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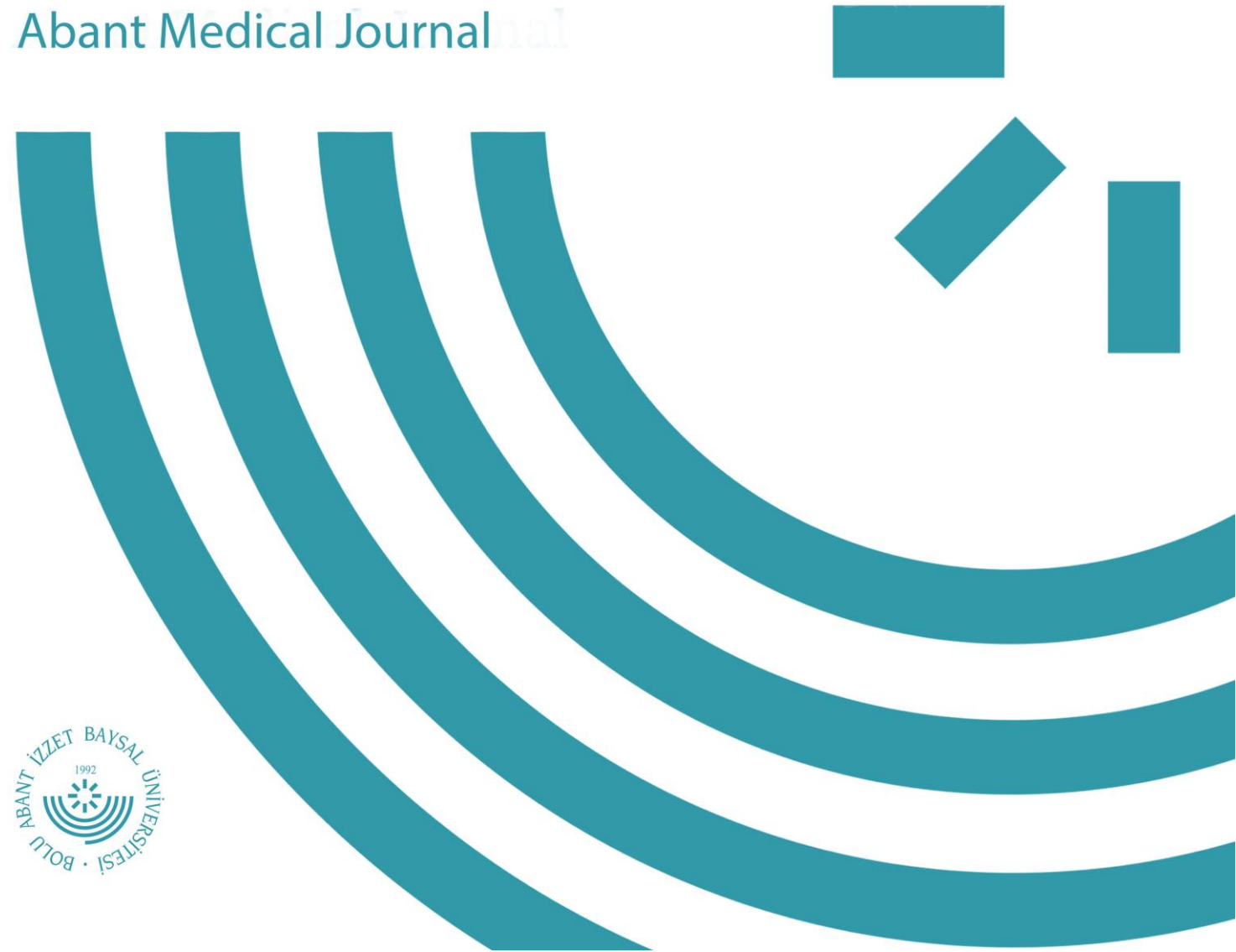

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Abant Tıp Dergisi

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A Call for Innovation in Drug Screening: Integrating Genetically Encoded Biosensors for Deeper Insights

İlaç Taramasında Yenilik Çağrısı: Daha Derin Bilgiler İçin Genetik Olarak Kodlanmış Biyosensörlerin Entegrasyonu

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Dear Editor,

We are writing to express our views on the urgent need for more informative and efficient methods in drug screening and testing within preclinical and translational medicine. The current state of the art primarily involves 2,5-diphenyl-2H-tetrazolium bromide (MTT) or similar cell viability assays, which provide limited information, predominantly focusing on cell toxicity. These methods are poor in providing insights into specific cellular mechanisms, long-term effects, or the drug's mode of action, thereby failing to deliver the comprehensive analysis required in modern drug development (1).

In vivo experiments, specifically in the context of drug development, are increasingly being abandoned in both the EU and the USA due to ethical concerns and regulatory changes. As a result, the reliance on in vitro systems and the development of innovative tools for drug screening have become more crucial than ever. Among these, genetically encoded biosensors for high-content drug screening represent a highly promising yet underutilized approach in the field.

Genetically encoded biosensors are advanced tools designed to provide real-time insights into cellular processes. Engineered from natural or synthetic genetic elements, these biosensors are optimized for high-throughput applications, allowing detailed monitoring of cellular responses. They track various biological signals or molecules, offering precise data on drug mechanisms and interactions at the molecular level (2). Integrating these biosensors into drug screening protocols can significantly enhance the efficiency and effectiveness of drug development processes by providing critical, functional insights into how drugs impact cellular functions.

Some of our previous studies have highlighted the significant value and effectiveness of genetically encoded biosensors in this field. These biosensors have proven particularly valuable in studying nitric oxide (NO), a crucial signaling molecule in the cardiovascular system (3). NO is essential for regulating vascular tone, blood pressure, and overall cardiovascular health by activating soluble guanylate cyclase (sGC), leading to vasodilation and maintaining endothelial function and vascular homeostasis. In the context of cardiovascular therapeutics, nitroglycerin (GTN) is a well-established antianginal drug that exerts its effects through NO release. The bioactivation of GTN by aldehyde dehydrogenase-2 (ALDH2) converts it to NO, which then activates sGC and induces vasodilation. Despite GTN's clinical success, understanding the precise mechanisms of its NO release and its impact on NO signaling pathways has been challenging due to limitations in traditional measurement techniques. Our research has demonstrated how advancements in genetically encoded biosensors can overcome these challenges. These innovative tools provide important insights into the real-time dynamics and spatial distribution of NO within cells, enabling a more precise visualization of NO production and its effects on cellular signaling. Our study, employing NO biosensors, has notably advanced the understanding of NO's role in cardiovascular pharmacology.

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It has addressed longstanding questions about NO signaling in response to GTN, highlighting the intricate interplay between drug metabolism and NO production in the vascular system (4).

In another study, we assessed the efficacy of two approved iron supplement drugs – Venofer and Ferinject- using our genetically encoded biosensor approach. This method effectively detects available iron (II) in cultured cells, demonstrating that genetically encoded biosensors are valuable tools for drug screening and testing at the (sub)cellular level (5).

Another crucial point we address is the critical importance of physiological oxygen levels in drug testing. We discovered that cells cultured under physiological normoxia (5 kPa O_2) require notably lower iron supplementation to activate metalloproteins compared to cells grown in standard room air (18 kPa O_2) (6). Additionally, we used genetically encoded biosensors to investigate the complex interaction between hydrogen peroxide (H_2O_2) and nitric oxide (NO) in endothelial cells under varying oxygen conditions. Traditionally, simultaneous measurement of these molecules has been technically challenging, leading to inconsistent results. By employing advanced biosensors -HyPer7 for H_2O_2 and geNOps for NO- for concurrent imaging in single cells, we found that, under ambient oxygen conditions, H_2O_2 did not significantly impact NO production. However, under physiological normoxia, we observed distinct oxidative stress and nuanced NO responses to H_2O_2 (7). These results underscore the necessity of incorporating physiological conditions into cellular studies to obtain accurate, meaningful insights, thereby enhancing the reliability of drug testing protocols.

We believe that integrating genetically encoded biosensors into standard drug screening protocols could significantly enhance the development of safer and more effective therapeutics. Their ability to provide detailed functional insights at the cellular level addresses a critical gap left by traditional drug testing methods.

Thank you for considering our perspectives on this matter. We look forward to further discussions and collaborations to advance the field of drug screening and testing.

Sincerely.

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Evaluation Of Plummer-Vinson Syndrome in Pediatric Patients with Dysphagia

Disfaji Olan Çocuk Hastalarda Plummer-Vinson Sendromunun Değerlendirilmesi

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Abstract

Objective: Dysphagia is a condition of increasing prevalence in childhood with numerous potential etiologies. Our study focuses on patients diagnosed with Plummer-Vinson syndrome (PVS), characterized by iron deficiency anemia and dysphagia, after excluding other contributing factors. We aim to highlight the importance of recognizing dysphagia cases responsive to anemia treatment and emphasize the potential for pediatricians to manage these patients effectively.

Materials and Methods: This study included pediatric patients presenting to our hospital with dysphagia between May 2019 and November 2020. After systematically ruling out other causes of dysphagia, patients diagnosed with PVS were evaluated retrospectively. We analyzed patient data including age, gender, dysphagia type, characteristics, and duration, and discuss these findings in the context of existing literature.

Results: The study included 200 pediatric patients presenting with dysphagia. Of these, 24 (14 female, 10 male) were diagnosed with Plummer-Vinson syndrome (PVS). The age range of patients was 12 to 213 months, with a mean age of 97.5 months (±72 months). The average duration of dysphagia symptoms was 11.2 months. Dysphagia characteristics were classified as follows: difficulty swallowing liquids only (n=4), solids only (n=12), or both solids and liquids (n=8). Anemia was diagnosed based on complete blood count results, with hemoglobin and hematocrit levels falling below two standard deviations for the patient's age. Cobalamin deficiency was defined as vitamin B12 levels below 200 pg/ml. Contrast esophagography revealed esophageal webs in 4 patients. Esophagogastroduodenoscopy (EGD) was performed, and web-associated stenosis was treated endoscopically in these patients. Following six months of iron deficiency anemia treatment, dysphagia resolved in 20 patients.

Conclusion: While Plummer-Vinson syndrome (PVS) is a less common diagnosis in pediatric populations, it remains an important consideration for children presenting with dysphagia and iron deficiency anemia. For patients whose symptoms persist despite appropriate iron supplementation, referral to a pediatric gastroenterologist is warranted for further evaluation and management.

Keywords: Child; Plummer-Vinson Syndrome; Iron-Deficiency Anemia; Esophageal Web, Dysafgia.

&

Öz

Amaç: Disfaji sıklığı çocukluk çağında giderek artmakta ve birçok nedene bağı olarak gelişmektedir. Çalışmamızda pediatrik çağda disfajinin diğer tüm nedenleri dışlandıktan sonra demir eksikliği anemisi ve disfaji olan Plummer-Vinson sendromu (PVS) tanısı ile takip ve tedavi edilen hastalar sunulmaya çalışılmıştır. Amacımız sadece anemi tedavisi ile düzelebilecek disfaji olabileceğini ve çocuk sağlığı ve hastalıkları uzmanı tarafından tedavi ile düzelebileceğini vurgulamaktır.

Gereç ve Yöntemler: Hastanemizde Mayıs 2019 ve Kasım 2020 arasında disfaji şikayeti ile başvuran, disfajinin diğer tüm nedenleri dışlandıktan sonra Plummer-Vinson sendromu tanısı alan hastalar retrospektif olarak değerlendirildi. Hastaların yaş, cinsiyet, disfaji şekli, özelliği ve süresi retrospektif olarak değerlendirilerek literatür eşliğinde sunuldu.

Bulgular: Disfaji şikayetiyle başvuran 200 çocuk hastadan 14' ü kız 10' u erkekti, toplam 24 çocuk hastada PVS saptandı. Hastaların yaşları en küçük 12 ay, en büyük 213 ay olup ortalama yaşları 97,5 (+-72 ay) aydı. Hastaların disfaji şikayet süresi ortalama 11,2 aydı. Dört hastada sadece sıvı gıdaları, 12 hastada katı gıdaları, 8 hastada ise hem katı hem de sıvı yutma güçlüğü vardı. Tam kan sayımı yapılarak ve hemoglobin, hematokrit düzeyleri yaşa uygun 2 standart sapma değerinin altında olanlar anemi; vitamin B12 düzeyi 200 pg/ml değerinin altında olanlar kobalamin eksikliği olarak tanımlandı. Kontraslı özofagografi çekilen 4 hastada özofageal web saptandı. Web saptanan hastaların özofagogastroduodensokopide darlık endoskopik olarak tedavi edildi. Yirmi hastada ise altı aylık demir eksikliğine bağlı anemi tedavisi sonrası yutma güçlüğünün devam etmediği görüldü.

Sonuç: PVS tanısı çocuklarda nadir görülür, demir eksikliği anemisi ile ilişkili yutma güçlüğü çeken tüm çocuklarda akla gelmeli ve tedavi verilmelidir. Uygun dozda ve sürede tedavi sonrası şikayeti devam eden hastalar çocuk gastroenteroloji değerlendirmesi için yönlendirilmelidir.

Anahtar Kelimeler: Çocuk; Disfaji, Plummer-Vinson Sendromu; Özofageal Web; Demir Eksikliği Anemisi.

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Introduction

Swallowing is a complex process enabled by the coordinated voluntary and involuntary actions of multiple structures, including the oral cavity, pharynx, larynx, and esophagus. Healthy, efficient swallowing requires the synchronized function of the oral cavity, pharyngeal muscles, cranial nerves, upper and lower esophageal sphincters, esophageal muscles, and stomach. Dysphagia, or difficulty swallowing, can result from mechanical obstruction during food transfer from the mouth to the stomach, or from decreased strength or impaired coordination of the muscles involved in the swallowing mechanism. Pediatric dysphagia can manifest at any age, often in conjunction with feeding or breathing difficulties, and potentially hindering growth and development.

First described by Plummer (1912) and Vinson (1919), Plummer-Vinson syndrome (PVS) is a triad characterized by dysphagia, iron deficiency anemia, and, in some cases, an upper esophageal web. Webs, a rare cause of upper cervical dysphagia, occur in approximately 5-15% of patients with dysphagia. While definitive data on PVS incidence and prevalence are lacking, it is considered very rare in childhood and generally presents as case reports within the literature (1,2). Improved nutrition and earlier diagnosis and treatment of iron deficiency likely contribute to the decreased incidence of PVS in children today. Dysphagia in PVS typically begins with solids and may be intermittent or progressive. Esophageal webs, thin transverse membranes extending into the esophageal lumen, can be single or multiple. While an esophageal web is not always present in PVS with iron deficiency, dysphagia remains a necessary diagnostic criterion (3).

Materials and Methods

This study included 200 pediatric patients presenting to our hospital's Pediatric Gastroenterology outpatient clinic with dysphagia complaints between May 2019 and November 2020. We evaluated patient data, including age, gender, dysphagia type, characteristics, and duration. To assess for iron deficiency anemia and potential concomitant vitamin B12 deficiency, the following laboratory tests were performed: hemogram, iron, iron-binding capacity, ferritin, and vitamin B12 levels. Contrast esophagography was performed to identify anatomical abnormalities, and patients with non-web anatomical etiologies were excluded from the study. We also excluded pediatric patients with burns from corrosive substance ingestion, esophagitis due to infection, eosinophilic esophagitis, and heterotopic gastric mucosal lesions within the esophagus. To investigate potential causes of dysphagia and anemia, esophagogastroduodenoscopy (EGD) with duodenal and stomach biopsies was performed. Patients received oral iron supplementation at a dose of 5mg/kg/day for the treatment of anemia.

Patients were instructed to return for follow-up after six months or sooner if dysphagia symptoms recurred. Data were analyzed retrospectively and discussed in the context of existing literature.

The study was approved by the Clinical Researches Ethics Committee of Adana City Training and Research Hospital (approval date: 17.08.2023, meeting number:133, decision no:2772).

Statistical Analysis

Descriptive statistics were calculated for numerical data, including mean, standard deviation, and median (min-max). Categorical data were expressed as percentages. A p-value of <0.05 was considered statistically significant.

Results

Among the 200 children presenting with dysphagia, we diagnosed 24 with Plummer-Vinson syndrome (PVS) after excluding all other potential causes. The average duration of their dysphagia complaints was 11 months, with the shortest complaint period being 1 month and the longest being 48 months. Our study included 10 male patients (37.5%) and 14 female patients (62.5%). We classified dysphagia into three groups based on the type of food causing difficulty: solid food (12 cases), liquid food (4 cases), and both solid and liquid food (8 cases). Table 1 provides a detailed breakdown of patient characteristics within these groups.

We performed complete blood counts to assess for anemia, defined as hemoglobin and hematocrit levels two standard deviations below the age-appropriate norm. Cobalamin deficiency was defined as a vitamin B12 level

below 200 pg/ml. Out of the 24 patients with PVS, 3.5% also exhibited cobalamin deficiency. Contrast esophagography was conducted in 79% of PVS cases, revealing esophageal webs in four patients.

Esophagogastroduodenoscopy (EGD) was performed in 14 patients (58.3%) who presented with both dysphagia and anemia. This procedure aimed to diagnose and treat potential esophageal webs, as well as rule out Helicobacter pylori gastritis and pernicious anemia (other potential causes of anemia). EGD confirmed the presence of webs in 4 patients, and endoscopic stenosis dilation was performed. Slight bleeding occurred as a procedural complication, but no other complications were observed. All patients received iron deficiency anemia treatment, and those with coexisting vitamin B12 deficiency received supplementation. Patients were followed up at 3-month intervals over a 6-month period. After six months of iron deficiency treatment, patients whose dysphagia resolved were discharged from follow-up (Table 2 provides a comparison of pre- and post-treatment values). Cases with confirmed webs remained under the care of pediatric surgery.

Table 1.

Demographic And Clinical Features of Patients by Groups.

	Solid dysphagia	Liquid dysphagia	Solid and Liquid dysphagia
Gender	10 F/ 2M	2 F/ 2 M	2 F/ 6 E
Average age	119 months	45.5 month	115 months
Contrast esophagography	9 patients	3 patients	7 patients
Esophagogastroduodenoscopy	9 patients	3 patients	2 patients

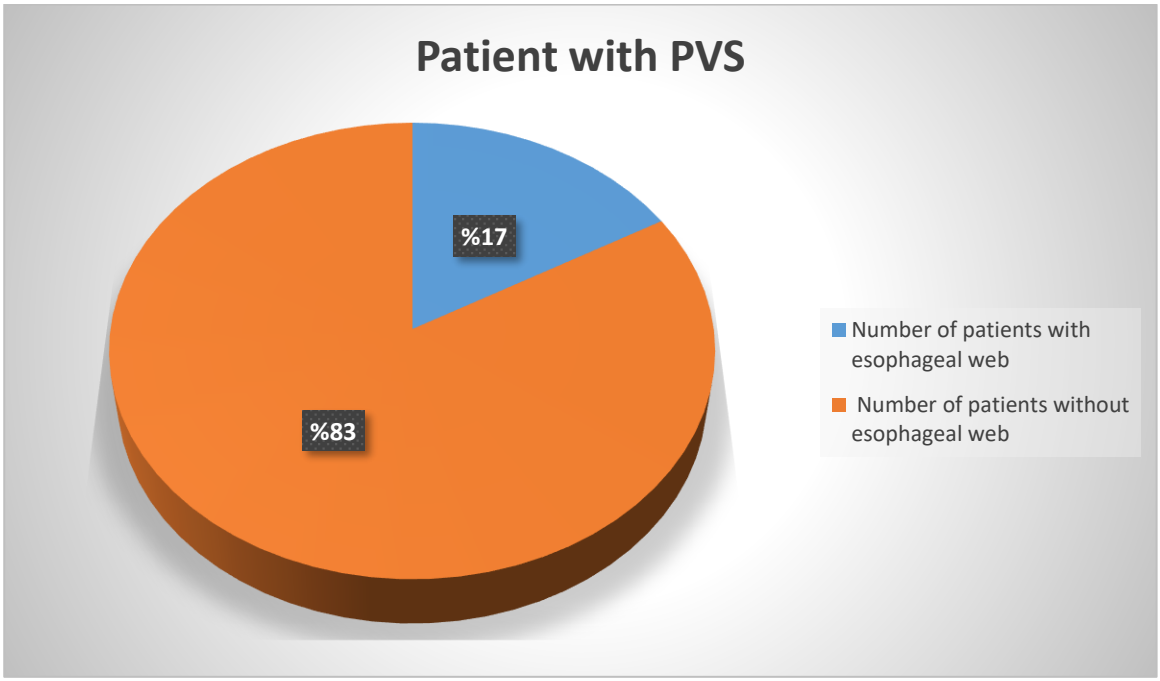

Figure 1. Distribution of pediatric patients with Plummer-Vinson syndrome according to webs.

Discussion

Plummer-Vinson syndrome (PVS) is named after the physicians who contributed to its understanding. Henry Stanley Plummer first described the condition in 1912, focusing on abnormal esophageal contractions without anatomical stricture. In 1919, Porter Paisley Vinson highlighted dysphagia caused by a surgically treatable esophageal stricture. Later, British physicians Donal Ross Paterson and Adam Brown-Kelly described the classic PVS triad: dysphagia, esophageal webs, and iron deficiency anemia. Due to this historical progression, the syndrome is known as Paterson-Brown-Kelly syndrome in the United Kingdom and Plummer-Vinson syndrome in the United States (4). Plummer-Vinson syndrome (PVS) is a clinical condition characterized by the triad of dysphagia, upper esophageal webs, and iron deficiency anemia (5, 6). Esophageal webs, a less common cause of upper cervical dysphagia in children, occur in approximately 5-15% of dysphagia cases (7). They are thin mucosal membranes composed of mucosa and submucosal tissue, typically found just below the cricopharyngeal muscle within the cervical esophagus. Esophageal webs often adhere asymmetrically to the anterior esophageal wall (8). Our study aligns with findings in adult literature, where PVS predominantly affects females (89% of cases with inflammatory PVS on biopsy) (9). In our pediatric cohort, we similarly observed a higher proportion of female patients (62.5%) compared to males (37.5%). The mean age of our patients was 97.5 months, with an average dysphagia duration of 11 months. The complaint duration ranged from a minimum of 1 month to a maximum of 48 months. Dysphagia in PVS typically presents with difficulty swallowing solid foods. It is often painless and may be intermittent or progressive. In some cases, it can evolve to include difficulty with liquids (2, 10). Out of our patient cohort, contrast-enhanced radiographs could not be obtained for one patient with liquid dysphagia, three patients with solid dysphagia, and one patient with both types. EGD results did not reveal significant differences across these groups. Esophagogastroduodenoscopy (EGD) was not performed in 10 patients due to family preference: 3 patients with solid food dysphagia, 1 patient with liquid dysphagia, and 6 patients with both types. We observed no statistically significant difference in average age between the dysphagia groups. While the liquid food dysphagia group appeared younger on average, the small sample size likely contributed to the lack of statistical significance. Esophageal webs can be multiple, and dysphagia typically presents when the esophageal lumen narrows below 2 cm. However, many webs remain asymptomatic (11). All webs identified in our study were singular and significantly narrowed the esophageal lumen (approximately 80%), contributing to dysphagia with both solids and liquids. All patients maintained normal body weight and height. Unfortunately, we could not access other physical examination findings due to incomplete records within the computer system. This limitation highlights the importance of comprehensive medical record-keeping for future studies.

The precise etiopathogenesis of PVS remains elusive, with potential contributions from genetic, environmental, nutritional, immunological, and infectious factors. The iron deficiency theory posits that reduced levels of iron-dependent oxidative enzymes lead to atrophy and myopathy in pharyngeal muscles and mucosa, promoting web formation. Interestingly, despite web persistence after iron treatment, esophageal motility normalization and dysphagia improvement support this theory. However, the reason why webs composed of squamous epithelium develop in the proximal hypopharynx secondary to submucosal inflammation and fibrosis remains unclear. Regardless of the underlying trigger, iron deficiency disrupts iron-dependent enzymes crucial for cellular renewal. This disruption leads to mucosal degeneration and mesh formation. Research indicates that iron deficiency impairs esophageal motility by reducing the amplitude of muscle contractions (11, 13). Miranda and Dantas demonstrated that iron deficiency anemia patients exhibited slower esophageal transit times in the proximal and middle esophagus compared to healthy individuals, but no difference in the distal esophagus (14). This finding could explain the propensity for web formation in the proximal esophagus. While motility studies, particularly manometry, offer valuable insights into esophageal function, they can be challenging to perform in pediatric populations. Successful esophageal manometry requires patient cooperation and responsiveness to instructions, which can be particularly challenging in young children (especially those under 7 years old). Despite having patients over the age of 7 in our study (41.6%), we were unable to conduct esophageal motility tests due to a lack of this specialized equipment at our center. Our findings highlight a critical need for larger multicenter studies incorporating motility assessments to deepen our understanding of this condition in pediatric patients.

An alternative theory proposes an immunological mechanism involving the formation of autoantibodies directed against the esophagus (11). In patients with PVS, the possibility of coexisting autoimmune disorders should be investigated. These may include rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, pernicious anemia, thyroiditis, or celiac disease (15, 16, 17). The potential link between PVS and autoimmune disorders (such as rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, pernicious anemia, thyroiditis, or celiac disease) warrants careful investigation (15, 16, 17). While the precise mechanisms remain unclear, these disorders could contribute to PVS through autoantibody production or by triggering inflammatory processes (18). In our study, we evaluated thyroid function tests and celiac antibodies to screen for other potential causes of dysphagia. These tests yielded normal results. Gastric biopsies obtained during esophagogastroduodenoscopy did not indicate pernicious anemia. While other autoimmune diseases were not specifically evaluated due to an absence of suggestive clinical findings, their potential role should be considered in future studies.

PVS is a clinical diagnosis based on dysphagia associated with chronic iron deficiency anemia. While esophageal webs are a characteristic finding, they are only detected radiologically or endoscopically in approximately 10% of cases. Dysphagia is the essential diagnostic criterion (3). Contrast-enhanced radiographs, especially lateral views, are crucial for visualizing webs and potential ring-shaped stenosis (19, 20). Even in the absence of abnormalities on contrast esophagography, severe cases may still present with stenosis. Nosher et al. (1975) demonstrated this, finding 5.5% of esophagi exhibiting one or more webs in their radiographic study (21). Chisholm et al. (1974) found esophageal webs in just 10% of patients with iron deficiency anemia, which aligns with our finding of webs in 17% of PVS cases. However, among the broader population of 200 children with dysphagia, we detected webs in only 2%. This highlights the challenges of evaluating barium radiographs, particularly for upper esophageal anomalies. Difficulty coordinating studies in children and a lack of experienced teams trained in serial image evaluation further complicate the process. With improved resources and expertise, we anticipate that web detection rates will increase. Upper endoscopy can also detect esophageal webs, though they can be easily missed, and there is a risk of perforation during the procedure. Godino et al. found iron deficiency anemia in 38.5% of patients with endoscopically detected webs and low serum ferritin levels (without anemia) in an additional 0.7% of cases (22). Our findings align with this study. We performed esophagogastroduodenoscopy (EGD) in 58.3% of our PVS cases, successfully visualizing and treating webs in 4 patients where they had also been detected by contrast-enhanced radiography. Treatment strategies for PVS include iron supplementation, esophageal dilation, or a combination of both. Iron therapy should continue until hematocrit and ferritin levels normalize. For patients without complete obstruction, this approach often leads to significant dysphagia improvement. Clinical studies demonstrate that iron repletion also enhances esophageal motility. In cases of severe, longstanding dysphagia unresponsive to iron supplementation, mechanical widening of the stenosis is typically necessary, with surgical intervention rarely required (23, 24, 25). The higher rate of endoscopic dilation performed in pediatric PVS patients (64%) suggests a reduced response to iron therapy compared to adults. Often, a single dilation procedure is sufficient in children, contrasting with adult cases (26). A three-year study of 37 PVS patients found a 94% resolution of dysphagia after one endoscopic dilation, with a 10% recurrence rate over a ten-month follow-up (27). Another study reported success with Savary-Gilliard bougie dilation in 153 patients, 132 of whom had PVS. Dysphagia resolved in 90.7% of these cases after a single dilation session (28). Within our pediatric cohort, we identified 12 PVS patients who also exhibited vitamin B12 deficiency alongside iron deficiency. We detected vitamin B12 deficiency in a significant portion of our pediatric dysphagia patients (13 out of 200 cases). Notably, all 12 PVS patients exhibited both iron and vitamin B12 deficiencies, while one patient had isolated vitamin B12 deficiency. Vitamin B12 deficiency can contribute to dysphagia through mechanisms like impaired cytokine expression, reduced oxidative enzymes, white matter demyelination, and atrophy in pharyngeal muscles. Our focus on PVS patients means we did not fully evaluate the broader relationship between dysphagia and isolated vitamin B12 deficiency. This highlights an important avenue for future research. The four patients with confirmed webs received a single endoscopic dilation session alongside iron therapy; we observed only minor bleeding as a complication. We treated all other PVS cases presenting with iron deficiency anemia (without webs) using oral ferrous iron (2+ valent form) at 5 mg/kg/day for 3-6 months. Following treatment, these patients reported complete resolution of dysphagia.

In conclusion, dysphagia is an increasingly common pediatric presentation with diverse etiologies. While Plummer-Vinson syndrome (PVS) remains a rare diagnosis in children, it warrants consideration in any child

presenting with dysphagia alongside iron deficiency anemia. Patients whose dysphagia persists despite six months of appropriate iron therapy should be referred to a pediatric gastroenterologist for further evaluation and management.

Ethics Committee Approval: The study was approved by the Adana City Training And Research Hospital Clinical Research Ethics Committee (date: 17.08.2023 and approval number: 133/2772).

Informed Consent: Written consent was obtained from the participants.

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Retrospective Comparison of Talon or Conventional Locking Nailing for Tibial Shaft Fractures

Tibia Gövde Kırıklarında Talon ve Geleneksel Kilitli Çivilemenin Retrospektif Karşılaştırması

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Abstract

Objective: Tibial shaft fractures are common orthopedic injuries that present challenges in treatment selection. The primary aim of this retrospective study was to compare the clinical outcomes of tibial shaft fractures treated with Talon and conventional locking nails.

Materials and Methods: Ninety-four patients who underwent tibial intramedullary nailing between 2019 and 2021 were included in the study. The patients were divided into two groups based on the type of distal locking used: Group 1 received conventional screw locking, and Group 2 received Talon locking. Patient age, gender, trauma mechanism, fracture type, and surgery data were analyzed. The complications and bone union processes during follow-up were evaluated and compared between the two nail designs.

Results: The age and gender of the patients included in the study were statistically similar in both groups. Furthermore, the Talon group demonstrated significantly shorter union times ($p < 0.001$). According to the OTA classification, there was a preference for screw-locking systems in more complex fractures ($p = 0.017$).

Conclusion: The results of this retrospective study suggest that Talon locking nails may offer advantages over conventional screw locking, especially in younger patients, resulting in earlier bone union. Further research is needed to investigate Talon nails' biomechanical stability and suitability for specific fracture types.

Keywords: Tibial Shaft Fractures, Locking Nails, Talon Nail, Conventional Locking Nail.

&

Öz

Amaç: Tibia gövde kırıkları, ortopedik tedavilerde yaygın ve zorlayıcı yaralanmalardır. Bu retrospektif çalışma, Talon ve geleneksel vida kilitleme çivileriyle tedavi edilen hastaların klinik sonuçlarını karşılaştırmayı hedeflemektedir.

Gereç ve Yöntemler: 2019-2021 yılları arasında tibia şaft kırığı nedeniyle intramedüller çivi operasyonu geçiren 94 hasta bu çalışmaya dâhil edildi. Hastalar, uygulanan distal kilitleme yöntemine göre iki gruba ayrıldı: Birinci grup geleneksel vida, ikinci grup ise Talon kilitleme yöntemi ile ameliyat edilen hastalar olarak belirlendi. Hastaların yaş, cinsiyet, travma mekanizması, kırık tipi ve cerrahi bilgileri incelendi. İyileşme sürecindeki komplikasyonlar ve kemik birleşme durumları her iki çivi tasarımı için değerlendirildi.

Bulgular: Çalışmaya alınan hastaların yaş ve cinsiyetleri her iki grupta da istatistiksel olarak benzerdi. Talon grubunda anlamlı derecede daha kısa kaynama süresi gözlendi ($p < 0.001$*). OTA sınıflandırmasına göre daha karmaşık kırıklarda vida kilitleme sistemlerinin daha sık tercih edildiği gözlendi ($p=0.017$).

Sonuç: Özellikle genç hastalarda, Talon kilitleme çivilerinin geleneksel vida kilitlemeye göre bazı avantajlar sunduğu ve daha hızlı kırık kaynamasına katkıda bulunduğu gözlemlenmiştir. Talon çivilerinin biyomekanik stabilitesi ve özel kırık tiplerine uygunluğu üzerine daha fazla araştırma yapılması önerilmektedir.

Anahtar Kelimeler: Tibia Şaft Kırığı, Kilitli Çivi, Talon Çivi, Geleneksel Kilitli Çivi.

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Introduction

Tibial shaft fractures are common injuries that pose significant challenges in orthopedic practice. The choice of fixation method plays a crucial role in achieving optimal outcomes for these fractures. In recent years, there has been growing interest in locking nails for tibial shaft fractures due to their biomechanical advantages and potential clinical benefits. The conventional locking nail technique has been widely utilized to treat tibial shaft fractures (1, 2). This technique involves using a non-locking nail with interlocking screws placed proximally and distally to provide stability. While this method has shown satisfactory outcomes in many cases, concerns have been raised regarding the risk of screw backout, rotational instability, and delayed fracture healing (3). The Talon nail, a newer generation locking nail system, has been introduced in response to these concerns. Despite the growing popularity of the Talon nail, limited comparative studies have been conducted to evaluate its efficacy and compare it with conventional locking nails. Therefore, this retrospective study aims to fill this knowledge gap by retrospectively comparing the clinical outcomes of tibial shaft fractures treated with either the Talon nail or conventional locking nails.

Materials and Methods

This study was conducted in accordance with the Declaration of Helsinki and received approval by the Clinical Researches Ethics Committee of Mersin University on May 8, 2023 (approval no: 215040260). We retrospectively analyzed 94 patients (81 males and 13 females) who underwent tibial intramedullary nailing for tibial shaft fractures between 2019 and 2021. The study included patients aged 18 and older who required surgical intervention with an intramedullary nail for tibial shaft fractures. Exclusion criteria were previous fractures at the same site, segmental tibial fractures, metabolic bone diseases, or prior surgeries on the affected limb.

The minimum follow-up period was 12 months, allowing for adequate assessment of post-surgical outcomes and long-term bone union. Surgeries were carried out by multiple surgeons with comparable levels of expertise, all adhering to the center's standardized surgical protocols to minimize variability in the outcomes. Patients were divided into two groups based on the distal locking method used: Group 1 received conventional screw locking, while Group 2 underwent Talon-locking.

Data on participants' age, gender, trauma mechanism, fracture type, and surgical details were collected. We also monitored complications and the bone union process during follow-up. Statistical analyses were performed using SPSS for Windows 25.0 (Armonk, NY: IBM Corp.). We used the Kolmogorov-Smirnov/Shapiro-Wilk tests to assess the normality of continuous variable distributions, with p-values above 0.05 indicating normal distribution. Descriptive statistics were presented as means, standard deviations, medians with ranges for quantitative variables, and frequencies and percentages for qualitative variables. The Mann-Whitney U test was utilized for quantitative comparisons and the chi-square test for qualitative data, with a significance threshold set at $p<0.05$. Radiological images of tibial shaft fractures treated with conventional and Talon-locking nails were reviewed to support the comparative analysis (Figure 1).

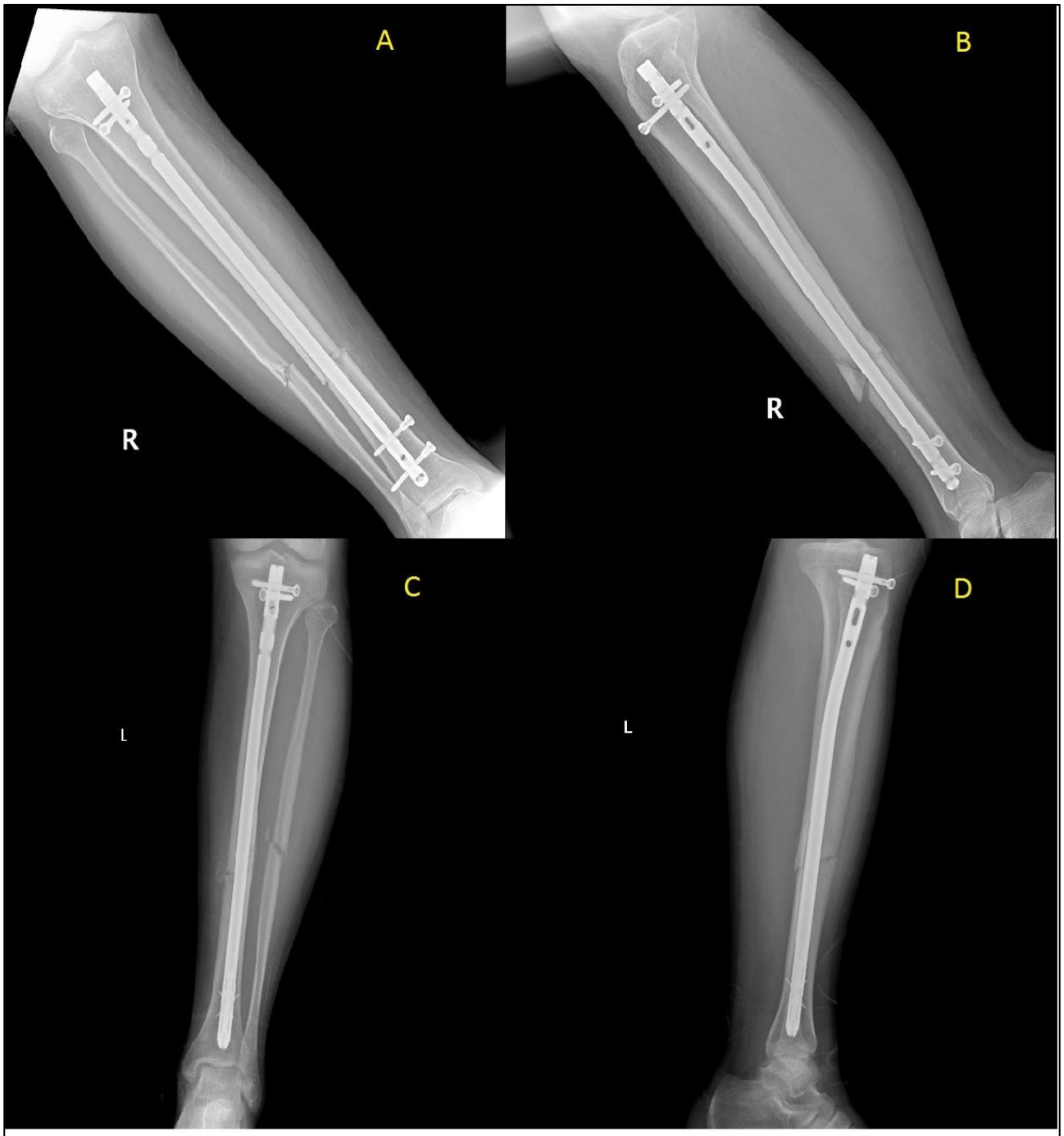
Results

A total of 94 patients were analyzed. Group 1 included 56 male patients, while Group 2 included 25 male patients. The average age was 34 years in Group 1 and 32 years in Group 2. There was no statistically significant difference in smoking habits between the groups.

The distribution of trauma mechanisms was similar between the groups, with falls from height, motorcycle accidents, and non-vehicular traffic accidents being equally represented. The incidence of open fractures was 30.3% in Group 1 and 20% in Group 2 ($p=0.368$).

Reduction types varied significantly between the groups. All patients in Group 2 underwent closed reductions, while in Group 1, 60.6% of patients underwent open reductions ($p<0.001$).

Alignment outcomes showed normal alignment in 87.9% of patients in Group 1 and 100% in Group 2 ($p=0.108$). Complications were observed in Group 1, including screw breakage (6.1%) and pseudoarthrosis (3%), while no complications were reported in Group 2 ($p=0.376$).



A) AP radiograph of the patient with conventional screw locking, B) Lateral radiograph of the patient with conventional screw locking, C) AP radiograph of the patient with talon distal locking, D) Lateral radiograph of the patient with talon distal locking

Figure 1. Patient X-rays operated with Talon and conventional locking nails

Healing times indicated a faster recovery for Group 2, with 70% achieving bone union by 3 months, compared to 18.2% in Group 1 within the same timeframe ($p<0.001$).

The AO classification showed different preferences for the treatment methods, with the screw-locking system being used more frequently for managing more complex fractures.

A retrospective analysis was conducted on 94 patients. In Group 1, there were 56 male patients, while Group 2 consisted of 25 male patients, indicating a predominance of male gender in both groups. The average age was 34 years in Group 1 and 32 years in Group 2, with similar age distributions across the groups. No

statistically significant difference was found in smoking habits between the groups. The mechanisms of trauma, including falls from height, motorcycle accidents, and non-vehicular traffic accidents, were similarly distributed between the groups. Table 1 summarizes the general characteristics of the patients.

Table 1

General Characteristics of Patients

	Locking Screw	**Talon**	**p-value**
Age, Median (min-max)	34 (17-58)	32 (18-58)	0.345
Gender, n (%)			0.417
Female	10 (15.2%)	3 (10.7%)	
Male	56 (84.8%)	25 (89.3%)	
Smoking habits, n (%)			0.258
No	22 (33.3%)	12 (42.9%)	
Yes	44 (66.7%)	16 (57.1%)	
Trauma type, n (%)			0.703
Fall down	22 (33.3%)	9 (32.1%)	
Motorcycle accident	22 (33.3%)	8 (28.6%)	
Pedestrian vehicle accident	22 (33.3%)	11 (39.3%)	

n: Number of Individuals. For statistical comparison, The chi-square test was used

The incidence of open fractures did not significantly differ between the groups, with 30.3% in Group 1 and 20% in Group 2 (p=0.368). Reduction type varied significantly; all patients in Group 2 underwent closed reductions, in contrast to Group 1, where 60.6% underwent open reductions (p<0.001).

Regarding alignment and complications, both groups reported high rates of normal alignment, 87.9% in Group 1 and 100% in Group 2, though this difference was not statistically significant (p=0.108). Group 1 experienced some complications, such as screw breakage (6.1%) and pseudoarthrosis (3%), whereas Group 2 reported no complications, but these differences were not statistically significant (p=0.376). Additional pathologies and trauma causes were similar across groups, with no significant differences observed in the presence of additional injuries or the causes of trauma.

Healing times indicated a faster recovery for Group 2, with 70% achieving bone union by 3 months, compared to 18.2% in Group 1 within the same timeframe (p<0.001).

The AO classification showed different preferences for the treatment methods, with the screw-locking system being used more frequently for managing more complex fractures.

Table 2 shows the comparison of the fractures and the findings between the groups after treatment.

Table 2

Comparative Analysis of Fracture Types and Treatment Outcomes Between Groups

	Locking Screw	**Talon**	**p-value**
OTA Classification (n%)			0.017
42a	26 (39.4%)	20 (71.4%)	
42b	28 (42.4%)	5 (17.9%)	
42c	12 (18.2%)	3 (10.7%)	
Trauma type (n%)			0.703
Fall down	22 (33.3%)	9 (32.1%)	
Motorcycle accident	22 (33.3%)	8 (28.6%)	
Pedestrian vehicle accident	22 (33.3%)	11 (39.3%)	
Open Fracture (n%)			0.269
No	46 (69.7%)	22 (78.6%)	
Yes	20 (30.3%)	6 (21.4%)	
Union time (months)			< 0.001*
Median (min-max)	5 (2-11)	3 (3-5)	
Alignment (n%)			
Normal	58 (87.9%)	28 (100%)	0.052
Valgus	8 (12.1%)	-	
Varus	-	-	
Other Trauma (n%)			
None			
2 Fracture	46 (69.7%)	17 (60.7%)	
3 Fracture	14 (21.2%)	6 (21.4%)	0.257
Head Trauma	2 (3%)	2 (7.1%)	
	4 (6.1%)	3 (10.7%)	

n: Number of Individuals. For statistical comparison, The chi-square test and *Mann-Whitney U test were used

Discussion

The patients who participated in our study were similar in age, gender, smoking, and fracture type, which may be related to fracture union. Additionally, our study corroborates previous literature, showing male dominance in both the Screw and Talon groups (4-6).

The most intriguing finding of our study is the significantly earlier union time observed in the Talon group. While the younger age of our study population may contribute to an expectation of earlier union regardless of the treatment type, it is noteworthy that this result contradicts some published data. For instance, Tekin et al. (4) reported earlier union in the Screw locking group compared to the Talon locking group. Similarly, Yalkın et al. (5) found longer union times in the Talon group. A study on Talon and conventional screw-locking nails in femur fractures also reported longer union time in the Talon group (6). However, with its younger patient population, our study demonstrated a shorter union time in the Talon group compared to conventional screw locking, which the age factor could explain.

Moreover, according to the OTA classification, we observed a preference for screw-locking systems in more complex fractures. In our study, eight patients in the screw-locking system group exhibited valgus misalignment, while no malalignment was observed in any patient in the Talon group. This discrepancy is likely due to the variation in fracture classes between the two groups.

Limitations of the study:

- Retrospective design
- Lack of randomization
- Single-center study
- Heterogeneity of fractures
- Limited follow-up duration
- Lack of biomechanical data
- Lack of control group

Conclusion

In the surgical treatment of tibial shaft fractures, intramedullary nails equipped with Talon distal locking have demonstrated advantages over conventional screw locking nails, including shorter healing times and lower complication rates. Further biomechanical studies and randomized prospective trials are essential to deepen our understanding of these outcomes. Such research will provide more definitive evidence on the efficacy of Talon locking systems, potentially leading to optimized treatment protocols for these common injuries.

Ethics Committee Approval: Approval was granted by the Clinical Researches Ethics Committee of Mersin University (date: 08.05.2023 and approval number: 215040260).

Informed Consent: Consent was not obtained as it was a retrospective study.

Conflict of Interest: Authors declared no conflict of interest.

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COVID-19 Pneumonia-Related ARDS – Can We Predict Mortality with Laboratory Parameters?

COVID 19 Pnömonisi Sonrası Gelişen ARDS'de Laboratuvar Parametreleri Mortaliteyi Öngörmede Kullanılabilir Mi?

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Abstract

Objective: To examine the laboratory characteristics of COVID-19 pneumonia-related ARDS patients who lived or died.

Materials and Methods: Retrospectively, two-center of patients who were hospitalized in the intensive care unit were researched in Abant Izzet Baysal University Education and Research Hospital in Bolu, Turkey. Between March 31 and December 31, 2020, data on the demographic characteristics, routine laboratory results, including arterial blood gas tests, and clinical outcomes were collected for both the survivor and non-survivor groups.

Results: The median age of the 509 patients was 70 years (interquartile range, 59-79 years); 326 patients (64%) were men, and 161 patients (31.6%) tested positive for RT-PCR. While 232 (45.6%) patients in the non-survivor group died, 277 patients were discharged (54.4%) as survivors. The mortality markers of WBC, RBC, HGB, Ph, pO_2, pCO_2, HCO_3, PLT, PCT, NEU, ALT, and D-dimer did not differ significantly ($p>0.05$). CRP, RDW, LDH, ferritin, urea, and creatinine levels were substantially higher and associated with death in the non-survivor group (p 0.05).

Conclusion: A greater risk of death was linked to older age and the number of days spent in the hospital, most likely as a result of persistent underlying issues and weakened immune responses. Risk variables for the progression were CRP, LDH, RDW, ferritin, urea, and creatinine. With the help of laboratory parameters to predict mortality, we can define earlier the changes in immune insufficiency, coagulation problems, hepatic injury, and kidney injury.

Keywords: ARDS, COVID 19, Laboratory Parameters, Mortality.

&

Öz

Amaç: Yaşayan veya ölen COVİD-19 pnömonisine bağlı ARDS hastalarının laboratuvar özelliklerini incelemek.

Gereç ve Yöntemler: Bolu Abant İzzet Baysal Üniversitesi Eğitim ve Araştırma Hastanesi'nde yoğun bakım ünitesinde yatan hastaların iki merkezi retrospektif olarak araştırıldı. 31 Mart ile 31 Aralık 2020 tarihleri arasında hem hayatta kalan hem de hayatta kalmayan gruplar için demografik özellikler, arteriyel kan gazı testleri dahil rutin laboratuvar sonuçları ve klinik sonuçlara ilişkin veriler toplandı.

Bulgular: 509 hastanın ortanca yaşı 70 (çeyrekler arası aralık, 59-79 yıl) idi; 326 hasta (%64) erkekti ve 161 hastanın (%31,6) RT-PCR testi pozitif çıktı. Hayatta kalan grupta 232 (%45,6) hasta hayatını kaybederken, 277 hasta (%54,4) sağ olarak taburcu edildi. WBC, RBC, HGB, Ph, pO2, pCO2, HCO3, PLT, PCT, NEU, ALT ve D-dimer mortalite belirteçleri anlamlı farklılık göstermedi ($p>0,05$). Hayatta kalmayan grupta CRP, RDW, LDH, ferritin, üre ve kreatinin düzeyleri önemli ölçüde daha yüksekti ve ölümle ilişkiliydi ($p < 0,05$).

Sonuç: Daha büyük ölüm riski, ileri yaş ve hastanede geçirilen gün sayısıyla bağlantılıydı; büyük ihtimalle kalıcı altta yatan sorunlar ve zayıflamış bağışıklık tepkilerinin bir sonucuydu. İlerlemeye ilişkin risk değişkenleri CRP, LDH, RDW, ferritin, üre ve kreatinindi. Mortaliteyi tahmin etmeye yönelik laboratuvar parametrelerinin yardımıyla bağışıklık yetersizliği, pıhtılaşma sorunları, karaciğer hasarı ve böbrek hasarındaki değişiklikleri daha erken tanımlayabiliriz.

Anahtar Kelimeler: ARDS, COVID 19, Laboratuvar Parametreleri, Mortalite.

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Introduction

Since the outbreak of Coronavirus disease 2019 (COVID- 19), the approach of severe and critical patients has remained a clinical challenge. Despite of the respiratory support, antiviral drugs and immunmodulators, it's still likely to develop acute respiratory distress syndrome (ARDS) for the patients and eventually invasive ventilation. The mortality rates of cases range from 1.7 to 2.23 percent belong to the geographic location, the virus's rate of transmission, and the proportion of the population at risks (1-3). In addition, some factors that affected these criteria were the health system's readiness, the availability of hospitals, and the number of beds in intensive care units (ICUs) (4). These results might also be due to variances in the categorization and reporting of COVID-19 cases and related fatalities. The WHO dashboard presently only includes real-time polymerase chain reaction (RT-PCR)-positive cases, which might cause the actual situation to be underestimated (1). A high proportion of PCR-negative people with clinical and radiographic traits consistent with COVID-19 are identified and handled as such in clinical practice (5). Furthermore, rates of false negative PCR tests are anticipated to vary between 2 and 29 percent (6).

Numerous investigations have demonstrated that COVID-19 pneumonia has had certain specific epidemiological and clinical features in the past (7,8). However, the risk factors for poor clinical outcomes have not yet been found, particularly in COVID-19 pneumonia-related ARDS. Even though several researchs have shown death rates and risk factors globally, we still don't have much information on the characteristics of proven or strongly suspected cases in Turkey, specifically forecasting fatality. In this research, the laboratory features of pneumonia-related ARDS in COVID-19 to death from two tertiary ICU units in Bolu, Turkey, are presented. We sought to explain the demographic and laboratory factors that distinguished critically sick patients who would survive from those who wouldn't, as these factors were crucial in predicting death.

Materials and Methods

Study Design

This multicenter registry study was approved by the Clinical Researches Ethics Committee of Bolu Abant Izzet Baysal University (2020/327). The clinical outcomes of patients were evaluated retrospectively from data hospitalized in tertiary ICU at Abant Izzet Baysal University Hospital and Izzet Baysal State Hospital in Bolu, Turkey. No informed consent was required, because of the retrospective design of the study. All patients were managed according to the guidelines of the Ministry of Health of Turkey (2). The demographic features, routine laboratory findings including arterial blood gas analyses, and clinical outcomes were recorded between March 31 and December 31, 2020.

Case Definition

The WHO COVID-19 case definition sheet was used to include the patients in the study. As a result, a confirmed case was defined as the presence of a positive nucleic acid amplification test or a positive fast antigen detection test, as well as clinical and radiographic features strongly suggesting COVID-19 (9). Despite matching clinical and radiographic signs in very likely occurrences, an RT-PCR assay was unable to confirm (9). The final diagnosis was made using the following criteria (9–11).

Procedures

Numerous procedures were administered to the patients, such as coagulation, hemograms, ferritin, C-reactive protein (CRP), D-dimer tests, and biochemical testing. The patients' vital status, length of hospital stay, and demographic data were also compared between the two of groups. Children, pregnant women, and patients who were in hospitals for other ARDS-related conditions were not included. 65 years of age or older were considered to be older. All patients had throat swabs obtained at the time of admission, and they were all tested using RT-PCR assays by a method that has previously been used to identify SARS-CoV-2 infection.

Data Management

The majority of the clinical data for this research was obtained on the discharge day of hospitalization in the survivor group and on the death day in the non-survivor group. WHO interim guidance was used to define COVID-19 pneumonia-related ARDS (9).

Statistical Analysis

The analysis of the data obtained as a result of the research was made in the SPSS 20 statistical package program. In addition to the Kolmogorov-Smirnov test, conformity to the normal distribution was evaluated based on the skewness and kurtosis coefficients and the range of ±2. Parametric data were compared with the Independent Sample t-test and expressed as standard deviation. The homogeneity of the variances was examined by Levene's test. Nonparametric data were compared with the Mann-Whitney U test and expressed as median (Q1-Q3). The relationship between categorical variables was examined with Chi-Square. Receiver Operative Characteristics (ROC) analysis was used to determine the cut-off values in estimating mortality. $p < 0.05$ was considered statistically significant.

Results

In this study, from March 31 to December 31, 2020, a total of 509 patients (mean age 67.25±16.00; 326 men [64%]; 161 RT-PCR positives [31.6%]) were hospitalized as ARDS in tertiary ICU and were retrospectively enrolled. They completed both thorax CT and laboratory viral nucleic acid testing (RT-PCR assay with throat swab samples). The patient's electronic medical records in our hospital information system were used to obtain the RT-PCR data. Despite having negative RT-PCR findings, radiologists discovered that 348 (68.4%) of the patients had traits that suggested they were highly susceptible to COVID-19. While 232 (45.6%) patients died in the non-survivor group, 277 patients were released (54.4%) as survivors.

There was no significant difference in mortality for white blood cell (WBC), red blood cell (RBC), hemoglobin (HGB), potential of hydrogene (pH), partial oxygen pressure (pO_2), partial carbon dioxide pressure (pCO_2), bicarbonate (HCO_3), platelet (PLT), plateaucrit (PCT), neutrophil (NEU), alanine transferase (ALT), and D-dimer indicators. ($p>0.05$) (Table 1).

Their mean ages, days spent in hospitals, C reactive protein (CRP), red blood cells distribution width (RDW), aspartate transferase (AST), lactate dehydrogenase (LDH), glucose, ferritin, urea, and creatinine levels were significantly higher ($p<0.05$) in the non-survivor group, despite their lower results for albumin, oxygen saturation (SO_2), lymphocyte (LYM), and monocyte (MONO).

The ROC analysis revealed that the albumin, SO_2, LYM, and MONO values were significant; however, the chi-square assumptions did not support the establishment of a relationship between these parameters and mortality. Table 2 presents the predictive value of many factors in relation to AUC, sensitivity, specificity, and 95% confidence intervals.

In patients with the non-survivor group of ARDS, CRP, RDW, ferritin, urea, LDH, and creatinine values were significantly higher and those on cut-off were related to mortality ($p<0.05$). The ROC curves of the parameters are shown in Figure 1.

Table 1.

Comparison Of Hemogram, Biochemical and Blood Gas Parameters

	Survivor (n=277, %54.4)	**Non-Survivor (n=232, %45.6)**	**All patients (n=509)**	**p-value**
Gender				
Female	74 (%40.4)	109 (%59.6)	183 (%36.0)	**<0.001[a,*]**
Male	203 (%62.3)	123 (%37.7)	326 (% 64.0)	
		$\bar{X}\pm ss$		
WBC, 10^9/L	13.79±6.88	13.54±9.25	13.68±8.04	0.717
RBC, 10^{12}/L	4.08±0.74	4.02±0.81	4.06±0.77	0.390
HGB, g/dL	11.53±2.28	11.44±2.27	11.49±2.27	0.648
Albumin, g/L	32.91±6.33	29.62±6.22	31.39±6.48	**<0.001[b]**
CRP, mg/L	53.58±72.62	105.82±85.59	78.22±83.13	**<0.001[b]**

		Median (Q1-Q3)		
Age, years	62.97±16.59 66 (54-74)	72.36±13.64 75 (66-82)	70 (59-79) 67.25±16.00	**<0.001**[b,*]
Days of hospitalized	6.46±10.28 2 (1-7)	12.45±18.06 6 (2-15)	4 (1-10) 9.19±14.65	**<0.001**[b,*]
pH	7.42 (7.39-7.47)	7.42 (7.37-7.48)	7.42 (7.37-7.47)	0.508
pO_2, mmHg	81.4 (49.5-106.4)	70.8 (43.7-96.95)	75.2 (45.25-101.5)	0.079
pCO_2, mmHg	39 (34.8-44.3)	40.35 (33.15-48.2)	39.60 (33.9-45.55)	0.342
SO_2, %	97.7 (92.8-99.2)	93.8 (83.9-98.75)	97.0 (88.65-99.0)	**<0.001**[b]
HCO_3, mEq/L	24.02 (21.9-27)	24.02 (21-26.45)	24.02 (21.6-26.9)	0.426
LYM, 10^9/L	1.19 (0.79-1.76)	0.84 (0.53-1.25)	1.03 (0.5-1.6)	**<0.001**[b]
PLT, 10^9/L	223 (177-276.5)	222 (147-299)	223 (167-288)	0.502
PCT, %	0.22 (0.18-0.28)	0.23 (0.16-0.31)	0.23 (0.17-0.29)	0.953
NEU, 10^9/L	9.63 (7.15-14.87)	9.9 (6.4-14.7)	9.75 (6.95-14.8)	0.362
MONO, 10^9/L	0.73 (0.48-1.06)	0.597 (0.3-0.91)	0.66 (0.37-1.04)	**<0.001**[b]
RDW, %	13.9 (13-15.8)	15.2 (13.8-17.5)	14.45 (13.2-16.7)	**<0.001**[b]
ALT, U/L	22 (14-39)	21 (14-45)	22 (14-41)	0.707
AST, U/L	29 (19-48)	34 (20-64)	30 (20-54)	**0.029**[b]
Glucose, mg/dL	143 (114-176)	152 (112-230)	146 (113-197)	**0.045**[b]
Ferritin, µg/L	172.5 (63.6-511.3)	556.3 (284.0-899.4)	369.2 (117.3-779.4)	**<0.001**[b]
Urea, mg/dL	39 (28-58)	66 (41-107)	47 (32-82.5)	**<0.001**[b]
D-dimer,	3.18 (1.32-8.19)	2.865 (1.49-5.29)	2.92 (1.4-6.54)	
LDH, U/L	309.5 (240-447)	432.5 (311-616)	365 (263.75-525.75)	**<0.001**[b]
Creatinine, mg/dL	0.87 (0.73-1.17)	1.15 (0.78-2.04)	0.97 (0.74-1.47)	**<0.001**[b]

White blood cell (WBC), red blood cell (RBC), hemoglobin (HGB), potential of hydrogene (pH), partial oxygen pressure (pO2), partial carbon dioxide pressure (pCO_2), bicarbonate (HCO_3), platelet (PLT), plateaucrit (PCT), neutrophil (NEU), alanine transferase (ALT), C-reactive protein (CRP), red blood cells distribution width (RDW), aspartate transferase (AST), lactate dehydrogenase (LDH), oxygen saturation (SO_2), lymphocyte (LYM), and monocyte (MONO). [a]Chi-Square test, [b]Independent Sample t test/Mann-Whitney U test.

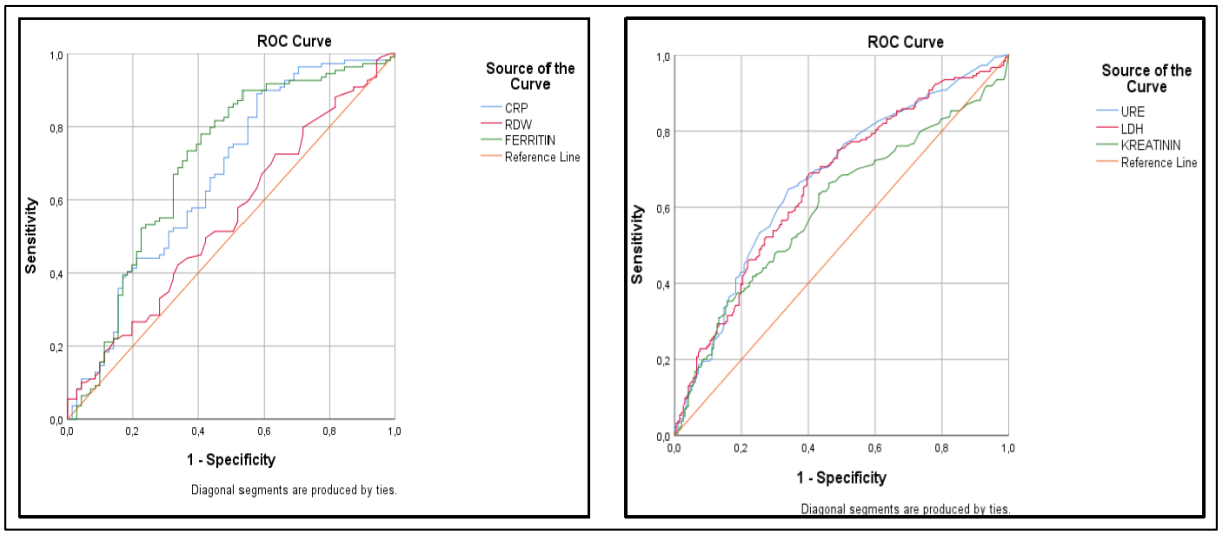
Table 2.

Cut-Off Values of Parameters and Their Relation to The Mortality

Parameters	**AUC (%95 CI)**	**Cut-Off**	**P value**	**Sensitivity (%)**	**Specificity (%)**
CRP, mg/L	0.708 (0.661-0.755)	34.65	<0.001	74.2	62.3
RDW, %	0.653 (0.606-0.700)	14.35	<0.001	65.4	59.6
AST, U/L	0.557 (0.506-0.607)	30.50	0.029	53.3	53.7
Glucose, mg/dL	0.552 (0.500-0.604)	145.50	0.045	52.8	52.0
Ferritin,µg/L	0.698 (0.619-0.778)	343.37	<0.001	67.3	67.1
Urea, mg/dL	0.711 (0.665-0.756)	50.00	<0.001	65.7	69.3
LDH, U/L	0.663 (0.609-0.718)	349.50	<0.001	68.5	60.1
Creatinine, mg/dL	0.632 (0.582-0.682)	0.985	<0.001	62.9	62.5
Albumin, g/L	0.350 (0.301-0.399)	31.55	<0.001	40.4	40.3
SO2, %	0.404 (0.353-0.455)	96.85	<0.001	40.1	39.7
LYM, 10^9/L	0.357 (0.309-0.406)	1.01	<0.001	39.0	38.8
MONO, 10^9/L	0.395 (0.345-0.445)	0.655	<0.001	42.9	42.8
	Sub-Groups Based on Defined Cut-Off	**Survivor, n (%)**	**Non-survivor, n (%)**	**X^2 value**	**P value***
CRP	0-34.640 ≥34.641	157 (%73.0) 95 (%36.3)	58 (%27.0) 167 (%63.7)	64.049	**<0.001**

RDW	0-14.340	164 (%67.2)	80 (%32.8)	31.437	**<0.001**
	≥14.341	111 (%42.4)	151 (%57.6)		
AST	0-30.490	146 (%57.7)	107 (%42.3)	2.403	0.128
	≥30.491	126 (%50.8)	122 (%49.2)		
Glucose	0-145.490	141 (%56.6)	108 (%43.4)	1.177	0.283
	≥145.491	130 (%51.8)	121 (%48.2)		
Ferritin	0-343.360	53 (%59.6)	36 (%40.4)	21.789	**<0.001**
	≥343.361	26 (%26.0)	74 (%74.0)		
Urea	0-49.00	190 (%70.6)	79 (%29.4)	61.533	**<0.001**
	≥49.01	84 (%35.7)	151 (%64.3)		
LDH	0-349.490	119 (%67.2)	58 (%32.8)	31.327	<0.001
	≥349.491	79 (%38.5)	126 (%61.5)		
Creatinine	0-0.984	173 (%66.8)	86 (%33.2)	32.556	<0.001
	≥0.985	104 (%41.6)	146 (%58.4)		

C reactive protein (CRP), red blood cells distribution width (RDW), aspartate transferase (AST), lactate dehydrogenase (LDH), oxygen saturation (SO2), lymphocyte (LYM), and monocyte (MONO). *Chi-Square analysis, AUC: Area under the curve. CI: Confidence interval,



C reactive protein (CRP), red blood cells distribution width (RDW), lactate dehydrogenase (LDH)

Figure 1. Receiver operating characteristic (ROC) curve for mortality

Discussion

In this retrospective study, the laboratory characteristics associated with clinical outcomes in patients with COVID-19 pneumonia-related ARDS and those who progressed from ARDS to death between two groups as a survivor and non-survivor group were evaluated. We aimed to predict the laboratory parameters that are linked to the onset of ARDS and the progression of ARDS to mortality in COVID-19 pneumonia. The older age and days of hospitalized stay were even associated with a higher risk of developing ARDS and mortality; this was not statistically significant. In patients with the non-survivor group of ARDS; CRP, RDW, LDH, ferritin, urea, and creatinine values were significantly higher and related to mortality ($p<0.05$).

The illness caused by COVID-19 spread rapidly, and significant studies have been done to determine which patients will be affected and what their clinical outcomes would be. We know that this virus mostly impacted the respiratory system, with some patients quickly developing ARDS which was mostly related to mortality; other organ functions were less affected (11). Thus, it is necessary for early detection and accurate therapy of COVID-19 pneumonia-related ARDS.

Patients with ARDS have been seen in ICUs across the world. Around 5% of patients infected with the new 2019 coronavirus disease necessitate hospitalization owing to ARDS, with a case-fatality rate ranging from

30% to 60% (11-13). Previous observational studies in Turkey found death rates ranging from 8.5 percent to 50%, depending on the healthcare environment, the age of the study group, and the severity of the condition (14-16). These studies were generally done in a single-center setting with a small number of patients. One big research, which used Ministry of Health records and included 16,942 hospitalized old people, found death rates ranging from 17.9% to 32.2% depending on when public limitations were in place (15). The research, however, did not give any clinical data about the patients. Our study evaluated a fatality rate of 45.5%. The groups in our research were not limited to mild to moderate cases but included a wide spectrum of severe patients with ARDS. This might explain why the death rate is so high when compared to prior findings from Turkey and other countries (17-19).

Several studies have evaluated the risk factors for mortality (20-23). The most well-known predictor of death in older age and countries with significant old populations have been proven to have higher case-fatality rates. The in-hospital mortality rate for patients aged 80 and over was estimated to be 32.8 percent in Turkey (15,16). Similarly, the non-survivors and survivors in our research had mean ages of 72.3 and 62.9 years, demonstrating that age was an independent variable associated with death. The median hospital stay was 6.4 days in the survivor group and 12.4 in the non-survivor group, as expected. Older age and days of hospital stay were significantly higher in the non-survivor group than in the survivor group but these were not predictable for mortality. Low immune response and comorbidities are all age-related disorders that may play a role infor the increased risk.

Some hematological and biochemical parameters about the prognosis of COVID-19, multiple recent studies have researched laboratory features of hospitalized patients. (17-19,23) Chidambaram et al. (22) looked at clinical and laboratory indicators related to mortality in a meta-analysis utilizing 109 published publications, 42 of which looked at mortality. Increased levels of CRP, LDH, and D-dimer were associated with a higher risk of severe disease and death. Huang et al. (23) found that increased serum CRP, PCT, D-dimer, and ferritin were linked with a poor outcome in a meta-analysis involving a total of 5350 patients. Another meta-analysis found that procalcitonin had the best predictor of mortality and disease severity (24). This may be caused by bacterial coinfection and cytokine storm according to the authors. In that study, parameters related to mortality were respiratory failure, high WBC-CRP-creatinine-LDH-D dimer-lactate, and low albumin, thrombocytopenia, and lymphopenia. In a recent study in Turkey, BUN and albumin levels at admission, as well as D-dimer and procalcitonin levels during follow-up, were shown to be linked with mortality (25). We found that CRP, LDH, RDW, ferritin, urea, and creatinine values were significantly higher and related to mortality like these studies. These parameters may be linked to the cytokine storm triggered by a viral infection, whereas coagulation activation is related to the long-term inflammatory response. Acute renal impairment caused by the infection, hypoxia, and shock might have resulted in elevated urea and creatinine levels.

Furthermore, because our study was single-center and had a limited sample size, our findings may not apply to all COVID-19 pneumonia-related ARDS patients. Secondly, we did not evaluate the comorbidities that can affect mortality. Also, the findings relied on data that were recorded at the time of hospitalization in the ICU, so there were no follow-up parameters. Finally, patients' ventilator parameters were not noted for both two groups even if that setting is being recommended to personalize at the bedside. To investigate the phenotypic, larger cohort studies are needed for ARDS caused by COVID-19.

Conclusion

In this study, we found that various laboratory indicators were linked to death in COVID-19 pneumonia-related ARDS and that clinicians should consider these factors while managing these patients. After these findings have been validated in prospective research, it may be advantageous to develop algorithms based on them.

Ethics Committee Approval: This study was approved by the Clinical Researches Ethics Committee of Bolu Abant Izzet Baysal Unıversity, (Approval No: 2020/327).

Informed Consent: Consent was not obtained as it was a retrospective study.

Conflict of Interest: Authors declared no conflict of interest.

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Comparison Of Three Methods for Calculation of Sacroiliac Joint Index in Different Age Groups in Bone Scintigraphy

Kemik Sintigrafisinde Farklı Yaş Gruplarında Sakroiliak Eklem İndeksinin Hesaplanmasında Kullanılan Üç Yöntemin Karşılaştırılması

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Abstract

Objective: The aim of this study is to evaluate three techniques for calculating the sacroiliac joint (SIJ) index by bone scintigraphy in patients.

Materials and Methods: Patients (n:160) who did not exhibit abnormalities on bone scan were analyzed and were divided into 4 groups; 3-20 years, 21-40 years, 41-60 years, and 61-86 years, respectively. Irregular and rectangular regions of interest (ROI) were used for the first and second methods, respectively. Horizontal rectangular ROI was selected for the last technique. The SIJ index was calculated by the following formula: SIJ count/sacrum count.

Results: There was no difference between the averages of all three methods according to the right and left SIJ index ($p>0.05$). The averages of all SIJ values differed for the three methods ($p<0.05$). The average of the first method's values for all three situations was lower than the averages of the other two methods' values ($p<0.05$). The first technique had a lower mean for the right SIJ index value than the other two techniques ($p<0.05$). The average of females was lower than males for all SIJ index values. The lowest average was detected at the age of 61 and above for three methods for both genders. All methods differed according to age ($p<0.05$). A relationship was detected between the age and all three index values of all techniques.

Conclusion: A threshold value for each method should be identified using a fixed reference point for each age group taking into account gender.

Keywords: Sacroiliac joint index, Bone scintigraphy, Sacroiliitis, Region of interest, Tc-99m MDP.

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Öz

Amaç: Bu çalışmanın amacı hastalarda kemik sintigrafisi ile sakroiliak eklem (SİE) indeksinin hesaplanmasına yönelik üç tekniğin değerlendirilmesidir.

Gereç ve Yöntemler: Kemik sintigrafisinde anormallik izlenmeyen hastalar (n:160) analiz edildi ve 4 gruba ayrıldı; sırasıyla 3-20 yaş, 21-40 yaş, 41-60 yaş, 61-86 yaş. Birinci ve ikinci yöntem için sırasıyla düzensiz ve dikdörtgen ilgi alanı (ROI) kullanıldı. Son yöntem için yatay dikdörtgen ROI seçildi. SİE indeksi şu formülle hesaplandı: SİE sayımı/sakrum sayımı.

Bulgular: Üç yöntemde sağ ve sol SiE indeksi ortalamaları arasında fark yoktu ($p>0,05$). Tüm SİE değerlerinin ortalamaları üç yöntem için farklılık gösterdi ($p<0,05$). Her üç durum için de birinci yöntemin değerlerinin ortalaması diğer iki yöntemin değerlerinin ortalamasından düşüktü ($p<0,05$). Sağ SİE indeks değeri için ilk metodun ortalaması diğer iki yönteme göre daha düşüktü ($p<0,05$). Kadınların ortalaması tüm SİE indeks değerleri için erkeklerden daha düşüktü. Her iki cinsiyette de üç yöntem için en düşük ortalama 61 yaş ve üzerinde tespit edildi. Tüm yöntemler yaşa göre farklılık gösterdi ($p<0,05$). Bütün metodlarda yaş ile her üç indeks değeri arasında korelasyon tespit edildi.

Sonuç: Her yöntem için cinsiyet dikkate alınarak her yaş grubu için sabit bir referans noktası kullanılarak bir eşik değeri belirlenmelidir.

Anahtar Kelimeler: Sakroiliak eklem indeksi, Kemik sintigrafisi, Sakroileit, İlgi alanı, Tc-99m MDP.

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Introduction

The sacroiliac joint (SIJ) provides a connection of the right ilium, sacrum, and left ilium. This joint also ensures body weight is transferred to the lower extremities. This joint's anatomy has a wide spectrum in adults (1). SIJ structure varies according to age, gender, and race. SIJ is more flexible in women to facilitate a baby's transition during birth. Therefore, women are more susceptible to stress on the structures surrounding the joint. On the other hand, SIJ is stronger in men, and as a result of that more load is added to the joint (1-4).

Sacroiliitis is an inflammatory disease and it causes SIJ dysfunction and pain. Patients generally complain of lumbar pain and ~ 70% of individuals are affected throughout their lifetime. While sports injuries and trauma cause pain in young patients, joint degeneration causes in an elderly population (1-4).

It can be difficult to differentiate SIJ pain from various diseases that cause similar symptoms. Patients with SIJ pain usually consult physicians with deep-rooted thigh pain that radiates to the lower extremities. The pain can be unilateral or bilateral and might increase with sitting down, long walking, or walking uphill. Therefore, detailed medical history is very important for diagnosis. Various tests are used to reveal SIJ pain during physical examination (1-3).

Dysfunction of this joint affects the life quality of individuals. Therefore, correct diagnosis is important. Imaging modalities play a vital role in sacroiliitis diagnosis. Various imaging methods have been used to demonstrate anatomical changes in sacroiliitis. Direct radiography is generally a preferred method by clinicians due to its easy accessibility. Furthermore, it is also a safe method and utilized with several advantages such as low radiation dose and low cost (4-5).

Computed Tomography (CT) provides detailed information about the SIJ anatomy, soft tissue surrounding the joint, and adjacent structures compared to radiography. It can show erosion, sclerosis, and narrowing of joint space (3-4).

Magnetic Resonance Imaging (MRI) demonstrates the early and inflammatory stage of sacroiliitis due to its high resolution. Therefore, it is accepted as the gold standard for the diagnosis of sacroiliitis. Furthermore, MRI usually detects bone marrow edema which is a key finding in active disease. It can visualize erosion, and changes in SIJ and soft tissues (4-7).

Nuclear medicine imaging methods can also be helpful for the evaluation of early sacroiliitis. Technetium (Tc)-99m labeled methylene diphosphonate (MDP) bone scintigraphy is the most commonly used nuclear medicine scan for sacroiliitis. Bone scintigraphy can detect early inflammatory and metabolic changes earlier than plain radiography (4,8,9). This method can also show the width of inflammation. Whole-body imaging is performed with a bone scan. Therefore, it provides valuable information about affected other joints in patients, especially with arthritis. However, this method is not specific and does not provide detailed anatomical information. It is combined with an X-ray or MRI.

Scintigraphic images are evaluated visually. The area where the radioactive substance accumulates pathologically is regarded as positive. SIJ value that is obtained by the ratio of SIJ counts to sacrum count as a quantitative parameter increases its specificity (10). If the SIJ count is greater than the sacrum count, it has clinical significance for the diagnosis of sacroiliitis.

Various studies that compare different regions of interest (ROI) methods in different age groups for the determination of the normal values of the SIJ index were reported in the literature (11-12).

From this point of view, we aimed to investigate the variability of normal values of the SIJ index according to different ROI methods. Therefore, we separated the cases into 4 groups based on these studies. It is known that Tc-99m MDP is physiologically distributed in the SIJ. It was reported that the normal SIJ value of each population is different. Based on this information, we also aimed to investigate the factors affecting the SIJ value in individuals whose bone scintigraphy was reported as normal in our society. Therefore, we analyzed whether this index varies according to age, gender, and laterality.

Materials and Methods

Patients who underwent bone scintigraphy from May 2015 to June 2016 at Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Nuclear Medicine were retrospectively analyzed. Local Ethics Committee approval was obtained with decision number 16 dated 29.06.2016.

Patients with a history of inflammatory arthritis, low back pain, orthopedic surgery, and multiple osteoblastic bone metastasis were excluded from the study.

One hundred sixty patients were included in this cross-sectional research. Patients who did not have pathological findings on bone scintigraphies were included in this study to assess normal values of the SIJ index as a control.

Scintigraphic imaging was carried out 3 hours after intravenous administration of 740 MBq Tc-99m MDP for adults. The pediatric dosage was calculated according to the guidelines. Imaging was performed with a dual-headed gamma camera (GE Healthcare Discovery NM630) equipped with a low-energy general-purpose collimator. Whole body bone scintigraphy (128x512 matrix) and static images (256x256 matrix) were performed for computer analysis.

Posterior pelvic images were used for analysis. Three different ROI methods were selected based on a literature search.

Irregular-shaped ROI was chosen for the first method. In this method, manual drawings were made around both SIJ and sacrum, separately (Figure 1). The average counts obtained from these drawings were recorded.

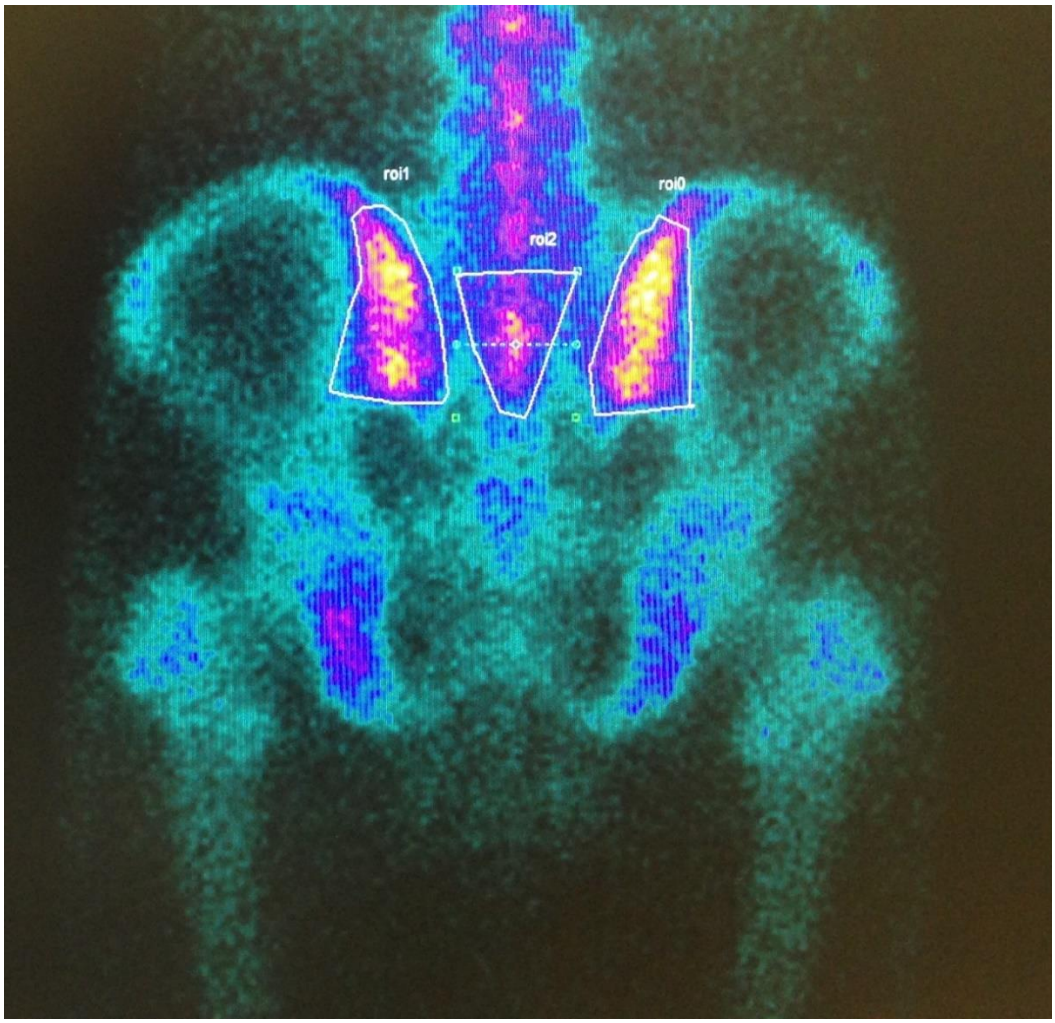


Figure 1. Irregular ROI method. Three ROIs are seen on both sacroiliac joints and sacrum were manually drawn in posterior pelvis image of bone scintigraphy.

Rectangular-shaped ROI was chosen for the second technique and it was automatically placed on the right SIJ, sacrum, and left SIJ, separately (Figure 2). The average counts obtained from these bones were recorded.

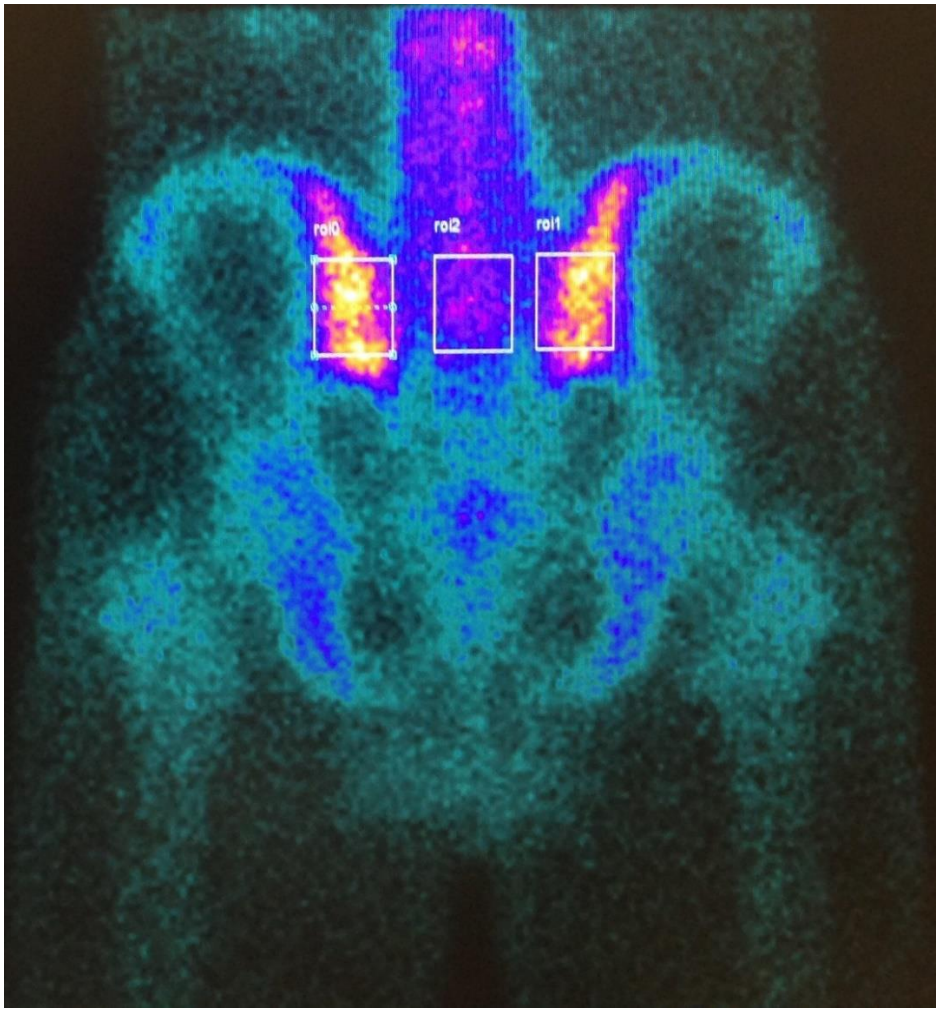


Figure 2. Rectangular ROI method. Same shaped rectangular ROI were placed on both sacroiliac joints and sacrum in posterior pelvis image of bone scintigraphy.

In the third method, a horizontal rectangular ROI was selected. This ROI was automatically placed on the same bone structures. A graph that shows profile peak counts of these bones was obtained and recorded (Figure 3).

The SIJ index was calculated by the following formula: SIJ count/sacrum count in all three methods.

Statistical Analysis

Statistical Package for the Social Sciences software (IBM SPSS Statistics for Windows, Version 25.0 IBM Corp., Chicago, IL, USA) was used for data analysis. Outlier analysis was performed to check the normality of the data and were excluded from the evaluation. To determine whether the data was suitable for normal distribution, it was first assessed with Kolmogorov-Smirnov/Shapiro-Wilk tests. Normality tests were also supported by skewness-kurtosis and a Q-Q plot graph. Descriptive data were expressed as number (n), percentage (%), and mean±SD (standard deviation) values. In cases where the normality assumption was met, paired sample t-test and if not met Mann Whitney U test, one of the non-parametric tests, were performed for two groups. One-way analysis of variance (ANOVA, F) test was performed to compare the means in more than two groups. Correlation analysis was performed to analyze the relationship between individual variables. Pearson correlation analysis was performed for normally distributed groups. A value of $p < 0.05$ was considered significant statistically.

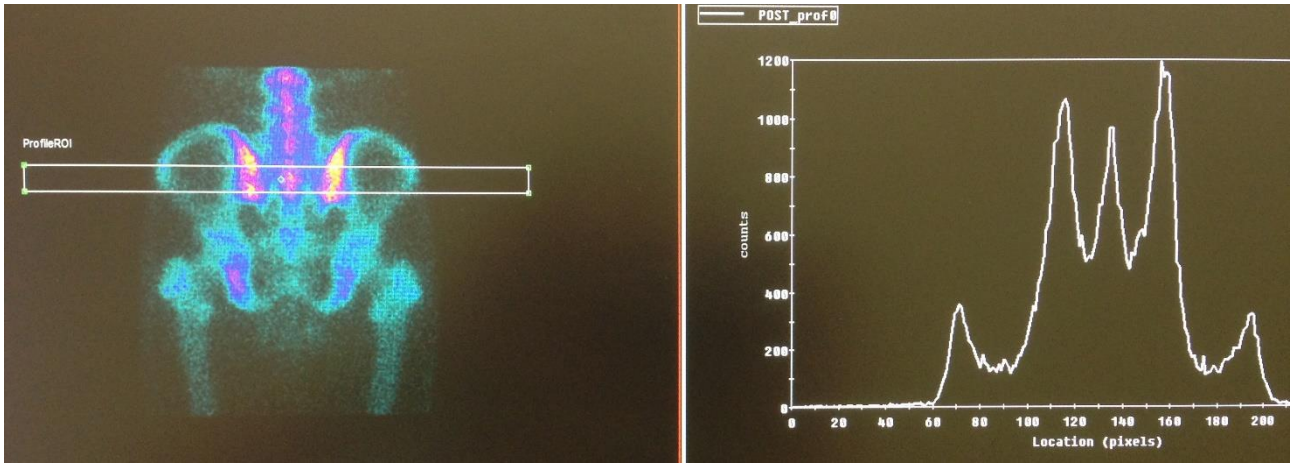


Figure 3. Horizontal rectangular ROI method. A horizontal rectangular ROI was placed on both sacroiliac joints and sacrum in posterior pelvis image of bone scintigraphy. Three separate peaks that shows maximum counts on the profile for both sacroiliac joints and sacrum.

Results

74 (46,2%) patients were females and 86 (53.8%) patients were males. The average age of the patients differed between females and males ($p<0.05$). The average age of males (90,54) was higher than that of females (68.83). The mean age of cases was found to be 51,85±18 years.

According to studies in the literature, patients were separated into 4 groups with an interval of 20 years. There were 12 patients in the first group (aged 3 to 20 years), 29 patients in the second group (aged 21 to 40 years), 54 patients in the third group (aged 41 to 60 years), and 65 patients in the fourth group (aged 61 to 86 years).

The averages of the three techniques were not different according to the right and left SIJ index as shown in Table 1 ($p>0.05$).

Table 1.

Evaluation of the averages of irregular-shaped ROI, rectangular-shaped ROI, horizonral rectangular ROI methods according to right SIJ index and left SIJ index

Variables	Groups	n	mean±SD	p value
Irregular-shaped ROI	Right SIJ index	160	1.03±0.11	0.681
	Left SIJ index	160	1.03±0.10	
Rectangular-shaped ROI	Right SIJ index	160	1.12±0.12	0.996
	Left SIJ index	160	1.12±0.11	
Horizontal rectangular ROI	Right SIJ index	160	1.13±0.16	0.169
	Left SIJ index	160	1.14±0.17	

ROI: Region of interest, SIJ: Sacroiliac joint

The averages of the right, left, and mean SIJ index values of the patients differed for the three techniques (p<0.05). The average of the first method values for all three situations was found to be statistically significantly lower than the average of the other two techniques' values (p <0.05) (Table 2).

Table 2.

Comparison of average of irregular-shaped ROI, rectangular-shaped ROI, horizonral rectangular ROI methods according to right, left and mean SIJ values

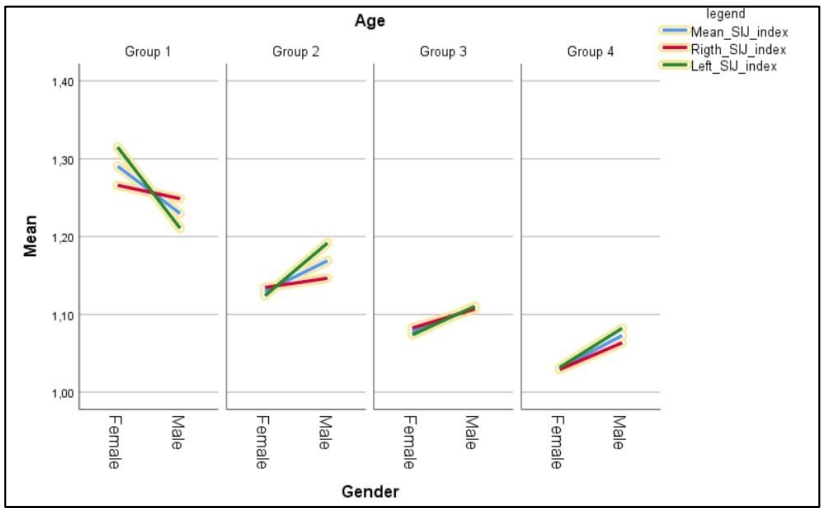
Variables	Groups	n	mean±SD	F	p value
Right SIJ index	Irregular-shaped ROI	160	1.03±0.10	28.893	**<0.001***
	Rectangular-shaped ROI	160	1.12±0.11		
	Horizontal rectangular ROI	160	1.13±0.16		
Left SIJ index	Irregular-shaped ROI	160	1.03±0.10	29.672	**<0.001***
	Rectangular-shaped ROI	160	1.12±0.11		
	Horizontal rectangular ROI	160	1.14±0.17		
Mean SIJ index	Irregular-shaped ROI	160	1.03±0.09	31.415	**<0.001***
	Rectangular-shaped ROI	160	1.12±0.11		
	Horizontal rectangular ROI	160	1.13±0.16		

F test; *p<0.05; ROI: Region of interest, SIJ: Sacroiliac joint.

The mean of three techniques and right, left, and mean SIJ index values were analyzed. The first method had a significantly lower mean for the right SIJ index value than the other two methods (p<0.05).

All SIJ index values were analyzed according to gender. The average of females was lower than males for all three SIJ index values. While the average of females was 1.09±0.14 for the right SIJ index, 1.08±0.14 for the left SIJ index, 1.08±0.13 for the mean SIJ index, the average of males was 1.10±0.13, 1.11±0.13, 1.10±0.13, respectively.

All SIJ index values according to gender were evaluated based on age (Graph 1). The lowest average was detected at the age of 61 and above for all three methods for females and males.



Graph 1. Graphical presentation of right SIJ index, left SIJ index and mean SIJ index values according to gender, based on age.

It was determined that all methods differed according to age as shown in Table 3 (p <0.05). The average of the first group was higher than the third and fourth groups, and the average of the second group was higher than the fourth group for the first and second methods. The average of the first group was higher than the second,

third, and fourth groups, and the average of the second group was higher than the fourth group for the third method ($p<0.05$).

Table 3.

Evaluation of the averages of the irregular-shaped ROI, rectangular-shaped ROI, horizonral rectangular ROI methods according to age

Methods	Age-Groups	n	mean±SD	F	p value
Irregular-shaped ROI	Group 1	12	1.13±0.11	7.662	**<0.001***
	Group 2	29	1.06±0.10		
	Group 3	54	1.02±0.09		
	Group 4	65	1.00±0.08		
Rectangular-shaped ROI	Group 1	12	1.23±0.12	8.773	**<0.001***
	Group 2	29	1.17±0.11		
	Group 3	54	1.11±0.10		
	Group 4	65	1.09±0.09		
Horizontal rectangular ROI	Group 1	12	1.34±0.13	11.816	**<0.001***
	Group 2	29	1.18±0.16		
	Group 3	54	1.12±0.15		
	Group 4	65	1.08±0.13		

ANOVA (F test); *p<0.05; ROI: Region of interest, SIJ: Sacroiliac joint.

A negative medium-level relationship was detected between the patient's age and the first method's right SIJ index value ($p<0.05$). A negative low-level relationship was detected between the patient's age and the first method left SIJ index value ($p<0.05$).

A negative medium-level relationship was detected between the patient's age and the second method's right SIJ index value ($p<0.05$). A negative medium-level relationship was found between the patient's age and the second method left SIJ index value ($p<0.05$).

A negative medium-level relationship was detected between the age of the patient and the third method's right SIJ index value ($p<0.05$). A negative medium-level relationship was detected between the patient's age and the third method left SIJ index value ($p<0.05$).

There was a difference between the averages of all three techniques for the 0-20 age group ($p<0.05$). The difference was found between the first and third techniques ($p<0.05$).

There was a difference between the averages of all three techniques for the 21-40 age group ($p<0.05$). The difference was found between the first and third techniques; the first and second techniques ($p<0.05$).

There was a difference between the averages of all three techniques for the 41-60 age group ($p<0.05$). There was a difference between the first and third techniques; the first and second techniques ($p<0.05$).

There was a difference between the averages of all three techniques for the age group of 61 years and above ($p<0.05$). There was a difference between the first and third techniques; the first and second techniques ($p<0.05$) (Table 4).

Table 4.

Evaluation of the averages of irregular-shaped ROI, rectangular-shaped ROI, horizonral rectangular ROI methods based on four age groups.

Age groups	Group	n	mean±SD	F	p value
0-20 age group	Irregular-shaped ROI	12	1.13±0.11	8.531	**0.001***
	Rectangular-shaped ROI	12	1.23±0.12		
	Horizontal rectangular ROI	12	1.34±0.14		
21-40 age group	Irregular-shaped ROI	29	1.06±0.10	7.353	**0.001***
	Rectangular-shaped ROI	29	1.17±0.11		
	Horizontal rectangular ROI	29	1.18±0.17		
41-60 age group	Irregular-shaped ROI	54	1.02±0.09	10.999	**<0.001***
	Rectangular-shaped ROI	54	1.11±0.10		
	Horizontal rectangular ROI	54	1.12±0.15		
≥ 61 age group	Irregular-shaped ROI	69	1.01±0.08	12.991	**<0.001***
	Rectangular-shaped ROI	69	1.10±0.10		
	Horizontal rectangular ROI	69	1.07±0.14		

F test; *p<0.05; ROI: Region of interest

Discussion

Quantitative sacroiliac bone scans have been used for a long time (13). In this study, a total of 160 patients with normal bone scintigraphy were retrospectively evaluated. Three ROI methods were used to calculate quantitative SIJ index in four different age groups. When the averages of the three methods were evaluated according to laterality in this study, no significant difference was found (p>0.05) (Table 1). The results of this study showed that right, left, and mean SIJ index values of the three methods were different (p<0.05) (Table 2). The mean value of the rectangular-shaped ROI method was lower than other methods in our study. In the first method, unlike the second and third methods, all counts from the bone structure are obtained. Additionally, the choice of count type and the distribution of radioactivity in the bone may have caused this result. Furthermore, the second and third methods were more practical than the first method. All SIJ index values were analyzed according to gender in this study. The results showed that females had lower SIJ index values than males. It may be caused by anatomical and physiological differences in the female and male pelvis. The male pelvis is adapted for weight bearing. Therefore, the male pelvis is narrower and the joint surface is wider. Unlike the male pelvis, the female pelvis is wider to facilitate birth (1-4). This can also be explained by the hormonal status of females.

This study showed that the age group ≥ 61 had the lowest SIJ values in both genders (Graph 1). The mean SIJ value in females was 1.02±0.11 for the right side, and 1.02±0.12 for the left side. The mean SIJ value in male was found 1.06±0.10 and 1.08±0.11 for right and left side, respectively. Radioactive agent uptake is related to blood flow and osteoblastic activity. Bone metabolism decreases with increased age. This result is correlated with this physiological process.

In this study, we found that three ROI drawing techniques in four groups were significantly different from each other (Table 3). The influence of ROI selection is important due to the variability of radiopharmaceutical distribution in the areas we used as a reference. A negative significant association between age and right/left

SIJ index values was found using all three methods in this study ($p<0.05$). This result shows that age affects the SIJ index. Osteoblast activity decreases with aging, thus bone density decreases. At the same time, the SIJ cartilage becomes weaker and degenerative changes can occur in the joint. We believe that the physiological aging process may cause this result. The average value range of the SIJ index of the three methods was determined as follows: 1.13-1.34 for the first group, 1.06-1.18 for the second group, 1.02-1.12 for the third group, 1.01–1.10 for the fourth group in this study (Table 4). ROI drawing methods may cause different results in different age groups. Differences in bone density, cartilage structure and ligaments of the SIJ as well as SIJ stability in children and adults can also lead to this result.

There are different results on this subject in the literature. In a research study, four different techniques were compared to calculate the SIJ index in a healthy group (n=100). Tiwari et al. reported that there was no difference between these methods in the SIJ index (11). Therefore, the authors underlined that the selection of ROI did not have importance in calculating this index. Elderly patients had the lowest SIJ values (11). The same authors also stated that SIJ values were changed between 1.06 and 1.36 (11). Additionally, in another study, authors documented that normal SIJ values ranged between 0.9 and 1.14 in eighty-two cases (13). Normal SIJ values can change in every population. Reyhan et al. reported that right SIJ was lower than left in both genders in 197 patients without any disease (12). SIJ value decreased with increasing age. The authors also stated that body mass index (BMI) and number of births affected the SIJ value. SIJ was decreased with increasing BMI in women.

SIJ value was higher in females in the first method using the sacrum as a background in research that was performed in pediatric patients (n=79). However, no difference was found in the second method using the L5 vertebra as background. Moreover, SIJ values were lower in the second method in this study (15). Rectangular ROI was used to calculate the SIJ index in a study conducted on 335 people. The lowest value was obtained in the group aged 5 and under (16). Min. et al. retrospectively evaluated bone scans in patients (n=53) and the SIJ to sacrum ratio was found helpful (17). Yoon et al. evaluated the diagnostic performance of quantitative single photon emission computed tomography (SPECT)/CT for identifying sacroiliitis. SPECT/CT had 87.5% sensitivity and 56.5% specificity. SIJ/sacrum ratio can be helpful for patients in whom MRI is contraindicated (18). There was a medium correlation between SPECT/CT and MRI in a study that was performed in 53 patients. The authors concluded that this method might have a role in the diagnosis of active sacroiliitis (19). In addition to conventional imaging methods, studies related to deep learning have been reported in the literature. Lee et al. developed and evaluated an artificial intelligence (AI) model using MRI images to show sacroiliitis in 296 patients. The authors reported that this model might be used for other clinical conditions (20). An AI model was developed using pelvic radiographs from patients by Li et al. (21). This model was found to be helpful for diagnosis and management of sacroiliitis. Bordner et al. developed a deep-learning model using MRI images of patients to show active sacroiliitis. The authors concluded that the diagnostic performance of this AI model was high for the detection of BME (22).

Limitations of this study were a low number of patients and a number of births, body mass index which might affect SIJ values could not evaluated.

Conclusion

Despite advances in imaging technologies, bone scintigraphy still maintains its importance in clinical practice. This method has been used for various clinical indications including detection of sacroiliitis. Bone scintigraphy is an easy-accessible, low cost and sensitive method. SIJ index is a quantitative parameter that increases, the bone scan's specificity. Due to SIJ's complex anatomy and the physiological distribution of the radiopharmaceutical, various factors might affect SIJ index values in individuals. Depending on the ROI selection, the normal SIJ index value varies in the same age group. For this reason, each society should know its own SIJ values considering other factors.

Ethics Committee Approval: The study was approved by the Sutcu Imam University Local Ethics Committee (date:29.06.2016 and decision number:16).

Informed Consent: Consent was not obtained as it was a retrospective study.

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Revision of The Total Hip Artroplasty Previously Placed False Acetabulum

Yalancı Asetabuluma Yerleştirilen Total Kalça Artroplastisinin Revizyonu

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Abstract

The initial management of coxarthrosis is conservative modalities; the final treatment is total hip arthroplasty. It is essential to place the acetabular cup in the true acetabulum. For a 43-year-old female patient, total hip replacement was performed, and it was seen that the acetabular cup was placed in the false acetabulum at a different medical center. Later, loosening of the prosthesis was detected, and revision total hip arthroplasty was performed about 26 months after the index surgery. The acetabular cup, previously placed in the false acetabulum, was left in place to act as a bone stock at the superior acetabulum. It was observed that there was no complication in the patient follow-up. There is no femoral head that can be used as a graft to support the superior region of the true acetabulum in some revision cases. The acetabular cup, placed at the false acetabulum, can be used as an abutment in cases of aseptic loosening.

Keywords: Dysplastic Coxarthrosis, Revision Total Hip Arthroplasty, False Acetabulum, Surgery.

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Öz

Koksartrozun ilk tedavisi konservatif yöntemler olmasına rağmen nihai tedavi total kalça protezidir. 43 yaşında kadın hastaya dış merkezde total kalça protezi ameliyatı uygulanmış ve asetabular komponentin yalancı asetabuluma yerleştirildiği görülmüştür. Daha sonra protezin gevşediği belirlendi ve ilk ameliyatından yaklaşık 26 hafta sonra revizyon total kalça artroplastisi yapıldı. Önceden yalancı asetabuluma yerleştirilen asetabular komponent asetabulum superiorunda kemik stoğu görevi görmesi için yerinde bırakıldı. Hastanın takiplerinde herhangi bir komplikasyon izlenmedi. Bazı revizyon vakalarında gerçek asetabulumun superior bölgesini desteklemek amacıyla greft olarak kullanılabilen femur başı yoktu, yalancı asetabuluma yerleştirilen asetabular komponent de aseptik gevşeme vakalarında destek olarak kullanılabilir.

Anahtar Kelimeler: Displastik Koksartroz, Revizyon Total Kalça Protezi, Yalancı Asetabulum, Cerrahi.

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Introduction

Developmental dysplasia of the hip (DDH) seen in infancy is the most common cause of secondary hip osteoarthritis in young patients (1). Although conservative treatment is the first step to managing dysplastic coxarthrosis, hip arthroplasty is the definitive treatment of pain and limitation of movement (2). Osteoarthritis patients secondary to developmental hip dysplasia (DDH) require total hip arthroplasty (THA) surgery at an earlier age than primary osteoarthritis patients. Surgery is more complex in these patients, and complication risk is higher than standard hip arthroplasties due to insufficient amount of acetabular bone, the disorder of the proximal femur anatomy, increased anteversion, muscle contractures, and limb length discrepancy (3).

In dysplastic coxarthrosis cases, the most crucial part of the surgery is acetabular reconstruction. Despite the superior placement of the acetabular component being accepted without lateral placement, it is recommended to place it in the true acetabulum as much as possible (3). Acceptable bone coverage is vital for adequate stability in placing the acetabular component in the true acetabulum (4). In Crowe type III and some types II and IV cases, the femoral head is used as an autograft for the insufficient superoposterior part of the acetabulum, or the acetabular component may need to be placed slightly above the true acetabulum (5). In cases where the acetabular component cannot be placed in the true acetabulum, the biomechanics of the hip will change significantly due to the change in the center of rotation of the hip, the durability of the reconstruction will be adversely affected, and this will cause premature loosening of the prosthesis (5).

The femoral head can be superiorly placed as a graft to support the acetabular component. The amount of the graft that covers the acetabular component should not exceed %40. (4). In this case, the previously placed acetabular component was left in place as an abutment since there was no femoral head. In the patient follow-ups, it was observed that the component placed in the false acetabulum acted as a support and remained stable.

Case Presentation

Writen informed consent for participating in the study was obtained from the patient. A 39-year-old female patient was diagnosed with DDH in infancy, and a spica cast was recommended as a treatment. The family refused the treatment and did not attend the follow-ups. In the last five years, pain in the right hip, especially at night time, and sleep disorder due to pain began to occur. The patient's resting pain started and gradually increased. As the patient's complaints did not regress and her complaints increased, the patient underwent primary total hip arthroplasty on 12.01.2015 at a different medical center. In this surgery, the patient's acetabular component was placed in the false acetabulum. The patient, who continued her active life after the surgery, did not have pain while walking, but the previous groin and hip pain continued during the resting period. In the first postoperative year, the patient started to have pain while walking and weight-bearing on the operated leg. When the patient was admitted to our hospital due to non-reducing pain, the physical examination revealed tenderness in hip movements and groin pain while walking. The patient was clinically unable to walk long distances, sometimes felt the need to use a cane, and had trouble sitting in a chair. The Harris hip score score was 51.1. On the posteroanterior (PA) pelvis radiograph, it was seen that the right hip acetabular component was placed in the false acetabulum, and there were minimal signs of osteolysis (Figure 1). Laboratory studies of the patient's blood sample resulted in C-reactive protein: 1.8 mg/L (N: 0-5), Sedimentation: 32 mm/h (N: 0-20), White blood cells: 4.4 K/uL (4.5-11.0). In the scintigraphy performed on 24.02.2017, it was reported that slightly increased activity uptake was detected in the superior portion of the acetabular component of the right hip prosthesis and trochanter major and minor, but these findings were not clear scintigraphic findings suggesting prosthesis infection/loosening. Since the patient's complaints continued and were not improved with medical treatment, revision total hip replacement surgery was performed, and the acetabular component was planned to be placed in the true acetabulum on 21.03.2017; the revision surgery was performed about 26 months after the index surgery.

On the first postoperative day, the patient was mobilized without any weight bearing. In-bed exercises and daily dressings were made. The patient was discharged on the fifth day because there were no complications in the postoperative period. On the 15th postoperative day, the sutures were removed at the outpatient follow-up. In the subsequent outpatient controls, it was observed that the patient's pain decreased, and her complaints were improved. In the postoperative evaluation at the sixth month, the patient's pain decreased, and there was

seldom pain. There was no need to use a cane; it was possible to sit in a chair. There was no limb incompatibility between both extremities preoperatively and postoperatively. There was no infective finding in place of the acetabular component, which was left in place during the intraoperative period. Acute phase reactants were normal both preoperatively and postoperatively. The walking distance had increased significantly, up to 10 times. The Harris hip score score was 85.55. The patient had no complaints in the 5th year following (Figure 2). No complications occurred.

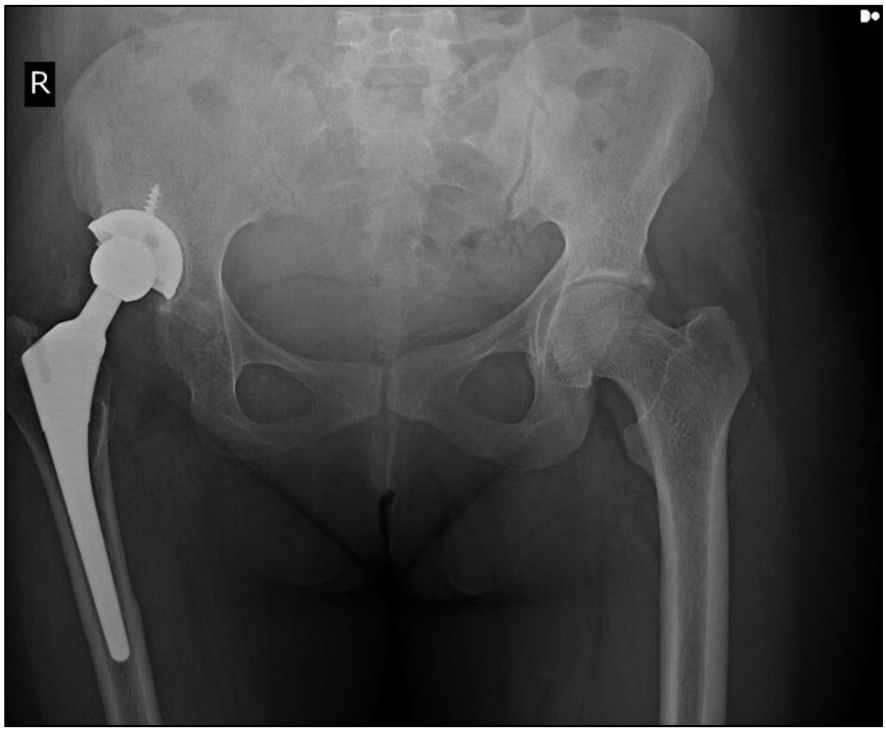

Figure 1. Pelvis x-ray of postoperative 24th months after the total hip arthroplasty, osteolysis of the acetabular cup at first operation at different center

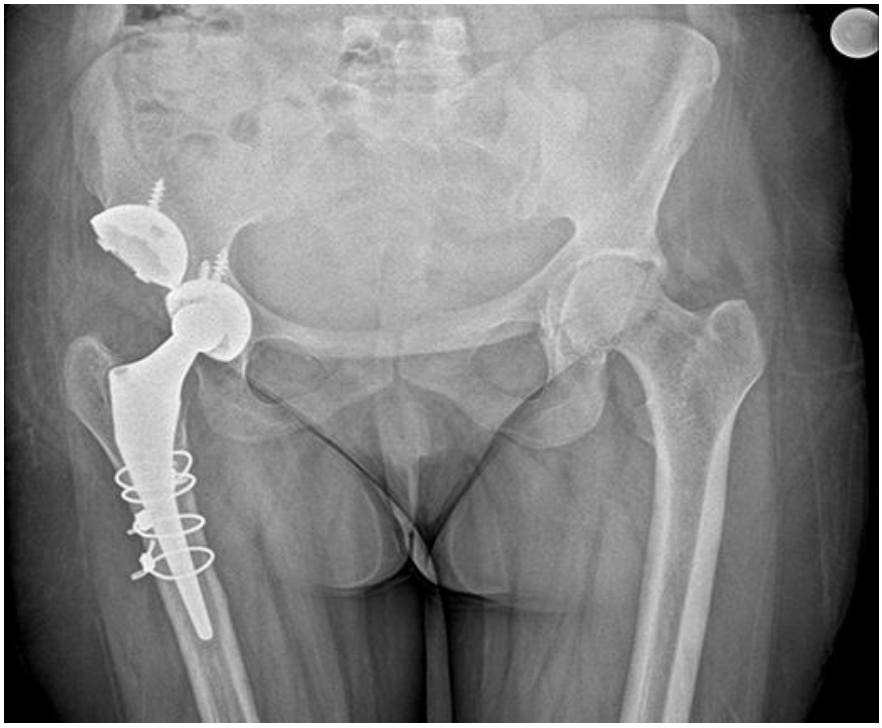

Figure 2. Pelvis x-ray of postoperative 5th years after the revision total hip arthroplasty

Discussion

This case report is the first revision hip replacement surgery in the literature in which the old acetabular component is left in place.

One of the most technically challenging parts of arthroplasty in dysplastic coxarthrosis patients is to obtain a stable and long-lasting acetabular component that can be covered with sufficient bone tissue (4). Indication of total hip arthroplasty in coxarthrosis due to DDH patients is not different from that in primary coxarthrosis cases (6). In this respect, one of the situations that should be considered is where the acetabular bone support is the greatest, the true acetabulum, or the region around it (7). As we move proximally towards the iliac bone, the bone support weakens, and the risk of loosening the acetabular component increases (7). In patients with dysplasia, placing the acetabular component as medial to the true acetabulum as possible will reduce the moment arm of the body weight, thereby reducing the pressure on the acetabular component (8). In the 15-year follow-up, Linde et al. reported that the loosening rate was 13% in the acetabular components placed in the true acetabulum and 42% in those places in superiorly (3). In a study by Johnston et al., they found that the abductor muscles spend 116% more force during normal walking as a result of 20 mm proximal, 20 mm lateral, and 10 mm posterior placement of the hip center (3).

The support of the acetabular component with bone grafts was brought to the agenda by Dunn and Hess (8) and the femoral head was used as an autograft by Harris for support in cemented acetabular components. (9). In Harris' study series, although the union of the graft placed in the early period was observed, loosening rates of 20% at the end of the 7th year and 46% at the end of the 11th year were found (9). The reason for these loosenings in the long term has been found to be the use of the sclerotic, cystic degenerated femoral head of the graft and the graft covering more than 40% of the acetabular component (10). Rodriguez, on the other hand, emphasized that the coverage rate of the acetabular component of the graft should be less than 40%, stated that the graft maintains its vitality and integrity, and noted that the main reason for loosening is the inadequacy of the cemented fixation rather than the collapse of the graft (10). In our case, due to the very few bone stocks between the false and true acetabulum, we did not remove the acetabular cup, previously placed in the false acetabulum, and provided superior support to the acetabular cup placed in the true acetabulum. By not using an extra autograft in this region, we prevented the resorption problem encountered in grafts. Thus, we forestalled the possibility of loosening the acetabular component due to graft resorption. Although there was no finding to suspect infection during the operation, we removed the polyethylene insert, which does not have any support function, so it does not constitute a source of infection.

Revision surgeries of patients with DDH who have undergone TKA are more challenging and have a higher risk of complications. Since there is no femoral head that can be used as a graft to support the superior region of the true acetabulum in these revision cases, the acetabular cup, placed at the false acetabulum, can be used as an abutment in cases of aseptic loosening.

Informed Consent: Written consent was obtained from the patient.

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Ceftazidime-induced Non-Convulsive Status Epilepticus (NCSE) in a pediatric patient with Literature Review

Pediatrik Hastada Seftazidime Bağlı Nonkonvülsif Status Epileptikus (NKSE) Olgusu; Seftazidime Bağlı NKSE

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Abstract

Cephalosporins are a class of antibiotics routinely prescribed for a variety of pediatric infections. Among uncommon adverse effects, cephalosporins can be neurotoxic and epileptogenic, particularly in patients with reduced renal function. Neurotoxic effects are most frequently observed in adults with impaired renal function, and they have rarely been recorded in children. An 11-year-old boy with chronic renal failure experienced non-convulsive status epilepticus two days after initiating intravenous cefazolin and ceftazidime with a pre-diagnosis of peritonitis. The patient's mental condition reverted to baseline within hours after intravenous antibiotic treatment was discontinued and appropriate antiepileptic and anticonvulsive therapy was started. Providers should investigate cephalosporin-induced non-convulsive status epilepticus clinically and electrophysiologically in any child with renal impairment who demonstrates acute changes in mental status or decreased awareness after initiating intravenous cephalosporins.

Keywords: Cephalosporin, Non-Convulsive Status Epilepticus, Renal Failure.

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Öz

Sefalosporinler, çeşitli pediatrik enfeksiyonların tedavisinde rutin olarak reçete edilen bir antibiyotik sınıfıdır. Seyrek görülen yan etkiler arasında, sefalosporinlerin özellikle böbrek fonksiyonu azalmış hastalarda nörotoksik ve epileptojenik olabileceği belirtilmiştir. Nörotoksik etkiler, özellikle böbrek fonksiyonu bozulmuş yetişkinlerde daha sık gözlenirken, çocuklarda nadiren bildirilmiştir. Kronik böbrek yetmezliği tanısı ile takip edilen 11 yaşındaki erkek hastada peritonit ön tanısı ile intravenöz sefazolin ve seftazidim tedavisine başladıktan iki gün sonra non-konvülsif status epileptikus tablosu gelişmiştir. Hasta intravenöz antibiyotik tedavisinin kesilmesi ve uygun antikonvülsan tedavinin başlatılmasının ardından birkaç saat içinde mental durumu normale dönmüştür. İntravenöz sefalosporin başlanmasının ardından akut mental durum değişiklikleri gösteren her çocuk hastada klinik ve elektrofizyolojik olarak sefalosporin kaynaklı non-konvülsif status epileptikus akla gelmesi gereken ön tanılardan biridir.

Anahtar Kelimeler: Sefalosporin, Nonkonvulzif Status Epilepticus, Renal Yetmezlik.

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Introduction

Cephalosporins are one of the most chosen classes of antibiotics for various types of infections because of their broad antibacterial spectrum and pharmacokinetic and pharmaco-dynamic features. Cephalosporins are classified into four generations according to their antibacterial ability. Neurotoxicity of cephalosporins was reported for all generations (1). While cephalosporin-related neurotoxicity can happen even with proper dose and during dialysis, predisposing variables include pre-existing central nervous system impairment, renal impairment, and excessive dosing (2).

Cephalosporin-related neurotoxicity can manifest as myoclonus, dystonic movements, tremor, asterixis, coma, seizure, encephalopathy, and status epilepticus. Non-convulsive status epilepticus (NCSE) is a rare but well-known side effect of cephalosporins in people with renal insufficiency (3). This disorder can result in varied degrees of altered consciousness in the absence of obvious motor signs. NCSE is defined as seizures that continue without convulsions for more than ten minutes without complete interictal recovery (4). The examination of an electroencephalogram (EEG) is essential for diagnosis of this illness, and EEG can reveal continuous or intermittent electrographic discharges. Here, we present a pediatric patient followed with renal failure and continuous ambulatory peritoneal dialysis (CAPD) who developed NCSE while being treated with intravenous cefazolin and ceftazidime for pre-diagnosis of peritonitis.

Materials and Methods

Case Report

An 11-year-old boy was brought to the outpatient clinic with complaints of fever, vomiting, and abdominal pain. He was diagnosed with chronic renal failure caused by posterior urethral valve. Since the patient had been receiving peritoneal dialysis for the previous six years, the current symptoms indicated peritonitis. He was hospitalized and administered intravenous cefazolin and intraperitoneal ceftazidime. During the fourth day of treatment, clinicians observed he was intermittently confused. At follow-up, he displayed a steady deterioration in his mental state, as well as disorientation and difficulty cooperating, occasionally featuring facial myoclonic jerks. He could be aroused, responded to queries, and obeyed directions at the time of the initial neurological evaluation. There were no focal neurological abnormalities found during the neurologic evaluation. Brisk deep tendon reflex and bilateral clonus were noted. His Glasgow Coma score was E4M6V4. Brain MRI showed periventricular white matter ischemic alterations (periventricular leukomalacia) in T1 series. Diffusion and SWI series were normal. His EEG (Figure-1) revealed constant 3-Hz bi/triphasic sharp waves, leading to the diagnosis of NCSE. After administering midazolam (0.1 mg/kg intravenously) and diazepam (10 mg intravenously), electrophysiological findings improved. He was treated with sodium valproate, which was initiated with loading dose of 20 mg/kg, intravenously and continued with oral maintenance therapy. His EEG background initially improved, nevertheless, throughout the course of the following hour, the persistent, widespread acute and slow wave activity reappeared. Intravenous levetiracetam and oral clonazepam were added as maintenance therapy because of the patient's intermittent drowsy state and EEG findings. As no alternate etiology for NCSE could not be identified, cephalosporin-induced NCSE was considered. Ceftazidime and cefazolin were discontinued, About two days after stopping the cephalosporin, clinical symptoms and EEG results improved. He was later discharged with full recovery. In the subsequent three months of follow-up, antiepileptic drugs were successfully discontinued and EEG results were entirely clear (Figure 2).

Discussion

Here, we report a male with renal failure who had developed NCSE with the treatment of cephalosporins. As a differantial diagnosis, we excluded if he had metabolic encephalopathy, severe hypertension, infectious diseases, and electrolyte imbalances which are the causes of altered consciousness in patients suffering from renal failure (5). His biochemical tests did not show electrolyte imbalance and, the renal function values were not increased compared to his baseline values. The blood pressure was at the 50th percentile for his age. During the NCSE period, the patient had been treated with antibiotics for peritonitis and, there was no increase in infectious biomarkers and he had no fever which is the main sign of the infections. However, since neurological deterioration occurred following antibiotic treatment, the lumbar puncture was planned to

exclude central nervous system infection by evaluating cerebrospinal fluid. However, the family did not consent to the procedure. The patient's EEG findings were consistent with NCSE. Clinical improvement was observed following the and the initiating antiepileptics and anticonvulsants and, discontinuation of the cephalosporins. This is proof that NCSE is related to cephalosporin treatment.

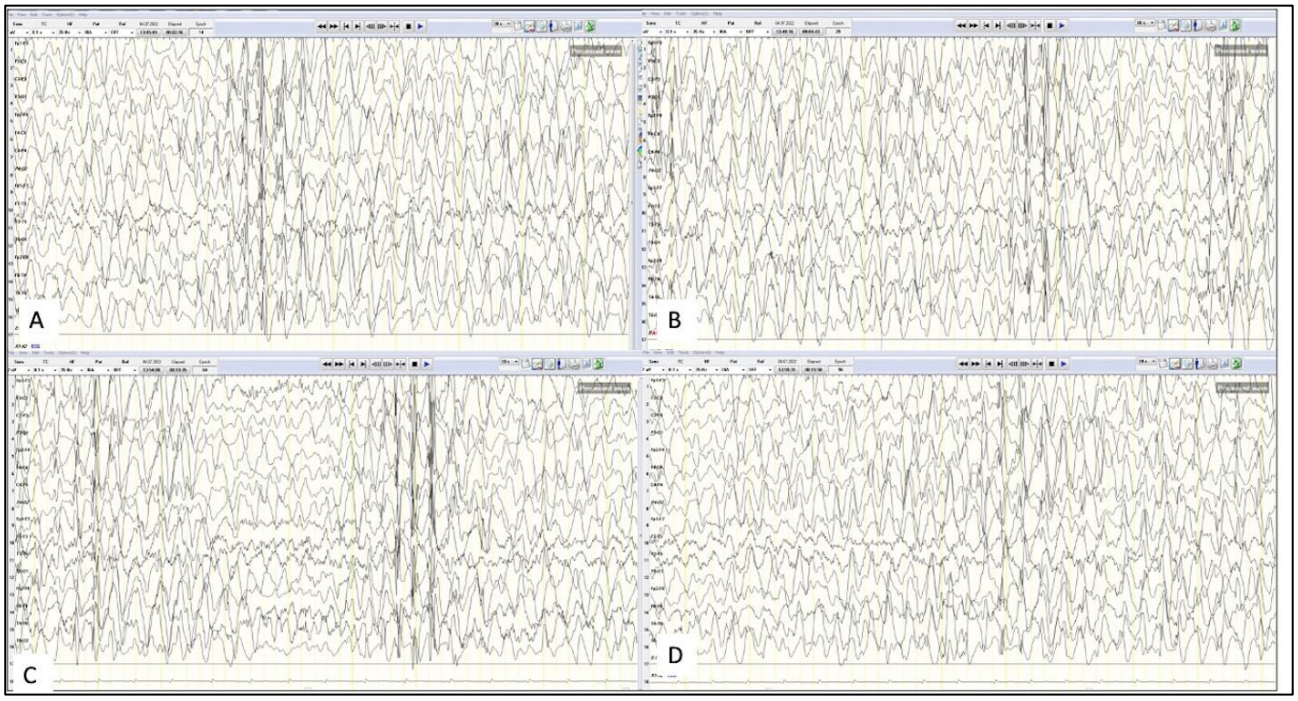

Figure 1. Preliminary electroencephalogram of the patient (during cephalosporin administration) suggestive of non-convulsive status epilepticus.
A)1st minute B) 5th minute C) 10 th minute D) 15 th minute

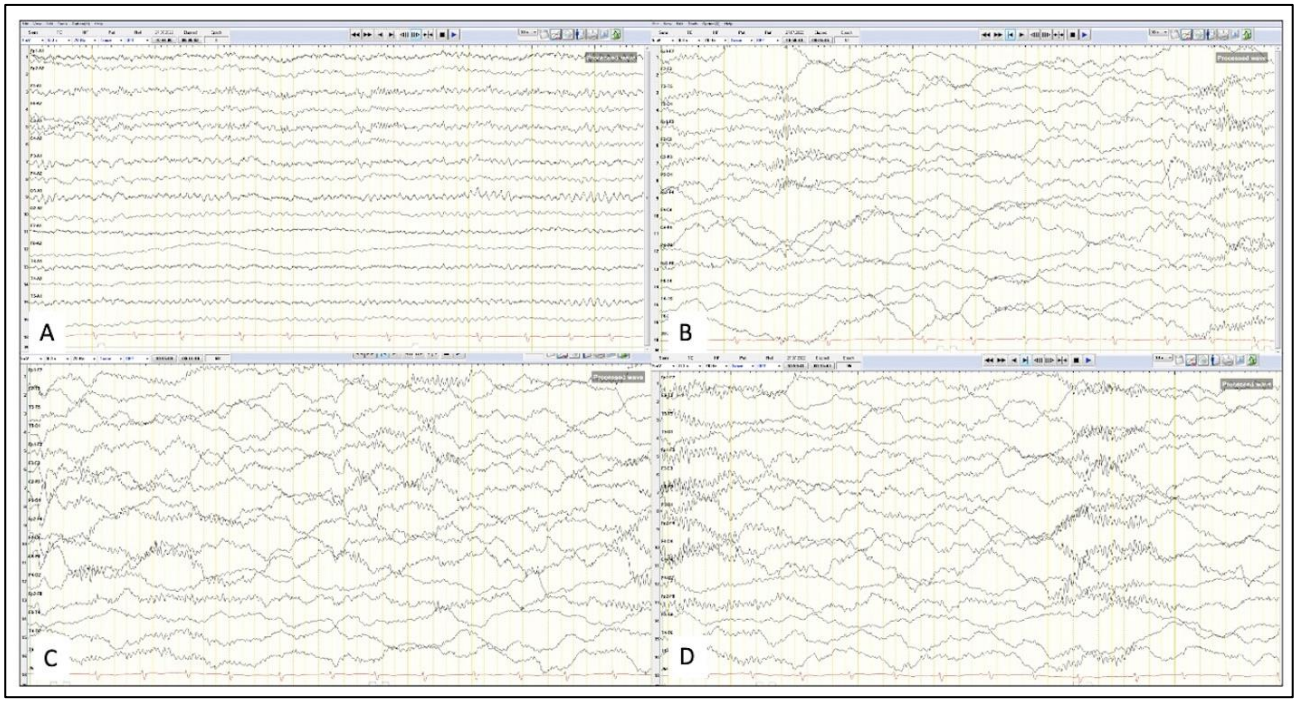

Figure 2. Control electroencephalogram – one week after discharge.
A)1st minute B) 5th minute C) 10 th minute D) 15 th minute

Neurotoxic adverse effects are caused by cephalosporins that can lead to status epilepticus, particularly NCSE, which is a well-known but unusual complication. Recent years have seen an increase in the number of reports

regarding the diagnosis of pediatric cephalosporin-induced NCSE. When a patient receives intravenous cephalosporin therapy and develops sudden changes in mental status, especially if they have any degree of renal failure, a diagnosis should be taken into consideration.It was reported that elderly patients are more likely to experience neurotoxicity since their creatinine clearance may decline with age. Here, we present a pediatric case with renal impairment diagnosed with NCSE, one of the neurotoxic effects of cephalosporins, while receiving intravenous cefazolin and intraperitoneal ceftazidime.

Cephalosporin-related neurotoxicity is thought to be associated with gamma aminobutyric acid (GABA)-A receptor antagonism because a part of the beta-lactam molecule resembles the chemical structure of the well-known GABA antagonist bicuculline (6,7). Inducing the release of endotoxins and TNF-alpha, which is associated with septic encephalopathy, and raising glutamate levels were considered as additional mechanisms contributing to neurotoxicity (8). Cefepime is the most frequently reported drug related to neurotoxicity among all generations of cephalosporins; however, ceftriaxone, ceftazidime, cefotaxime, and cefazolin were all cited (8). It is common practice in acute peritonitis to administer a combination of first and third-generation cephalosporins, cefazolin and ceftazidime, intraperitoneally on an intermittent or continuous basis (8). The size of the substituents at positions 7 (R1) and 3 (R2) in their 7-cephalosporanic acid structures determines the epileptogenesis of cephalosporin. Positions 7 and 3 on a cefazolin heterocyclic ring may increase the possibility of epileptogenesis.

Prior central nervous system (CNS) disorders, high dosage consumption, and renal insufficiency are risk factors for cephalosporin-induced neurotoxicity (3). Patients suffering from renal insufficiency are more susceptible to neurotoxic effects because of changed pharmacokinetics that lead to raised blood urea nitrogen and cephalosporin concentrations in circulation. Additionally, the permeability of the blood-brain barrier is increased by glycated and carbamylated proteins (10). However, active peritonitis may raise membrane permeability and hence raise antibiotic absorption, raising the possibility of systemic toxicity (9). From the peritoneal cavity, ceftazidime is absorbed and enters the bloodstream. Compared to individuals who are not infected, patients with peritonitis absorb more medication from the peritoneal cavity (3). Despite being administered at authorized dosages, patients with renal impairment are more susceptible to ceftazidime neurotoxicity because the medication is not digested by the body and is eliminated unchanged in the active form in the urine by glomerular filtration (11). As a result of renal failure and peritonitis, our patient was in the risk group for cephalosporin neurotoxicity.

The onset of neurotoxicity can occur one to ten days later. After stopping cephalosporin medication, documented neurological problems frequently subside in two to seven days (1,12). The clinical condition of our patient worsened on the fourth day of cephalosporin medication. Symptoms began to improve two days after cephalosporin discontinuation.

Although NCSE was reported in patients with renal disease, neurotoxicity was also reported in cases without renal function problems (13). The diagnosis of drug-induced NCSE has become more common in recent years, and patients who experience sudden changes in their mental state while receiving intravenous cephalosporin treatment—especially those with some degree of renal dysfunction—should have this condition evaluated. An urgent EEG should be taken into account. The use of electroencephalography is necessary for precise diagnosis (4). Working criteria for the EEG diagnosis of NCSE were proposed by a consensus panel at the 4th London-Innsbruck Colloquium on status epilepticus and acute seizures, which was held in Salzburg in 2013 (Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus, SCNC). Our patient was diagnosed with NCSE with continuous 3 Hz generalized spike and wave activity based on these criteria.

Myoclonic seizures, aberrant conduct, mutism, ataxia, asterixis, hallucinations, tremor, clonus, and hyperreflexia are among the clinical signs other than altered awareness that have been documented (6). Case reports have shown brief myoclonic seizures prior to NCSE, as was the situation with our patient (10).

Our case is an example of NCSE due to the neurotoxicity of cephalosporin at a therapeutic dosage in a pediatric patient with renal failure. It is important that this event should be considered in pediatric patients, although the majority of cases were reported at older ages. A summary of the previously reported pediatric patients with cephalosporin-induced NCSE is shown in Table 1. Most of the pediatric cases reported in the literature were related to cefepime. However, our case is significant due to its association with ceftazidime.

Tablo 1.

The Summary of Patients with The Diagnosis of Cephalosporin-Induced Non-Convulsive Status Epilepticus

References	Age of patient/ sex	Comorbidities	Drug	NCSE symptoms	Cranial imaging	EEG findings	Treatment	Follow up
Chedrawi et al., 2004 (13)	12-years/ Female	Chronic renal insufficiency secondary to congenital renal dysplasia.	ceftriaxone for possible sepsis	progressively more confused and unresponsive occasional myoclonic twitches of the face	CT: normal	Bursts and runs of generalized spike and spike wave discharges *are recorded over a period of 90 seconds.* Generalized triphasic and slow waves	diazepam , phenytoin,, benzodiazepine Ceftriaxone was discontinued	the following day, mental status dramatically improved , became awake, coherent and able to follow verbal commands. complete resolution of the epileptiform discharges within 24 hours after discontinuing ceftriaxone background remained slow, likely a postictal effect.
Alpay et al., 2004 (14)	15years/Male	End-stage renal disease secondary to focal segmental glomerulosclerosis	intravenous cefepime for pneumonia	gait abnormality, difficulty in writing and reading, memory problems. progressive confusion	CT: did not show any acute abnormalities. MRI : normal	consistent with status epilepticus	diazepam phenytoin Cefepime therapy was discontinued	No neurological findings and with normal EEG (after 1 year follow-up)
Thabet et al., 2009 (15)	15-years / Female	End stage renal disease secondary to polycystic kidney on hemodialysis	IV cefepime for blood culture showed Pseudomonas aeruginosa	Lethargic and confused. (Glasgow coma scale of 8), myoclonic jerks	CT scan brain were unrevealing	Generalized spike and sharp wave activity compatible with NCSE	Midazolam con-tinuous infusion. İntubation Cefepime was discontinued	the patient regained full consciousness (Glasgow coma scale of 15) after 48 hours repeated EEG was normal

Nichols et al., 2011 (16)	A 15-year-old,	Cystic fibrosis Acute kidney injury	IV cefepime for lower respiratory cultures contained MSSA and *Stenotrophomonas maltophilia*, with past cultures significant for *P. aeruginosa*.	Sleepy poorly responsive.	Not available	An electroencephalogram (EEG) was not obtained due to extubation of the patient	Hemodialysis	At a 2-week follow-up clinic visit, the patient was recovering well,
Landgrave et al., 2012 (17)	14 years / Female	McCune-Albright syndrome, hypoparathyroidism, hypothyroidism, asthma, hypogammaglobulinemia, factor V Leiden deficiency, deep vein thrombosis, worsening kidney failure during antibiotic treatment.	intravenous cefepime and meropenem for septic hip artiritis	deteriorated right-sided face twitching sleeping, sedated	CT: mildly prominent lateral ventricles, with otherwise normal findings.	Requent, irregular, generalized polyspike wave discharges High-amplitude nonrhythmic slowing, and 2-second periods of background suppression or attenuation. After pentobarbital infusion :burst suppression	midazolam drip levetiracetam. pentobarbital infusion Cefepime was discontinued Meropeme was discontinued	
Ekici et al., 2012 (18)	Case1(C1) : 15 years / Female Case2 (C2) : 7 years / Female	C1: Chronic renal failure who was on continuous ambulatory peritoneal dialysis (CAPD) C2: Hypertension and chronic renal failure secondary to bilateral vesico-ureteral reflux	C1: Intraperitoneal and intravenous (IV) ceftazidime and vancomycin for peritonitis C2: IV cefepime for open bilateral ureteroneocystostomy	C1: Headache, drowsiness, myoclonic jerks and ataxia. C2: confused demonstrated inappropriate crying, agitation involuntary movements of the head and hands.	C1: (MRI) was normal. C2:not available	C1: diffuse slow-spike waves and triphasic waves C2: diffuse slow-spike waves	C1: ceftazidime was discontinued oral valproate C2: cefepime was discontinued, iv diazepam , oral sodium valproate	C1: Began to communicate after 24 hours. Myoclonus disappeared (on the fifth day of treatment) the EEG normalized after 6 days. C2: symptoms were disappeared after 2days EEG findings were normalized after 10 days.

Shah et al. , 2021(19)	13years/ Female	major depressive and behavioral disorder, focal segmental glomerulosclerosis, subsequent hemodialysis dependent end-stage renal diseas	intravenous cefepime for cathether infection	difficulty in walking and grasping items. aphasia visual hallucinations	CT: did not show any acute abnormalities. MRI :unremarkable	mild background slowing, multifocal and diffuse epileptiform discharges, generalized excessive beta intermittently, slowing in the right posterior quadrant, left posterior quadrant, and central head regions	lorazepam levetiracetam phenobarbital Cefepime therapy was discontinued hemodialysis	back to her neurologic baseline with normal GCS within 24 hours
Nguyen et al. 2022 (12)	16 years/ Female	Chromosome 10-15 unbalanced translocation, spastic quadriplegic cerebral palsy, epilepsy, hydrocephalus with VP shunt, tethered cord syn-drome Tracheostomy fundoplication, scoliosis, and thoracic lordosis status post spinal fusion, and global developmental delay.	intravenous cefepime, linezolid and vancomycin for positive Escherichia coli urine cultures, positive Pseudomonas spp. respiratory cultures, Clostridium difficile prophylaxis	less responsive than usual Intermittent extensor posturing was noted with tactile stimuli, no other response to noxious stimuli.	CT head : showed expected pneumocephalus with mild soft tissue swelling over the left frontal scalp	Rhythmic 2.5-3 Hz generalized epileptiform discharges	levetiracetam, lorazepam, phenobarbital Cefepime was discontinued	Back to her baseline state of health within 2 days after discontinuing cefepime
Hambrick et al., 2022 (20)	2 years /	Chronic kidney diseas	IV cefepime for *Serratia marcescens* bacteremia	Agitation, tremor, and inconsolability	No data avaliable (abstract only)	No data avaliable (abstract only)	Cefepime was discontinuation	No data avaliable (abstract only)

In conclusion; while there are no defined standard criteria for the therapy of this condition have not been established, discontinuation of antibiotics, administration of antiepileptic drugs, and receiving supportive treatment are suitable measures to take. In this potentially curable illness, prompt detection and diagnosis are critical because protracted diagnostic delays may raise morbidity or death. Clinicians and doctors should be more aware of the possible neurotoxicity of ceftazidime and other cephalosporins because their usage is growing more widespread.

Informed Consent: Written informed consent was obtained from the parents of the patient.

Conflict of Interest: Authors declared no conflict of interest.

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A Case Report: Lipomatous Hypertrophy of the Interatrial Septum

Olgu Sunumu: İnteratriyal Septumun Lipomatöz Hipertrofisi

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Abstract

Lipomatous hypertrophy of the interatrial septum is a benign condition characterized by the deposi-tion of fat into the interatrial septum. It is often mistaken for atrial masses and can be associated with conditions such as obesity, and steroid use. In this case presentation, we describe the comput-ed tomography (CT) findings of an incidentally detected and asymptomatic case of lipomatous hy-pertrophy of the interatrial septum in an 81-year-old male patient with a history of nephrolithiasis. The patient underwent CT imaging, revealing a nodular thickening of the interatrial septum. Despite the presence of moderate cardiomegaly, the patient did not exhibit any symptoms related to the cardiac mass. Lipomatous hypertrophy of the interatrial septum is often asymptomatic but can rarely cause cardiac symptoms and arrhythmias. Differential diagnoses include other cardiac masses. Ac-curate diagnosis is crucial to avoid unnecessary surgery and to provide appropriate management. Diagnostic assessment involves multiple imaging modalities, such as echocardiography, cardiac CT, and magnetic resonance imaging (MRI) scans, with CT and MRI being particularly useful in charac-terizing the tissue properties. The recognition and understanding of lipomatous hypertrophy of the interatrial septum are important for radiologists to ensure accurate diagnosis and appropriate patient management.

Keywords: Lipomatous Hypertrophy Of The Interatrial Septum, Atrial Mass, Computed Tomography.

&

Öz

İnteratriyal septumun lipomatöz hipertrofisi, interatriyal septumda yağ birikmesiyle karakterize be-nign bir durumdur. Sıklıkla atriyal kitlelerle karıştırılır ve obezite, steroid kullanımı gibi durumlarla ilişkilendirilebilir. Bu vaka sunumunda, 81 yaşında, nefrolitiazis öyküsü olan bir erkek hastada, rastlantısal olarak tespit edilen ve semptomsuz interatriyal septumun lipomatöz hipertrofisinin bilgi-sayarlı tomografi bulgularını sunacağız. Hastaya yapılan BT görüntülemede interatriyal septumda nodüler kalınlaşma tespit edildi. Hastanın orta derece kardiomegali dışında, kardiyak kitle ile ilişkili herhangi bir semptomu yoktu. İnteratriyal septumun lipomatöz hipertrofisi genellikle semp-tomsuzdur ancak nadiren kardiyak semptomlara ve aritmilere neden olabilir. Ayırıcı tanı diğer kardi-yak kitleleri içerir. Gereksiz cerrahiyi önlemek ve uygun hasta yönetimini sağlamak için doğru tanı konulması hayati öneme sahiptir. Tanıda ekokardiyografi, kardiyak BT ve manyetik rezonans görüntüleme (MRG) gibi çeşitli yöntemleri içerir; BT ve MRG, dokunun özelliklerini karakterize etmede özellikle yararlıdır. İnteratriyal septumun lipomatöz hipertrofisinin tanınması ve anlaşılması, doğru tanı konulması ve uygun hasta yönetimini sağlamak için radyologlar için önemlidir.

Anahtar Kelimeler: İnteratriyal Septumun Lipomatöz Hipetrofisi, Atriyal Kitle, Olgu Sunumu, Bilgisayarlı Tomografi.

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Introduction

Lipomatous hypertrophy of the interatrial septum is an entity was described in autopsy examinations in 1964 (1). It is characterized by non-capsulated, dumbell-shaped infiltration of fatty tissue in the interatrial septum (2,3). To be considered lipomatous hypertrophy of the interatrial septum, the sep-tum must reach a thickness of over 20 mm while preserving the fossa ovalis (4). With the frequent use of echocardiography, cardiac computed tomography (CT) imaging, and magnetic resonance im-aging (MRI), it is increasingly recognized and tissue characterization can be done more clearly (1,3). In this case presentation, we aimed to increase awareness of this condition among radiologists by sharing an CT findings of incidentally detected and remained asymptomatic case of lipomatous hy-pertrophy of the interatrial septum, which can be mistaken for atrial masses. In this case presenta-tion, we aim to raise awareness among radiologists about lipomatous hypertrophy of the interatrial septum by sharing CT findings of an incidentally detected and asymptomatic case. This condition can be mistaken for atrial masses.

Case Presentation

Written informed consent was obtained from the participant for publication of medical records and images of the patient. An 81-year-old male patient with a history of nephrolithiasis underwent fur-ther evaluation with non-contrast and contrast enhanced CT imaging during his visit to the urology clinic due to macroscopic hematuria. The patient underwent extracorporeal shock wave lithotripsy (ESWL) in 2015 due to kidney stones. Abdominal CT scan is revealed a 12 mm stone in the right ureter at the constriction at pelvic brim and an atrophic right kidney. Urogram phase was delayed at the right kidney. Due to advanced age of the patient, he was recommended to be monitored for the ureteral stone. At the same time, a nodular thickening reaching 24 mm diameter with increased fat density at the level of the interatrial septum drew attention on the chest included in this examination (Figure). The patient had moderate cardiomegaly and did not exhibit any accompanying symptoms related to cardiac mass during cardiac examination and an electrocardiogram showed sinus rhythm.

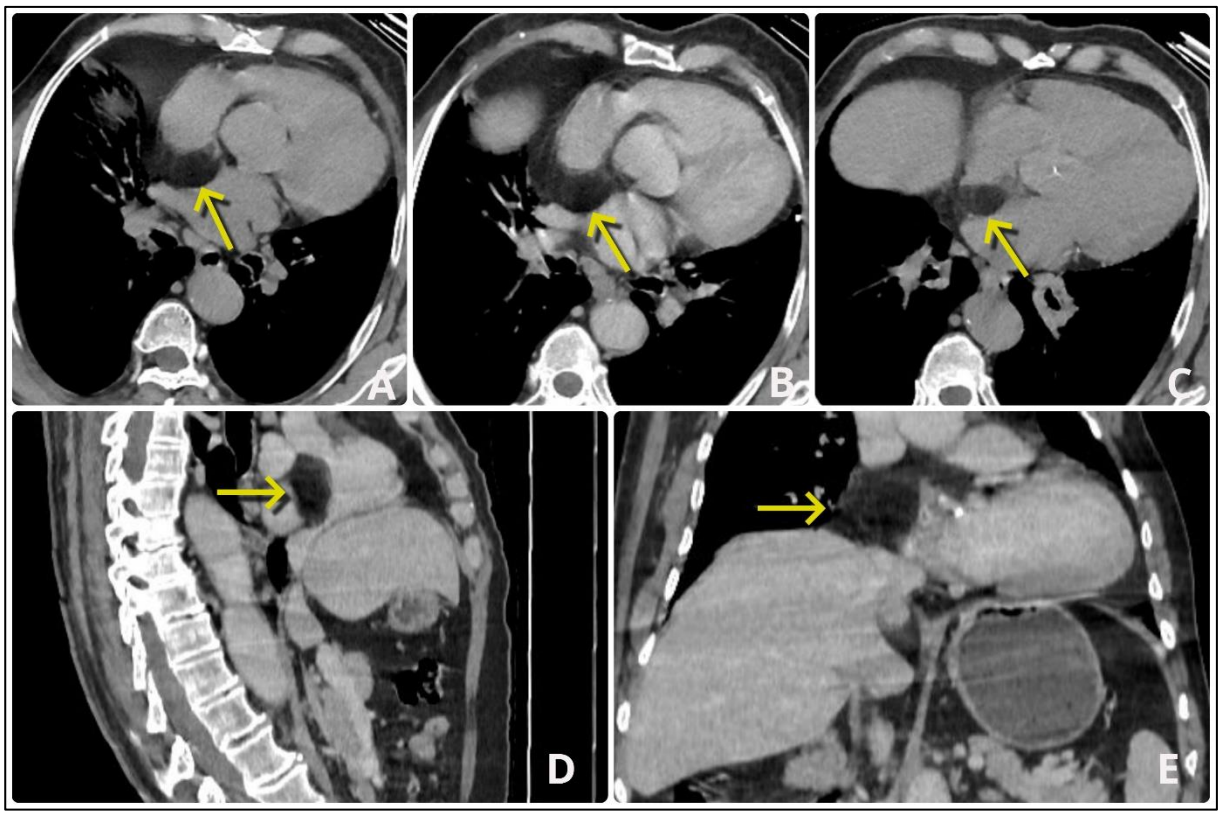

Figure 1. Axial and multiplanar views of lipomatous hypertrophy of the interatrial septum on computerized tomography (CT) images. (A-C) Axial CT images, these images show the presence of fat density (low attenuation) within the interatrial septum. The yellow arrows indicate areas where the fat den-sity is causing a mass effect on the adjacent cardiac structures. (D) Sagittal CT view provides a lon-gitudinal perspective of

the heart, illustrating the extent of the lipomatous hypertrophy. (E) Coronal CT view is particularly useful for assessing the vertical extent and impact of the hypertrophy on the atrial chambers.

Discussion

Lipomatous hypertrophy of the interatrial septum is a finding characterized by adipose tissue infil-tration in the interatrial septum, which is believed to be associated with conditions such as obesity, steroid use, and emphysema, and is more commonly seen in women and older age groups (3). Alt-hough the incidence of lipomatous hypertrophy is not exactly known, the reported incidence in the literature varies between %1 to 8 (2,5). While lipomatous hypertrophy of the interatrial septum is a benign condition, it is important for radiologists to be aware of this entity to prevent unnecessary surgery and exaggerated diagnoses, as its differential diagnosis includes tumors such as lipoma, liposarcoma, myxoma, metastasis, rhabdomyoma, fibroma, and iatrogenic hematoma in cases with previous history of percutaneous coronary interventions. Recognizing this entity is important as it can be mistaken for atrial masses (4). Although lipomatous hypertrophy of the interatrial septum is mostly asymptomatic, when they originate from the atria, they can rarely cause premature atrial con-tractions, dyspnea, chest discomfort, right atrial obstruction, or even sudden cardiac death (4,5,6). The underlying mechanism of arrhythmia is not clear but there are hypotheses have been suggesting as a result of involvement of interatrial septum and right atrial wall which may distort the structure and conducting pathways (2,7). Surgical interventions like removal of the lipomatous mass or septal myectomy may be considered in severe cases with significant hemodynamic impairment or malig-nant arrhythmias (7). Diagnostic assessment of lipomatous hypertrophy of the interatrial septum involves multiple imaging modalities including echocardiography, cardiac CT or MRI scans. The initial evaluation often start with an echocardiography exam which provides valuable information regarding the location and size of the lesion, however it is not always possible to differentiate fat from the connective tissue on echocardiography The initial evaluation often starts with an echocar-diography exam, which provides valuable information regarding the location and size of the lesion. However, it is not always possible to differentiate fat from connective tissue on echocardiography (2,7). Therefore for further characterization of the tissue characteristics the role of cardiac CT and MRI is critical. Sparing of the fossa ovalis gives the lesion typical dumbbell-shaped apperance which makes the diagnosis easier (2).

The initial evaluation often starts with an echocardiography exam, which provides valuable infor-mation regarding the location and size of the lesion. However, it is not always possible to differenti-ate fat from connective tissue on echocardiography.

Conclusion

Lipomatous hypertrophy of the interatrial septum is a relatively common, usually asymptomatic, benign condition that may mimic interatrial masses. The diagnosis is more frequently and easily made nowadays with the accelerating use of multimodality imaging techniques in which we are able to characterize tissue properties in daily clinical practice.

Informed Consent: Written consent was obtained from the patient.

Conflict of Interest: Authors declared no conflict of interest.

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