirmed that the observed difference was clinically negligible. Consequently, our data reinforce the premise that nodule size alone is insufficient as an independent predictor for surgical intervention in the specific population referred for thyroidectomy. This observation might be influenced by our specific focus on patients who were preoperatively classified in the benign Bethesda category. While these results may not be directly applicable to all conservatively managed thyroid nodules in the general population, they provide critical evidence for the surgical management of macronodules.

The literature recommends direct surgical removal for large thyroid nodules (4). However, other studies have shown that nodule size alone is not a decisive factor in surgical decision-making (14,15). In our cohort, we observed that the false-negative rate remained high regardless of size, suggesting that the "size-rule" for surgery may lead to overtreatment of benign disease without significantly improving detection of malignancy. While nodule diameter is an insufficient independent predictor of the need for surgery, clinicians must remain cognizant of the elevated potential for false negatives, which warrants a highly individualized, cautious follow-up protocol. The reliability of cytology, especially in large nodules, should be questioned, and results should be supported by repeat biopsies. In the surgical decision-making process, nodule size alone is not sufficient; clinical and pathological factors must also be considered. This approach can prevent unnecessary surgeries while enabling early detection of the risk of malignancy.

Adherence to the ATA guidelines, the use of the Bethesda classification, and procedures performed by specialized professionals enhance the study's alignment with international standards. Compliance with international standards increases the reliability of our data and the scientific value of the study. With these strengths, our study can contribute to clinical practice and serve as a foundation for future research.

Study Limitations

We must acknowledge the presence of a significant selection bias inherent in our study design, as our cohort consists exclusively of surgically treated patients. In our clinical practice, nodules ≥4 cm were often operated on based on size alone, whereas smaller nodules (<4 cm) typically required additional indications for surgery, such as compressive symptoms or suspicious sonographic features. This discrepancy in surgical indications, known as indication bias, means that our findings primarily apply to patients already selected for surgical intervention and may

not be generalizable to the broader population of patients with benign thyroid nodules managed conservatively. Additionally, interpretations of these findings are constrained by the study's single-institution scope and retrospective methodology, which may limit the broader applicability of the data across regions with differing iodine status. Additionally, the more selective approach to surgical decision-making for benign nodules <4 cm may have introduced bias in this group. Specifically, smaller nodules were more likely to be operated on because of suspicious sonographic features or clinical symptoms. In contrast, macro-nodules (≥4 cm) were often sent for surgery based on size alone, which indicates a common selection bias in surgical series. This difference in surgical indications reflects the "real-world" clinical challenge where size often matters more than cytological findings in macro-nodular disease. Additionally, the high rate of occult malignancy may result from technical difficulties in sampling large-volume lesions or from differences in interpretation among cytopathologists. A significant limitation of our study is the lack of direct lesion-to-lesion correlation between the specific nodule biopsied and the final histopathological focus of malignancy. In multinodular cases, the detected cancer might represent an incidental finding in a non-targeted nodule, which precludes the calculation of a true lesion-specific false-negative rate for FNAB. Despite these limitations, our study offers a significant dataset that questions the use of size as a standalone reason for surgery.

CONCLUSION

The present investigation found that, in a surgical cohort, nodule dimensions are not independent predictors of either malignancy risk or the likelihood of postoperative detection of malignancy in cytologically benign cases.. However, we found the incidence of detected malignancies was relatively high. This finding highlights that nodule size alone is not a sufficient criterion for decisions regarding thyroid surgery. Based on our findings within this surgically selected cohort, clinical decision-making should avoid relying solely on size thresholds. Instead, management should favor an integrated strategy incorporating sonographic risk features and multidisciplinary evaluation to optimize patient outcomes and reduce unnecessary surgeries.

ETHICS

Ethics Committee Approval: This study was conducted after approval was obtained from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Research and Training Hospital Non-Interventional Clinical Research Ethics Committee (approval no: 2025-03-18, date: 05.02.2025).

Informed Consent: Due to its retrospective nature, informed consent was waived.

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FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: B.A., F.C., S.B., A.G., D.G., Concept: B.A., H.A., S.B., A.G., D.G., Design: B.A., H.A., F.C., A.G., D.G., Data Collection or Processing: B.A., S.B., Analysis or Interpretation: B.A., S.B., D.G., Literature Search: B.A., F.C., Writing: B.A., H.A., F.C., S.B., A.G., D.G.

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

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Research

Association Between Nutritional Status and Proximal Re-Amputation in Patients Undergoing Amputation for Diabetic Foot Ulcers: The Role of GNRI and CONUT Scores

Diyabetik Ayak Ülseri Nedeniyle Ampütasyon Uygulanan Hastalarda Beslenme Durumu ile Proksimal Reampütasyon İlişkisinin Değerlendirilmesi: GNRI ve CONUT Skorlarının Rolü

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ABSTRACT

Objective: Diabetic foot ulcers (DFUs) are a major cause of lower extremity amputation; identifying patients at risk for progression to more proximal amputation levels remains a significant clinical challenge. This study aimed to evaluate the association between nutritional status and amputation level progression in patients undergoing surgical treatment for DFUs.

Methods: In this retrospective cohort study, 151 patients who underwent surgical amputation for DFUs between 2020 and 2025 were included. Nutritional status was assessed using the Geriatric Nutritional Risk Index (GNRI) and the Controlling Nutritional Status score. The primary outcome was amputation level progression, defined as the transition from minor to major amputation or to a more proximal level. Clinical, laboratory, and metabolic parameters were compared between patients with and without progression. Multivariable logistic regression was performed to identify independent predictors.

Results: Amputation progression occurred in 64 patients (42.3%). Patients with progression had significantly lower GNRI scores and levels of albumin, cholesterol, and lymphocytes, and significantly higher levels of C-reactive protein, HbA1c, and serum creatinine. In multivariable analysis, serum creatinine [odds ratio (OR): 4.06, 95% confidence interval (CI): 2.04-8.09, p<0.001], GNRI (OR: 2.72, 95% CI: 1.30-5.65, p=0.008), and Wagner grade ≥3 (OR: 3.25, 95% CI: 1.07-9.83, p=0.037) were independently associated with amputation progression.

Conclusion: Poor nutritional status, renal dysfunction, and advanced ulcer severity are independently associated with an increased risk of progression to a higher level of amputation in patients with DFUs. GNRI may serve as a practical and accessible tool for early risk stratification and clinical decision-making.

Keywords: Amputation, diabetic foot ulcer, malnutrition, nutritional status, risk assessment

ÖZ

Amaç: Diyabetik ayak ülserleri (DAÜ), alt ekstremite ampütasyonlarının başlıca nedenlerinden biridir ve daha proksimal ampütasyon düzeylerine ilerleme riski taşıyan hastaların belirlenmesi önemli bir klinik zorluk olmaya devam etmektedir. Bu çalışmanın amacı, DAÜ nedeniyle cerrahi tedavi uygulanan hastalarda nütrisyonel durum ile ampütasyon düzeyi progresyonu arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif kohort çalışmasına, 2020-2025 yılları arasında DAÜ nedeniyle cerrahi ampütasyon uygulanan 151 hasta dahil edildi. Nütrisyonel durum, Geriatrik Nütrisyonel Risk İndeksi (GNRI) ve *Controlling Nutritional Status* skoru kullanılarak değerlendirildi. Birincil sonlanım noktası, minör ampütasyondan majör ampütasyona veya daha proksimal bir ampütasyon düzeyine geçiş olarak tanımlanan ampütasyon progresyonuydu. Progresyon gelişen ve gelişmeyen hastalar klinik, laboratuvar ve metabolik parametreler açısından karşılaştırıldı. Bağımsız belirleyicileri saptamak amacıyla çok değişkenli lojistik regresyon analizi yapıldı.

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ÖZ

Bulgular: Ampütasyon progresyonu 64 hastada (%42,3) gözlendi. Progresyon gelişen hastalarda GNRI skorları, albümin, total kolesterol ve lenfosit düzeyleri anlamlı olarak daha düşük; C-reaktif protein, HbA1c ve serum kreatinin düzeyleri ise daha yüksekti. Çok değişkenli analizde serum kreatinin düzeyi [olasılık oranı (OR): 4,06; %95 güven aralığı (GA): 2,04-8,09; p<0,001], GNRI (OR: 2,72; %95 GA: 1,30-5,65; p=0,008) ve Wagner evresi ≥3 olması (OR: 3,25; %95 GA: 1,07-9,83; p=0,037) ampütasyon progresyonu ile bağımsız olarak ilişkili bulundu.

Sonuç: Kötü nütrisyonel durum, böbrek fonksiyon bozukluğu ve ileri ülser şiddeti, DAÜ olan hastalarda ampütasyon düzeyi progresyonu riskinde artış ile bağımsız olarak ilişkilidir. GNRI, erken risk sınıflandırması ve klinik karar verme süreçlerinde kullanılabilecek pratik ve kolay uygulanabilir bir araç olabilir.

Anahtar Kelimeler: Ampütasyon, diyabetik ayak ülseri, malnütrisyon, nütrisyonel durum, risk değerlendirmesi

INTRODUCTION

Diabetes mellitus remains a major global health challenge, with an estimated 537 million adults affected worldwide, a number that continues to rise and reflects the increasing burden of diabetes-related complications (1). Among these complications, diabetic foot ulcers (DFUs) are particularly devastating, leading to substantial morbidity, reduced quality of life, recurrent hospitalizations, and significant healthcare expenditure (2,3). The lifetime risk of developing a DFU ranges between 19% and 34% among individuals with diabetes, emphasizing its global impact (4). DFU-related infections contribute to approximately 85% of non-traumatic lower extremity amputations (5), and patients who undergo amputation face five-year mortality rates comparable to many malignant diseases (6). Identifying factors associated with progression to higher amputation levels is therefore crucial for improving clinical outcomes in this high-risk population.

The clinical trajectory of DFUs is shaped by a multifactorial interplay, including glycemic control, infection severity, vascular insufficiency, systemic inflammation, and overall disease burden (7). Recently, the influence of nutritional status on wound healing, immune function, and infection control has gained increasing recognition. Malnutrition is known to impair immune responses, delay tissue repair, and contribute to adverse outcomes in individuals with chronic wounds (8). Objective nutritional assessment tools such as the Geriatric Nutritional Risk Index (GNRI) and the Controlling Nutritional Status (CONUT) score have emerged as practical, laboratory-based measures reflecting systemic nutritional impairment. Previous studies have demonstrated associations between poor nutritional scores and unfavorable clinical outcomes—including mortality, prolonged hospitalization, and delayed wound healing—in patients with DFUs (9-11). In diabetic foot surgery, determining the appropriate level of amputation is a central concern for orthopedists, and evaluating nutritional impairment may provide valuable prognostic insight. Despite increasing recognition of nutritional status as a prognostic factor, the potential role of GNRI and CONUT in predicting amputation progression—particularly from minor to major amputation—remains insufficiently explored, leaving a notable gap in the current literature.

Therefore, this study was designed to evaluate the association of GNRI and CONUT scores with progression in amputation level among patients undergoing surgical treatment for DFUs. The research question of this study was whether preoperative nutritional status, measured using the GNRI and CONUT scores, predicted progression of amputation level in patients undergoing amputation for DFUs. Specifically, we evaluated whether patients who progressed from minor to major amputation differed from those who did not progress with respect to these nutritional indices. We aimed to determine whether these nutritional indices could serve as reliable predictors of adverse surgical trajectories. We hypothesized that lower GNRI and higher CONUT scores would be associated with an increased likelihood of amputation progression.

METHODS

This study was approved by the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Health Practice and Research Center Clinical Research Ethics Committee (approval no: 5001, date: 05.08.2025), and all procedures were conducted in accordance with the Declaration of Helsinki. This retrospective cohort study was conducted at a tertiary referral center between January 2020 and January 2025. During this period, all patients who underwent surgical amputation due to DFU were screened. Demographic characteristics (age, sex), metabolic parameters (glucose, HbA1c, total cholesterol), nutritional indicators (albumin, lymphocyte count, hemoglobin), inflammatory markers [C-reactive protein (CRP), white blood cell (WBC)], and renal function parameters [serum creatinine, estimated glomerular filtration rate (eGFR)] were extracted from electronic medical records. Additional clinical information, including diabetes duration, smoking status, comorbidities such as end-stage renal disease (ESRD), cardiovascular or cerebrovascular disease, and body mass index (BMI), was also recorded. Ulcer severity was

assessed using the Wagner classification and dichotomized as Wagner grades <3 for low-to-moderate severity and ≥3 for limb-threatening ulcers, as commonly applied in previous literature.

A total of 216 patients who underwent surgical amputation for DFU between January 2020 and January 2025 were identified, and their medical records, operative notes, laboratory data, and follow-up information were retrospectively reviewed. After this evaluation, 65 patients were excluded for the following reasons: missing laboratory data preventing calculation of the CONUT or GNRI scores; insufficient follow-up or lack of postoperative control records; death during treatment before progression assessment; primary presentation with major amputation precluding evaluation of progression; coexistence of non-diabetic foot conditions such as traumatic injuries, vasculitis, tumors, or non-diabetic Charcot; being under 18 years of age; or having inconsistent clinical data. Following these exclusions, 151 patients met all criteria and constituted the final analytical cohort. The inclusion criteria were: a diagnosis of type 2 diabetes mellitus; a DFU requiring surgical amputation; availability of complete preoperative laboratory parameters; and a minimum of one month of postoperative follow-up. The exclusion criteria were: age under 18 years; primary major amputation at presentation; missing clinical or laboratory data; pregnancy; and non-diabetic foot pathology (Figure 1).

Amputation levels were categorized as minor when the procedure was performed distal to the ankle joint (including toe, ray, and transmetatarsal amputations) and as major when the procedure occurred through or proximal to the ankle joint (including below-knee and above-knee amputations). Amputation progression, defined as the primary outcome, referred exclusively to the transition from a minor amputation to a major amputation or the advancement of a major amputation to a more proximal level. Changes between minor amputation types (e.g., transitions from toe to ray or from ray to transmetatarsal amputation), were not considered progression because such revisions typically reflect limited local tissue loss or management of localized infection rather than clinically meaningful deterioration. In contrast, progression to a major amputation reflects a substantial increase in limb-loss severity and a significant decline in function; therefore, it was deemed an appropriate indicator of true progression. Accordingly, patients were classified into two groups: those with no progression, defined as having experienced no shift to a more proximal amputation level; and those with progression, defined as having undergone a minor-to-major or a major-to-more-proximal amputation.

Nutritional status was evaluated using the CONUT and GNRI scores. The CONUT score was calculated from serum albumin, total lymphocyte count, and total cholesterol values, and categorized as normal (0-1), mild malnutrition (2-4), moderate malnutrition (5-8), or severe malnutrition (9-12). The GNRI score was computed using the formula GNRI=1.489×albumin (g/L)+41.7×(current weight/ideal body weight), with ideal body weight calculated using the Lorentz formula. GNRI categories included: no nutritional risk (>98), mild risk (92-98), and moderate-to-severe risk (<92). Clinical variables collected for analysis included age, sex, BMI, duration of diabetes, comorbidities (ESRD, cardiovascular and cerebrovascular disease), smoking status, and Wagner grade. Laboratory parameters included albumin, CRP, hemoglobin, glucose, HbA1c, total cholesterol, lymphocyte count, WBC, serum creatinine, and eGFR.

Statistical Analysis

All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation, and categorical variables as numbers and percentages. Differences between groups were assessed using the Mann-Whitney U test for continuous variables and the chi-

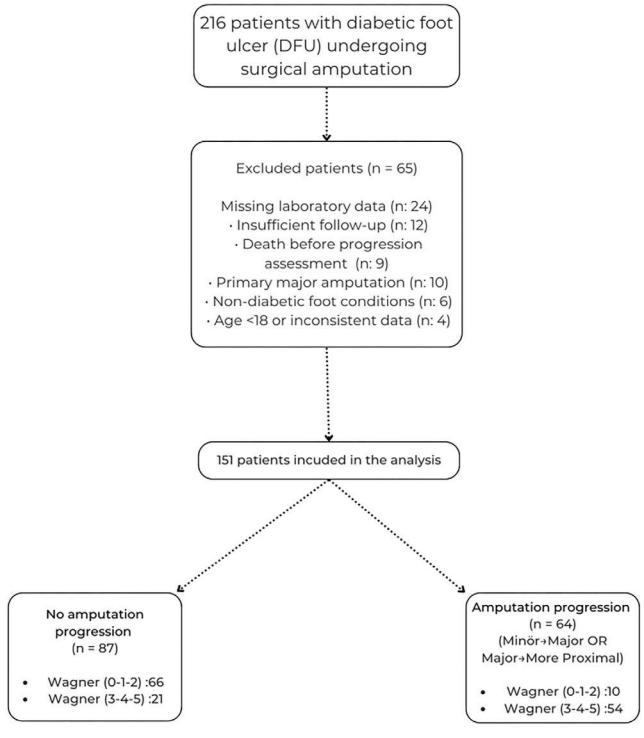

Figure 1. Study flow diagram. Flow diagram of patient selection. Of 216 patients with diabetic foot ulcer (DFU), 151 met inclusion criteria and were analyzed. Patients were categorized into groups with and without amputation progression, with corresponding Wagner grade distributions

square test for categorical variables. Variables associated with amputation progression in univariate analyses at a significance level of p<0.10, or those deemed clinically relevant, were entered into a multivariable logistic regression model. This model was developed using the backward stepwise likelihood ratio (Backward LR) method. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Model fit was assessed using the Hosmer-Lemeshow test, and explanatory power was evaluated using Nagelkerke R^2. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 151 patients who underwent surgical amputation for DFUs were included in the analysis. The mean age of the cohort was 66.9±9.2 years, 61.5% (n=93) were male, and the mean BMI was 28.09±4.6 kg/m^2. The mean duration of diabetes was 11.85±2.6 years. Laboratory parameters showed a mean albumin level of 2.97±0.64 g/dL, CRP of 108±39 mg/L, HbA1c of 10.1±1.47%, and total cholesterol of 142±41 mg/dL. The mean lymphocyte count was 1307±392/μL, serum creatinine was 2.04±1.03 mg/dL, and the mean eGFR was 46±19 mL/min. Baseline characteristics of the study population are summarized in Table 1.

Of the 151 patients, 64 (42.3%) experienced amputation progression and 87 (57.7%) did not. Patients with progression were older, had lower BMI , and had a longer duration of diabetes than those without progression. Albumin levels, lymphocyte counts, and total cholesterol concentrations were lower in the progression group. CRP and WBC values were higher among patients with progression. Glucose and HbA1c levels were also higher in this group. Serum creatinine levels were higher and eGFR values were lower in patients with progression. Hemoglobin levels were lower in the progression group. Significant associations were observed among CONUT scores, Wagner grade, GNRI categories, and amputation progression (all p<0.001). Higher CONUT scores were more frequent among patients with higher Wagner grades (3-5), higher GNRI-defined nutritional risk categories, and higher progression rates. A significant association was observed between CONUT and GNRI classifications (χ^2=198.1, p<0.001). These relationships are illustrated in Figures 2, 3, and 4.

Table 1. Baseline demographic and laboratory characteristics of the study population by amputation progression status

Characteristic	Total (n=151)	No progression, (n=87) mean±SD	Progression, (n=64) mean±SD	p-value
Age (years), mean±SD	66.9±9.2	65.0±8.7	69.8±9.2	0.024
BMI (kg/m^2), mean±SD	28.09±4.6	30.20±3.43	25.23±4.33	<0.001
Duration of DM (years), mean±SD	11.85±2.6	11.06±1.59	12.69±3.10	<0.001
Gender, n (%)				
Male	93 (61.5)	49 (%56)	44 (%69)	0.167[a]
Female	58 (38.5)	38 (%44)	20 (%31)	
Smoking, n (%)				
Yes	60 (40)	40 (%46)	20 (%31)	0.097[a]
No	91 (60)	47 (%54)	44 (%69)	
Albumin (g/dL)	2.97±0.64	3.31±0.39	2.48±0.57	<0.001
CRP (mg/L)	108±39	88.7±34.1	136.6±26.9	<0.001
HbA1c (%)	10.1±1.47	9.21±1.46	11.49±0.96	<0.001
Total cholesterol (mg/dL)	142±41	160.9±34.2	114.8±34.0	<0.001
Lymphocyte count(/μL)	1307±392	1496±318	1020±298	<0.001
Serum creatinine (mg/dL)	2.04±1.03	1.42±0.52	2.87±0.96	<0.001
Glucose (mg/dL)	248±52	227.2±40.0	281.0±51.8	0.031
Hemoglobin (g/dL)	9.9±1.07	10.43±0.90	9.10±0.77	<0.001
WBC (×10^3/μL)	8.17±2.71	7.17±2.12	9.54±2.67	<0.001
eGFR (mL/min)	46±19	56.6±17.6	32.4±12.2	<0.001

Values are expressed as mean ± SD. Mann-Whitney U test was used for continuous variables
[a]: Pearson Chi-Square Test, p<0.05 considered statistically significant
Comparison of patients with and without amputation progression. The "total" column reflects the overall study population (n=151), while the "no progression" and "progression" columns present subgroup characteristics. p-values represent comparisons only between the two subgroups (progression vs. no progression)
Continuous variables are shown as mean±SD and compared using the Mann-Whitney U test; categorical variables were analyzed using Pearson's chi-square test
SD: Standard deviation, WBC: White blood cell, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, BMI: Body mass index, DM: Diabetes mellitus

In the multivariable logistic regression model, serum creatinine, GNRI, and Wagner classification were independently associated with amputation progression. Serum creatinine was associated with progression (OR: 4.06, 95% CI: 2.04-8.09, p<0.001). GNRI was also associated with amputation progression (OR: 2.72, 95% CI: 1.30-5.65, p=0.008). Wagner grade ≥3 was independently associated with progression (OR: 3.25, 95% CI: 1.07-9.83, p=0.037). The final regression model demonstrated good calibration (Hosmer-Lemeshow p=0.786) with a Nagelkerke R^2 of 0.651 (Table 2). CONUT was associated with progression in univariate analyses but was not retained in the multivariable model.

DISCUSSION

DFUs represent a complex clinical condition associated with substantial morbidity, mortality, and a frequent need for surgical intervention (12). Despite increasing awareness of the role of systemic factors in DFU outcomes, the impact of nutritional status on amputation level progression has not been clearly defined. The potential effects of malnutrition, inflammation, and metabolic disturbances on wound healing are well established (13). The present study aimed to evaluate the association of GNRI and CONUT scores with progression in amputation level in patients undergoing surgical treatment for DFUs. The findings support our initial hypothesis and demonstrate that impaired nutritional

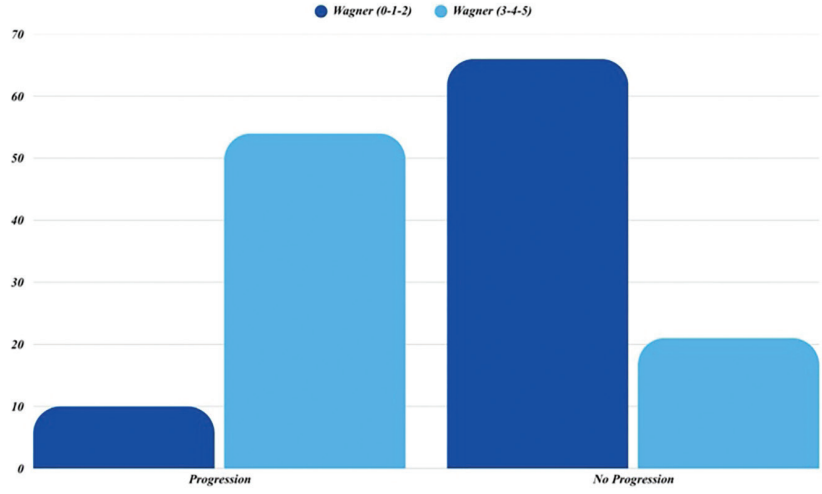

Figure 2. Distribution of Wagner ulcer grades by amputation progression status. This bar chart illustrates the distribution of Wagner grades (0-1-2 vs. 3-4-5) among patients with and without amputation progression. Higher-grade ulcers (Wagner 3-5) were notably more frequent in the progression group, whereas lower-grade ulcers (Wagner 0-2) were predominantly observed in patients without progression

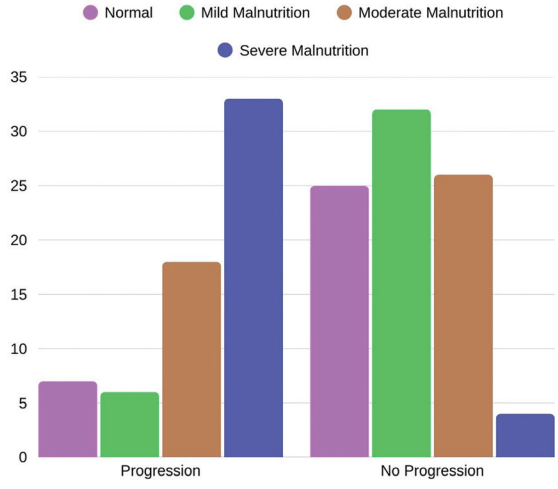

Figure 3. CONUT-based nutritional status categories in patients with and without amputation progression. This figure shows the distribution of nutritional status according to CONUT scoring (normal, mild malnutrition, moderate malnutrition, and severe malnutrition). Severe malnutrition was more common in the progression group, while normal and mild malnutrition categories were more prevalent among patients without progression

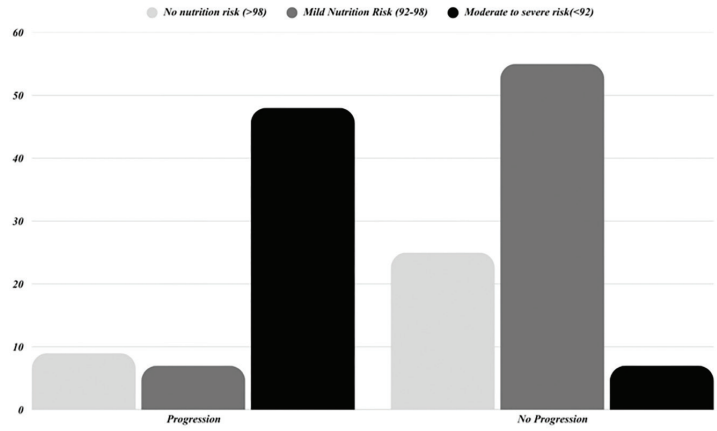

Figure 4. GNRI-based nutritional risk categories by amputation progression status. This bar graph presents the frequency of GNRI nutritional risk levels (no nutrition risk, mild nutrition risk, and moderate-to-severe nutrition risk) across the two patient groups. Moderate-to-severe nutrition risk (<92) was markedly higher in the progression group, whereas mild or no nutrition risk was more common in patients without progression
GNRI: Geriatric Nutritional Risk Index

Table 2. Independent predictors of amputation progression

Variable	OR	95% CI	p-value
Serum creatinine	4.06	2.04-8.09	<0.001
GNRI	2.72	1.30-5.65	0.008
Wagner grade ≥3	3.25	1.07-9.83	0.037

The multivariable logistic regression model identified serum creatinine, GNRI, and Wagner grade ≥3 as independent predictors of amputation progression. Higher serum creatinine levels and poorer nutritional status were associated with a significantly increased risk of progression. The final model demonstrated good calibration (Hosmer-Lemeshow p=0.786) and strong explanatory power (Nagelkerke R^2=0.651)
GNRI: Geriatric Nutritional Risk Index, OR: Odds ratio, CI: Confidence interval

status, along with adverse metabolic and inflammatory profiles, is significantly associated with an increased likelihood of progression to amputation. Notably, patients with progression exhibited poorer nutritional indices, greater inflammatory burden, worse glycemic control, and more pronounced renal dysfunction compared with those without progression.

The pathophysiology of DFUs is multifactorial, primarily driven by peripheral neuropathy, ischemia related to peripheral arterial disease, and superimposed infection (14). In addition to these mechanisms, systemic metabolic disturbances play a critical role in determining wound healing capacity. Reductions in albumin, cholesterol, and lymphocyte levels reflect impaired immune competence, diminished tissue repair capacity, and reduced metabolic reserve (15,16). The elevated CRP and WBC levels observed in patients with amputation progression are indicative of an intensified inflammatory response, which is known to adversely affect wound healing (17,18). Furthermore, renal dysfunction contributes to this process by impairing immune function, promoting systemic inflammation, and disrupting microvascular circulation (19). Anemia, commonly observed in chronic disease states, further compromises tissue oxygenation and healing potential (15). Persistent hyperglycemia, reflected by elevated HbA1c and glucose levels, remains a central driver of metabolic dysregulation, impairing leukocyte function and collagen synthesis, thereby delaying wound healing (20). Collectively, these findings demonstrate that the clinical and biochemical differences observed between groups are physiologically plausible and consistent with established mechanisms.

In addition to systemic factors, local wound characteristics are critical determinants of clinical outcomes. The Wagner classification remains one of the most widely used systems for assessing DFU severity (21,22). Although lower Wagner grades are generally associated with favorable outcomes, grades ≥3 indicate advanced tissue involvement and a higher risk of adverse progression. In the present study, higher Wagner grades were independently associated with amputation progression, consistent with previous reports emphasizing the prognostic significance of ulcer severity (22). The combined predictive value of GNRI, serum creatinine, and Wagner classification suggests that both systemic and local factors should be considered when evaluating the risk of disease progression.

From a clinical perspective, these findings highlight the importance of incorporating nutritional assessment into routine DFU management. Early identification of patients at nutritional risk, using simple and accessible tools such as GNRI, may facilitate timely intervention. Multidisciplinary approaches, including formal dietary consultation, individualized nutritional supplementation, and patient education, may help improve overall outcomes and potentially reduce the risk of progression to amputation. In addition, close monitoring and optimization of renal function and glycemic control appear essential in this high-risk population.

The present study has several strengths. The simultaneous evaluation of GNRI and CONUT scores in relation to amputation level progression provides a novel contribution to the literature, as most previous studies have focused primarily on mortality or major amputation outcomes rather than progression patterns (9,23-28) . The inclusion of comprehensive biochemical and clinical parameters allowed for a multidimensional assessment of the interplay between nutritional status, inflammation, renal function, and metabolic control. Furthermore, the use of multivariable regression analysis enabled the identification of independent predictors, enhancing the robustness of the findings and their potential clinical applicability.

Study Limitations

However, several limitations should be acknowledged. First, the retrospective, single-center design limits causal inference and may affect the generalizability of the results. Second, although multiple clinical and laboratory variables were included, important confounding factors such as peripheral arterial disease status, vascular imaging findings, and revascularization procedures were not systematically assessed, representing a significant limitation given their known impact on DFU outcomes. Third, standardized wound classification systems that incorporate infection and ischemia severity, such as the Wound, Ischemia, and foot Infection classification, were not available in this dataset, potentially limiting the ability to fully account for disease complexity. Fourth, information regarding in-hospital nutritional support or supplementation was not consistently available, precluding assessment of its potential modifying effect on outcomes. Fifth, although amputation progression was selected as a clinically meaningful endpoint reflecting functional deterioration, it may be influenced by surgeon decision-making and patient-related factors, thereby introducing potential subjectivity. Finally, collinearity between nutritional indices such as GNRI and CONUT limited their simultaneous inclusion in multivariable models; therefore, the independent contribution of each index should be interpreted with caution.

CONCLUSION

Poorer nutritional status, impaired renal function, and higher Wagner grade were associated with an increased likelihood of progression to a higher amputation level among patients with DFUs. Future research should incorporate prospective multicenter designs and more standardized analytical methods to refine risk prediction models and validate the clinical utility of nutritional indices in this population.

ETHICS

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Health Practice and Research Center Clinical Research Ethics Committee (approval no: 5001, date: 05.08.2025).

Informed Consent: Patient consent was waived due to the retrospective nature of this study.

FOOTNOTES

Authorship Contributions

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

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

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Research

The Relationship Between Chronic Total Occlusion Morphology and Procedure Success in Percutaneous Endovascular Treatment of Left Subclavian Artery

Sol Subklavyen Arterin Perkütan Endovasküler Tedavisinde Kronik Total Oklüzyon Morfolojisi ile İşlem Başarısı Arasındaki İlişki

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ABSTRACT

Objective: In this study, we aimed to investigate results of percutaneous endovascular interventions (PEI) in symptomatic proximal left subclavian artery (LSA) chronic total occlusions (CTOs) and its relationship with angiographic and morphological typing.

Methods: This study enrolled retrospectively evaluated 60 patients (41 males 68.3%, mean age 61.2±7.727 years) treated by PEI symptomatic proximal LSA CTOs between April 2010 and December 2021. Technical success was defined as residual stenosis of <30%, the absence of major complications (any access side complications, flow-limiting dissection, rupture). CTOs were classified mainly into 4 types according to their angiographic appearance [rat-tail n=12 (20%), plain n=18 (30%), hilly n=18 (30%) and peak n=10 (16.7%) types, also n=2 (3,3%) in-stent CTOs].

Results: The study cohort was divided into 2 groups as technically successful (n=49) and technical unsuccessful (n=11). Symptoms were due to 15 (25%) vertebrobasilar insufficiency 17 (28.3%) coronary ischemia had a left internal mammary artery by-pass graft and 28 (46.7%) arm claudications. Plain type CTO of LSA (81.8 vs. 18.4%, p<0.001), dual approach (femoral and radial) (100 vs. 65.3%, p=0.017) and lesion crossing-retrograde (90.9 vs. 44.9%, p=0.022) were notably higher in the technical successful group than in the technical unsuccessful group. In the logistic regression analysis, the presence of plain-type CTO lesions (odds ratio: 14.85, 95% confidence interval: 2.498-88.334, p=0.003) was found to be the independent predictor of technical failure.

Conclusion: PEI is a safe and effective treatment for LSA CTOs; the antegrade approach is the preferred initial method, although this choice may necessitate a retrograde approach depending on certain anatomical and clinical characteristics.

Keywords: Chronic proximal left subclavian artery, chronic total occlusions, endovascular therapy

ÖZ

Amaç: Bu çalışmada, semptomatik proksimal sol subklavyen arter (LSA) kronik total oklüzyonlarında (KTO) perkütan endovasküler girişimlerin (PEG) sonuçlarını ve bunların anjiyografik ve morfolojik sınıflama ile ilişkisini araştırmayı amaçladık.

Gereç ve Yöntem: Bu çalışmaya, Nisan 2010 ile Aralık 2021 tarihleri arasında semptomatik proksimal LSA KTO'su nedeniyle PEI ile tedavi edilen ve geriye dönük olarak değerlendirilen 60 hasta (41 erkek %68,3, ortalama yaş 61,2±7,727 yıl) dahil edildi. Teknik başarı; %30'un altında rezidüel stenoz varlığı ve majör komplikasyonların (herhangi bir giriş yeri komplikasyonu, akımı kısıtlayan diseksiyon veya rüptür) yokluğu olarak tanımlandı. KTO'lar, anjiyografik görünümlerine göre temelde 4 tipe ayrıldı: *rat-tail* (n=12; %20), *plain* (n=18; %30), *hilly* (n=18; %30), *peak* (n=10; %16,7). Ayrıca 2 olguda (%3,3) stent içi total oklüzyon saptandı.

Bulgular: Çalışma grubu, teknik başarı olan (n=49) ve teknik başarı olmayan (n=11) olmak üzere iki gruba ayrıldı. Semptomlar; 15 hastada (%25) vertebrobaziler yetmezlik, 17 hastada (%28,3) koroner iskemi (sol iç meme atardamarı bypass grefti mevcut) ve 28 hastada (%46,7) kol kladikasyosu kaynaklıydı. Teknik başarı olmayan grupta LSA'da *plain* tip KTO (%81,8'e karşı %18,4; p<0,001), ikili yaklaşım (femoral ve radial) (%100'e karşı %65,3; p=0,017) ve retrograd lezyon geçişi (%90,9'a karşı %44,9; p=0,022) oranları, teknik başarı olan gruba kıyasla belirgin şekilde daha yüksekti.

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ÖZ

Lojistik regresyon analizinde, *plain* tip KTO lezyonlarının varlığı (olasılık oranı: 14,85; %95 güven aralığı: 2,498-88,334; p=0,003], teknik başarısızlığın bağımsız bir öngördürücüsü olarak saptandı.

Sonuç: PEI, LSA KTO'ları için güvenli ve etkili bir tedavi yöntemidir; antegrad yaklaşım tercih edilen ilk yöntem olmakla birlikte, belirli anatomik ve klinik özelliklere bağlı olarak bu tercih retrograd bir yaklaşımı gerektirebilir.

Anahtar Kelimeler: Proksimal sol subklavyen arter, kronik total oklüzyonlar, endovasküler tedavi

INTRODUCTION

Some of symptomatic extracranial cerebrovascular diseases consist of chronic total occlusions (CTOs) of the subclavian artery (SA) (1). SA CTOs are usually atherosclerotic. Inflammatory arteritis and other rare causes are less common. The prevalence of SA stenosis in the general population is estimated at approximately 2% (2). They occur 1.5 to 2 times more frequently in men and are more common in the population over the age of 50 (3). The most affected part of left SA (LSA) by atherosclerosis is proximal first 2 centimeter from aorta origin (Figure 1) (4). CTOs were classified into 4 types according to their angiographic appearance (rat-tail, plain, hilly and peak type) (Figure 2) (5). CTO of the proximal LSA occurred four times more frequently than right side even when imnominate artery include two main branch originated (6). LSA stenosis or CTOs require treatment when symptomatic (7). The main three reasons for endovascular treatmant are vertigo caused by subclavian steel syndrome, arm claudication and ischemia in coronary vascular system due to patent left internal mammarian artey-left anterior descending artery (LIMA-LAD) bypass greft (8). CTO of the proximal LSA occurred four times more frequently than right side even when imnominate artery include two main branch originated (6). Since first successful percutoneus transluminal angioplasty (PTA) was done by Bachman and Kim (9) in 1980 PTA and stenting is becoming first treatment strategy in left subclavian atherosclerotic disease. Stenting after PTA is superior to PTA alone strategy for long term patency rate (10). However the success of percutaneous therapy is hıgh in high-grade stenozis of the LSA, the percutaneous success rate is lower in CTOs (11) . Standart open surgical carotid-subclavian bypass (CSB) surgery operation is required when PTA is failed . They are few report and case series including endovasculer treatment (ET) of left subclavian CTO lesions (12-14). With advances in stent technology and increased usage rates, short- and long-term success rates have increased, and it has become the first-choice treatment compared with bypass surgery (15). Here we aim to report our ET of isolated proximal left subclavian CTOs results and its relationship with angiographic and morphological features.

METHODS

Our retrospective cohort study included percutaneous interventions for symptomatic, isolated CTO of the left proximal SA in 60 patients between April 2010 and December 2021. Approval was obtained from the

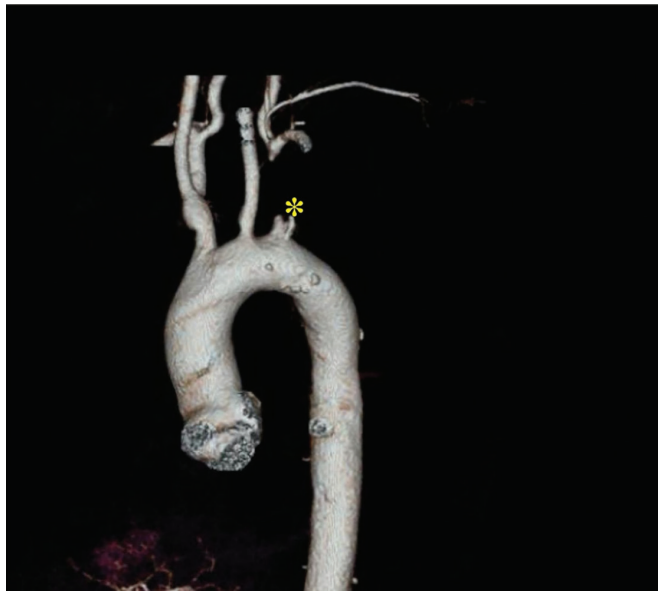

Figure 1. Computed tomography angiography image of left subclavian artery chronic total occlusion

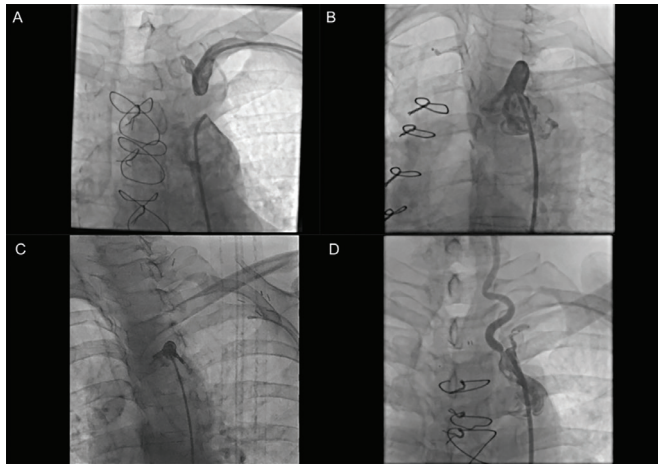

Figure 2. Conventional angiography depicts 4 different morphological types of chronic total occlusion of the proximal left subclavian artery. A: Plain type, B: Hilly type, C: Peak type, D: Rat-tail type

Table 1. Baseline clinical and demographical variables of the study population

Parameters	All (n=60)	Successful (n=49)	Unsuccessful (n=11)	p-value
Age (years)	61.2±7.727	60.6±7.1	64.0±9.8	0.191
Gender (man), n (%)	41 (68.3)	34 (69.4)	7 (63.6)	0.484
Weight (kg)	79 (70-84)	75 (70-84)	80 (76-85)	0.237
Height (cm)	168 (163-173)	169 (163-173)	165 (159-173)	0.315
BMI (kg/m^2)	27.2±3.71	26.8±3.75	29.0±3.01	0.074
Smoking n(%)	32 (53.3)	26 (53.1)	6 (54.4)	0.929
HTN n (%)	50 (83.3)	40 (81.6)	10 (90.9)	0.409
DM n (%)	23 (38.3)	21 (42.9)	2 (18.2)	0.118
HPL n (%)	55 (91.7)	44 (89.8)	11 (100)	0.349
CAD n (%)	35 (58.3)	28 (57.1)	7 (63.6)	0.483
CABG n (%)	21 (35)	15 (30.6)	6 (54.5)	0.125
CKD n (%)	10 (16.7)	8 (16.3)	2 (18.2)	0.591
COPD n (%)	10 (16.7)	9 (18.4)	1 (9.1)	0.409
CVD n (%)	2 (3.3)	2 (4.1)	0	0.664
CHF n (%)	9 (15)	6 (12.2)	3 (27.3)	0.206
AF n (%)	9 (15)	7 (14.3)	2 (18.2)	0.525
HB (g/dL)	13.8 (12.2-14.6)	13.9 (12.9-14.8)	11.5 (10.3-13.8)	0.015
HTC (%)	41.1 (36.1-43.5)	41.2 (39.1-43.7)	35.6 (32.4-42.8)	0.045
PLT (10^9/L)	256 (221-302)	255 (221-299)	266 (223-329)	0.586
WBC (10^9/L)	9 (7.4-10.7)	9.1 (7.4-10.8)	8.3 (7.5-10.5)	0.871
MPV (fL)	9.8 (9.1-10.8)	9.9 (9.2-10.8)	9.6 (9.1-11.1)	0.939
Neutrophil (10^9/L)	5.5 (4.5-7)	5.4 (4.51-7.04)	5.87 (4.72-8.5)	0.325
Lymphocyte (10^9/L)	2.2 (1.8-2.7)	2.25 (1.87-2.79)	2.15 (1.46-2.28)	0.172
ALT (U/L)	15 (11.2-20.7)	16 (13-22)	14 (10-16)	0.083
AST (U/L)	17 (14-21.7)	17 (14-22)	15 (12-21)	0.416
Creatinin (mg/dL)	1.0±0.75	1.05±0.81	1.08±0.44	0.906
Bun (mg/dL)	16 (13-23)	16 (14-23)	19 (12-27)	0.863
Sodium (mmol/L)	138 (136-140)	138 (136-140)	136 (136-139)	0.107
Potasium (mmol/L)	4.4 (4.1-4.7)	4.4 (4.2-4.8)	4.3 (4.0-4.6)	0.189
Uric acid (mg/dL)	5.4 (4.8-6.3)	5.4 (4.85-6.25)	5.85 (5.1-6.3)	0.734
Albumin (mg/dL)	4.4 (4.1-4.6)	4.4 (4.25-4.6)	4.25 (4-4.5)	0.088
Calcium (mg/dL)	9.3 (8.9-9.6)	9.36 (9.09-9.62)	9.2 (8.8-9.3)	0.106
Glucose (mg/dL)	106 (91-131)	103 (91-131)	108 (92-125)	0.848
TRG (mg/dL)	191.8±134.1	202.4±143.9	139.8±42.6	0.181
Total cholesterol (mg/dL)	194.4±49.5	196±50.8	±186.8	0.442
HDL (mg/dL)	40 (35-46)	40 (36-46)	43 (35-46)	0.887
LDL (mg/dL)	113.1±42.3	112.57±43.9	115.5±36.3	0.836
CRP (mg/L)	5 (3.2-8)	5 (3.1-8)	8.6 (4.1-11)	0.139

BMI: Body mass index, CRP: C-reactive protein, Hb: Hemoglobin, Htc: Hematocrit, WBC: White blood cell, PLT: Platelets, MPV: Mean platelet volume, Neut: Neutrofil, Lym: Lymphocytes, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BUN: Blood Urea Nitrogen, TRG: Triglycerides, HDL: High density lipoprotein, LDL: Low density lipoprotein, DM: Diabetes mellitus, HTN: Hypertension, CKD: Chronic renal failure, CAD: Coronary artery disease, CHF: Chronic heart failure, COAD: Chronic obstructive airway disease, AF: Atrial Fibrilation, CVD: Cerebrovascular Disease, CABG: Coronary Artery Bypass Greft, HPL: Hyperlipidemia

local ethics committee for our study. All patients were older than 18 years. Demographic data, clinical history, and laboratory values of the patients were obtained from the patient files with the hospital information operating system. All lesions were of atherosclerotic etiology and were located in the LSA proximal to the left internal mammary artery. Interventions for true and pseudoaneurysmal lesions of the LSA were excluded from the study. In our study, SA CTO was diagnosed by Doppler ultrasound (retrograde reverse flow observed in the left vertebral artery), computed tomographic angiography, magnetic resonance angiography or conventional anjiography. Patients were included in the procedure if they had a systolic arterial pressure difference of at least 20 mmHg between the two upper extremities before the procedure. In our study, reproducible left arm pain with exercise, vertigo (due to SA steal syndrome), and the presence of a patent LIMA-LAD graft constitute the 3 main indications for intervention. After the intervention, all patients were assessed in outpatient clinics during the first month and then were followed up annually. In post-intervention follow-up assessments, clinical symptom relief was recorded, and distal pulse palpation and inter-arm blood pressure difference were monitored. Technical success was defined as residual stenosis of <30%, absence of major complications (any access-site complications, flow-limiting dissection, rupture), and a difference in blood pressure between the two arms below 10 mmHg after the procedure.

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the University of Health Sciences Türkiye, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Clinical Researchs Ethics Committee (approval no: 2023.06-67, date: 22.08.2023). Written informed consent was obtained from each patient.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). Data are expressed as n (%) for categorical variables. Pearson's chi-square and Fisher's exact tests were performed for categorical variables. After normal distribution was analyzed with the Kolmogorov-Smirnov test, the data were expressed as median (25^{th} and 75^{th} percentiles) for variables without a normal distribution and mean±standard deviation for variables with normal distribution. Student's t-test was used to compare quantitative variables with a normal distribution, while the Mann-Whitney U test was used to compare quantitative variables with a non-normal distribution. Univariate and multivariate logistic regression analyses were used to determine the independent predictors of technical success.

RESULTS

Sixty (41 males 68.3%) patients with a mean age 61.2±7.72 years were performed percutaneous angioplasty and stenting procedure. Fourty nine patients (81.6%) achieved technical success, whereas 11 patients (18.4%) failed to achieve technical success. There were no differences in baseline characteristics between the two groups, except for left ventricular ejection fraction (p<0.045), hemoglobin (p<0.015), and hematocrit (p<0.045) (Tables 1 and 2). Baseline laboratory test results are also shown in Table 2. Procedural indications were 15 (25%) vertebrobasilar insufficiency, 28 (46.7%) coronary ischemia had a LIMA coronary artery by-pass greft and 17 (28.3%) arm claudications.

Left subclavian total occlusion was diagnosed in the patients by Doppler ultrasound (n=11), computerized tomographic angiography (n=30), DSA (n=18), and magnetic resonance imaging angiography (n=1).

The arcus aorta morphology of the patients in the study was categorized either by arcus aortogram or by computed tomographic angiography. Thirty (55%) patients had type 1, 18 (30%) patients had type 2, and 9 (15%) patients had type 3 arcus aorta; there were no statistical differences in procedural success between the groups (Table 3).

The preprocedural systolic and diastolic blood pressure between the upper extremities did not differences between two group.

In the percutaneous procedure, only the femoral route was used in 17 (28.3%) of the patients, while the dual approach (femoral+brachial or radial access) was preferred in 43 (71.7%). Dual access side was attempted in all 11 unsuccessful patients and retrograde crossing of the total lesion was not attempted in only 2 patients. Although the length of the CTO segment was longer in the unsuccessful group, the difference was not statistically significant. The impact on procedural success of CTO segment length (p=0.232) and of the presence of calcification (p=0.317) within the segment has not been determined. Guidewire diameter and structure (hydrophilic or non-hydrophilic) did not differ between the two groups with respect to procedural success (p=0.273) (Table 3).

All CTO lesions were initially attempted to be crossed with the antegrade method. Success was achieved in 26 of 27 (45%) patients in whom only the antegrade route, and not retrograde crossing, was attempted. In the remaining

Table 2. Physical examination and etiology variables of the study population

Parameters	All (n=60)	Successful (n=49)	Unsuccessful (n=11)	p-value
LUESP (mmHg)	77.31±14.45	78.42±15.6	72.45±5.82	0.220
LUEDP (mmHg)	52.5±8.9	52.88±9.51	51.09±6.10	0.556
RUESP (mmHg)	134.9±12.9	135.8±13.7	131.1±8.02	0.289
RUEDP (mmHg)	81.8±7.5	81.59±7.99	82.73±5.17	0.655
PİSGBUE (mmHg)	3.8±10.6	1.86±3.87	52.50±3.53	<0.001
Indications				
VBI	15 (25)	13 (26.5)	2 (18.2)	0.100
Arm claudication	28 (46.7)	25 (51)	3 (27.3)	
Coronary ischemia with patent LIMA-LAD graft	17 (28.3)	11 (22.5)	6 (54.5)	
Diagnostic tools				
Doppler USG	11 (18.3)	8 (16.3)	3 (27.3)	
CTA	30 (50)	28 (57.1)	2 (18.2)	0.100
MRA	1 (1.7)	1 (2.0)	0	
DSA	18 (30)	12 (24.5)	6 (54.5)	
LV EF (%)	60 (55-60)	60 (55-65)	59 (55-60)	0.045

VBI: Vertebrobasilar insufficiency, LVEF: Left ventricular ejection fraction, USG: Ultrasonography, CTA: Computed tomographic anjiography, MRA: Magnetic resonance angiography, LUESP: Left Upper Extremity Systolic Pressure, LUEDP: Left Upper Extremity Diastolic Pressure, RUESP: Right Upper Extremity Systolic Pressure, RUEDP: Right Upper Extremity Diastolic Pressure, PISGBUE: Post-intervention Systolic Pressure Gradient between upper extremities, DSA: Digital Subtraction Angiography, LIMA-LAD: Left internal mammamry artery-left anterior descending artery

32 (53.3%) patients, retrograde true lumen transition was attempted, of whom 22 were successful and 10 were unsuccessful. Successful recanalization with reverse controlled antegrade and retrograde tracking technique was achieved in 1 (1.6%) patient.

Balloon-expandable stents were implanted in 47 of the successful patients, and self-expandable stents were implanted in 2 of them. Post-dilatation was performed in 13 patients after stent implantation. In 2 patients, a second stent was implanted distally because of edge dissection following implantation of the first stent. In one patient, brachial artery dissection and occlusion were observed due to the uncontrolled advancement of the distal end of the 0.035 hydrophilic guidewire, and they were successfully treated with balloon angioplasty. The mean diameter of the implanted stents was 8.37±1.06 mm and the length was 40.56±14.22 mm.

Among the proximal left SA CTOs included in the study, the morphological subgroup counts were 10 (16.7%) peak type, 18 (30%) hilly type, 18 (30%) plain type, 12 (20%) rat-tail type, and 2 (3.3%) in-stent restenosis. Frequencies of plain type CTO of LSA (81.8 vs. 18.4%, p<0.001), dual approach (femoral and radial) (100 vs. 65.3%, p=0.017), and lesion crossing-retrograde (90.9 vs. 44.9%, p=0.022) were notably higher in the technical success (-) group than in the technical success (+) group. Logistic regression analysis showed that the presence of plain-type CTO lesions (odds ratio: 14.85, 95% confidence interval: 2.498-88.334, p=0.003) was an independent predictor of technical success. Among the CTO morphological types, only the plain type differed with respect to procedural success (Table 3).

There was no statistically significant difference in the complication rate during the percutaneous procedure between the two groups (Table 4). No procedure-related transient ischemic attack or cerebrovascular accident was observed in either group. CSB operations were performed in 5 of 11 patients in whom the percutaneous procedure was unsuccessful.

DISCUSSION

Our study is one of the largest isolated left subclavian proximal segment CTO PTA series in the literature so far. The main findings of this study are: (1) only the plain type, as a CTO morphology, negatively predicted the success of the procedure; (2) arcus aorta type did not affect the success of the procedure; and (3) lesion length and the presence of calcification did not affect procedure success.

The procedural success rate observed in our study is similar to that reported in previous publications. Among the CTO morphological classification subtypes, only the plain type was found to be effective for processing success. We think that one major reason for this may be that the CTO segment is very close to the aorta and that the proximal cap region is ambiguous in the current morphological subtype. For this reason, it may be more appropriate to start cases of this CTO morphology primarily via the retrograde route.

Table 3. Data regarding morphological and technical characteristics affecting procedural success

Parameters	All (n=60)	Successful (n=49)	Unsuccessful (n=11)	p-value
Morphological type, n (%)				
Peak type	10 (16.7)	10 (20.4)	0	0.109
Hilly type	18 (30)	16 (32.7)	2 (18.2)	0.289
Plain type	18 (30)	9 (18.4)	9 (81.8)	<0.003
Rat-tail type	12 (20)	12 (24.5)	0	0.066
ISR-CTO	2 (3.3)	2 (4.1)	0	0.664
Arcus aorta type, n (%)				
1	33 (55)	28 (57.1)	5 (45.5)	0.447
2	18 (30)	15 (30.6)	3 (27.3)	
3	9 (15)	6 (12.2)	3 (27.3)	
Approach, n (%)				
Femoral	17 (28.3)	17 (34.7)	0	0.017
Dual (BA or RA with FA)	43 (71.7)	32 (65.3)	11 (100)	
Lenght of occlusion (mm)	25 (17.2-32.7)	24 (17-32)	29 (25-36)	0.232
Calsifications, n (%)	30 (50)	23 (46.9)	7 (63.6)	0.317
Guidewire covering, n (%)				
Hydrophilic	40 (66.7)	34 (69.4)	6 (54.5)	0.273
Non-hydrophilic	20 (33.3)	15 (30.6)	5 (45.5.)	
Guidewire diameter, n (%)				
0,014 inches	26 (43.3)	21 (42.9)	5 (45.5)	0.567
0,035 inches	34 (56.7)	28 (57.1)	6 (54.5)	
Microcatheter, n (%)				
None	9 (15.0)	9 (18.4)	0	0.148
1.8 Fr coronary	12 (20)	8 (16.3)	4 (36.4)	
4 Fr peripheral	39 (65)	32 (65.3)	7 (63.6)	
Lesion crossing, n (%)				
Antegrade	27 (45)	26 (53.1)	1 (9.1)	<0.022
Retrograde	32 (53.3)	22 (44.9)	10 (90.9)	
CART	1 (1.7)	1 (1.7)	0	
Baloon predilation, n (%)	49 (81.6)	49 (100)		
Stent type, n (%)				
Baloon expendable	46 (95.8)	46 (95.8)		N/A
Self expendable	2 (4.2)	2 (4.2)		
Stent diameter (mm)	8.37±1.06	8.37±1.06		
Stent lenght (mm)	40.56±14.22	40.56±14.22		
Post-dilatation PTA	13 (27.1)	13 (27.1)		

ISR-CTO: Instent restenozis chronic total occlusion, CART: Controlled antegrade and retrograde tracking technique, PTA: Percutaneous transluminal angioplasty, BA: Brachial artery, FA: Femoral artery, RA: Radial artery, Fr: French catheter size

Table 4. Complications associated with interventional procedures

Parameters	All (n=60)	Successful (n=49)	Unsuccessful (n=11)	p-value
Complications, n (%)				
None	54 (90)	45 (91.8)	9 (81.8)	0.302
SA dissection	4 (6.7)	3 (6.1)	1 (9.1)	
Access side Cx	1 (1.7)	0 (0)	1 (9.1)	
Stent migration	1 (1.7)	1 (2.0)	0	

SA: Subclavian artery, Cx: Complications

Contrary to popular belief, clinical conditions in which canalization of the LSA ostium is difficult, especially type 3 arcus aorta, are not statistically associated with procedural success.

Our study, consistent with other studies in the literature, showed that lesion length and the presence of calcification did not have a significant effect on procedural success. In our study, since routine CT angiography and quantitative calcium scoring were not performed on all patients before the procedure, the presence of calcification was mainly evaluated angiographically. Because the quantitative evaluation of calcification was not performed in our study, further studies are necessary.

Unlike other studies, the most common indication for intervention in our study was coronary ischemic symptoms in the presence of a patent LIMA-LAD graft rather than vertebrobasilar insufficiency or arm claudication. Our center is a tertiary cardiovascular branch hospital may have contributed to this clinical picture.

Our study showed that the success of the procedure in patients planned to undergo PTA can be increased by appropriate clinical indication, detailed morphological imaging, and careful procedural planning.

Study Limitations

Our study has some limitations. Although it is one of the largest isolated left SA CTO intervention series described, the small number of cases,single center , the retrospective nature of the study, and the difference in intervention preferences between operators constitute the main limitations. For this reason, prospective multicenter studies are needed.

CONCLUSION

Balloon angioplasty and stenting for isolated proximal LSA CTO cases is a safe, effective treatment , preferred over surgical intervention and antegrade approach is the first method of choice and, depending on some anatomical and clinical features, it increases the success of the procedure in the retrograde approach.

ETHICS

Ethics Committee Approval: This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the University of Health Sciences Türkiye, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Clinical Researchs Ethics Committee (approval no: 2023.06-67, date: 22.08.2023).

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

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: A.Y.Ç., A.G., S.K., A.A.Y., F.U., Concept: A.Y.Ç., A.G., S.K., Design: A.Y.Ç., A.G., S.K., Data Collection or Processing: A.Y.Ç., K.Ç., E.G.G., N.G.S., F.F.B., A.D., K.G., B.S., Analysis or Interpretation: A.Y.Ç., S.K., Literature Search: A.Y.Ç., A.G., E.G.G., N.G.S., A.D., K.G., B.S., Writing: A.Y.Ç., A.G., S.K.

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

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Case Report

Dedifferentiated Pleural Liposarcoma

Dediferansiye Plevral Liposarkom

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ABSTRACT

Ninety percent of primary pleural malignancies are malignant mesotheliomas. Pleural liposarcoma (LS) is a rare form of primary pleural malignancy. Among pleural LSs, the dedifferentiated subtype is even rarer and is considered a negative prognostic factor. In this report, we present the case of a 56-year-old male patient who was evaluated for the etiology of a right-sided pleural effusion. Over time, the disease progressed to involve the entire right hemithorax, circumferentially, with radiological findings resembling malignant mesothelioma. The diagnosis was confirmed by a tru-cut biopsy performed under thoracic ultrasonography guidance. This patient's prognosis remained poor during follow-up, and we present this case in light of the current literature.

Keywords: Liposarcoma, pleural malignancy, dedifferentiated pleural liposarcoma

ÖZ

Plevral primer malignitelerinin %90'ını malign mezotelyoma oluşturur. Plevranın liposarkomu oldukça nadir görülen bir primer plevral malignitedir. Plevral liposarkomlar içerisinde dediferansiye plevranın liposarkom ise daha da nadir görülen ve görülmesinin plevral liposarkomlar içerisinde negatif prognostik faktör olduğu kabul edilen bir alt tiptir. Bu yazıda; sağ plevral sıvı etyolojik incelenmesi için tetkik edilen, ilerleyen zaman içerisinde sağ hemitoraksı çepeçevre tutan ve radyolojik olarak malign mezotelyoma ile benzeşen, tanısını torasik ultrasonografi eşliğinde tru-cut biyopsi ile alan 56 yaşında takiplerinde prognozu çok kötü seyreden bir olgu güncel literatür eşliğinde paylaşıldı.

Anahtar Kelimeler: Liposarkom, plevral malignite, plevral dediferansiye liposarkom

INTRODUCTION

Liposarcoma (LS) is one of the most common types of sarcoma, accounting for 15-25% of all sarcoma types, and represents one of the most challenging entities in diagnostic pathology. The World Health Organization classifies LS into five main subtypes: well-differentiated LS (WDLS), dedifferentiated LS (DDLS), myxoid LS, pleomorphic LS (PLS), and myxoid PLS. These tumors most commonly originate from deep soft tissues, such as the retroperitoneal area, extremities, and intramuscular fascia. Intrathoracic LSs are extremely rare, accounting for only 1-2% of all LSs. LSs are aggressive tumors characterized by a high rate of recurrence and metastasis (1,2).

The exact incidence of primary pleural LS, a very rare pleural malignancy, remains unclear, as most cases have been reported as isolated case studies in the literature. It is believed to be more common in males and in individuals over the age of 50. The symptoms in most cases are non-specific, typically consisting of chest pain, cough, and dyspnea (3).

A review of the English literature reveals approximately 50 reported cases to date, and, due to its rarity in pulmonary practice, we present a case of dedifferentiated pleural LS located in the right hemithorax, accompanied by a brief review of the literature (4).

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CASE REPORT

A 56-year-old male patient presented to the emergency department with complaints of shortness of breath and was subsequently referred to the pulmonology clinic for further evaluation of pleural effusion (PE). His medical history included hypertension, coronary artery disease, and a prior cerebrovascular event. The patient had a 40 pack-year smoking history, with no notable family history. On physical examination, bilateral early inspiratory rales were auscultated. Laboratory test results are summarized in Table 1. A posteroanterior chest X-ray revealed PE in the right lung, volume loss in the right hemithorax, and multiple metastatic nodules in both lungs (Figure 1). Chest computed tomography (CT) demonstrated mediastinal pleural thickening in the right hemithorax, along with PE and multiple bilateral pulmonary nodules suggestive of metastasis (Figure 2).

Thoracentesis was performed under thoracic ultrasonography (USG) guidance. Cytological analysis of the pleural fluid revealed atypical cells suspicious for malignancy; however, the cell count was insufficient to establish a definitive diagnosis. A positron emission tomography-CT scan was performed, which showed multiple nodular lesions that were intensely hypermetabolic in both lungs (SUV_{max}: 9.4). In the right hemithorax, PE was noted along with intense hypermetabolism on the pleural surfaces, and a minimally hypermetabolic lesion was observed in the posterior aspect of the right lower lobe, measuring 47 mm (SUV_{max}: 12.5). In the mediastinum, intense hypermetabolic lymph nodes were detected in the right upper, bilateral lower paratracheal, subcarinal, and right hilar lymphatic stations, with the largest node located in the right hilar region, suggesting metastasis (SUV_{max}: 12) (Figure 3).

An informed consent form was obtained. For diagnostic purposes, a tru-cut biopsy of the right hemithorax was performed under thoracic USG guidance (Figure 4). Histopathological examination revealed tumoral cell infiltration embedded within dense fibrous stroma, with evidence of muscle and adipose tissue invasion at the periphery. The majority of the areas showed spindle cells without visible nucleoli. Extensive tumor necrosis was present. A comprehensive immunohistochemical panel was conducted, with no staining observed for smooth muscle actin, desmin, *SOX10*, cluster of differentiation 31 (*CD31*), *CD34*, Cam5.2, osteoclast associated receptor, cytokeratin, epithelial membrane antigen, D2-40, *SATB2*, WT1, *CALB2*, *STAT6*, anaplastic lymphoma kinase, *CD163*, immunoglobulin G4, *S100*, *CD45*, and *CD68*. Focal weak positivity was noted for cyclin-dependent kinase 4 and MDM2. The Ki-67 proliferation index was approximately 60% in the hotspot area. *BAP1* expression was retained. The differential diagnosis included pulmonary artery intimal sarcoma, sarcomatoid mesothelioma, DDLS, solitary fibrous tumor, malignant peripheral nerve sheath tumor, synovial sarcoma, inflammatory myofibroblastic tumor, malignant melanoma, IgG4-related diseases, histiocytic lesions, hematologic malignancies, extraskeletal osteosarcoma, and pleomorphic carcinoma with spindle cell features. Based on histopathological and immunohistochemical findings, the final diagnosis was consistent with DDLS (Figure 5).

A medical oncology consultation was requested for the case. However, as the patient and their relatives expressed that they do not wish to pursue oncological treatment despite initially considering it, the patient was advised to apply to the medical oncology outpatient clinic if they reconsider, and were subsequently discharged. Unfortunately, two months after the diagnosis, the patient passed away without receiving any oncological treatment.

Table 1. Laboratory values of the case

Parameter	Conclusion	RR
WBC (10^3 U/L)	12.4	4.00-10.00
Hemoglobin (g/dL)	6.6	13-17
Hematocrit (%)	22	40.00-54.00
Urea (g/dL)	35	16.6-48.5
Kreatinin (mg/dL)	0.39	0.7-1.2
ALT (U/L)	80	0-40
AST (U/L)	73	0-41
LDH (U/L)	224	135-225
CRP (µg/L)	138	0-5
Procalcitonin (mg/dL)	0.111	<0.5
Sedimentation mm/hour	26	0-15

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, LDH: Lactate dehydrogenase, mm: Millimeters, RR: Reference range, WBC: White blood cell

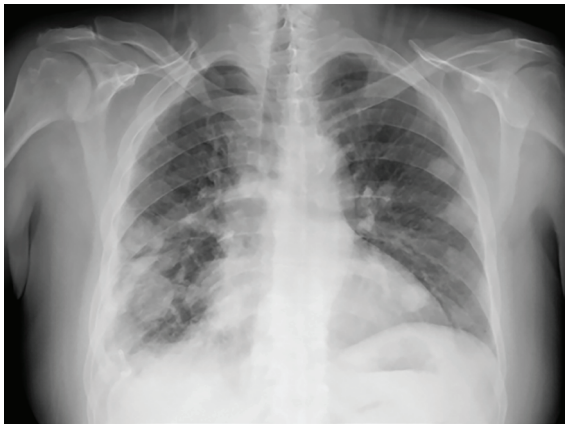

Figure 1. Lung X-ray of the case

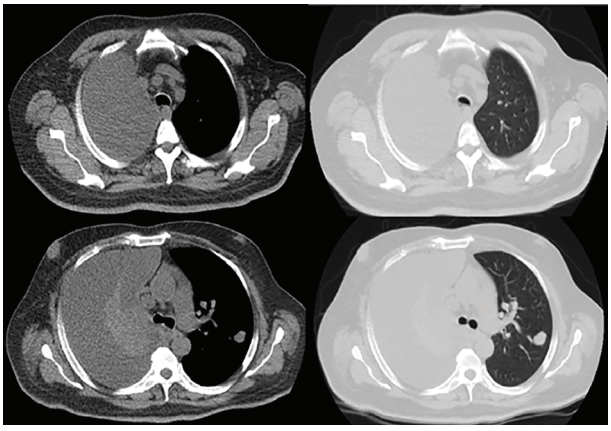

Figure 2. A computed tomography scan: mediastinal pleural thickening in the right hemithorax, circumferential involvement of the pleura in the right hemithorax, pleural effusion and multiple bilateral metastatic nodules

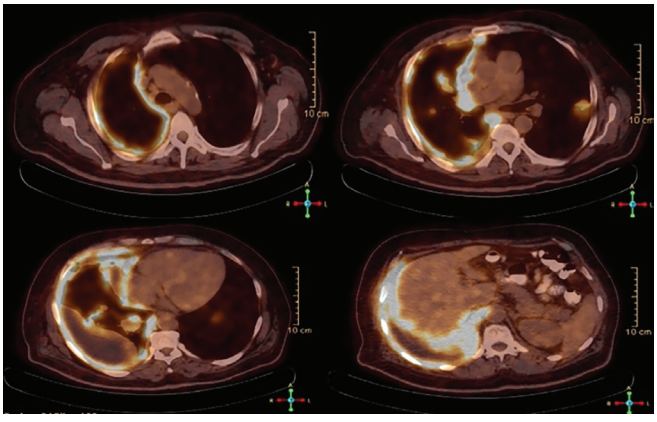

Figure 3. Positron emission computed tomography of the case

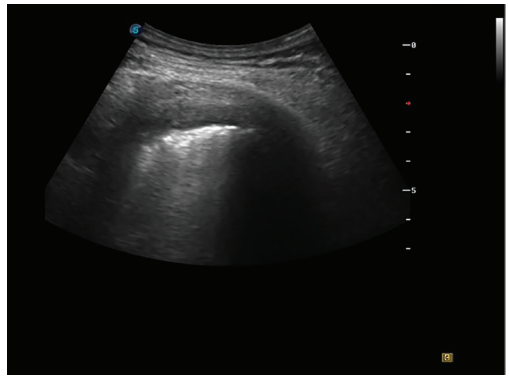

Figure 4. Appearance of thickened pleura on thoracic ultrasonography

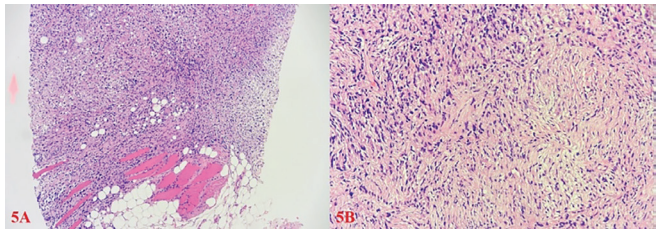

Figure 5. A) The tumor shows infiltration of adipose and muscle tissue at its periphery (hematoxylin and eosin x200). **B)** Within the fibrous stroma, tumoral infiltration with spindle-shaped cells and hyperchromatic nuclei lacking visible nucleoli was observed (hematoxylin and eosin x400)

DISCUSSION

This article presents a case of a 56-year-old male pleural LS, a rare and aggressive malignancy characterized by frequent recurrence and metastatic potential, which was diagnosed through a tru-cut biopsy guided by thoracic USG.

Malignant mesothelioma accounts for the majority of pleural malignant lesions (90%). The remaining cases include rare entities such as PLS, malignant solitary fibrous tumor, localized malignant mesothelioma, pleuropulmonary blastoma, synovial sarcoma, angiosarcoma, and pleural lymphoma. Although the exact etiology of PLS remains unclear, it is believed to arise from residual primitive mesenchymal cells. Additionally, although not definitive, the malignant transformation of pre-existing pleural lipomas is also suspected (5).

Upon reviewing the patient's chest CT from two years prior to admission, no findings suggestive of lipoma, pleural lipoma, or pleural pathology were identified. The most comprehensive study to date on pleural LS was conducted by Kawai et al. (4) and published in 2023. In their review of 45 reported cases, the authors aimed to evaluate the clinicopathological and immunohistochemical

characteristics of PLS and to identify prognostic factors. The results of the study indicated that the average patient age was 51, and 66% of cases were male. Dedifferentiated PLS was identified as the rarest histologic subtype with only five reported cases. *CDK4-MDM2* positivity was emphasized as a key marker for definitive diagnosis. The WDLS subtype was associated with a more favorable prognosis. Our case involved a 56-year-old male with *CDK4-MDM2* positivity and was consistent with dedifferentiated PLS, a rare and aggressive variant. This case supports previous findings highlighting the diagnostic value of *CDK4/MDM2* immunostaining and the poor prognosis associated with the dedifferentiated subtype.

Due to the rarity of PLS, it is not possible to provide definitive data regarding average tumor size, tissue density, or SUV_{max} values based on the current literature. In a study by Matsukuma et al. (6), which included their own case report and a review of 31 PLS cases, tumor sizes were found to range from 3.5 cm to 29 cm. Similarly, Chen et al. (7) reported tumor sizes ranging from 4 cm to 39 cm in a series of 23 cases. SUV_{max} values were reported to vary between 3.3 and 10.2 (5,6). Regarding CT density, Carrillo et al. (8) reported a density of 18 Hounsfield units (HU) in one PLS case on chest CT, while Prabhakar et al. (9) observed a density of 10 HU in their cases. Our case involved a dedifferentiated PLS, circumferentially surrounding the right hemithorax, with a maximum diameter of 10 cm, an SUV_{max} of 12.5, and a CT density of 18 HU.

One of the largest studies on PLS, conducted by Matsukuma et al. (6), emphasized that dedifferentiated histology is a negative prognostic factor. A review of the literature suggests that overall survival in PLS cases ranges between seven months and eight years (10). Our patient did not receive any oncological treatment and passed away two months after the diagnosis. Following the oncology consultation, no oncological treatment was planned for the patient due to the refusal by the patient and their relatives. The primary reasons for this decision may include the patient's poor overall performance status at the time of diagnosis, the presence of metastatic lesions in both lungs, and a high tumor burden in the right hemithorax. As emphasized in the literature, this is consistent with the limited response to treatment and generally poor prognosis observed in cases of dedifferentiated pleural LS (11).

CONCLUSION

In conclusion, the most common primary malignancy of the pleura is malignant mesothelioma. Although rare, other primary pleural malignancies that may radiologically mimic mesothelioma can also be encountered. There is a significant gap in the literature regarding these rare entities. Studies involving large case series of pleural malignancies, such as PLS, are needed to better understand their clinical, radiological, and pathological characteristics. However, even individual case reports, like this one, provide valuable contributions to the growing body of literature on rare pleural tumors.

ETHICS

Informed Consent: An informed consent form was obtained.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: D.Y., Concept: C.D., Design: C.D., B.B., Data Collection or Processing: D.Y., A.N.T.Y., Analysis or Interpretation: B.B., Literature Search: D.Y., Writing: C.D.

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

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